

**MONITORING HIV DISEASE PROGRESSION AMONG
ANTIRETROVIRAL THERAPY PATIENTS IN ZIMBABWE
FROM 2004 TO 2017: SPATIAL AND MULTISTATE MODEL
APPROACHES**



By

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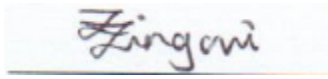
BIostatISTICS AND EPIDEMIOLOGY

October 2020

DECLARATION

I, Zvifadzo Matsena Zingoni, declare that this research report is my own, except where specific references cited to the work of others. This work has not been submitted elsewhere for any other degree or award except for this current fulfilment of the Doctor of Philosophy degree at The University of Witwatersrand. This research work reflects my independent work except in instances where explicit references have acknowledged other sources.

(Signature of candidate)

A rectangular box containing a handwritten signature in dark ink that reads "Zingoni".

25th day of October 2020

DEDICATION

This work is a special dedication to two important men in my life. Firstly, to my beloved husband Nathan Zingoni for believing in me and giving me a chance to take up space by attaining my doctoral qualification. I also dedicate this work to my late dad, Alexious Matsena, who passed-on on the 29th of June, 2011. My dad saw this season before me; unfortunately, he could not live to see it unfolding. However, he always reminded me to put God first in everything for with Him (God) nothing is impossible!

THESIS ABSTRACT

Background

Globally, remarkable progress has been made on the treatment of HIV-infected people using antiretroviral therapy (ART), particularly in sub-Saharan Africa (SSA). SSA region is disproportionately affected by the pandemic as it accounts for more than 50% of people living with HIV (PLWHIV). With the global efforts to achieve zero HIV incidences by 2030, the 90-90-90 UNAIDS targets were launched, whereby 90% of the PLWHIV should know their status, 90% of those diagnosed should be initiated on ART, and 90% of those on ART should achieve viral suppression(1). In Zimbabwe, strides have been made towards achieving these targets; however, limitations exist. Statistical modelling approaches like multistate models framework and geostatistical models can be used to determine how well ART patients are adhering to ART by estimating the ART attrition rate due to loss to follow-up (LTFU), immune deterioration patterns using CD4 cell counts and viral rebound trajectories. Geo-spatial modelling techniques can also be used to determine the spatial patterns of ART drop-out at the health facility and district levels and identify hot spots for ART drop-out to guide policy.

Study objectives

The main focus of this study was to answer the following questions crucial in HIV disease progression and monitoring: 1) what are the LTFU patterns after ART decentralization?; 2) what are the immune-deterioration patterns among ART patients?; 3) what are the underlying factors associated with poor viral suppression rates?; 4) what are the viral suppression among ART patients?; 5) which regions are heavily affected by poor ART outcomes (drop-outs, viral rebound or immune–deterioration) in Zimbabwe?; 6) and which statistical tools can be most appropriate

to answer these epidemiological questions using routinely collected individual-level data and partially observed aggregated data?

The specific objectives of this study were:

1. To demonstrate the use of Kolmogorov's forward equations in estimating transition probabilities if data is partially observed using Bayesian estimation approach as an application in the multistate models' review.
2. To describe the spatio-temporal patterns of ART drop-out at the health facility and district levels and identify cold spots and hot spots for ART drop-out
3. To determine the time to occurrence of LTFU with mortality as a competing event over 13 years follow-up period across health facility levels and other associated factors
4. To describe the HIV disease progression, and immune recovery patterns based on CD4 cell counts among adult patients on ART in Zimbabwe accounting for decentralization of ART services to all levels of care
5. To determine spatial heterogeneity of viral suppression and viral rebound trajectories among patient on ART in Zimbabwe adjusting for individual frailty, non-linear and spatial effects using Bayesian estimation
6. To jointly model viral load (VL) and CD4 cell counts prognostic markers in a multistate model framework and identify the shared geographical patterns of low CD4 cell counts and viral rebound patterns

Methods

This study was a secondary data analysis of routinely collected individual-level data of HIV-infected patients who initiated ART between 2004 and 2017. The data was compiled through the

electronic patient management system (ePMS) under the Zimbabwe national ART programme. The final study sample had 390,771 participants from 538 health facilities aged 15 years and above. The study endpoints were mortality if a patient was reported to have died, loss to LTFU defined as a failure of a patient to report for drug refill for at least 90 days from last appointment date or if the patient missed the next scheduled visit date and never showed up again; withdrawal and drop-outs. CD4 cell counts and VL prognostic markers were used to define the finite states of the HIV disease progression models. Semi-parametric time-homogeneous Multistate Markov model was used in the CD4 cell counts model: State 1($CD4 \geq 500 \text{ cells/uL}$), State 2($350 \text{ cells/uL} \leq CD4 < 500 \text{ cells/uL}$), State 3($200 \text{ cells/uL} \leq CD4 < 350 \text{ cells/uL}$), State 4($CD4 < 200 \text{ cells/uL}$) and the absorbing state death (State 5). The geoadditive Bayesian regression multistate model was fitted in the VL model. The geoadditive Bayesian regression multistate model accounted for the nonlinear effects of continuous variables, fixed effects and spatial variation. In this model, we assumed that individuals from state 1 ($VL < 50 \text{ copies/uL}$) with an undetectable viral load may die (state 3) via state 2 ($VL \geq 50 \text{ copies/uL}$) which indicates a viral load rebound or detectable viral load, or directly from state 1 ($VL < 50 \text{ copies/uL}$). Again individuals may move back to state 1 ($VL < 50 \text{ copies/uL}$) once they are in state 2 ($VL \geq 50 \text{ copies/uL}$) after ART which shows a reversible transition. Time-varying log-baseline effects of the transition intensities and nonlinear effects of continuous covariates were estimated as smoothed functions of time using penalized splines (P-splines). Non-parametric effects of fixed covariates and frailty effects to account for individual variability were also considered. Lastly, adjusted transition intensities, hazard ratios (HR) and regression coefficients were estimated from the joint modelling of CD4 cell counts and VL. Joint mapping of HIV disease progression conditions was done using the Bayesian intrinsic Multivariate Conditional

Autoregressive (MCAR) prior model. The Kolmogorov-Chapman forward equations were also used to estimate transition rates on a partially observed aggregated data.

Results:

From a total of 390,771 participants enrolled in 538 health care facilities, the proportions of mortality, becoming LTFU and attrition were 4.7% (n=18,328), 22.7% (n=88,744) and 31.2% (n=121,875), respectively. LTFU rate was 5.75(95% confidence interval (CI): 5.71-5.78) per 100 person-years. Those who had CD4 cell counts below 200cells/uL had a mortality rate of 5.7 per 100 person-years (4,541 deaths). Adjustment for the competing event independently increased LTFU rate ratio in provincial and referral (adjusted sub-hazard ratios (AsHR) 1.24; 95%CI: 1.20-1.28) and district and mission (AsHR 1.47; 95%CI: 1.45-1.45) hospitals; higher-level health facilities were associated with an increased risk of ART drop-out (RR=1.46; 95%CI: 1.43-1.48 (secondary level facilities) and RR=1.41; 95%CI: 1.43-1.45 (tertiary level facilities); higher levels of care had an increased risk of high rate ratios of LTFU and mortality while primary health care (PHC) facilities had an increased risk of poor immune recovery.

Adolescence and young adults (15-24 years) group had an increase rate ratio of becoming LTFU. The effects of patients' age on mortality increased with age while the effects of age on LTFU increased with age for the 15-20 years age group and decreased after that; patients aged 20-60 years had a high risk of attrition, and patients aged 45+ years were more likely to immune deteriorate. Male patients had a higher risk of becoming LTFU; 32% increased risk of death; and a higher risk of immune deterioration. The longer the individuals were on ART, the less likely they were to drop-out (district level: RR=0.7552; 95%CI: 0.69-0.83); health facility level: RR=0.8194; 95%CI: 0.81-0.83).

There existed a strong shared geographical pattern of 66% spatial correlation between the relative risks of VL rebound and low CD4 cell counts from the joint mapping model. High relative risks of $VL \geq 50 \text{ copies/uL}$ and $CD4 \text{ cell counts} < 350 \text{ cells/uL}$ after ART initiation was observed in Matabeleland North and Mashonaland East provinces. The geosadditive Bayesian model showed that mortality rates decreased with increase in the time since ART initiation and viral rebound transition was significantly prevalent among patients living on the long-distance truck route region (Matabeleland North province) which borders with Botswana and Zambia. The southern and northern parts of Zimbabwe show a high risk of ART drop-out based on the structured effects.

Conclusions:

ART drop-outs or "leakages" within the ART treatment cascade persist after the decentralization of ART services. Interventions which immediately link HIV patients to care and strengthen patients' retention are a priority to achieve viral suppression among ART patients. Though ART uptake has increased after ART decentralisation, poor immune recovery and viral suppression are high in PHC; hence, there is need to upgrade PHC infrastructure and strengthen their VL monitoring capacity for better outcomes. The observed poor immune recovery and viral rebound among subpopulation groups confirm the low viral suppression estimates. The poor viral suppression among males could be due to them being a blind spot in HIV response. Interventions which reach out to men in their "male spaces" and target their risk masculinity norms are encouraged to boost their HIV services uptake. The poor immune recovery among adolescents requires the launching of the social deprivation programmes to break food insecurity pathways and financial support, and the paediatric to adult transition programme to mitigate treatment lapses. Moreover, targeted interventions to highly burdened regions to improve patients'

retention coupled with strategies which will enhance ART adherence are core in the global HIV control campaign.

The main strength of this study was the statistical rigour which involves extending the Bayesian multistate model with the spatial covariate accounting for individual frailty terms and joint modelling of VL and CD4 cell counts. HIV decision-making programmes, model inferences based on BE perspective are the preferred as they provide coherent estimates despite model fitting challenges associated with Bayes models. However, future studies should consider assessing the time-varying effects of covariates; determine underlying latent covariates associated with ART outcomes, but the issues on the generalizability of research finding remain a priority to epidemiologists. Strategies which strengthen data quality of routinely collected programme data are a priority in this era of evidence-based decision making, for valid and precise findings.

Keywords:

ART monitoring, Bayesian estimation, CD4 cell counts/viral load, HIV disease progression, multistate models, hierarchical spatial-temporal models

PREFACE

This thesis is submitted to the University of the Witwatersrand, Faculty of Health Sciences for the fulfilment of the requirements for the degree of doctor of philosophy by publication in the major area-subject of Biostatistics and Epidemiology. The doctoral research has been undertaken at the School of Public Health in the Department of Biostatistics and Epidemiology with Professor Eustasius Musenge as the main supervisor and; Professor Tobias Freeman Chirwa and Professor Jim Todd both as co-supervisors.

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I would like to thank my funders, the African Academy of Science through the Developing Excellence in Leadership, Training and Science (DELTAS) Africa Initiative Sub-Saharan Africa Consortium for Advanced Biostatistics (SSACAB) funding scheme. It was an honour and a privilege to receive the SSACAB doctoral fellowship, and I am grateful to have walked this journey with the SSACAB family. Not only, did I receive financial support but mentorship. Through SSACAB, my dream came true!

I would also like to thank the Ministry of Health and Child Care, Zimbabwe through the AIDS/TB Unit for permitting me to use part of the national ART program data compiled through the electronic patient management system (ePMS). The secondary data provided was huge and helped me achieve my set objective in line with my doctoral work. I hope these doctoral research findings will be useful to formulate future studies and come up with appropriate interventions as guided by the research results to better the Zimbabwe HIV population and Africa at large. Special thanks to the former National Institute of Health Research (NIHR) director, Dr Susan Lily Mutambu for spearheading women in science at NIHR for the encouragements throughout the whole academic journey and continuously telling me that is it possible.

I extend my gratitude to the Witwatersrand School of Public Health (SPH) for being my home in the past three years. Though the Wits SPH, I received support from the PhD administration unit and being constantly supported with writing retreats within and outside the school in addition to other individual tailored assistances. Special thanks to the Witwatersrand Biostatistics Unit for their encouragements and support during my PhD journey, which kept me going over the years. Thanks to Professor Jonathan Levin, who always says PhD is a solo journey with low and high moments, but you don't give up. Recalling such words revived my determination and gave me the zeal to soldier on, especially in my lowest moments. I also thank Professor Thomas Kneib for his prompt responses to my emails and assisting me with some analysis codes which I used in one of my papers. Thanks to the SSACAB programme directorate for always making sure that our welfare was taken care of during the fellowship period. Not forgetting my friend, Rutendo Birri Makota for being a true friend who wants nothing but the best out of me. I am here because you made it, so I cherish you always.

Special thanks to my family for being there for me. My mom, my sisters (Christina and Miyetani) and brothers (Antony, Benjamin and Dzikamai), thank you for always cheering on me! Thanks to my in-laws (the Zingoni family) for supporting me in this journey and understanding how demanding it is. Last but not least, hearty thanks to my beloved husband, Nathan Zingoni, for putting my career life first. You believed in me, and you stood with me when I needed you the most.

Thank you, God, for your blessings on me!

MY CONTRIBUTION TO THE THESIS

My involvement in the PhD research work includes being the first and corresponding author in all the thesis papers in addition to the following:

1. **The review paper:** This paper forms part of chapter 1 as it reviews the multistate models from a broad perspective. We extended the work by Machado *et al.* (2009) and Hougaard (1999) in multistate models review; however, the focus was on the use of Bayesian estimation in multistate models. I took part in the conceptualization of the research question, structuring of the paper, analysing and interpreting the results, drafting of the manuscript, addressing co-authors' comments, submitting to agreed journals for review and addressing peer reviewers' comments.

Paper under interactive review:

Matsena Zingoni Z, Chirwa TF, Todd J, Musenge E. A review of multistate modelling approaches in monitoring disease progression: Bayesian estimation using Kolmogorov-Chapman forward equations. Under interactive review in the *Statistical Methods in Medical Research Journal*

2. **The structured additive regression models paper:** This paper is presented in chapter 3 of the thesis and aimed at describing the spatial variation explained by ART drop-out. We used the R Integrated Nested Laplace Approximation (INLA) modelling approach assuming the conditional autoregressive prior proposed by Besag *et al.* (1991). I was involved in the conceptualization of the research question, structuring of the paper,

analyzing and interpreting the results, drafting of the manuscript, addressing co-authors' comments and submitting to agreed journals for review.

Paper submitted for review :

Matsena Zingoni Z, Chirwa TF, Todd J, Musenge E. Hierarchical Bayesian spatio-temporal Poisson modelling of ART drop-out among HIV patients in Zimbabwe at health facility and district levels. Submitted for review in *Spatial and Spatio-temporal Epidemiology Journal*

3. **The competing risk paper:** This paper results appear in chapter 4 of the thesis. We used the modelling approach as described by Putter *et al.* (2007) to understand the loss to follow-up risk in the presents of mortality outcome as a competing event. I was involved in the conceptualization of the research question, structuring of the paper, analysing and interpreting the results, drafting of the manuscript, addressing co-authors' comments, submitting to agreed journals for review and addressing peer reviewers' comments.

Published paper:

Matsena Zingoni Z, Chirwa TF, Todd J, Musenge E. Competing risk of Mortality on Loss to follow-up Among Adult Antiretroviral Therapy Patients from 2004 to 2017: Zimbabwe National ART Programme. *BMJ Open* 2020;10:e036136.
<http://doi:10.1136/bmjopen-2019-036136>

4. **The multistate model based on CD4 cell counts paper:** The findings of this paper are provided in chapter 5 of the thesis. We used the frequentist (maximum likelihood estimation) modelling approach implemented in R software using the “msm” library developed by Jackson (2011). I did the data management including cleaning and structuring before performing the analysis in R. I prepared the initial draft of the manuscript, work of supervisors’ comments, submitting the paper to journals for review and respond to peer reviews.

Published paper:

Matsena Zingoni Z, Chirwa TF, Todd J, Musenge E. HIV Disease Progression Among Antiretroviral Therapy Patients in Zimbabwe: A Multistate Markov Model. *Frontiers in Public Health*. 2019; 7:1–15. <http://doi.org/10.3389/fpubh.2019.00326>

5. **The multistate model based on viral load measurements:** This paper is covered in chapter 6 of this thesis and adopted and extended the Bayesian multistate model by Kneib *et al.* (2008) with the inclusion of the spatial covariate. With the guidance of my supervisors’ to conceptualize the research question, I performed the analysis, drafted the paper, and submitted the manuscript to agreed journals for review. I addressed co-authors’ and peer reviewers’ comments before publication.

Published paper:

Matsena Zingoni Z, Chirwa TF, Todd J, Musenge E. Spatial Heterogeneity of Viral Suppression and Viral Rebound Patterns among ART Patients in Zimbabwe from 2004 to

2017 : A Bayesian Mixed Effects Multistate Model. International Journal of Statistics in Medical Research.2019;8:98–113. <http://doi.org/10.6000/1929-6029.2019.08.13>

6. The joint modelling and mapping of CD4 cell counts and viral load measurements:

This paper aimed at joint modelling of viral load and CD4 cell counts in HIV disease progression, which is often ignored in most studies. We further used the multivariate intrinsic conditional autoregressive model in WinBUGs to describe the shared geographical patterns of the multidimensional data. I conceptualized the idea, wrote the initial draft, submit to journals for peer review. The findings from this paper are provided in chapter 7 of this thesis.

Paper under review:

Matsena Zingoni Z, Chirwa TF, Todd J, Musenge E. Joint modelling and mapping HIV disease progression patterns based VL and CD4 cell count prognostic markers in monitoring ART patients. Under review in the *BMC Journal in Theoretical Biology in Medical Modeling*

CONFERENCE PRESENTATIONS

1. **Z. Matsena Zingoni**, T. Chirwa, J. Todd and E. Musenge, Antiretroviral therapy outcomes in adults HIV patients of the Zimbabwe National ART programme from 2004-2016. *SSACAB Annual Conference in Windhoek*, Namibia (2017), Oral presentation
2. **Z. Matsena Zingoni**, T. Chirwa, J. Todd and E. Musenge, Antiretroviral therapy outcomes in adults HIV patients of the Zimbabwe National ART programme from 2004-2017. *School of Public Health Research Day at Witwatersrand University in Johannesburg, South Africa* (2017), Oral Presentation
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8. **Z. Matsena Zingoni**, T. Chirwa, J. Todd and E. Musenge, Hierarchical Bayesian spatio-temporal Poisson regression of ART drop-out among HIV patients in Zimbabwe at health facility and district levels. *2020 DELTAS SSACAB Virtual Annual Conference, 2020*, Oral Presentation

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral therapy
AZT	Zidovudine (ART drug)
AIC	Akaike's information criterion
AsHR	Adjusted sub-distribution hazard ratio
BE	Bayesian estimation
BIC	Bayesian information criterion
CAR	Conditional autoregressive
CCR5	C-C chemokine receptor type 5
CD4	Cluster of differentiation 4
CIF	Cumulative incidence function
CIP	Cumulative incidence distribution
CR	Competing risk
DIC	Deviance information criterion
DNA	Deoxy-ribose nucleic acid
D4T	Stavudine (ART drug)
EFV	Efavirenz (ART drug)
ePMS	Electronic patient management system
GAM	Generalized additive models
GAMM	Generalized additive mixed models
GIS	Geographic information system
GLM	Generalized linear models
GMRF	Gaussian Markov random field
GMAR	Gaussian Markov autoregressive
GSSEM	Generalized spatial structural equation models
GOF	Goodness of fit
HIV	Human immunodeficiency virus
HR	Hazard ratio
HLA	Human leukocyte antigen
IDU	Injecting Drug Users
INLA	Integrated nested Laplace approximation
ILWS	Iteratively weighted least square
LRT	Likelihood ratio test
LTFU	Loss to follow-up
MAR	Missing at random
MCAR	Missing completely at random/ Multivariate conditional autoregressive
MCMC	Monte Carlo Markov Chain

MH	Metropolis-Hastings
MLE	Maximum likelihood estimation
MOHCC	Ministry of Health and Child Care
MRF	Markov random field
NRTI	Nucleotide reverse transcriptase inhibitor
NVP	Nevirapine (ART drug)
OI	Opportunistic infections
PCA	Principal component analysis
pdf	Probability density function
PHC	Primary health care
PHR	Posterior hazard ratio
PLWHIV	People living with HIV
PMR	Patients monitoring records
PMTCT	Prevention to mother and child transmission
POR	Posterior odds ratio
PrEP	Pre-exposure prophylaxis
P-splines	Penalised -splines
REML	Restricted maximum likelihood
RHS	Right hand side
RNA	Ribose nucleic acid
RR	Relative risk
SAR	Spatial autoregressive
SEM	Structural equation model
SSA	Sub-Saharan Africa
STAR	Self-testing Africa
STAR	Structural autoregressive (model)
TB	Tuberculosis
TDF	Tenofovir (ART drug)
UNAIDS	United Nations AIDS
VL	Viral load
VMMC	Voluntary medical male circumcision
WHO	World Health Organization
WinBUGS	Windows version of Bayesian inference Using Gibbs Sampling
WinDiff	WinBUGS Differential Interface
ZIMPHIA	Zimbabwe Population-based HIV impact assessment
3TC	Lamivudine (ART drug)

GLOSSARY

Multistate models	These are state transition models for a stochastic process allowing individuals to move among a finite number of states
States	Intermediate compartments within a course of disease progression, e.g. CD4 cell counts can be used to define HIV/AIDS states
Transition	Moving from one state to another, it is an event
Adsorbing state	A state which does not have any states emerging from it, e.g. death
Transition intensities	These are hazard rates for an event to occur or parameter estimations to define the occurrence of an event
Reversible state	A transition is bidirectional or regressive leading to the recovery
Irreversible state	A transition is unidirectional or progressive
Maximum likelihood estimation	A method of estimating population characteristics from a sample by choosing a parameter value that will maximize the probability of getting a particular sample
Bayesian estimation	A method of estimating population parameters from posterior distribution by combining the prior knowledge about the parameters with evidence from the observed data sample
CD4 percentage (CD4 %)	The CD4 percentage refers to the percentage of total lymphocytes in the body that are CD4 cells
ePMS	Electronic patient management system used to track HIV patients on ART
Gibbs sampling	A special MCMC algorithm used to sample random variable from the joint (posterior) distribution model according to its full conditional distribution

CHAPTER 1

This chapter introduces the research thesis by providing an overview of Human Immunodeficiency Virus (HIV) global, regional distribution; antiretroviral therapy (ART) coverage; approaches to monitoring HIV disease progression among ART patients and statistical models in HIV. The thesis objectives, justification and literature review which highlights the evolving process of multistate model and the gaps which have not been considered in multistate models, especially in answering HIV disease progression research are provided in this chapter. Chapter 1 also knits together the thesis framework and inter-linkages with the papers which emerged from this research work.

1. INTRODUCTION

1.1. Human Immunodeficiency Virus (HIV) biology and replication

The HIV pathogen is a retroviruses type of virus which causes disease slowly (2). HIV requires a human host to replicate; therefore, it infects the CD4 cells within the human immune system. The CD4 cells are white blood cells which play a fundamental role in helping the body fight against infections (3). HIV destroys these CD4 cells, and the body's immune response declines gradually. In the absence of antiretroviral therapy (ART) treatment, the loss of CD4 cells results in the development of opportunistic infections which subsequently lead to full-blown AIDS condition or death (4). HIV replication in the human body involves seven stages, as illustrated in **Figure 1-1** (5,6).

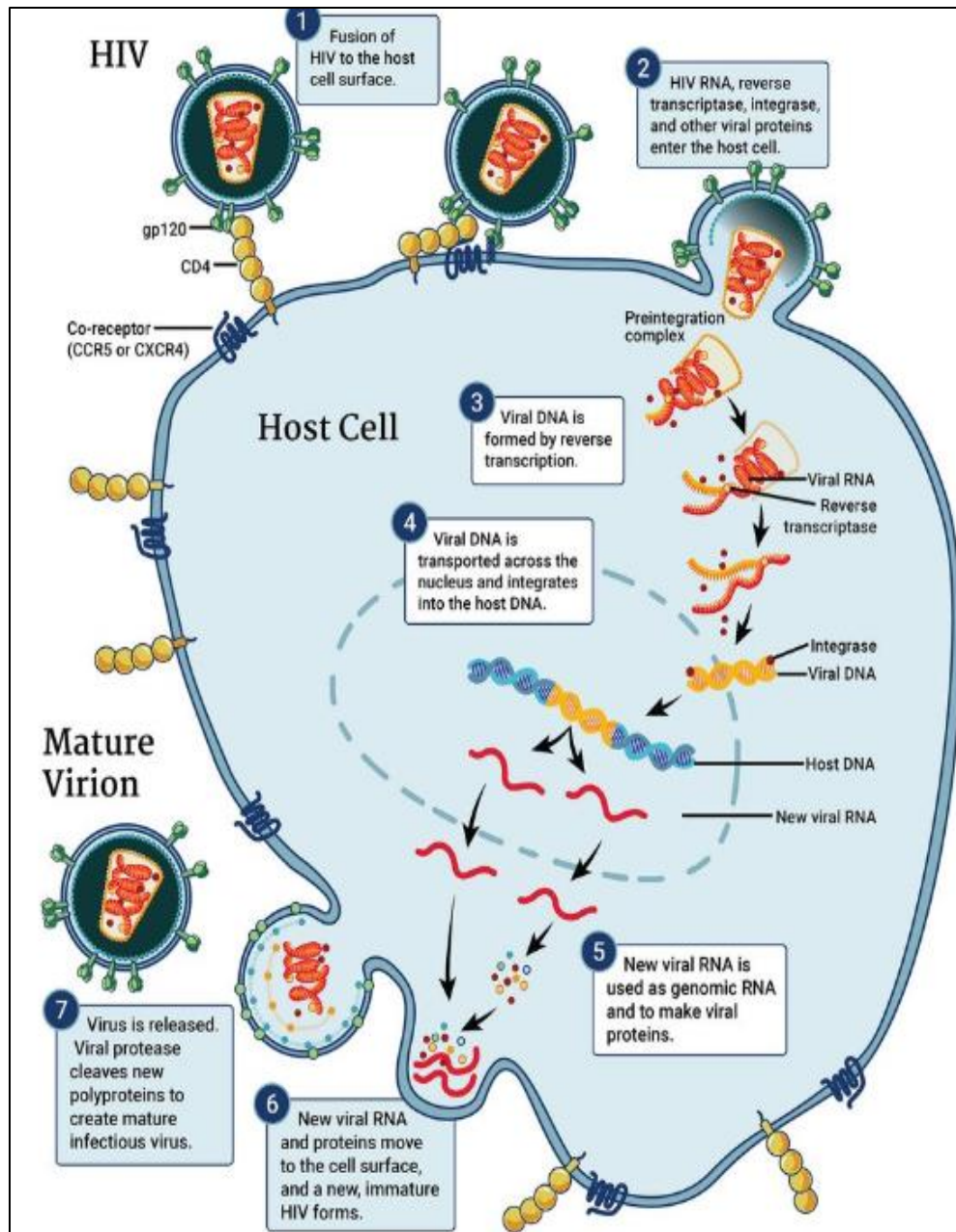


Figure 1-1: The human immunodeficiency virus replication process in the absence of antiretroviral therapy treatment
 (Source: <https://www.niaid.nih.gov/diseases-conditions/hiv-replication-cycle>, (5,6))

In summary, the seven stages of the HIV life cycle are: 1) the *binding stage* whereby the HIV attaches itself to the CD4 receptors on the surface of the CD4 cell; 2) the *fusion stage* whereby the CD4 cell membrane and the virus envelop join together allowing the virus to enter the cell; 3)

the *reverse transcription stage* whereby HIV releases HIV transcriptase enzyme to convert HIV ribose nucleic acid (HIV RNA) into HIV deoxy-ribose nucleic acid (HIV DNA); 4) the *integration stage* whereby HIV DNA releases HIV integrase enzyme inside the CD4 cell nucleus which catalysed the insertion of viral DNA onto CD4 cell DNA; 5) the *replication stage* whereby HIV uses the CD4 cell machinery to synthesize HIV proteins which are the building block of more HIV; 6) the *assembly stage* whereby newly synthesized protein and viral RNA move to the CD4 cell surface and assemble into a non-infectious HIV; 7) the *budding stage* whereby the newly formed non-infectious HIV sprout out of the host CD4 cell. The new HIV releases protease enzyme which transforms the non-infectious HIV into an infectious form, and all these steps are described in detail elsewhere (5,6). This whole process of HIV replication is highly dependent on the CD4 cell machinery in the human body.

1.2. Human Immunodeficiency Virus (HIV) Overview

HIV pandemic remains a global public health challenge which requires continual action to mitigate it, particularly in Africa; however, it is no longer an urgent issue in developed countries. Globally, there were 37.9 million (32.7 million–44.0 million) people living with HIV (PLWHIV) by the end of 2018 (7). In the same year, the estimated number of new HIV infections was 1.7 million (1.4 million–2.3 million) people while HIV-related deaths were estimated at 770,000 (570,000–1.1 million) people (7). The HIV pandemic has disproportionately affected the African continent, which accounts for approximately two-thirds of the global HIV infections; however, a considerable portion of these infections are in the Sub-Saharan Africa (SSA) region (7) as depicted on the worldwide map in **Figure 1-2**.

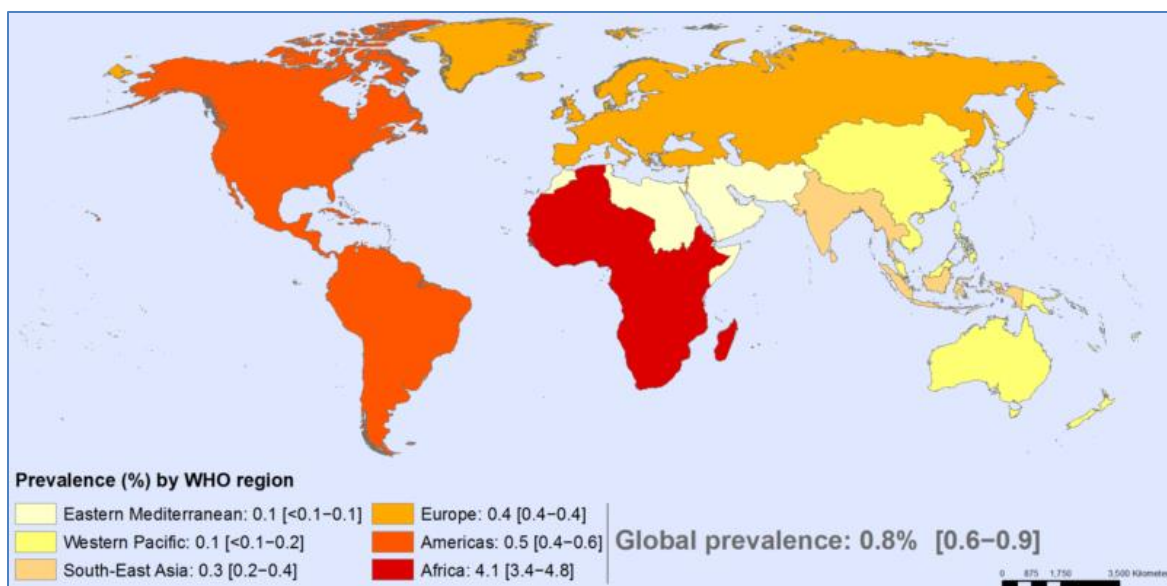


Figure 1-2: Human immunodeficiency virus prevalence global distribution among adults patients aged 15-49 years by World Health Organization region
(Picture Source: <https://www.who.int/gho/hiv/en/>)

In the SSA region, there were 20.6 million (18.2 million- 23.2 million) PLWHIV by the end of 2018 (7). New HIV infections in the same year were estimated at 800,000 (620,000-1 million) people while HIV-related illnesses claimed 310,000 (230,000-400,000) people, which is 70% of all the global HIV-related deaths (7). Zimbabwe, one of the countries in the SSA region, is heavily affected by the HIV pandemic; however, there has been a significant decrease in adult HIV prevalence over the years as depicted by the epidemic curve in **Figure 1-3** (8). Adult HIV prevalence was estimated at 13.7 % (12.9%-14.3%) in 2018 (9). The estimated number of PLWHIV was 1.3 million people in 2018, while the estimated number of new HIV infections was 41,000 people (8). In that same year, the estimated number of death due to HIV-related illnesses was 22,000 people. These estimates strongly indicate that HIV is one of the major causes of mortality in Zimbabwe.

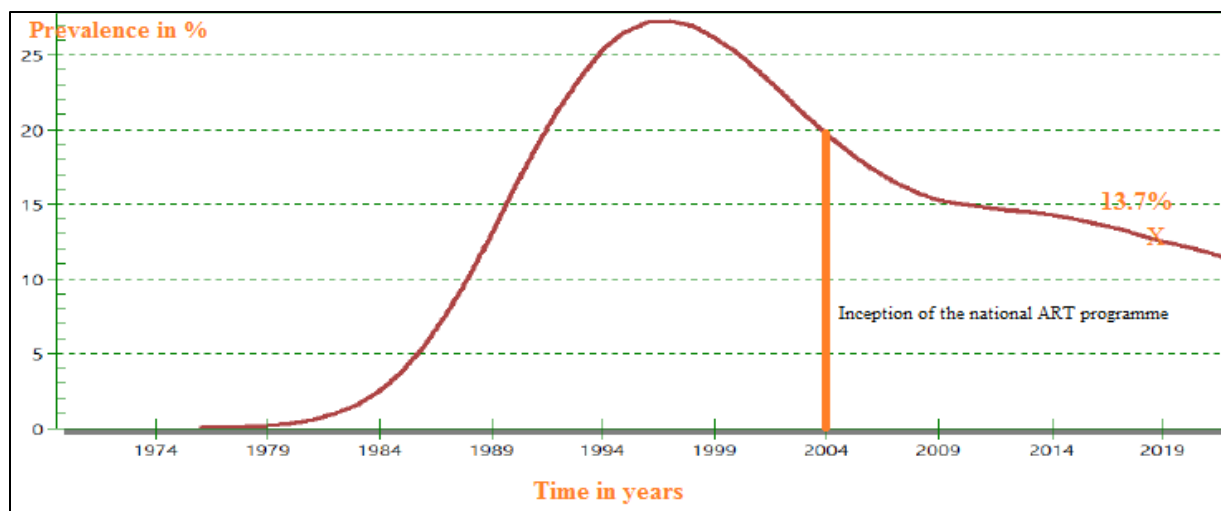


Figure 1-3: The HIV epidemic curve showing the trend in the aggregated adult HIV prevalence (in percentage) for the Zimbabwe population

(Graph source: <http://www.unaids.org/sites/default/files/country/documents/ZWE>)

The HIV burden in Zimbabwe varies by province due to significant heterogeneity in social, cultural and population dynamics which are mainly influenced by geographical correlation of the epidemic, **Figure 1-4** (10).

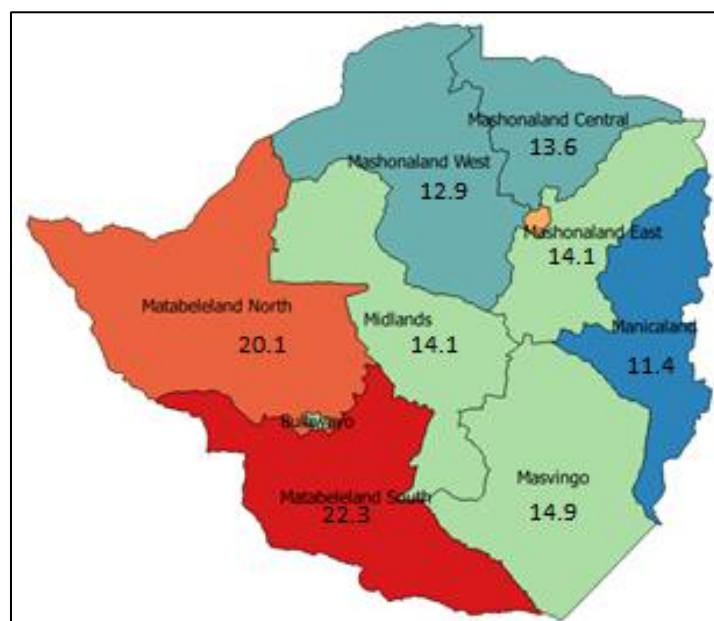


Figure 1-4: Geographical distribution of HIV prevalence estimates among adult Zimbabwean population aged 15-49 years as reported by ZIMPHIA survey in 2015/2016

Based on the Zimbabwe Population-based HIV impact assessment (ZIMPHIA) survey in 2015/16, Matabeleland South and Matabeleland North provinces had the highest HIV prevalence of 22.3% and 20.1%, respectively. In comparison, Manicaland province had the lowest prevalence, of 11.4% (10). This same provincial HIV burden pattern was consistent with the 2018 HIV incidence estimates (8).

1.1.1. HIV prevention strategies and ART coverage

There is a remarkable achievement towards fighting against HIV worldwide. Comprehensive integrative strategies have been implemented across the world from HIV testing, HIV prevention and HIV treatment. ART has been the backbone of HIV prevention and control as it provides comprehensive care and supports package to PLWHIV (11). ART does not only slow disease progression (12), preserve health by prolonging survival outcomes (13) and improve the quality of life (14), but it also minimizes HIV transmission to others by reducing viral load. The initial regimen for an ART naïve patient is the first-line ART, a combination of two nucleoside reverse transcriptase inhibitors (NRTI), the first drug can be Zidovudine (AZT), Tenofovir (TDF) (the most common) or Stavudine (D4T) and the second drug is mainly Lamivudine (3TC); and one non-NRTI which can either be Nevirapine (NVP) or Efavirenz (EFV). These drugs target the *reverse transcriptase stage* of the HIV life cycle.

There has been a remarkable expansion in the availability of ART to those in need globally. The estimated number of people accessing ART increased to 23.3 million (20.5 million–24.3 million) people by the end of 2018 from 7.7 million (6.8 million–8 million) in 2010 (7). New HIV infections decreased by 16% from 2.1 million (1.6 million–2.7 million) in 2010 to 1.7 million (1.4 million–2.3 million) in 2018 (7). The impact of ART has been felt vividly through the

reduction of deaths due to HIV-related illnesses by 33% from 1.2 million (860,000-1.6 million) in 2010 to 770,000 (570,000-1.1 million) in 2018 globally (7). In the SSA region, similarly, significant strides have been made in the fight against HIV. The estimated number of HIV patients with access to ART was estimated at 13.8 million (12.1 million-14.3 million) people which equates to an ART coverage of 67% (52%-78%) in the SSA region (7). New HIV infections were estimated at 800,000 (620,000-1 million) while HIV-related mortalities were estimated at 310,000 (230,000-400,000) people (7). Such success as reflected by these statistics has positioned ART access at the centre of global HIV response to prevent HIV transmission, HIV-related morbidity and HIV-related mortality through the "Treat All" approach regardless of the cluster of differentiation 4 (CD4) cell counts or clinical staging across all age groups as per World Health Organization (WHO) guidelines (15). However, continual expansion of treatment is of urgency to further reduce the HIV-related mortality.

Zimbabwe, one of the countries in the SSA region, has made plausible strides towards fighting against the HIV pandemic through ART. The estimated number of patients on ART has drastically increased from 362,817 people in 2010 to 1,119,909 people in 2017 (8), and this upsurge can be attributed to the decentralization campaign of ART services from tertiary health care to primary health care facilities (16,17). The ART coverage in Zimbabwe was estimated at 84.5% for both adults and children in 2018 (8). Not only has the decentralization campaign made ART treatment available and accessible to everyone in need, but it also resulted in task-shifting among the health practitioners by lessening the workload of doctors and bringing in the nurses on board.

1.1.2. Monitoring HIV disease progression among ART patients

Potent ART drugs can reverse and improve clinical status by hindering immune deterioration and keeping with viral suppression. Once patients are initiated on ART, there is a need to be observed to determine how well they are responding to ART treatment. Monitoring individuals on ART is imperative to ensure treatment efficacy, support ART adherence, identify treatment failure, improve health outcomes among PLWHIV, guide the country's response to HIV pandemic and inform policy (18). Through patient monitoring, the effectiveness of ART intervention can be assessed, and its bottlenecks can be detected. Identification of such gaps can improve HIV patients management by recommending new treatment regimens (18).

To help gauge how the HIV management is progressing towards the set goals, and direct HIV prevention resources most effectively at country-level, the "HIV continuum of care" and "HIV treatment cascade" are tracked (**Figure 1-5**). The continuum of care focuses on HIV risk reduction through a series of steps from diagnosis to successful treatment of HIV. These steps include prevention, testing, linking to care, treatment and chronic care. The HIV treatment cascade is also another essential tracking system in HIV management which measures the number of PLWHIV, and the type of care HIV positive individuals require from diagnosis through to viral suppression. The monitoring frameworks also help to assess the level of ART patients participation in HIV control by understanding their adherence patterns, treatment defaulting, retention in care and attrition. It is these indicators at patients-level coupled with the programme inputs and resources which give the overall performance of the ART programme and pinpoint the areas which require to be strengthened.

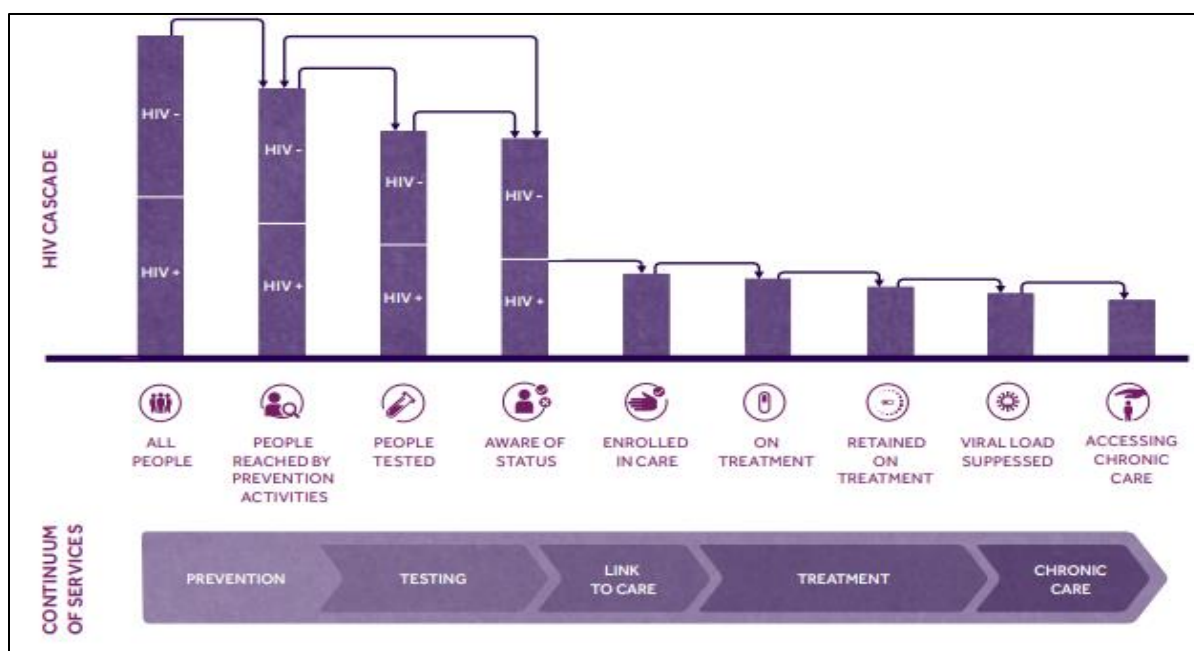


Figure 1-5: The HIV continuum of care and ART retention cascade

(Picture source: <https://apps.who.int/iris/bitstream/handle/10665/246178/WHO-HIV-2016.05eng.pdf?sequence=1>)

Within the HIV continuum of care are the HIV RNA viral load and CD4 cell counts immunological assessments; and the clinical assessment. These monitoring assessments are useful to guide clinicians on when to change ART regimen when to give prophylaxis and other HIV-related interventions which may benefit the patients(15). The **WHO clinical staging** is used for baseline assessment (initial diagnosis of HIV infection) and in the follow-up of patients in care and ART treatment programmes. The WHO spectrum of HIV- related symptomatology has four classes which are the asymptomatic stage (WHO I), the mild symptoms stage (WHO II), the advanced symptoms stage (WHO III) and the severe symptoms stage (WHO IV) (19). The recurrence of HIV-related opportunistic infections (OIs) on an ART patient is not only used as a clinical guide to recognizing ART failure or intolerance and the need to change treatment regimens; but also these clinical events may reflect immune deterioration for other patients which is a sign for HIV disease progression. Clinical assessment is vital in a resource-

constrained setting where access to laboratory monitoring may be limited; however, it is critical to note that clinical assessment has a low sensitivity in assessing disease progression (20).

CD4 cell counts are used in HIV monitoring to characterize the severity of immune-deficiency among HIV patient. To assess the immune status of an HIV patient, the absolute number of CD4 cell count per microliter of blood for patients who are five years and older is used while relative CD4 cell counts (CD4%) is preferred in children less than five years (21). The CD4 cell counts form the basis of the historical evolution in guiding ART treatment initiation clinically and regimen switching. The normally used four CD4 cell counts bands of HIV-related immunodeficiency are the no significant immunodeficiency ($CD4 \geq 500 \text{ cells/uL}$), the mild immunodeficiency ($350 \text{ cells/uL} \leq CD4 \leq 499 \text{ cells/uL}$), the advanced immunodeficiency ($200 \text{ cells/uL} \leq CD4 \leq 349 \text{ cells/uL}$) and the severe immunodeficiency ($CD4 < 200 \text{ cells/uL}$). Progressive depletion of CD4 cell counts is related to HIV disease progression and this is associated with an increased likelihood of OIs and subsequently the development of poor ART outcomes (21,22). Though CD4 count monitoring is often used in monitoring disease progression, CD4 count measurement is prone to measurement variability (23,24). There can be within-patient variability in CD4 cell count quantification, either day to day or diurnal variability such that an individual may be classified as not responding while in fact, is recovering (25). Absolute CD4 cell count measurement variability can be as a result of bone marrow-suppressive medications use, presence of acute infections or co-infections (23).

Viral load (VL) is much more sensitive and specific prognosis marker recommended by WHO for detecting HIV treatment failure and monitoring disease progression. The levels of HIV viremia are used to characterize HIV disease progression or recovery (23). Optimal viral suppression is defined as a VL, which is below the detection level ($HIV \text{ RNA} < 50 \text{ copies/uL}$) or a

range of HIV RNA <20 to 75 copies/uL (26). VL monitoring is more sensitive, provides early and more accurate detection of therapy failure than CD4 or clinical monitoring (25). The VL measurement technique is the standard practice in developed countries for routine monitoring of HIV disease progression among ART. However, in developing countries, VL monitoring has been rarely available just a couple of years ago due to high costs associated with it. Nonetheless, progress has been made to expand VL monitoring rapidly in developing countries (52). Use of VL measurement helps to improve the tracking of ART treatment outcomes and inform a timely switch of ART regimen to either second-line or third-line therapy when needed. Also, point-of-care technologies can be thought of an opportunity for further expand VL testing to all people accessing ART treatment and to achieve a more precise HIV disease monitoring of both individual and community viral loads (27).

Within the HIV treatment cascade emerged the 2014 UNAIDS fast track 90-90-90 targets of 2020, which became a fundamental pillar of the global quest towards achieving zero HIV incidence in 2030 (1). The 90-90-90 targets put forward the fact that viral load (VL) measurements are the primary prognostic laboratory marker to evaluate HIV disease progression with viral suppression as the ultimate goal of ART. The first 90 focuses on 90% of PLHIV know their status; the second 90 focuses on 90% of those who know their status are initiated on ART treatment, and the third 90 focuses on 90% of patients on ART are virally suppressed, **Figure 1-6**. Globally, it was estimated that by the end of 2018, 79% (67%-92%) of the 39.7 million PLWHIV knew their HIV status, 78% (69%-82%) of those who knew their HIV status were receiving ART and 86% (72-92%) of those on ART achieved viral suppression. Of all the PLWHIV in 2018, 62%(47-74%) were accessing ART, and 53% (43-63%) attained viral

suppression (28). These statistics show how far the world is from achieving viral suppression among HIV patients.



Figure 1-6: Illustration of the 2014 UNAIDS 90-90-90 fast track targets for HIV prevention and treatment by 2020

(Picture source: <https://www.avert.org/global-hiv-targets>)

Zimbabwe has made some impressive progress in attaining the 90-90-90 UNAIDS targets. However, the first 90 target has been trailing at 74% based on the 2018 estimates, and this affects the other subsequent targets (8). This indicator can be improved through strengthening and intensifying index testing, lay testing and community mobilization of HIV-testing musical galas campaigns. Rapid roll-out and promotion of self-testing campaigns is another possibility to promote community-based testing (29,30). Self-testing campaigns have been pilot tested in Zimbabwe and were found to be effective as well as the UNITAID-supported HIV Self-Testing Africa (STAR) study which reported that self-testing strategy is useful especially those people who do not usually go and seek voluntary HIV testing in health facilities (31). The second 90 is estimated at 84.4% as of 2018 estimates (8). This indicator has been boosted by the decentralization of ART services as far as the hard to reach areas which have resulted in more

than a million HIV-infected people receiving ART. However, going forward, models which expedite treatment uptake for the newly diagnosed patients; and provision of potent and effective ART regimens with minimum side-effects and less prone to resistance should be the focus in addition to sustaining the already implemented interventions (8). The third 90 was estimated at 73% in 2018, and its trailing is of concern in the country's progress since this is the ultimate goal of ART (8). Therefore, intensified efforts are required to understand factors contributing to low rates of achieving and sustaining viral suppression.

1.1.3. Statistical models in monitoring HIV disease progression

In longitudinal studies, participants are followed-up, and patient's information is collected repeatedly. In such studies, individuals may experience multiple events, and longitudinal failure time data is captured. Mathematical and statistical models are a useful tool in monitoring HIV disease progression as they give an in-depth understanding of time to event patterns among ART patients (32). Traditionally in time to event longitudinal studies, survival models are used to estimate the hazard rates (transition intensities) or compare the survival (hazard) functions between groups (33). However, in disease progression monitoring, it is more beneficial to partition the alive state into a finite number of intermediate states which may offer greater insight and understanding of the disease evolution(34). This gives rise to multistate modelling approach which allows one to estimate transition intensities, transition rates, the total length of stay in a defined stage before experiencing an adverse event like death (absorbing state) and mean sojourn times which defined the total time spent in each state before moving to the next state (34). The model states can be defined by CD4 cell counts or VL range of values as transient states and ART outcomes (mortality) can be used to define the absorbing state. Though intensive research

has been done on the use of multistate modelling in HIV monitoring, most of the studies have used the frequentist estimation compared to the Bayesian inference approach.

The Geographic information system (GIS) is about capturing, management, evaluation and visualization of geographically referenced data (35). Use of geospatial analysis techniques is on the rise and continues to take significant hikes forward as the software and computing power brings solutions to previously unanswered questions. Spatial modelling is essential in monitoring HIV disease programmes since health risks, and illnesses have a geographical linkage. Statistical modelling approaches which handle spatial data are useful in HIV disease monitoring to visually pinpoint the heavily burdened regions for policymakers and programme managers so that region-specific interventions can be developed and implemented. However, geospatial modelling has not been extensively used in HIV disease monitoring.

1.1.4. Research problem and justification: What is novelty?

Although HIV-related deaths are on the decrease, the numbers are relatively high. To date, approximately 32 million HIV-related deaths have occurred with 770,000 reported in 2018 only (8). Of the global HIV-related mortalities, Zimbabwe contributed 22,000 death (8) which makes HIV one of the top-ranking causes of death in the country. Also, in the last decade, the main focus of the fast track targets has been on the second 90-to increase ART access- and less on the third 90-viral suppression and this has been a gap in HIV monitoring research, especially after ART services decentralisation in Zimbabwe.

PLWHIV are known to be vulnerable to many structural barriers that inhibit them from achieving viral suppression and subsequently sustaining it. This study sets to understand the magnitude of ART “leakages” in the HIV continuum of care; immune recovery and deterioration

trajectories; and viral rebound and suppression patterns among ART patients after ART services decentralisation in Zimbabwe. This study sets to identify the heavily burdened regions with poor viral suppression and ART dropouts, which sub-population groups are at risk of poor viral suppression, determine ART outcome patterns after ART decentralization in Zimbabwe which can help understand how well PLWHIV are adhering to ART.

Unlike most studies which have used the maximum likelihood estimation (MLE) approach to estimate the transition rates in the multistate model framework, this study implemented models from the Bayesian estimation (BE) perspective. The BE approach was preferred since it can handle nonlinear effects, individual frailty, time-varying covariates and spatial frailty terms normally impossible in the MLE approach and this was the main gap this study aimed to cover. What is novel in this study is the extension of BE multistate models with the inclusion of the spatial covariate to give a pictorial view of heavily burdened regions which may require targeted interventions. Use of spatial models to pinpoint high-risk regions to guide policy has been a gap in HIV disease monitoring studies and this research work incorporated geostatistical techniques within the multistate model framework (36). Spatial-temporal models were also implemented to describe ART drop-out which is a threat to viral suppression and these techniques have not been extensively used in monitoring HIV disease. Lastly, in HIV monitoring CD4 cell counts prognostic markers have been used in most studies, this current research used VL measurement and jointly model the joint model the CD4 cell counts and VL prognostic markers which has not been done often in many studies.

Findings from this study are useful in HIV monitoring programme in terms of adding knowledge to HIV programme (know the affected population and groups, attrition rates in HIV treatment cascade and the disease progression trajectories); and guide policy on the region-specific

interventions to be implemented. Moreover, this study can help ART patients to see the importance of ART adherence and showing up for routine VL monitoring to guide treatment change in instances where ART failure occurs. Once the patients have suppressed VL, transmission to uninfected partners becomes negligible.

1.1.5. Thesis epidemiological research questions

- ❖ With the global agenda to achieve zero HIV incidences by 2030 spearheaded by the UNAIDS 90-90-90 fast track targets, how well are PLWHIV adhering to ART to achieve viral suppression after ART services decentralization in Zimbabwe?
- ❖ Which subpopulation groups (health facility type, age, gender) are heavily affected by immunological ART outcomes, LTFU and mortality among the adults HIV patients in Zimbabwe?
- ❖ Assuming the spatial variation of the HIV burden in Zimbabwe by province due to significant heterogeneity in social, cultural and population dynamics, which geographical areas (provinces, districts) are heavily affected by poor viral suppression, LTFU and mortality in Zimbabwe?

1.1.6. Thesis broad and specific objectives

The main objective of this thesis was to employ multistate Markov statistical models in monitoring HIV disease progression amongst adults ART patients who initiated ART between 2004 and 2017 in Zimbabwean cohort. The multistate models were based on CD4 cell counts and VL prognostic markers. This study also aimed to determine the spatial-temporal heterogeneity of ART drop-out and viral rebound among this same cohort. The constructed objectives covered

both the epidemiological and statistical modelling aspects employed in this research. The modelling inferences were based on both the MLE and the BE perspective.

The specific objectives were:

1. To review multistate modelling approaches and illustrate the use of Kolmogorov-Chapman forward equations in estimating transition probabilities if data is partially observed

Paper 1 title: A review of multistate modelling approaches in monitoring disease progression: Bayesian estimation using the Kolmogorov-Chapman forward equations

2. To describe the spatio-temporal patterns of ART drop-out at the health facility and district levels and identify cold spots and hot spots for ART drop-out

Paper 2 title: Hierarchical Bayesian spatio-temporal Poisson modelling of ART drop-out among HIV patients in Zimbabwe at health facility and district levels

3. To determine the time to occurrence of LTFU with mortality as a competing event over 13 years follow-up period across health facility levels and other associated factors

Paper 3 title: Competing risk of Mortality on Loss to follow-up Among Adult Antiretroviral Therapy Patients from 2004 to 2017: Zimbabwe National ART Programme

4. To describe the HIV disease progression, and immune recovery patterns based on CD4 cell counts among adult patients on ART in Zimbabwe accounting for decentralization of ART services to all levels of care

Paper 4 title: HIV Disease Progression among ART Patients in Zimbabwe: A Multistate Markov Model

5. To determine spatial heterogeneity of viral suppression and viral rebound trajectories among patient on ART in Zimbabwe adjusting for frailty, non-linear and spatial effects using Bayesian estimation

Paper 5 title: Spatial heterogeneity of viral suppression and viral rebound patterns among ART patients in Zimbabwe from 2004 to 2017: A Bayesian mixed-effects multistate model

6. To jointly model viral load (VL) and CD4 cell counts prognostic markers in a multistate model framework and identify the shared geographical patterns of low CD4 cell counts and viral rebound patterns

Paper 6 title: Joint modelling and mapping HIV disease progression patterns based VL and CD4 cell counts prognostic markers in monitoring ART patients

1.3. Literature Review

1.3.1. Evolution of multistate models use in routine HIV monitoring

In HIV monitoring, patients are followed over time, and the data is collected repeatedly. In such longitudinal studies, multistate models are commonly used to describe time to event history data. One of the strengths of multistate models is its ability to predict an individual's disease progression trajectories through time. The earliest work to model HIV disease progression using multistate models was performed by Longini *et al.*, (1989) who fitted a 5-stages Markov model to estimate the average length of the incubation period for acquiring AIDS from HIV-infected individuals. The model fitted had four progressive stages: (1) HIV-infected but antibody-negative; (2) antibody-positive but asymptomatic; (3) pre-AIDS symptoms or abnormal hematologic indicator; and (4) clinical AIDS; and death as an absorbing stage (37). This model

was fitted on a cohort of 513 homosexual and bisexual men and was the first study to estimate the waiting times for HIV infection to understand the natural history of HIV. This model also managed to handle heavily censored (left, right and interval) data which standard methods could not do; however, the researchers did not take into account the effects of cofactors with influence HIV disease progression rates.

Another study was the work by Longini *et al.* (1991) that fitted an 8-staged continuous-time Markov process among 1,796 HIV positive individuals to determine immune deterioration based on the decline of CD4⁺ T-lymphocytes (T4-cells). The model had six progressive states: (1) T4-cells ≥ 900 , (2) $700 \leq \text{T4-cells} < 900$, (3) $500 \leq \text{T4-cells} < 700$, (4) $350 \leq \text{T4-cells} < 500$, (5) $200 \leq \text{T4-cells} < 350$ and (6) T4-cells < 200 ; and a definitive HIV-infection endpoint, either AIDS diagnosis or an OI stage. In this study, the researched accounted for age as a possible risk factor, assuming that the transition rates were age-dependent. This study reported that age was a strong risk factor of HIV progression with high rates observed among individuals aged less than 25 years. However, this study did not consider reversible transitions and model the long term behaviour of CD4 cell counts in these individuals (38).

The first study to incorporate the use of CD4 cell counts was work by Bwayo *et al.*, (1995). This study examined the decline in CD4 cell counts among 485 HIV positive female sex worker in Kenya (39). This was the first study to incorporate reversible transitions between CD4 cell counts states. The model states were defined as: (1) $\text{CD4} \geq 900$, (2) $700 \leq \text{CD4} < 900$, (3) $500 \leq \text{CD4} < 700$, (4) $350 \leq \text{CD4} < 500$, (5) $200 \leq \text{CD4} < 350$ and (6) $\text{CD4} < 200$. This study observed a rapid disease progression among the female sex workers, which could be explained by multiple HIV strains and the presence of sexually transmitted infections which made the CD4 cell counts more susceptible to HIV infections. However, the multistate model considered in this study did

not consider any absorbing states which were then considered by Hendriks *et al.*, (1998) in a study of 173 Injecting Drug Users (IDU) in Netherlands(40).

Much more recently, extensive work on HIV disease progression using multistate models has been done including the work by Grover *et al.*, (2013) who fitted a 5-staged multistate model based on CD4 cell counts with death as an absorbing state. This study accounted for cofactors like age, gender and method of HIV transmission among the Indian population (41). Another work by Ayele *et al.*, (2013) was a 5-staged HIV disease progression based on CD4 cell counts among Ethiopians was fitted and a study by Dessie (2014) which fitted a 4-staged multistate model; however, no cofactors were accounted for, and only death was considered as an absorbing state (42,43). These two studies concluded that patients with lower CD4 counts were more likely to experience a worse health state or die.

Earlier studies have used the CD4 cell counts marker more often to describe HIV disease progression because of the availability of data or based on the fact that CD4 cell counts have been used to guide ART treatment initiation clinically before and regimen switching. However, the CD4 prognostic marker is prone to measurement variability when staging HIV-1 infection (25). In such cases, the focus now is on the use of VL in HIV monitoring as the VL is sensitive and much more superior to predict ART outcome compared to CD4 cell counts model (44). Studies have shown that VL monitoring is more sensitive, provides early and more accurate detection of therapy failure than CD4 monitoring(25). Moreover, within an ART program, patients are exposed to various ART outcomes which include mortality, LTFU, withdrawal and drop-outs. A study by Shoko *et al.*, (2018) included the withdrawal stage which defines the ART outcomes (45); however, outcomes like LTFU have never been considered yet which is a major contributor of attrition within an ART program. Joint modelling of these two prognostic makers

is just emerging following the work done in South Africa (44,45). This has been lagging in most African studies which have considered multistate models in HIV disease progression. One of the reasons which might have made most researchers, not to joint model these two prognostics markers might be lack of VL data. However, with the main thrust to achieve viral suppression, viral monitoring becomes a requirement. There is a need to refocus HIV disease progression based on VL, which is much sensitive and specific compared to CD4 cell counts.

Moreover, most of these studies which have models HIV disease progression have only used the MLE which cannot account for individual frailty effects, nonlinear covariates and spatial covariates. BE model within the multistate model framework can be used and can give relatively robust inference (46). These methods have been used in non-infectious disease studies, but the methods can be adopted in public health research. Majority of the studies have not considered modelling the spatial patterns of ART outcomes and HIV disease progression transitions. This is an important area to try and understand any geographical variation in the occurrence of HIV within a country. An emerging study which applied spatial modelling was work by Odhiambo *et al.*, (2019), which model viral suppression patterns in Kenya (47). Therefore, these gaps in monitoring HIV disease progression among ART patients are what this thesis is set to investigate extending the existing statistical modelling approaches.

1.4. Thesis framework and inter-linkages with papers

The identified themes for this thesis linked to the six papers which emerge from this research work are summarised in **Table 1-1**. A summary of the manuscripts which came out from this thesis, manuscript status and key messages in each manuscript is shown in **Table 1-2**.

Key Introductory Points

- HIV remains a public health concern, particularly in developing countries including Zimbabwe
- Monitoring HIV disease progression is a priority in the quest to fight HIV to attain zero new infection
- Viral load monitoring should be strengthened in developing countries since it is a more sensitive marker compared to CD4 cell counts
- Multistate models provide a flexible framework to model time to event history data
- Spatial models are an emerging tool in HIV studies

Table 1-1: Thesis themes and inter-linkages with the manuscripts

Themes	Theme 1: Factors associated with ART drop-out, LTFU, mortality, viral suppression and immune deterioration/ recovery)	Theme 2: Spatial heterogeneity of ART drop-out, viral suppression and immune deterioration/ recovery	Theme 3: Use of multistate models in HIV disease monitoring using CD4 and viral load	Theme 4: Bayesian inference in HIV disease progression monitoring
Papers				
Paper 1: A review of the multistate model in HIV disease progression				
Paper 2: Hierarchical Bayesian spatio-temporal Poisson modelling of ART drop-out among HIV patients in Zimbabwe at health facility and district levels				
Paper 3: Competing risk of mortality on LTFU				
Paper 4: CD4 cell counts transition rates trajectories				
Paper 5: Spatial heterogeneity of viral suppression and rebound patterns				
Paper 6: Joint modelling and mapping of CD4 cell counts and viral load				

Table 1-2: Thesis papers titles, status, comparative features and summary of key results

Paper	Title, type and status	Data features and software used	Analyses methods used and duration of computing	Key messages
1	A review of multistate modelling approaches in monitoring disease progression: Bayesian estimation using the Kolmogorov-Chapman forward equations Review paper Under interactive review in the <i>Statistical Methods in Medical Research Journal</i>	The illustration example had aggregated data from 5,596 patients followed up for a year. The model was implemented in WinBUGS	A search of articles which used multistate models in the literature. The Kolmogorov-Chapman differential equations illustration took less than 5 minutes.	Various types of multistate models, different assumption and implemented in different software. Kolmogorov-Chapman forward equations are useful in the multistate model estimation, especially if data are aggregated
2	Hierarchical Bayesian spatio-temporal Poisson modelling of ART drop-out among HIV patients in Zimbabwe at health facility and district levels Application paper Submitted for review in the <i>Spatial and Spatio-temporal and Epidemiology Journal</i>	Used ART drop-out count data aggregated at the health facility and district level.	Used separable space-time hierarchical Bayesian Poisson spatio-temporal models fitted in R-INLA models and ordinary kriging to interpolation outcome values at locations. Models took less than 10 minutes	Spatial mapping of ART drop-out is essential in identifying hot spots with high risk so that targeted interventions and be implemented. This is useful in resource-constrained settings so that interventions are channelled where they are needed the most.
3	Competing risk of Mortality on Loss to follow-up Among Adult Antiretroviral Therapy Patients from 2004 to 2017: Zimbabwe National ART Programme Application paper Published in the <i>BMJ Open Journal</i>	Used data from 390,771 patients with complete ART outcomes and aged 15years and above adjusting for health facility level, age, gender and tuberculosis Implemented in STATA	A competing risk model of mortality of LTFU. Sensitivity analysis using Cox regression (complete case and multiple imputations), Gompertz Parametric regression (frequentist and Bayesian). Competing risk model took three and a half days The Bayesian model took 16 hours	There are superior ART outcomes at primary care levels, and this supports the fact that ART services and task shifting have been well absorbed into these lower levels of care. Interventions and policies should encourage adolescence ART uptake and continual support of treatment adherence to reduce HIV transmission.
4	HIV Disease Progression among ART Patients in Zimbabwe: A Multistate Markov Model Application paper Published in the <i>Frontiers in Public Health Journal</i>	Used data from 63,422 patients with at least 2 CD4 cell count measurements and include health facility level, age, gender and ART initiation period Implemented in R and STATA	A 5 staged multistate model assuming time homogenous and Markov property. There were 16 transitions to be estimated. Frequentist perspective model It took three days to run the model	Early therapeutic interventions when the immune system is relatively stable across gender and age may contain mortality and increase survival outcomes. Interventions which strengthen ART services in primary health care facilities are essential.
5	Spatial heterogeneity of viral suppression and viral rebound patterns among ART patients in Zimbabwe from 2004 to 2017: A Bayesian mixed-effects multistate model Methodological paper Published in the <i>International Journal of Statistics in Medical Research</i>	Used data from 9,273 patients with at least two viral load measurements adjusting for spatial effects, age and WHO staging Implemented in STATA, R and BayesX	A multistate model with three states assuming time inhomogeneous and Markov property. Bayesian perspective model It took six days to run	Assessing for the spatial effects on viral suppression transitions is useful in detecting high burdened region. Interventions which improve ART adherence and encourage viral monitoring are crucial in HIV control
6	Joint modelling and mapping HIV disease progression patterns based viral load and CD4 cell counts prognostic markers in monitoring ART patients Application paper Under review in the <i>BMC Journal in Theoretical Biology in Medical Modelling</i>	Used data from 3,896 patients with at least two viral loads and CD4 cell counts measurements.	The multistate models were implemented in R using the msm. The principal component analysis was used to generate orthogonal covariates accounted for in the multistate model. The multivariate intrinsic CAR model was fitted in WinBUGS. It took 15-20 minutes to run	The viral load multistate model, which accounted for CD4 cell counts effects, was a superior model. Observed high transition rates for viral rebound compared to viral suppression. The joint mapping of CD4<350cells/uL and viral load>50copies/uL showed a 66% shared spatial correlation of these two conditions.

CHAPTER 2

Chapter 2 describes the study methodology with main highlights on the study design, study site, data sources and data description. This chapter also describes the data management process from the point of receiving the data file to analysis. In this chapter, detailed information on the models considered in subsequent thesis chapters is provided. The thesis themes are outlined and linked to the papers taking note of comparable features and the key findings of each paper. Lastly, the study ethical consideration statement is provided.

2. STUDY METHODOLOGY

2.1. Study Design and Study Site

We conducted a secondary data analysis of the routinely collected longitudinal HIV-infected patient-level data (cohort data). The study was carried out in Zimbabwe, a country with eight provinces (Masvingo, Mashonaland East, Mashonaland West, Mashonaland Central, Matabeleland North, Matabeleland South, Manicaland and Midlands) and two metropolitans (Harare and Bulawayo). The country is land-locked bordered by South Africa, Botswana, Mozambique and Zambia.

2.2. Data Sources and Description

The data used in this research came from the Zimbabwe national ART programme, which started in 2004. The data included patients who started ART between 2004 and 2017. The number of health facilities providing ART services increased steadily from 395 sites in 2005/6 to 1,478 sites at the end of 2013 (48), as shown in **Figure 2-1**. By the end of 2017, there were 1,566 sites

providing ART services from the 1,722 health facilities nationwide(8). This means approximately 91% of the health facilities in Zimbabwe are offering ART services. This swift increase in ART sites can be attributed to the decentralization of ART services campaign in Zimbabwe.

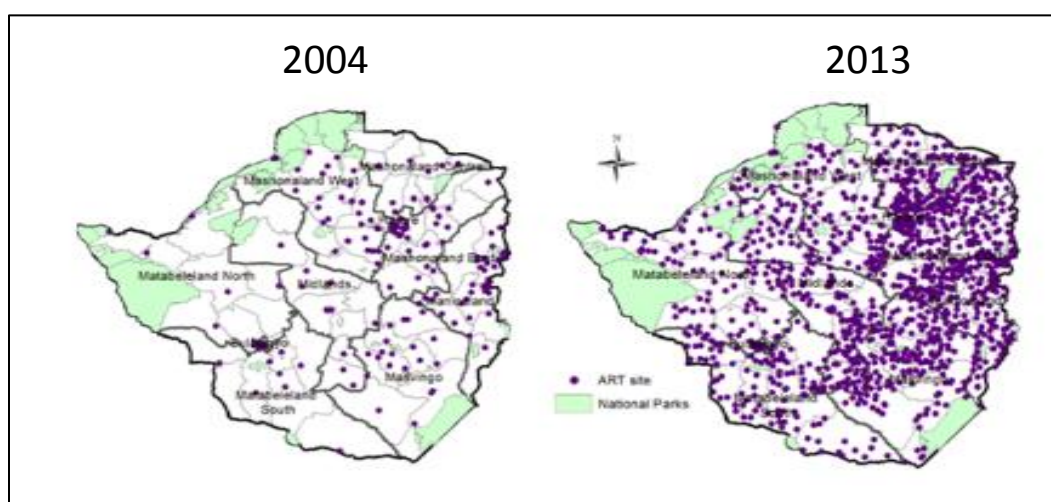


Figure 2-1: The distribution of health facilities which offer ART services in Zimbabwe between 2004 and 2013

Picture source: http://www.unaids.org/sites/default/files/country/documents/ZWE_narrative_report_2015.pdf

The monitoring and evaluation system of the ART programme in Zimbabwe has been described elsewhere(49). Briefly, since the inception of ART, all patient monitoring records (PMR) had been collected manually using a paper-based system and kept at the health facility where the patient is registered. Since 2012 the paper-based system was no longer functioning properly due to high volumes of ART patients (8). This upsurge in patients' volumes began to affect the accurate ART monitoring and reporting process as the paper-based system could not cope. Moreover, the paper-based system translated into huge workloads and became strenuous to the already over-burdened health workers. As a result, the electronic patient management system (ePMS) was launched in 2012.

The ePMS increased efficiency and effective management of ART patients through improving follow-ups to subsequently increase ART adherence(49). The ePMS provided a platform to compile quality patient-level data to accurately make forecast and evaluate the ART intervention, enabling a more effective program (8). The ePMS was rolled out in systematic phased approach with priority given to those HIV sites with high volumes of HIV patients at the same time maintaining a good representation of the four health care levels in the country (49). From the ePMS Strategic Plan document, the first phase target was 83 sites in 2013 comprising of central, provincial and district hospitals which covered approximately 61% of ART patients nationwide. Additional 267 city polyclinics, rural/large mission hospitals sites were included to make a total of 350 sites by the end of 2014(49). The last phase included 184 static ART follow up sites to bring the total to 534 sites by the end of 2017. By the end of 2018, there were 622 sites with a functional ePMS with the inclusion of private hospitals which meant that approximately 95% of all patients receiving ART were linked to the ePMS database (8).

The final database of the ePMS has patients' information from all levels of care (quaternary, tertiary, secondary and primary health care levels). It, therefore, reflects the overall ART management services in the country, although the database includes all HIV-related data. At enrolment, the patient's demographic data are captured including age, sex, marital status, level of education and the name of the health facility. Patient's past medical history is collected and at ART initiation (baseline), WHO clinical stage, tuberculosis status, body functional status and ART regimen type the patient receives (first-line or second-line regimen) information is captured. Patients' follow-up visits are recorded and at each subsequent visit, clinic visit date, information on clinical data, laboratory investigations including CD4 and viral load (VL) measurements), and physical examination is obtained. At the end of each visit, patients'

outcomes are assessed and captured as death, loss to follow-up (LTFU) if a patient has missed appointment date in 90 days since the last observed date (27), transfer-out to another health facility or alive and active on treatment. Attrition outcome was defined as a composite outcome after combining all the observed mortality, LTFU, withdrawal and drop-outs outcomes. Already existing patient's information prior to 2012 from the paper-based system was retrospectively transcribed into the electronic database at each clinic, and all subsequent clinic visits were recorded prospectively with a real-time entry of patient records.

The introduction of the ePMS for monitoring HIV patients in 2012 has provided a platform for huge data repository in the country which may be used to answer some of the public health questions on the HIV aspects using statistical models. Moreover, the ePMS platform provides readily available data archiving for robust statistical analysis approaches to guide evidence-based decision-making and programme interventions planning at patients-level while eliminating the aggregated data. Therefore, this rich, huge patient-level database was of preference and suitable to answer our study objectives.

This research work considered different types of ART outcomes from different angles as per the specific objectives listed in chapter 1. Chapter 3 focuses on ART drop-out outcome; chapter 4 focuses on LTFU with mortality as a competing event; chapter 5 focuses on mortality among patients with CD4 cell counts; chapter 6 focuses on mortality among patients with VL measurements while chapter 7 focuses on mortality and LTFU among patients with CD4 cell counts and VL measurements. Patients, who were once indicated to have become LTFU and returned to the same health facility, were classified as alive and active on treatment.

2.3. Study Population and Selection of Study Participants

The selection of study participants occurred in two phases, the ePMS implementation and roll-out phase and data management phase of this current research. In the ePMS phase, the ePMS was implemented to 38% of the total health facilities offering ART services in Zimbabwe, **Figure 2-2**; however, these sites were selected based on the areas with the majority of patients on ART. At the time of receiving the data file, only 538 health facilities had complete updated data.

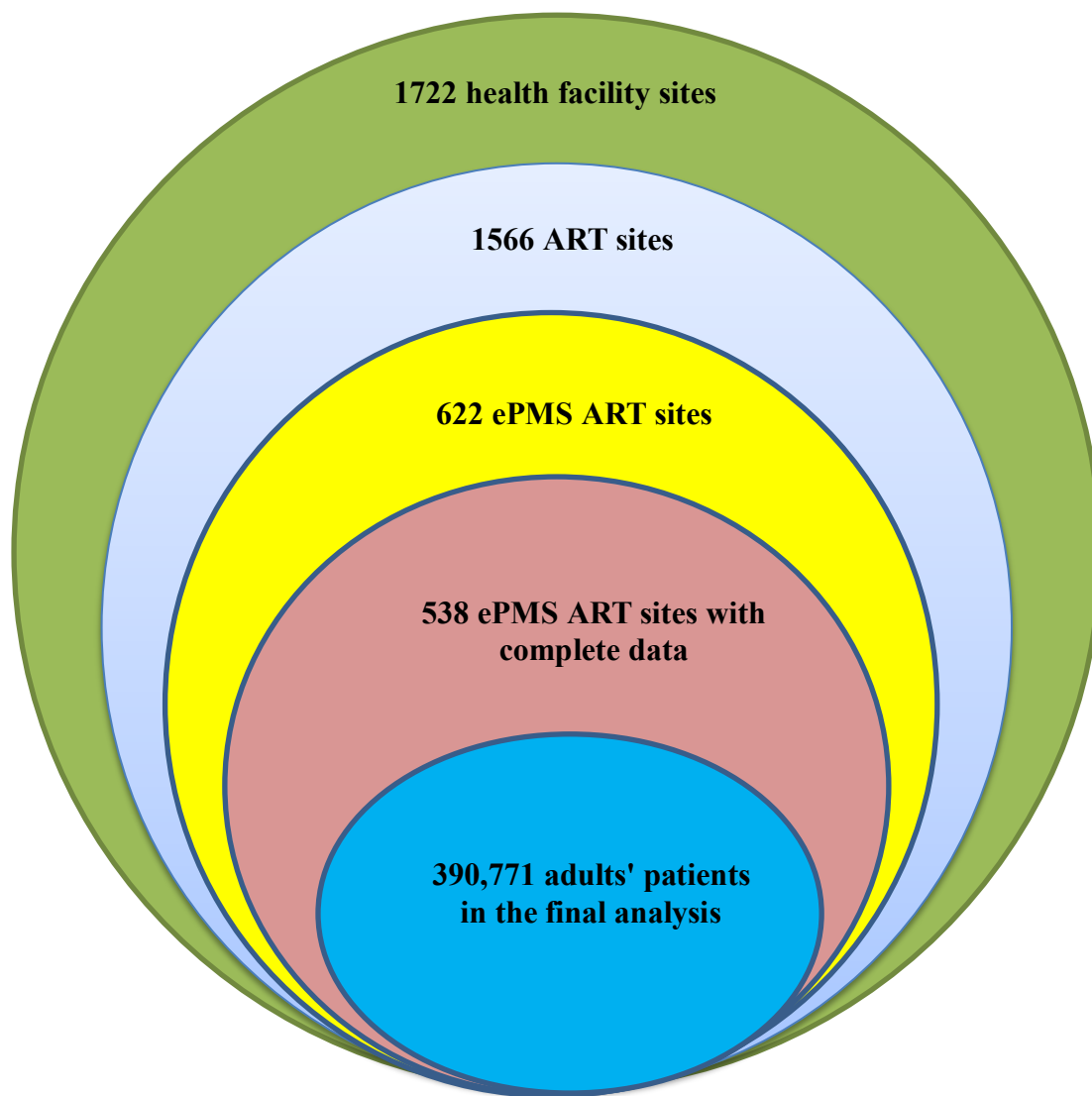


Figure 2-2: Diagrammatic illustration of the inclusion and exclusion criteria for the selection of health facilities in this study at the ePMS roll-out phase

The data cleaning and inclusion criteria steps for this current study are summarised in **Figure 2-**

3.

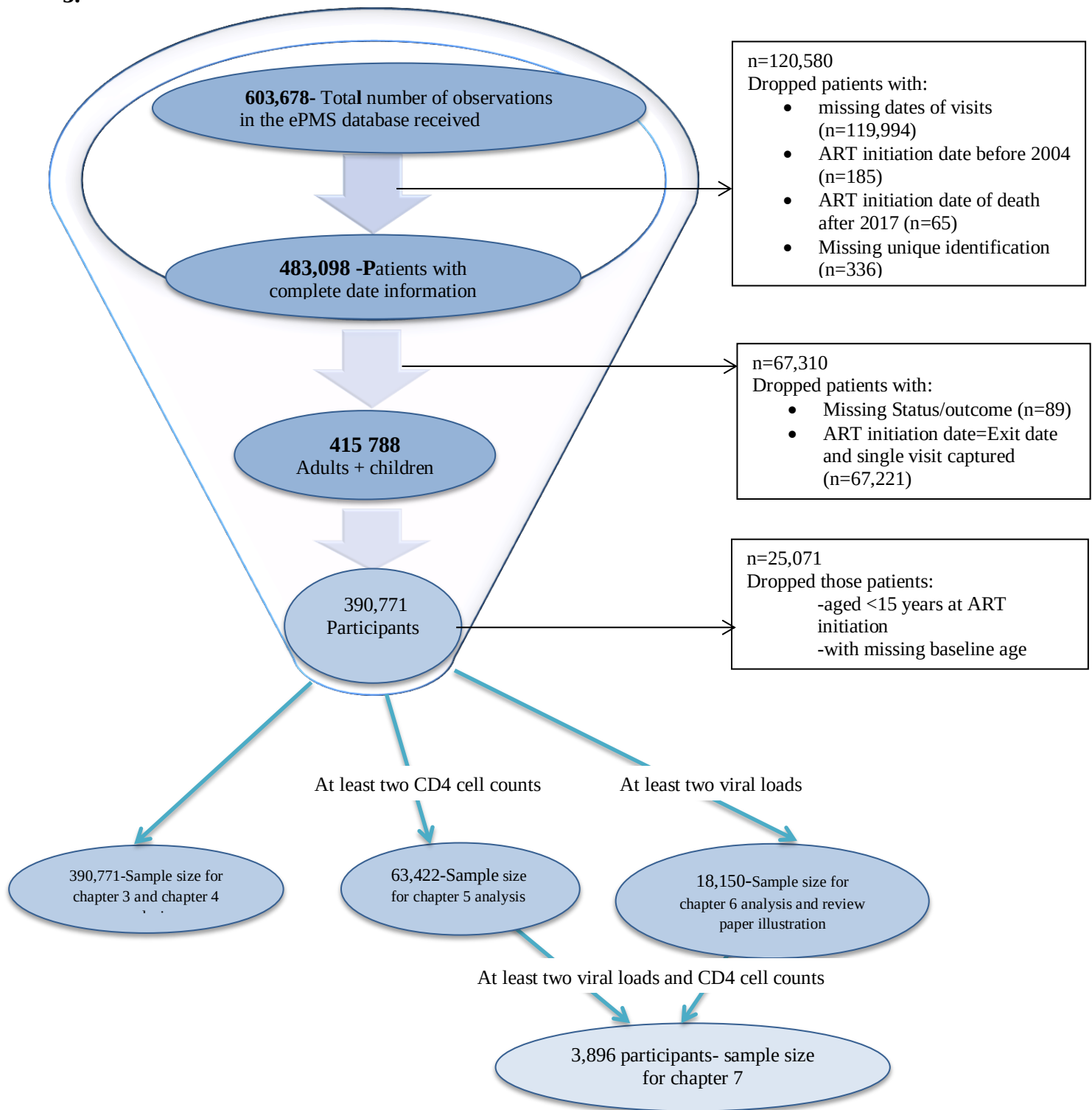


Figure 2-3: Flow chart of how patients were conveniently selected into this current study for analysis

In this current research phase, the main interest was to analyse adults patients aged 15 years and above at ART initiation to maintain consistency in patient care across the follow-up period considered in this study. From the 603,678 participants whose information were captured in the received data file, observations with missing dates of visits, missing ART initiation date, missing date of death or date of death after the study end date were excluded in the database. Observations with missing unique identifier, missing outcome status and with inconsistent dates were excluded in the analysis. The final sample size for this research work was 390,771 participants.

All 390,771 participants were considered in chapter 3 and chapter 4 analyses while in chapter 5 only those patients who had at least two CD4 cell counts measurements from the 390,771 participants were considered which resulted in a sample size of 63,422. In chapter 6, only those patients with at least two VL measurements from the 390,771 participants were considered which resulted in a final sample size of 9,273 participants. Lastly, from those with at least two consecutive measurements of both CD4 cell counts or VL measurements, only those participants who were monitored for both laboratory markers were extracted giving a final sample size of 3,896 participants, and these were considered the results reported in chapter 7.

2.4. Statistical Analysis Outline

This study extensively used various types of multistate models in a single context to answer research gaps in the HIV treatment cascade from ART attrition outcomes. The multistate models used were the competing risk model implemented in chapter 4; the disease progression (Illness-death model) in chapter 5, chapter 6 and chapter 7. This study also made use of spatial models to describe spatial heterogeneity of various ART outcomes, that is, ART drop-outs (attrition rates)

using conditional autoregressive models and kriging approaches in chapter 3, poor viral suppression in chapter 6 and chapter 7. The detailed rationale behind the suitability of these statistical models is described in subsequent sections.

2.4.1. Multistate models in infectious disease monitoring: A comprehensive review

*A review paper on multistate models has been submitted to the **Statistical Methods in Medical Research Journal**. The paper is currently at the interactive review stage.*

Paper Title: *A review of multistate modelling approaches in monitoring disease progression: Bayesian estimation using the Kolmogorov-Chapman forward equations*

The rationale of the paper: *There is an extensive review of multistate models in the literature. However, most review papers on multistate models have focused on the frequentist or maximum likelihood estimation (MLE) or the frequentist approach within the multistate model framework (34,50,51). None of these reviews has discussed Bayesian estimation (BE) within the multistate models, which is equally a robust method in multistate statistical modelling. Therefore, the manuscript extended previous reviews on multistate models with primary emphasis on Bayesian estimation (BE) inference. The theoretical aspects of the transition rate estimation using the MLE and BE are provided in **Appendix A and B** respectively. An illustration of the BE multistate modelling using Kolmogorov-Chapman forward equations on partially observed data is provided in **Appendix C** while information on the various statistical software and challenges in implementing multistate models is provided **Appendix D**).*

In chapters 4, 5, 6 and 7, multistate models were fitted to estimate time to event history processes among ART patients. Multistate models provide a flexible framework for longitudinal data

which can describe more than one possible time to event outcomes for a single individual (38,41,43). Since antiretroviral drug use suppresses VL by inhibiting the viral replication and boosting CD4 cell counts, multistate models can be used to give an in-depth understanding of the disease progression patterns using these surrogate markers among immune-compromised individuals and this was the focus in chapters 4, 5, 6 and 7.

2.4.1.1. Types of multistate models

A multistate model is defined as a continuous-time stochastic process which allows participants to move among a finite discrete number of compartments or states which could be clinical symptoms, biological markers, disease stages or disease recurrence in biomedical research (34,50). Multistate models are useful in infectious disease monitoring programs which aim to gain an in-depth understanding of the disease progression patterns. Commonly for these models, the disease state is partitioned into a finite number of intermediate states which may offer greater insight and understanding of the disease evolution (34).

Movement from one state to another is called a transition (event has occurred); states can be transient (if a transition can emerge from the state) or absorbing (if no transition can emerge from the state). Movement between transitions can be reversible or irreversible, and these movements contribute to the intricacy of the multistate model in addition to the number of states defined. The transition intensities (hazard rates) provide the transition specific hazards for movement from one discernible state to another. These transition intensity functions can also be used to compute the mean sojourn time (the average time spent in a single state before an outcome of interest occurs), the total length of stay in a state (total time spent in a state before making a transition), the number of transitions made from start to end of the study and the

transition probabilities(52). Also, the effect of covariates on each transition can be assessed to quantify the influence of the covariate on the different model transitions. The covariates effects may not be the same since the severity of the disease progression differs by each intermediate state(51).

There are different types of multistate models which can be used to answer a different research question, as shown in **Figure 2-4**. The *mortality model* for survival analysis with only two states and one transition from “alive” state to “dead” state is the simplest multistate model, **Figure 2-4 A**. This model was fully implemented in chapter 4 of this thesis to estimate time to become LTFU among ART patients. These mortality models are useful, mostly in answering etiological research questions (53). The hazard rates are usually estimated using a semi-parametric approach which has a less stringent assumption (33) and assumed to be an arbitrary, unspecified, non-negative function of time (54). The incidence or hazard rate is estimated by assuming independence of survival times between distinct individuals in a sample and a constant hazard ratio regardless of time (33).

Another type of multistate models is the *competing risks model* which extends the mortality model depicting a scenario whereby an individual may experience one of the several failure outcomes (55,56), **Figure 2-4 B**. In such models, competing risk analysis is performed whereby the interest is in the occurrence of the primary outcome but have other contesting events which may preclude the occurrence of the primary outcome or significantly alter the chances of observing the primary outcome; or situations where the different types of events may be relevant, but the analysis focuses on both time and occurrence of the first event(57).

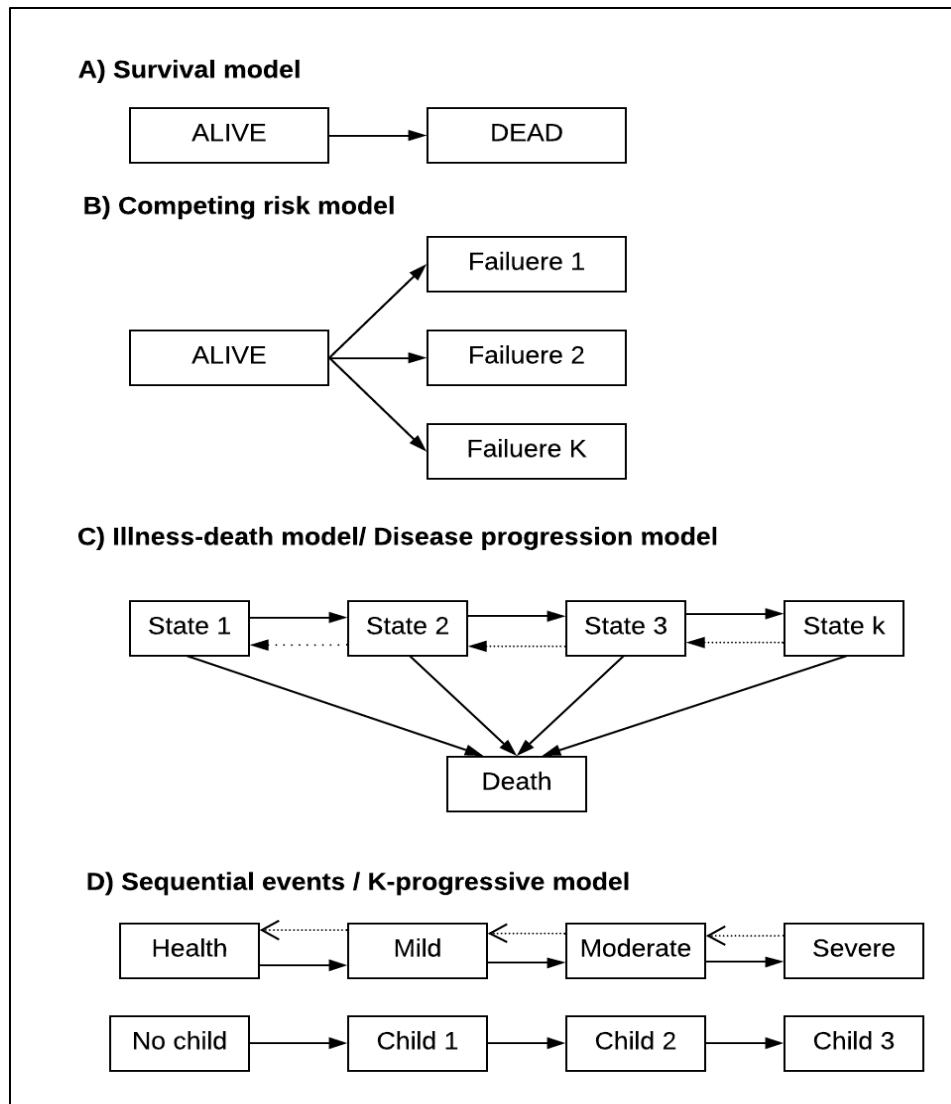


Figure 2-4: Schematic illustration of different types of multistate models

This model was fully implemented in chapter 4 of this thesis with mortality as a competing event for becoming LTFU. In this model, the interest was in modelling the occurrence of the primary outcome (LTFU) taking into account the competing outcome (mortality) which precludes the occurrence of the primary outcome or significantly alters the chances of observing the primary outcome. Moreover, the competing events models can be used in situations where the different types of events may be relevant but the analysis is focused on both the time and occurrence of the first event (57). The reason why the competing risk analysis is considered to be appropriate

over the Kaplan-Meier estimation in such situations described above is that the Kaplan-Meier estimation treats the competing events as censored observations which bring in bias since the independence assumption is violated. The baseline hazard may differ between these competing events(58). The competing risk models also provide in-depth insight on the effect of interventions on separate outcomes observed and are useful in exploring the relationship between explanatory covariates and the absolute risk which is critical particularly in decision-making and prognostic research work(53).

Partitioning the “alive” state of the mortality model into two or more transient (intermediate) states yields another type of a multistate model known as the *disease progressive multistate model* of which the simplest is the three-state model (34), **Figure 2-4 C**. This model was fitted in chapters 5, 6 and 7 of this thesis with states defined based on CD4 cell counts or VL measurements. In biomedical research, *illness-death models* or *disability models* which are a special type of a disease progression model, are usually used in estimating disease incidence rates and the mortality transition intensities(59). The disability model is considered in irreversible models when the disease increases the risk of death. In scenarios whereby the absorbing state is not considered, the *K-progressive models* which follow a sequential process(59) for instance health, mild, moderate and severe sequence or the *fertility model* which is used to describe the reproductive life history of a woman, **Figure 2-4 D**, where each state is defined by the number of children born.

2.4.1.2. Multistate models assumptions

The model assumptions behind these modelling approaches in these two packages overlap as both can assume the Markov process (assessed using the *markovchain* library in R), time homogenous transition rates (normally default set in most analysis packages) (60), and right censoring of observations. A flow chart for multistate model assumptions, methods of estimation, possible censoring patterns and covariates types is shown in **Figure 2-5**.

Multistate models can either be fitted assuming *discrete-time or continuous-time*. In discrete-time models, the movements between states occur at a fixed time, and the transition probabilities are usually reported. In contrast, in the stochastic continuous-time models, the transitions can occur at any time point, and these model inferences are usually based on the estimation of hazard rates or transition intensities (61). These transition rates describe the instantaneous rates at which the continuous-time multistate model transitions between states. In biomedical studies **of naturally occurring phenomena**, the continuous-time model reflects reality since the transitions occur at random.

Different assumptions can be made on multistate models about the dependency of the hazard rates (transition intensities) on time. The *Markov property* assumes that the transition to a future state is only dependent on the present state occupied not the ones before; hence, the model has a “memory loss”. This type of model is usually used because of its simplicity (62). Alternatively, multistate models can assume a semi-Markov process meaning that the next future transition depends on both the currently occupied state and also the time of entry into the current state. The *semi-Markov model* is considered flexible in most cases; however, there are some drawbacks in using this model. Firstly, the semi-Markov model contains many parameters which make the model much more problematic to fit and the distribution of the sojourn times in each state is a requirement which in most instances might be unavailable(42,43,51,63). Lastly, multistate

models can assume a non-Markovian process. This model is dependent arbitrarily on the previously occupied states; hence, there is no “memory loss” in the model. The implementation of *non-Markovian models* has been challenging until the introduction of the “Markov-free” estimators for transition probabilities in the last decade(50).

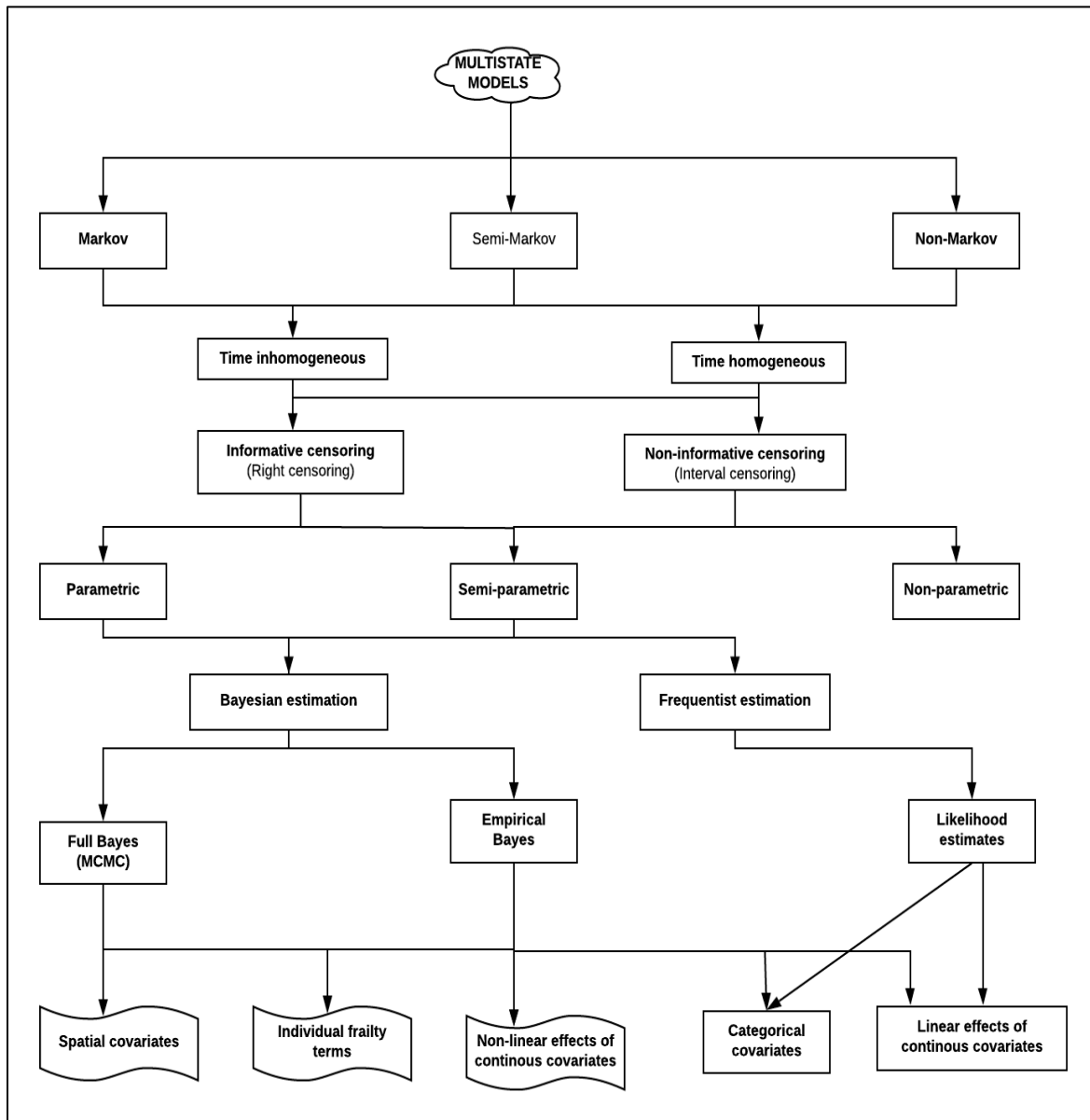


Figure 2-5: The multistate model assumptions, estimation types and possible covariates flow chart

Another assumption normally made in the multistate model is that of *time homogeneity*. In a time-homogeneous model, the transition intensities are assumed to be constant over time; that is, the rates are independent of time(42,50,64). In such models, the Kolmogorov differential equations can be solved explicitly using the decomposition of the transition matrix into both eigenvalues and eigenvectors(61). Models which assume time homogeneity are used more often possibly due to well-developed software at disposal and their less intimidating theoretical framework. This assumption was made for models fitted in chapter 5 and chapter 7. However, if time homogeneity assumption is violated, an inhomogeneous time model is used which assume that the transition intensities change with time(64). In chapter 5, the multistate model assumed time inhomogeneous (time-varying) assumption as it reflects reality.

2.4.1.3. Multistate models data features and contrasts between Bayesian estimation and the maximum likelihood estimation

Multistate models can be characterised by the way the data have been captured. Censoring is a crucial feature in time-to-event data analysis(65). In observational studies, follow-up studies often end before the outcome occurs, leading to right-censoring of observation times(66). At the same time, left-censoring occurs when the study begins after the event has occurred, but the event times are unknown(65). Frequently, non-informative censoring occurs when participants are followed up intermittently such that the period between visits is missing. This means that the transition times are not precisely observed, and the states occupied between follow-up time points are unknown. These non-informative censoring observations are considered to be interval-censored(65). A special case of interval censoring is grouped survival data, in which the intervals for the subjects are completely identical or non-overlapping. Grouped survival data have been documented to be simpler to analyse (67). The mechanisms which give rise to censoring are

essential in statistical inference within the multistate framework, and these data features need to be taken into account during analysis to avoid getting biased estimates since their likelihood functions will be different(68). In this study, the data used was right-censored, and the multistate models fitted can handle such heavily right censored data (37).

Moreover, intermittent follow-up of participants leads to incomplete spaced data points or missing information as a result of incomplete disease history of participants. In intermittent follow-ups, participants are observed for a short time, not to completion of their disease history as other visits are missed, and the specific time of occurrence of an event is usually unknown. The missing data in longitudinal studies and programmatic data frequently occurs with different missing mechanisms to define the process(69). Missing data may be missing completely at random (MCAR) if the probability of missingness is not dependent on the unobserved or observed data. Suppose a study is comparing time to change of viral load level after ART initiation and the follow-up viral load values were not measured on some individuals because they transferred to another health facility. These missing viral load values may be considered to be MCAR if the decision by participants to move is not related to the running study. Missing at random (MAR) occurs if the probability that data are missing does not depend on unobserved data but may depend on observed data. Suppose that individuals who leave the study (become LTFU and never return) are those with severe illness (high viral load), it is unlikely that the missing viral load measurements are MCAR, but the missing is due to severely immune-deterioration of the patients; hence, the data is monotone MAR, which can be simpler to analyse than non-monotone missing data (70).

In contrary, if the patients who are severely immune deteriorating do not have viral load follow-up measurements because of their severity, the missing viral load values would not be MAR but

missing not at random (MNAR). For such missing data mechanism, the reason for missingness has to be accounted for in the model to obtain precise results. In practice, it is a challenge to distinguish the MAR mechanism from MNAR mechanism; therefore, a sensitivity analysis is encouraged to compare estimated of analysis under various missing data models to verify the stability of the inference. The multistate model framework allows one to use the likelihood-based method for MAR or MNAR covariates, assuming a continuous-time Markov multistate model(71). Work by Kalbfleisch and Lawless equips one to fit a time-homogeneous Markov model with arbitrary transitions structure for such incomplete history data(71). However, if any covariates are missing, convergence problems are more likely with this method; hence, most studies prefer to work with fully observed complete case data.

The dataset used in this research was compiled through the ART program; hence, it was prone to missing information on both the dependent and independent covariates. At the data cleaning stage, all observations with missing outcome information, start or end dates were excluded in the analysis, and this is called a listwise (casewise) deletion. However, with an enormous number of missing observations, this method may lead to biased results with less efficient estimates. Large standard errors may yield wider interval estimates and less power; therefore, this method is not encouraged since the remaining observations with complete information may not be a perfect representation of the target population. In this study, the listwise deletion was only limited to the missing information of the dependent (outcome) variables. Multiple imputations (MI) was performed on all independent (explanatory) covariates with missing information using the Rubin method to maintain the study power, assuming that the data are MAR (72). The Rubin method ignores the process that causes missing data and simplifies the imputation steps ensuring correct

inference which is not possible if data are MNAR. A sensitivity analysis of the complete case model estimates and the multiple imputation model estimates was done.

Also, in longitudinal studies, the follow-up visits for participants are often intermitted, and the number of visits varies across participants. In such situations, the first visit and the last observed visit can be used. Such an approach results in partially observed data within a multistate model, that is, only the initial state and the final state information is known but the intermediate experiences of an individual are unknown. This happens typically in programme data which is usually reported and summarised in an aggregated format at national-level reports. In such cases, multistate models can be used to estimate transition rates using the partially observed aggregated data, which is a useful step as it forms the basis of future research formulation (73).

Multistate models can handle various types of covariates depending on the modelling approach used and the software the model is implemented in. Both methods of estimation can handle parametric effects of fixed covariates or categorical variables to assess their influence on the estimated transition processes(74). The maximum likelihood (MLE) multistate models fitted within R *msm* library assume that the functional form of the effects of predictive factors is linear by default (or log-linear) which might not be the case always. This precludes the assessment of non-linear effects on the transitions rates using the MLE models. The violation of this assumption may lead to inaccurate statistical conclusions, the increased bias in estimates and decreases statistical power for statistical significance tests in MLE(52). In contrast, the Bayesian estimation (BE) multistate models within BayesX using the *bayesreg* object (75) can handle non-linear covariates effects of continuous covariates using penalised splines through their flexible predictor component(74). Besides, BE multistate models can handle time-varying effects and nonparametric baseline effects using penalised splines, which MLE multistate models cannot do.

Another strength of the BE multistate models over MLE models is their ability to account for frailty (random-effects) terms to explain unobserved heterogeneity in the collected information either at the individual level or spatial level which R *msm* library cannot do (74). For instance, in HIV disease progression model, it is vital to account for individual-level heterogeneity to estimate transition rates since patients respond differently to ART treatment, and these transitions may also vary by location. BE multistate models with spatial random effects were proposed by Kneib *et al.* (2008) with a demonstration on human sleep data(46). Their application to disease progression studies has been on the rise with recent work involving their application to HIV disease progression based on viral suppression and viral rebound model(76). This is one of the first papers to include the spatial effects within BE multistate models framework.

Moreover, in longitudinal studies with intermitted follow-up visits of participants, the number of visits may vary across participants. In such scenarios, the first visit (baseline) and the last observed visit assessment points (end of study) can be used. Such a data capturing process results in partially observed data which can be implemented within a multistate model framework. In such a scenario, only the initial state (baseline) and the last state (end of study) information is known but the intermediate experiences of an individual are unknown (or might not have been recorded). This happens typically in programme data where the data is usually reported and summarised in an aggregated format in national-level reports whereby detailed information of intermediate processes is usually missing or clinical trials whereby only the clinical endpoints are reported. Nonetheless, this data can be used within a multistate framework using the method proposed by Welton (2005) on handling partially observed aggregated data to estimate transition rates using Kolmogorov-Chapman forward equations(73). Such modelling approach of partially

observed data provides a useful step in the research agenda as it forms the basis of future research formulation. This is one of the strengths of BE multistate models, which is not easily implemented in the MLE multistate models. However, there is still under-utilised of BE approach in epidemiological studies though BE multistate models are much more flexible and can handle most of the data features which are not possible with the MLE multistate models.

2.4.2. Spatial models in infectious disease monitoring

In chapters 3, 6 and 7, spatial and spatio-temporal models were considered to describe the spatial heterogeneity of different ART outcomes considered. The HIV continuum of care focuses on populations and geographic locations which are experiencing the greatest HIV burden to come up with location-specific intervention tailor-made for each location (36). Spatial models point out which populations and geographical areas are experiencing the greatest HIV burden (in terms ART attrition, unsuppressed VL or decrease in CD4 cell counts) which will guide resource allocations and implementation of area-specific interventions (77). Spatial distribution of regions with poor patient retention and poor viral suppression are viewed in pictorial outputs. Not only does spatial models useful in monitoring ART retention patterns and viral suppression but also may help to identify geographical barriers which may have a negative influence on ART adherence (poor ART uptake) like inadequate transport network, poor terrain and long-distance to clinics.

The geospatial analysis technique is on the upsurge and continues to take significant hikes as it has brought solutions to some of the previously unanswered questions. In general, spatial maps aim to estimate the spatial patterns of an outcome of interest since health risks vary geographically due to many factors and pinpoint the marginalized groups of people (78). The

spatial heterogeneity can be described through a map by partitioning non-overlapping areal locations and calculate the weighted outcome of interest for the population living in each location. This is a useful strategy in health issues mapping, especially for low-middle income countries which are resource-constrained. There are different types of spatial data namely the areal (lattice) data which includes administrative areas like villages, wards, districts, provinces or counties and geostatistical (centroids) locations which are fixed such as household location, health facility location or cluster locations (79,80).

2.4.2.1. Types of geostatistical models

There are different modelling techniques which may be used to investigate spatial heterogeneity. **Structured autoregressive (SAR) models** fitted in STATA are based on the MLE of the spatial effects of the outcome of interest. Within the SAR models, the spatial effects are modelled in a model which can assume any of the following: 1) spatial lag of the outcome variable, 2) spatial lag of the explanatory variables, 3) the spatially autoregressive error term of the spatial contiguity or inverse distance matrix and 4) all these three types of spatial lag terms fitted at once. These models are much more useful if the outcome is assumed to have "spillover" (indirect) effects to neighbouring regions. The SAR models are biased towards outcome variables measured on a continuous scale which then restricts the fitting of binary or count data. However, non-continuous outcomes can be fitted as proportions if data is aggregated.

Structured additive regression (STAR) models provide a flexible framework for modelling possible nonlinear effects of continuous covariates. This class of models contains the well-established frameworks of generalized linear models (GLM), generalized additive models (GAM), generalized additive mixed models (GAMM) and varying coefficient models as

exceptional cases. These models also allow a broader class of effects, for instance, spatio-temporal or geographical data which may be incorporated in a geographically weighted regression model. The spatial effects can be decomposed into structured (correlated) or unstructured (uncorrelated) random effects which can be modelled independently in the spatial model. Ordinarily, spatial modelling focus of space collected data but in some instances, data can be collected across time and space meaning the data has both spatial and temporal properties. The temporal random effects can be modelled using autoregressive models or first-order random walk models and the time variable can either be discrete or continuous (81,82). There are many studies which have implemented these STAR models (79,80,83,84). The STAR models can be fitted within R software using the “R2BayesX” library (83) which provides an interface to the standalone software package BayesX or can be implemented in WinBUGS software.

There are different types of spatial data namely the areal (lattice, spatial polygon) data which includes administrative areas like districts; and geostatistical (centroids) locations which are fixed such as health facility locations (79,80,85). Within the Bayesian framework, spatial polygon data can be modelled using the conditional autoregressive (CAR) prior and these spatial models are often termed **conditional autoregressive (CAR) models** and are normally fitted in WinBUGS or within R using “R2Winbugs” package(86) proposed by Besag-York-Mollie` (81) which assumes spatial dependence between spatial polygons. Besides, **multivariate conditional autoregressive (MCAR) prior models** are used to jointly map the relative risks of two conditions or diseases. The MCAR model assumes that the occurrence of one condition coincidentally affect the other condition due to shared geographical pattern. If geo-coordinates spatial data is used, the Bayesian models can assume the Gaussian Markov Random Fields (GMRF) prior or kriging in BayesX (81,82).

Often, these spatial models fitted in BayesX and WinBUGS are estimated based on the Bayesian inference and the Markov Chain Monte Carlo (MCMC) simulation is normally employed. However, other estimation approaches within BayesX include the restricted maximum likelihood (REML) or stepwise selection. However, the MCMC method makes inference tractable for complex models and may present convergence and computational challenges. To overcome this challenge, Integrated Nested Laplace Approximation (INLA) models are a better alternative as this is a computationally less-intensive method which approximate Bayesian inference in latent Gaussian models which include the spatial models. The INLA package uses optimized algorithms and can handle hierarchical Gaussian Markov random fields (GMRF) priors; however, the Bayesian inference is not based on the Gibbs sampling. The Gibbs sampling is useful if the joint distribution is unknown and is difficult to sample from directly while the Metropolis Hasting is useful when the distribution is known (87). As much as the INLA models can help overcome the mixing and convergence of the model challenges; these models require quite an advanced mathematical and numerical tool for implementation. Besides, complex hierarchical prior structures like Bayesian lasso or complex models with a larger number of hyper-parameters are more challenging to fit in INLA framework (83).

2.4.3. Types of covariates considered in this study

The HIV disease progression patterns are influenced by several cofactors, some as risk factors or confounders. The effects of covariates on each transition within the multistate model were assessed, assuming that the effects of the covariate on the different transitions may vary since the severity of the disease progression differs by each intermediate state. Similarly, the spatial models accounted for the covariate effects. The models adjusted for age reported as mean

(standard deviation) for continuous variable or as proportions and frequencies for the categorical variable (15-24, 25-34, 35-44, 45 and above years) in descriptive analysis. We also adjusted for sex (male, female), degree of urbanization (rural, urban), WHO clinical stage at ART initiation (I/II, III/IV), treatment regimen at the time of data extraction (first-line, second-line), tuberculosis status at ART initiation (positive, negative, not assessed), functional body status (working, ambulatory, bedridden) and marital status (single, married, widowed, divorced). Acknowledging that the period covered in this study encompasses change in treatment guidelines for ART initiation, this study adjusted for the calendar period of starting ART with intervals based on when the new treatment guidelines were effected in Zimbabwe assuming that the effect was uniform across the country (2004-2007, 2008-2011, 2012-2014, 2015-2017). Moreover, the multistate models fitted can account for the time within the model implementation framework, which supports the strength of the multistate model in modelling time to event history data. The health facility type (primary health care (PHC), district or mission hospitals, and provincial or referral hospitals) was a crucial variable accounted for since this study focused on ART outcomes after the decentralization of ART services. In sub-analysis of chapter 7 results, CD4 cell counts and VL covariates effects were accounted for in the covariate matrix.

The schematic presentation of the conceptual framework used in this study is shown in **Figure 2-6**. We assumed that the factors associated with adherence to ART included but not limited to programmatic factors (drug supply, treatment access, laboratory services access and patient-provider service); clinical factors (baseline VL, CD4 cell counts, body functional status and comorbidities (tuberculosis, diabetes, hypertension or cancer) and individual-level factors (socio-demographic factors, beliefs towards ART and behavioural characteristics like alcohol intake and smoking). Treatment adherence will influence the follow-up measurements of CD4 cell counts

and VL measurements. Through the laboratory markers, we can estimate the viral suppression patterns (objective 5) and CD4 cell counts immune deterioration (objective 4) which jointly answer objective 6. Through the laboratory marker trajectories, ART outcomes occur (death, LTFU, drop-out and withdrawals).

2.4.4. The inter-linkages of the different model fitted in this research

The inter-linkage of the different multistate models (survival model, competing risk model, disease progression model) utilized in this thesis is depicted in **Figure 2-7**. The "green" colour entries depict the simplest multistate model, the survival model and the competing risk models. These models were fitted in **chapter 4**, and only the competing risk of mortality on LTFU outcome was assumed. The "blue" colour entries represent the HIV disease progression model based on CD4 cell counts. This model assumed time homogenous and nonhomogeneous Markov assumptions; the model is described fully in **chapter 5**. The "purple" colour entries represent the VL multistate model which assumed time inhomogeneous Markov processed and is the first model to incorporate spatial effects. This model is fitted in **chapter 6**. The mortality outcome ("grey" colour) was universal for all the multistate models.

The CAR models using the INLA approach illustrated in **Figure 2-8** were fitted in **chapter 3** to describe the ART drop-out heterogeneity. The joint multistate models of CD4 cell counts and VL and joint spatial models were fitted in **chapters 7**. These models are linked by the spatial random effects (health facility level and district as the spatial units for models in Chapter 3 and province as a spatial unit for chapter 7).

2.4.5. Conceptual framework of this research

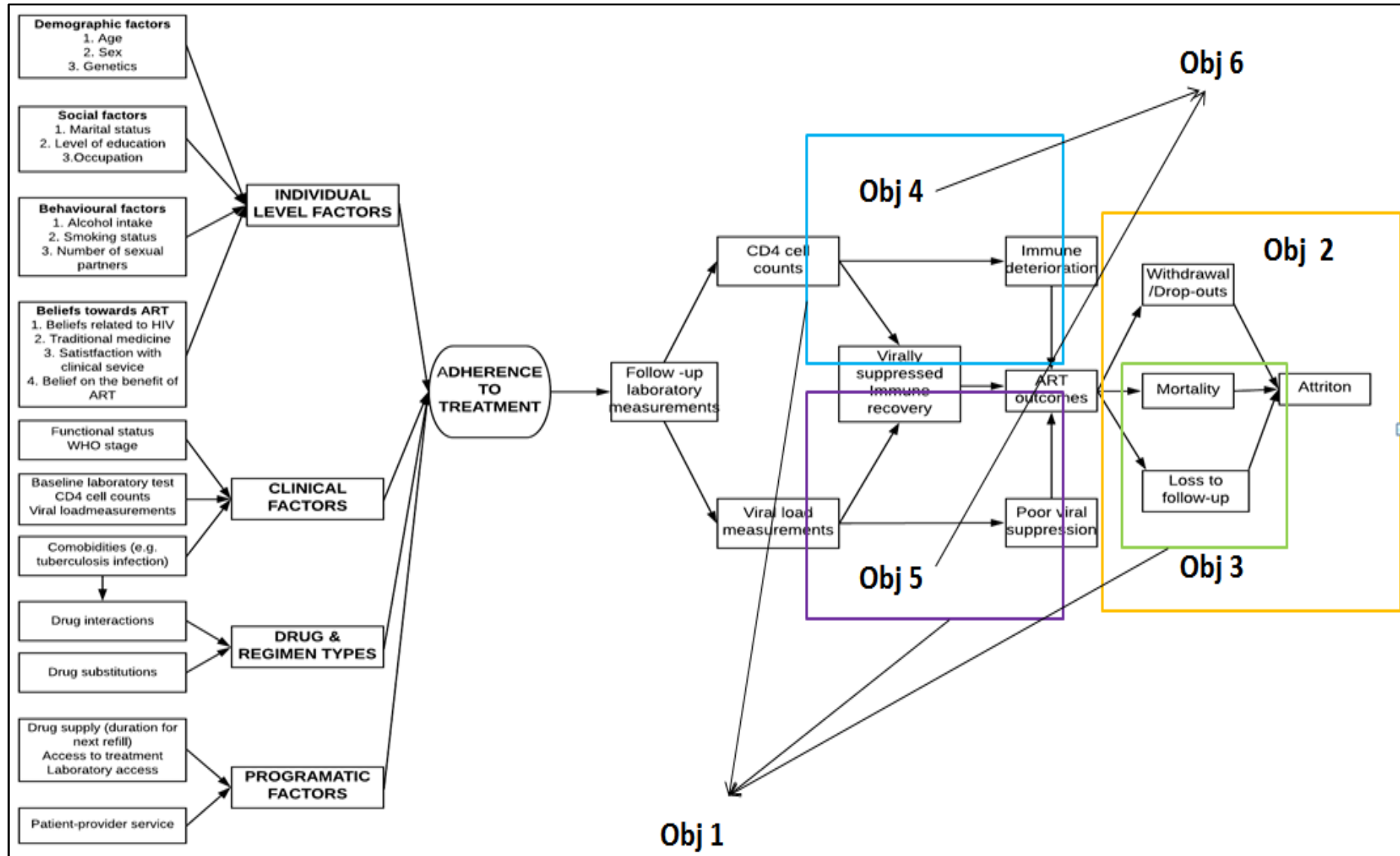


Figure 2-6: The schematic presentation of the thesis conceptual framework linking to the thesis objectives

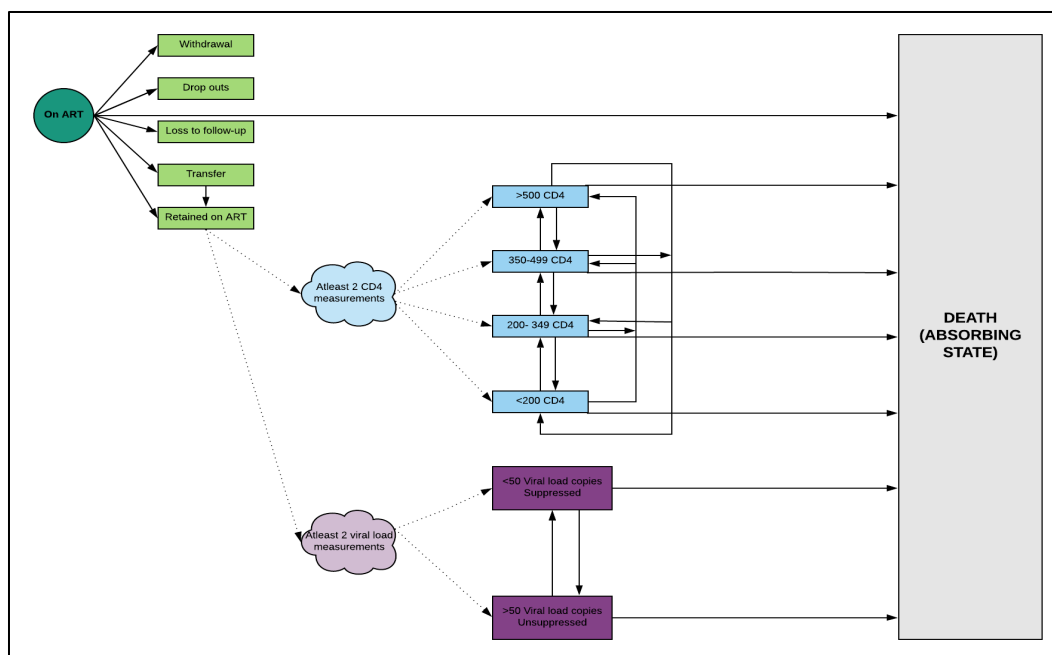
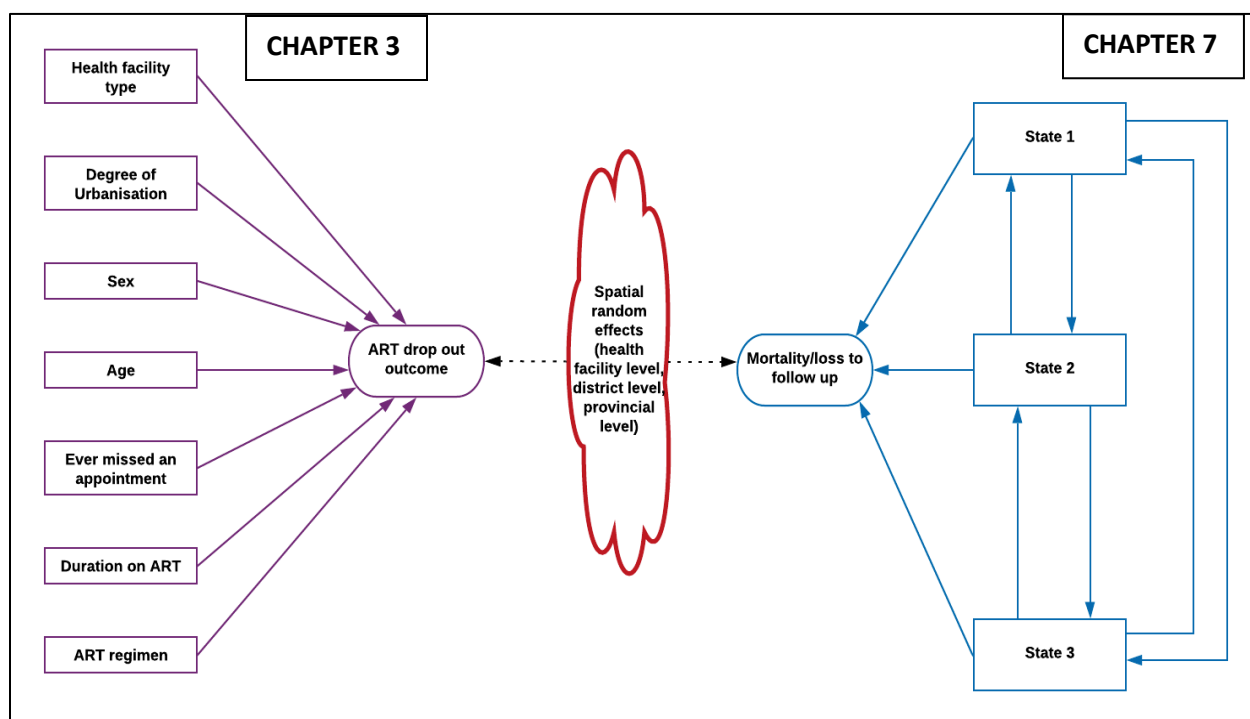


Figure 2-7: Schematic presentation of the linkage of the multistate models for HIV disease progression



State 1(VL<50 or CD4 ≥ 800), State 2 (50 ≤ VL<1000 or 350 ≤ CD4<800), State 3 (VL ≥ 1000 or CD4<350)

Figure 2-8: The inter-linkage of the ART drop-out spatial model using INLA and the joint modelling of VL and CD4 multistate model

2.4.6. Ethical considerations

The data used in this study had no personal identification; however, we used the individual unique identifier for the analysis. Permission to use the dataset was sort and granted by the Ministry of Health and Child Care, Zimbabwe through the AIDS/TB Units. This doctoral research was granted ethical approval by the University of Witwatersrand's Human Research Ethics Committee (Medical) (Clearance Certificate No. M170673), and a copy of the ethical clearance letter is attached in the thesis appendices (**Appendix F**).

The remaining parts of this thesis (chapters 3, 4, 5, 6 and 7) provide an outline of the detailed research findings presented as stand-alone chapters of this thesis. Each subsequent chapter in this thesis should be viewed as an independent written work contributing to a unique manuscript; hence, there could be repeated usage of symbols in equations with different meaning per chapter and repeated definition of some acronym terms per chapter. Chapter 8 is left for discussion, conclusion and future research focus in addition to public health contribution of this research work.

CHAPTER 3

This chapter is structured as a manuscript format following the targeted journal article guidelines. The main objective of this paper was to describe the spatio-temporal patterns of ART drop-out at the health facility and district levels and identify hot spots and cold spots for ART drop-out to guide policy using Integrated Nested Laplace Approximation (INLA). The kriging technique was used to interpolate ART drop-out values at health facility-level. In general, we observed a significant spatial variation of ART drop-out in the northern and southern parts of Zimbabwe. Higher-level of care health facilities were associated with an increased risk of ART drop-out compared to primary level facilities. The longer the individuals at the health facility level and district levels were on ART; the less likely they were to drop-out. This puts forward the need to strengthen ART adherence and implement interventions which retain patients in care.

This paper has been submitted to the Spatial and Spatio-Temporal Epidemiology Journal and is currently under review.

3. HIERARCHICAL BAYESIAN SPATIO-TEMPORAL POISSON MODELLING OF ART DROP-OUT AMONG HIV PATIENTS IN ZIMBABWE AT HEALTH FACILITY AND DISTRICT LEVELS

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3.1. Abstract

Background: Patient drop-out in an antiretroviral therapy (ART) programme remains one of the fundamental challenges in HIV prevention and control. We aimed to describe the spatio-temporal patterns of ART drop-out at the health facility and district levels and identify hot and cold spots for ART drop-out to guide policy.

Methods: Routinely collected aggregated count data of HIV patients who initiated ART between 2004 and 2017 from the Zimbabwe national ART programme was used. To estimate the adjusted spatial posterior relative risk (pRR) of ART drop-out counts, separable space-time hierarchical Bayesian spatio-temporal Poisson regression models were using the Integrated Nested Laplace Approximation package. Spatial random effects decomposed into structured and unstructured were assigned conditional autoregressive prior and Gaussian Markov Field priors respectively. Temporal random effects were modelled assuming first-order random walk Gaussian priors. Time series plots and trellis plots were used to describe the spatio-temporal effects of ART drop-out. Kriging technique was used to interpolate ART drop-out “exceedance probability” values at health facility-level.

Results: Generally, there is a steady decrease in the ART drop-out effects over time. In the health facility level model, individuals in secondary level health facilities were 1.31times more at risk of ART drop-out (pRR=1.31;95%CI:1.29-1.33) while those registered in tertiary institutions were 2.22 times more at risk of ART drop-out (pRR=2.22;95%CI:2.16-2.28) compared to primary level of care. Those who were registered in health facilities in the urban areas were 1.63 times more at risk of ART drop-out compared to those who were registered in rural health facilities (pRR=1.63;95%CI:1.61-1.65). In the district level model, an increase in the meantime

duration on ART increased the risk of ART drop-out by 14% (pRR=1.14;95%CI: 1.12-1.16). Mean duration time since ART initiation was 9%-11% protective against ART drop-out. Regions around Victoria Falls and those bordering Mozambique were hot spots for ART drop-out. The spatio-temporal distribution of the ART drop-out varied across districts over time. Structured random effects showed highest ART drop-out risk along the southern and northern parts bordering Botswana.

Conclusions: The spatio-temporal patterns of ART drop-out vary across districts over time though there is a steady decrease of ART drop-out risk in Zimbabwe. With ART drop-out risk in the southern and northern parts of the country, region-specific interventions are of priority to increase ART patients' retention. Community-based interventions and programmes which strengthen ART adherence remain essential in the global HIV control campaign to improve health and prolong survival among HIV infected patients.

Keywords: ART drop-out, aerial interpolation, conditional autoregressive models, R-INLA, kriging, health facility spatial mapping, Poisson regression

3.2. Introduction

The Human immunodeficiency virus (HIV) is a complex retrovirus that progressively destroys the body's immune system, making it harder for infected individuals to battle other infections (88). However, the introduction of antiretroviral therapy (ART) which aims to suppress the HIV viral load, thus decreasing the aggression of the immune system and enabling it to recover, has left an indelible mark in the HIV fight. Slowing down the HIV progression and suppressing the virus to undetectable levels using the ART treatment results in un-transmittable HIV(26). This ultimately lowers HIV incidences in the general population.

The UNAIDS 90-90-90 fast track targets were launched with the global vision to achieve a zero HIV incidence by 2030. The fast track targets aimed to ensure that 90% of the people living with HIV (PLWHIV) know their status, 90% of the PLWHIV are initiated on ART and ensure that 90% of those on ART are virally suppressed by 2020 (1). The last 90% is the prime focus of HIV prevention and control; however, achieving the last 90% is strongly dependent on how well these HIV patients are adhering to ART. In Zimbabwe, the last 90% was estimated at 73% in 2018, but still below expected (8). One of the challenges which may contribute to the slow rate of viral suppression is poor ART adherence among HIV patients. Poor ART adherence has been documented to be due to patients' attrition in the HIV continuum of care through "leakages" of patients from the ART programme. Individuals may drop-out from treatment, withdraw from treatment, become loss to follow-up or miss appointments for treatment refill for various reasons. Possibly due to misconceptions over ART benefits, health literacy, cultural beliefs and inclination for traditional medicine (89).

The geospatial analysis techniques are on the rise and continue to take significant hikes forward as the software and computing power brings solutions to previously unanswered questions. Geospatial modelling is an essential tool in advanced public health since epidemiological data have a geographical linkage and has been used extensively in malaria (84), chronic obstructive pulmonary disease(36), perinatal mortality (90,91), female genital mutilation (92) and HIV infection (47,93). As much as geospatial analysis thrives to become the gold standard in health issues mapping to guide programme planning and monitoring (94); this tool has not been extensively used in monitoring HIV. The tool encompasses maps with information about point locations and mapping variations in risk factors associated with the specified outcome through partitioning non-overlapping spatial units.

Spatial modelling also involves the use of complex statistical analysis to make inference of the risk factors. Spatial modelling can be performed on areal (lattice, spatial polygon) data which includes administrative areas like districts; and geostatistical (centroids) locations which are fixed such as health facility locations (79,80,85). Bayesian inference has been the predominant method of estimation used in spatial modelling. Within the Bayesian framework, spatial polygon data can be modelled using the conditional autoregressive (CAR) priors while the kriging method or Gaussian Markov Random Field (GMRF) prior for the geo-coordinate data (81,82). The spatial effects can be decomposed into structured (correlated) or unstructured (uncorrelated) random effects which can be modelled independently in the spatial model. Ordinarily, spatial modelling focus of space collected data but in some instances, data can be collected across time and space meaning the data has both spatial and temporal properties. The temporal random effects can be modelled using autoregressive models or first-order random walk models and the time variable can either be discrete or continuous (81,82). In public health outcome mapping, the most commonly used model is the Poisson distribution to handle count data of the health outcome of interest.

With the global efforts to achieve zero HIV incidences by 2030, ART drop-out spatial analysis may help to pinpoint cold and hot-spot regions to guide program planning and rolling-out region-specific ART interventions to improve ART patients' retention. This study aims to describe ART drop-out spatio-temporal risk at district and health facility levels and pinpoint cold and hot-spot regions of ART drop-out in Zimbabwe using separable space-time hierarchical Bayesian spatio-temporal Poisson regression model. ART drop-out risk mapping to describes the geographical distribution ART drop-out is quite useful for policymakers and programme managers to have a pictorial view of the high-risk regions to guide in resource distribution and implement region-

specific interventions or policy formulation (36). Besides, the gained knowledge helps in the formulation of hypothesis for further research and guide surveillance in high-risk regions. Once ART drop-out has been reduced, ART adherence is likely to improve, and subsequently, viral suppression can be attained and maintained.

3.3. Materials and Methods

3.3.1. Study design

We did a secondary data analysis of the routinely collected aggregated count data at the health facility and district levels from the electronic patient management system (ePMS) which is a sample of all PLWHIV in Zimbabwe (8). The main interest was to map the ART drop-out counts distribution across the country.

3.3.2. Study site

This study was done in Zimbabwe, which is a landlocked country located in sub-Saharan Africa bordering with South Africa, Mozambique, Botswana and Zambia. The country is made up of eight provinces (Matabeleland North, Matabeleland South, Masvingo, Midlands, Mashonaland East, Mashonaland Central, Mashonaland West and Manicaland) and two metropolitan cities (Harare and Bulawayo). These provinces are further divided into 60 districts which are the spatial unit of analysis for this study; however, these districts are further partitioned into 1,980 administrative wards (**Figure 3-1**). The ART services have been decentralized to approximately 1,566 health facilities across the country in 2017 (8). The decentralization of these health facilities resulted in increased access of ART to all those in need and improved ART uptake in the country. The overall adult HIV prevalence at country level was estimated at 13.7%; however,

the HIV prevalence varies by province due to significant heterogeneity in social, cultural and population dynamics which are mainly influenced by geographical correlation of the epidemic. From the Zimbabwe Population-based HIV impact assessment (ZIMPHIA) survey in 2015/16, Matabeleland South and Matabeleland North provinces had high HIV prevalence of 22.3% and 20.1%, respectively (10).



Figure 3-1: The map of Zimbabwe partitioned and labelled at the district level

3.3.3. Data source

The data for this study was extracted from the Zimbabwe national ART program database among HIV patients aged 15 years and above who initiated ART between 2004 and 2017. The database captures individual-level monitoring information; however, in this study aggregated drop-out count data at health facility levels (quaternary, tertiary, secondary and primary levels of care) and district were used. The degree of urbanisation of health facilities was adjusted for in addition to

gender, ever missed appointment, tuberculosis infection and ART regimen type (AZT=Zidovudine, 3TC=Lamivudine, NVP=Nevirapine combination therapy) as proportions. Mean age at last observed visit and average duration of patients on ART at the health facility and district spatial units of analysis were also considered. The distribution of the 538 health facilities considered in this study, whose coordinates are defined by the red dots, is shown in **Figure 3-2**.

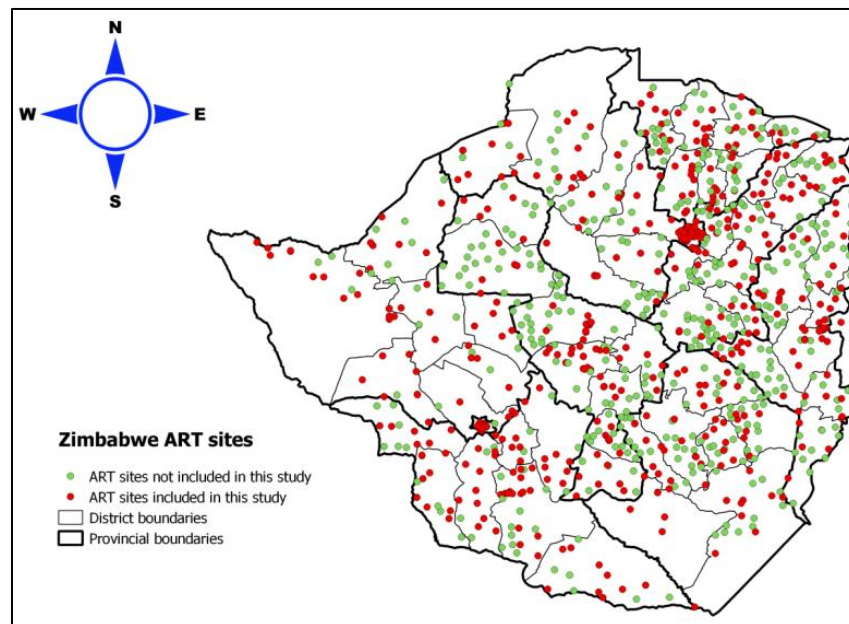


Figure 3-2: The map of Zimbabwe with provinces and district demarcations showing the geographical points of the ART health facilities used in this study (red dots)

3.3.4. Statistical analysis

The hierarchical Bayesian spatio-temporal Poisson regression model

Likelihood specification

To estimate the ART drop-out risk and quantify the risk associated between ART drop-out and selected covariates in Zimbabwe, we fitted a separable space-time hierarchical Bayesian spatio-

temporal Poisson regression model. In Bayesian analysis, estimates are based on the posterior distribution (likelihood x prior) and this approach contrasts the maximum likelihood approach which derives estimates from the likelihood alone. The ART drop-out counts were modelled based on the Poisson distribution function with the following probability density function:

$$P(Y_{it}) = \frac{\mu_{it}^{Y_{it}}}{Y_{it}!} \exp(-\mu_{it}) ; i = 1, 2, \dots, n \text{ and } t = 1, 2, \dots, Z \quad (3.1)$$

where Y_{it} defines the observed ART drop-out counts at region i in time t measured in years (2004-2017) and the mean of the observed ART drop-out counts $\mu_{it} = \lambda_{it} E_{it}$. The parameter E_{it} defines the total number of drop-out counts expected at region i in time t compared to the standard population and λ_{it} is the unknown relative ART drop-out risk at region i in time t . The known expected (E_{it}) ART drop-out counts for the study regions (538 health facilities or 60 districts) were calculated using direct standardization, that is, $E_{it} = R(P_{it})$, where R is the overall ART drop-out rate of the standard population, and P_{it} is the number of ART patients at risk in region (health facility or district) i at time t .

To summarise the distribution of the count data:

$$Y_{it} \sim Po(\mu_{it}) = Po(\lambda_{it} E_{it}) \quad i = 1, 2, \dots, n \text{ and } t = 1, 2, \dots, Z \quad (3.2)$$

The likelihood of the data is defined as:

$$\begin{aligned}
P(\mathbf{Y}_{it} | \boldsymbol{\theta}_{it}) &= P(Y_{1t}, Y_{2t}, \dots, Y_{nt} | \lambda_{1t}, \lambda_{2t}, \dots, \lambda_{nt}) \\
&= \prod_{t=1}^Z \prod_{i=1}^n \left[\frac{\mu_{it}^{Y_{it}}}{Y_{it}!} \exp(-\mu_{it}) \right] = \prod_{t=1}^Z \prod_{i=1}^n \left[\frac{(\lambda_{it} E_{it})^{Y_{it}}}{Y_{it}!} \exp(-\lambda_{it} E_{it}) \right] \\
&\propto \sum_{t=1}^Z \sum_{i=1}^n (\lambda_{it} E_{it})^{Y_{it}} [\exp(-\lambda_{it} E_{it}) nZ]
\end{aligned} \tag{3.3}$$

Taking the log-likelihood of equation 3.3, differentiation with respect to λ_{it} gives

$$\begin{aligned}
\log(\lambda_{it} E_{it}) &= \log \left[(\lambda_{it} E_{it})^{\sum_{t=1}^Z \sum_{i=1}^n Y_{it}} \right] - (\lambda_{it} E_{it}) nZ \\
&= \sum_{t=1}^Z \sum_{i=1}^n [Y_{it} (\log \lambda_{it} + \log E_{it}) - \lambda_{it} E_{it}] \\
\frac{\partial \log(\lambda_{it} E_{it})}{\partial \lambda_{it}} &= \sum_{t=1}^Z \sum_{i=1}^n \left(\frac{Y_{it}}{\lambda_{it}} - E_{it} \right) = \sum_{t=1}^Z \sum_{i=1}^n \left(\frac{Y_{it}}{\lambda_{it}} \right) - \sum_{t=1}^Z \sum_{i=1}^n (E_{it}) = \frac{nZY_{it}}{\lambda_{it}} - nZE_{it}
\end{aligned} \tag{3.4}$$

Setting the derivative to zero gives a maximum likelihood estimate of the rate

$$\frac{nZY_{it}}{\lambda_{it}} - nZE_{it} = 0 ; \quad \frac{Y_{it}}{\lambda_{it}} - E_{it} = 0 ; \quad \text{SIR}_{it} = \hat{\lambda}_{it} = \frac{Y_{it}}{E_{it}} \tag{3.5}$$

which defines the crude yearly Standardised Incidence Ratios (SIRs) of the ART drop-out counts for a specific region. The use of SIRs is the standard maximum likelihood approach which can be used to describe spatial heterogeneity of the outcome; however, in instances where very extreme values occur in regions with small populations due to the small sample sizes are involved; this may result in the overestimation or underestimation of the associated outcome risk. Moreover, if the likelihood is complex and the number of parameters is large, this approach may become difficult to implement. To overcome this limitation, Bayesian inferential models are preferred to obtain the outcome risk estimates accounting for confounding factors; adjusting for

the neighbouring areas random effects and parameter estimates can be smoothed or shrunk to improve the precision (95).

The likelihood function linear predictor in Bayesian inference can handle additional components.

If we consider the log function of the Poisson mean parameter and let $\log(\lambda_{it}) = \psi_{it}$:

$$\log(\mu_{it}) = \log(\lambda_{it} E_{it}) = \log(E_{it}) + \log(\lambda_{it}) = \log(E_{it}) + \psi_{it} \quad (3.6)$$

This shows that $\lambda_{it} = \exp(\psi_{it})$ where ψ_{it} can be assumed to be a random-effects parameter. This random effect component can be split into more additional components to have a convolutional regression model with separable spatial and temporal components:

$$\log(\mu_{it}) = \log(E_{it}) + \alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t \quad (3.7)$$

where α is the mean log overall risk ART drop-out risk over all areas and $\mathbf{X}_{it}^T \boldsymbol{\beta}$ denotes the fixed effects regression coefficients $\boldsymbol{\beta} = (\beta_1, \beta_2, \dots, \beta_m)$ associated with explanatory variables $(\mathbf{X}_i^T = X_1, X_2, \dots, X_m)$, $\boldsymbol{\phi} = \phi_1, \phi_2, \dots, \phi_n$ and $\boldsymbol{\eta}_i = \eta_1, \eta_2, \dots, \eta_n$ components define the decomposed structured and unstructured spatial random effects for region i respectively. In other words, spatial random effects $\mathbf{S}_i$ are partitioned into two components $(\mathbf{S}_i = \boldsymbol{\phi} + \boldsymbol{\eta}_i)$. These spatial random effects accounted for the extra-Poisson variability in the observed ART drop-out counts data(95). The component $\boldsymbol{\varphi}_t = \varphi_1, \varphi_2, \dots, \varphi_p$ defines the overall temporal random effects common to all regions.

Prior specification

All unknown parameters and hyper-priors were assigned some prior information. The α parameter was $\alpha \sim U(-\infty, +\infty)$ to have a “sum to zero” constraint for the structured spatial parameter. The regression coefficients for the selected covariates $\beta = (\beta_1, \beta_2, \dots, \beta_m)$ were assumed to follow a non-informative Gaussian distribution with a mean ($\mu_\beta = 0$) and a wide variance, that is, $\beta \sim iid N(\mu_\beta, \sigma_\beta^2)$ with a precision of $\tau_\beta = 1/\sigma_\beta^2$. The temporal random effects $\phi_t = \phi_1, \phi_2, \dots, \phi_p$ were assumed first-order random walk priors $\phi_t - \phi_{t-1} \sim N(0, \tau_\phi)$ $t = 2, \dots, Z$ with a precision of $\tau_\phi = 1/\sigma_\phi^2$. The unstructured spatial random effects were assumed Gaussian priors, that is, $\eta_i \sim iid N(\mu_\eta, \sigma_\eta^2)$ where σ_η^2 is the variance component specified as a precision $\tau_\eta = 1/\sigma_\eta^2$. Structured spatial polygon random effects were modelled using the intrinsic conditional autocorrelated (CAR) normal prior proposed by Besag-York-Mollie` (81) which assumes spatial dependence between neighbouring spatial polygons expressed as:

$$\phi_i | \phi_{-i} \sim N\left(\frac{\phi_i}{\phi_i}, \frac{\sigma_\phi^2}{N_i}\right) = N\left(\frac{\phi_i}{\phi_i}, \frac{1}{\tau_\phi N_i}\right) \quad (3.8)$$

where N_i is the number of neighbours of region i and a Gamma hyper-prior for the precision parameter $\left(\tau_\phi = 1/\sigma_\phi^2\right)$ which controls for the strength of local spatial dependency. The stationary Gaussian Markov Random Field (GMRF) prior was considered for the geographical locations of health facilities (centroid data), Let $\phi = (s_{ix}, s_{iy})$ defines the health facility

coordinates and $f(\phi_i) = \kappa_\phi$ be the structured spatial component which follows a zero-mean stationary GMRF with variance τ_ϕ and isotropic correlation function $Cov(\kappa_\phi, \kappa_{\phi+h}) = C(\|\vec{h}\|)$. The correlations between health facility sites that were $\|\vec{h}\|$ units apart were assumed to be equal regardless of direction and position. The Gamma priors for $\kappa_\phi = (\kappa_1, \kappa_2, \dots, \kappa_S)$ were considered:

$$P(\kappa | \tau_\phi) \propto \frac{1}{(\tau_\phi)^{\text{rank}(\mathbf{Q})/2}} \exp\left(-\frac{1}{2\tau_\phi} \kappa_\phi' \mathbf{Q}_\phi \kappa_\phi\right) \quad (3.9)$$

where $\mathbf{Q}$ is the penalty matrix. The hyper-priors for all the variance components $\tau = \{\tau_\beta, \tau_\phi, \tau_\eta, \tau_\phi\}$ were assumed to follow a conjugate Gamma distribution ($\tau \sim \text{Gamma}(\alpha_\tau, \beta_\tau)$) with $\alpha_\tau = 0.01$ and $\beta_\tau = 0.001$.

The ordinary kriging method was performed to predict the unmeasured locations at health facility level(96). Kriging method assumes that the spatial variations can be modelled by random process with spatial autocorrelation. Suppose the kriged ART drop-out rate at region i located at s_i in time t is defined by

$$\hat{N}(s, t) = \sum_{j=1}^{n_i} \gamma_{j, (s_i, t)} N(s, t) \quad (3.10)$$

where n_i is the number of observation in region i at time t and $\gamma_{j, (s_i, t)}$ is the kriging weight derived from the semivariogram functions accounting for the spatio-temporal dependence among the observations. Let $\{Y(s_i) : i = 1, \dots, n\}$ define the data corresponding to spatial locations $\{s_i : i = 1, \dots, n\}$ coordinate data for each centroid. From these data, an unknown data entry $Y(s_0)$ is

predicted at a known location. This means, if $Y(s_0)$ has a measurement error component $\varepsilon(s_i)$, then a smooth version can be predicted (96). The ordinary kriging model is defined as:

$$Y(s_i) = \mu + \varepsilon(s_i) \quad i = 1, 2, \dots, n \quad (3.11)$$

where μ is an unknown constant. The kriging approach was used to predict values for unmeasured locations to identify hot and cold spots regions. The health facility or districts with high RR of ART drop-out would mean that these regions have an increased risk of ART patients' attrition; hence, ART patients are not well retained in care.

The posterior estimates

The posterior estimates were obtained through the marginal distribution of each parameter to be estimated. In other words, the posterior estimates are obtained by multiplying the likelihood and the prior distributions.

$$P(\Omega \equiv \alpha, \beta, \phi, \varphi, \eta, \tau_\phi, \tau_\eta, \tau_\varphi | Y_{it}) \propto L(Y_{it} | \alpha, \beta, \phi, \eta, \varphi) \times P(\beta_m) \times P(\varphi_i | \tau_\varphi) P(\tau_\varphi) \times P(\eta_i | \tau_\eta) P(\tau_\eta) \times P(\phi_i | \tau_\phi) P(\tau_\phi) \quad (3.12)$$

The full posterior model specifications and derivations implemented in this study are shown in chapter 3 appendix section. The spatio-temporal posterior relative risks (RR_{it}) are defined as:

$$RR_{it} = \mu_{it} = E_{it} \exp(\alpha + X_{it}^T \beta + \phi + \eta_i + \varphi_t) \quad (3.13)$$

An $RR_{it} > 1$ indicates an increased risk of the outcome, $RR_{it} < 1$ indicates a low risk (protective effect) while $RR_{it} = 1$ indicates no effect. Often, it is of interest to estimate the excess RR of an outcome in a region based on a threshold value T known as the “exceedance probability”, that

is, $P(RR_{it} > T)$. The “exceedance probability” helps identify the regions with a high risk of ART drop-out.

3.3.5. Bayesian model fitting and model comparison

Hierarchical Bayesian spatial-temporal Poisson regression models were fitted in R using the Integrated Nested Laplace Approximation (INLA) package while kriging of the health facility posterior estimates was handled using ArcMap. Four models were fitted namely 1) a model without the spatial random effects, 2) model with unstructured spatial random effects, 3) model with structured random effects and 4) a convolutional model with both the correlated (structured) and uncorrelated (unstructured) spatial random effects. All models had temporal random effects. Fixed effects covariates were assessed in each of these models to account for any confounding and identify possible risk factors associated with the ART drop-out (75). Traditionally, Bayesian models are fitted by drawing random samples from the Markov chain Monte Carlo (MCMC) simulations methods; however, inferences may be tractable for complex models and may present convergence and computational challenges, the INLA was used. INLA is a computationally less-intensive method which approximate Bayesian inference in latent Gaussian models which include the spatial models. The INLA models for observed data have a generic form:

$$Y_i | x, \theta \sim \pi(Y_i | x, \theta) ; x | \theta \sim N(0, Q(\theta^{-1})) ; \theta \sim \pi(\theta) \quad (3.14)$$

where x represents a Gaussian field, and θ are hyper-parameters. The outcome observations assume an exponential family with mean $\mu_i = g^{-1}(\eta_i)$ where η_i is a linear predictor which can contain linear effects of covariates on the response, non-linear effects or smooth functions of some covariates. This generic form accommodates different functions, including the risk models.

The INLA method uses analytical approximation and numerical integration to obtain the posterior distribution of the parameters. To compare the model with no spatial covariate and the adjusted spatial models, we used the Deviance Information Criterion (DIC) values. The model with the lowest DIC value was selected as the best fitting model with the lowest complexity and was the one used for the interpretation of the results (97).

3.3.6. Ethical approval of the dataset

The permission to use the routinely collected HIV data amongst ART patients was sort and granted from the Zimbabwe Ministry of Health and Child Care through the AIDS/TB Unit who oversees the data collection and storage. Ethical approval was granted by the University of Witwatersrand's Human Research Ethics Committee (Medical) (Clearance Certificate No. M170673).

3.4. Results

3.4.1. The hierarchical Bayesian spatio-temporal Poisson regression models estimates at the health facility level

Table 3-1 summarises the results for the hierarchical Bayesian spatio-temporal Poisson regression models at the health facility level. Looking at the DIC values, the model without spatial random effect and the model with structured spatial random effects had the same DIC values (DIC=893121.90); however, adding unstructured spatial random effects only did not improve the model (DIC=924671.38). Though the convolutional model was better than the unstructured spatial random-effects model with a lower DIC value, simultaneous modelling of the structured and unstructured effected did not improve the structured spatial random-effects model.

Table 3-1: Multiple variable Bayesian spatio-temporal Poisson regression models estimates of the ART drop-out counts at the health facility level

Variables	Health facility level spatial unit			
	Without spatial random effects	Unstructured spatial random effects	Structured spatial random effects	Convolutional
Health facility level				
Primary	Reference	Reference	Reference	Reference
Secondary	1.31(1.2-1.33)	1.26(1.22-1.28)	1.31(1.29-1.33)	7.19(2.83-11.55)
Tertiary	2.22(2.16-2.28)	2.26(2.16-2.36)	2.22(2.16-2.28)	1.36(0.93-1.79)
Degree of urbanisation				
Rural	Reference	Reference	Reference	Reference
Urban	1.63(1.61-1.64)	3.16(1.67-4.65)	1.63(1.61-1.65)	1.79(1.56-2.02)
Sex				
Female	Reference	Reference	Reference	Reference
Male	0.99(0.97-1.01)	1.01(0.97-1.05)	0.99(0.93-1.05)	1.01(0.96-1.06)
Age (mean age in years)	1.09(1.07-1.11)	1.47(1.27-1.67)	1.09(1.00-1.18)	1.46(1.34-1.58)
Ever missed an appointment				
No	Reference	Reference	Reference	Reference
Yes	0.99(0.97-1.01)	0.99(0.97-1.01)	0.99(0.89-1.08)	1.00(0.89-1.11)
Tuberculosis co-infection				
No	Reference	Reference	Reference	Reference
Yes	1.01(0.99-1.03)	1.04(1.01-1.07)	1.01(0.91-1.10)	1.04(0.95-1.13)
Duration on ART (average time since ART initiation)	0.89(0.88-0.90)	0.89(0.80-0.97)	0.89(0.83-0.95)	0.89(0.82-0.96)
ART combination				
Other drugs	Reference	Reference	Reference	Reference
AZT+3TC+NVP	1.01(0.99-1.01)	1.01(0.99-1.01)	1.00(0.96-1.04)	1.02(0.94-1.10)
Model intercept	0.08(0.07-0.09)	1.52(1.43-1.61)	0.08(0.06-0.10)	2.97(2.83-3.13)
Information criterion				
DIC	893121.90	924671.38	893121.90	914671.22

AZT=Zidovudine, 3TC=Lamivudine, NVP=Nevirapine, DIC=Deviance Information Criterion, Significance was set at 5%

With regards to the structured spatial random-effects model, the variables which showed high-risk values for ART drop-out at health facility level were health facility levels type and degree of urbanisation while mean duration on ART was protective after adjusting for other covariates. With reference to the primary levels of care; individuals who were registered in secondary level health facilities were 1.31 times more at risk of ART drop-out (posterior relative risk (pRR)=1.31; 95%CI: 1.29-1.33) while those registered in tertiary institutions were 2.22 times more at risk of ART drop-out (pRR=2.22; 95%CI: 2.16 -2.28). Those who were registered in health facilities in the urban areas were 1.63 times more at risk of ART drop-out compared to those who were registered in rural health facilities (pRR=1.63; 95%CI: 1.61-1.65). The mean duration on time since ART initiation was protective against ART drop-out. An increase in meantime duration on ART reduced the risk of ART drop-out by 11% (pRR=0.89; 95%CI: 0.83-0.95). This means the longer the individuals were on ART, the less likely they were to drop-out at the health facility level.

The “exceedance probability” for the health facility spatial units was mapped using the kriging technique with the district boundaries superimposed over the smoothed map (**Figure 3-3**). The temporal risk estimates were aggregated at the health facility level to give an overall pictorial view of the areas which experienced a higher risk of ART drop-out during the study period. This means the cold and hot spots for the ART drop-out risk were identified. The regions with $P(RR_i \leq T = 1)$ close to zero are the regions with the ART drop-out RR exceeding one and these hot-spots regions are depicted by the red colour. The regions with $P(RR_i \leq T = 1)$ close to one are regions which had a protective effect of ART drop-out and these cold-spots regions are depicted by the blue colour. The yellow colour depicts moderate ART drop-out zones. The hot spots were spread across the country covering the central district linking the two metropolitan

cities and up the region which borders with Zambia. The region around Victoria Falls was a hot spot as well as some of the regions which border with Mozambique

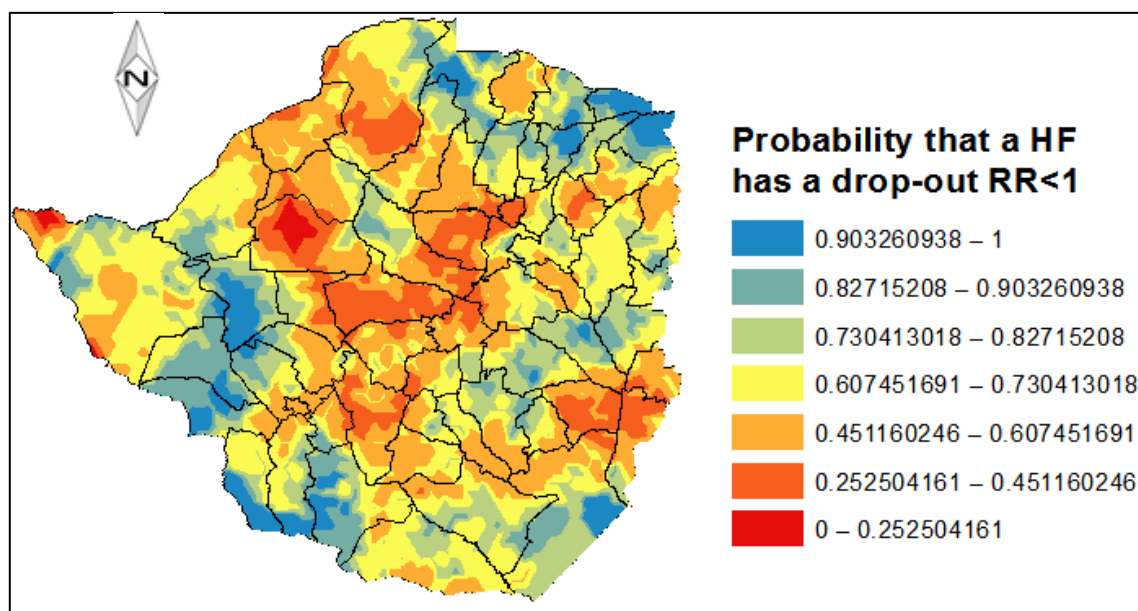


Figure 3-3: The overall spatial interpolation of the probability relative risk map for ART drop-out at health facility level in Zimbabwe using the kriging technique

3.4.2. The hierarchical Bayesian spatio-temporal Poisson regression models estimates at the district level

Table 3-2 summarises the results for the hierarchical Bayesian spatio-temporal Poisson regression models at the district level. Looking at the DIC values, the model without spatial random effect had the highest DIC value (DIC=96299.76) and adding structured spatial random effects slightly improved the model (DIC= 95255.61). Adding unstructured spatial random effects only improved the model (DIC=54823.57) and this model was comparable to the convolutional model (DIC=54823.54).

Table 3-2: Multiple variable Bayesian spatio-temporal Poisson regression models estimates of the ART drop-out counts at the district level

Variables	District level spatial unit			
	Without spatial random effects	Unstructured spatial random effects	Structured spatial random effects	Convolutional
Health facility level				
Primary	Reference	Reference	Reference	Reference
Secondary	1.01(1.00-1.02)	1.01(1.00-1.02)	1.01(1.00-1.02)	1.01(1.00-1.02)
Tertiary	1.00(1.00-1.03)	0.99(0.98-1.01)	1.00(1.01-1.03)	0.99(0.98-1.01)
Degree of urbanisation				
Rural	Reference	Reference	Reference	Reference
Urban	0.94(0.93-0.95)	0.91(0.90-0.92)	0.94(0.93-0.95)	0.91(0.90-0.92)
Sex				
Female	Reference	Reference	Reference	Reference
Male	0.99(0.97-1.01)	1.00(0.99-1.01)	1.00(0.97-1.03)	1.00(0.99-1.01)
Age (mean age in years)	1.12 (1.10-1.14)	1.14(1.12-1.16)	1.12 (1.10-1.14)	1.14(1.12-1.16)
Ever missed an appointment				
No	Reference	Reference	Reference	Reference
Yes	1.02(1.01-1.03)	0.98(0.96-1.00)	1.02(1.00-1.04)	0.98(0.97-0.99)
Tuberculosis co-infection				
No	Reference	Reference	Reference	Reference
Yes	1.02(1.01-1.03)	1.01(1.00-1.02)	1.02(1.01-1.03)	1.01(1.00-1.02)
Duration on ART (average time since ART initiation)	0.75 (0.73-0.77)	0.67(0.65-0.69)	0.75 (0.73-0.77)	0.67(0.65-0.69)
ART combination				
Other drugs	Reference	Reference	Reference	Reference
AZT+3TC+NVP	0.91(0.89-0.93)	1.02(1.00-1.04)	0.91(0.89-0.93)	1.09(1.07-1.11)
Model intercept	0.15(0.12-0.14)	1.27(1.09-1.45)	0.17(0.09-0.32)	2.16(2.02-2.30)
Information criterion				
DIC	96299.76	54823.57	95255.61	54823.54

AZT=Zidovudine, 3TC=Lamivudine, NVP=Nevirapine, DIC=Deviance Information Criterion, Significance was set at 5%

With regards to the structured spatial random-effects model, the variables which showed high-risk values for ART drop-out at district level were mean age and ART combination therapy while the degree of urbanisation and mean duration on ART were protective after adjusting for other covariates. With reference to the districts in rural areas, individuals who were registered in urban districts were 9% less likely to drop-out from ART compared to those in the rural districts (pRR=0.91; 95%CI: 0.90-0.92). An increase in the meantime duration on ART increased the risk of ART drop-out by 14% (pRR=1.14; 95%CI: 1.12-1.16). Individuals who were on AZT+3TC+NVP combination therapy had a 9% increased risk of ART drop-out in this study compared to other ART combinations (pRR=1.09; 95%CI: 1.07-1.11).

3.4.3. First-order random walk model plots for the models fitted at the district level

The first-order random walk models for the temporal ART drop-out effects at district levels are shown in **Figure 3-4**.

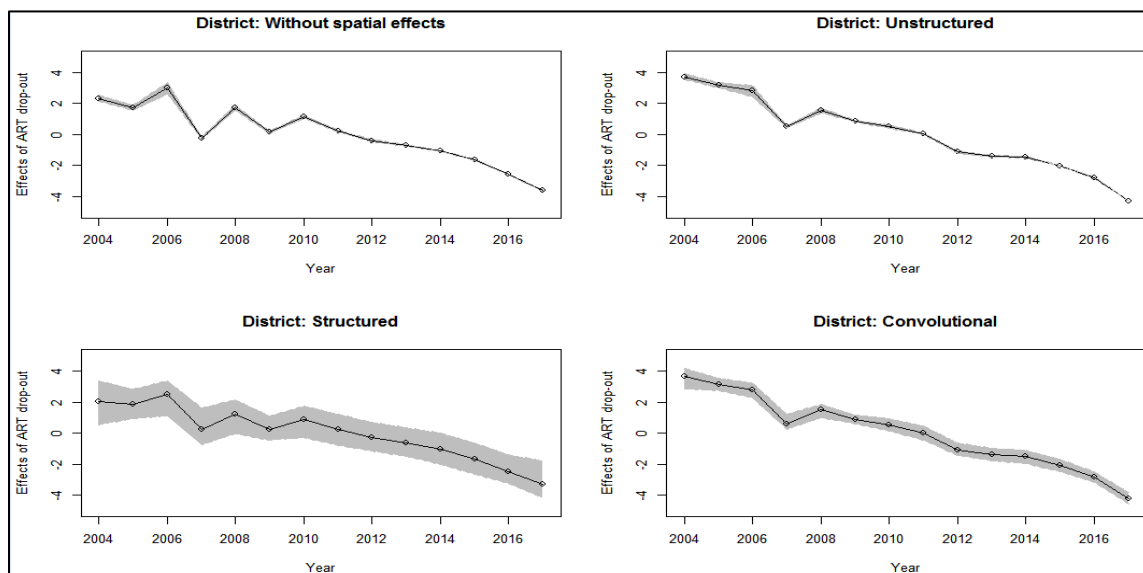


Figure 3-4: The first order random walk models for the temporal ART drop-out effects at the district level

Generally, there is a decrease in the ART drop-out effects over time. The main difference of the time series plots is between 2005-2010 period. There was a sharp drop in the ART drop-out effects in 2007 in all models. The precision ART drop-out effects over time models varied with the inclusion of the spatial random effects. The model with structured spatial random effects had wider 95%CI width compared to the model with the unstructured spatial random effects.

3.4.4. The Standardised Incidence Ratio and posterior relative risk spatio-temporal estimates for the ART drop-out at the district level

Figure 3-5 displays the spatio-temporal estimates of SIR and pRR from the convolutional model of ART drop-out at the district level. The darker colour shows the districts with the highest SIR values and pRR values while the lighter colour shows the districts with the lowest values. The SIRs were estimated using the maximum likelihood estimates while the pRR were estimated using the Bayesian inference method. The pRR estimates smooth out the ART drop-out effects and most of the districts showed an increased risk of ART drop-out compared the SIR estimates. The spatio-temporal distribution of the ART drop-out varied across districts over time. Regarding the SIR spatio-temporal estimates, the risk of ART drop-out was highly observed among the districts in the southern parts of the country in 2005, 2012 and 2016 while in 2007, 2010, 2014 and 2017, the risk of ART drop-out was highly observed among the districts in the northern parts of the country. In 2006, 2011 and 2013, there was a random distribution of ART drop-out in the districts. Regarding the spatio-temporal estimates of pRR estimates, the risk of ART drop-out was highly observed in the northern parts of the country in 2005, 2008, 2012 and 2016. The Hwange district which borders with Zambia and Botswana showed a consistent high risk of ART drop-out over time, particularly in 2005, 2008, 2009, 2012, 2013, 2015 and 2016 compared to other districts.

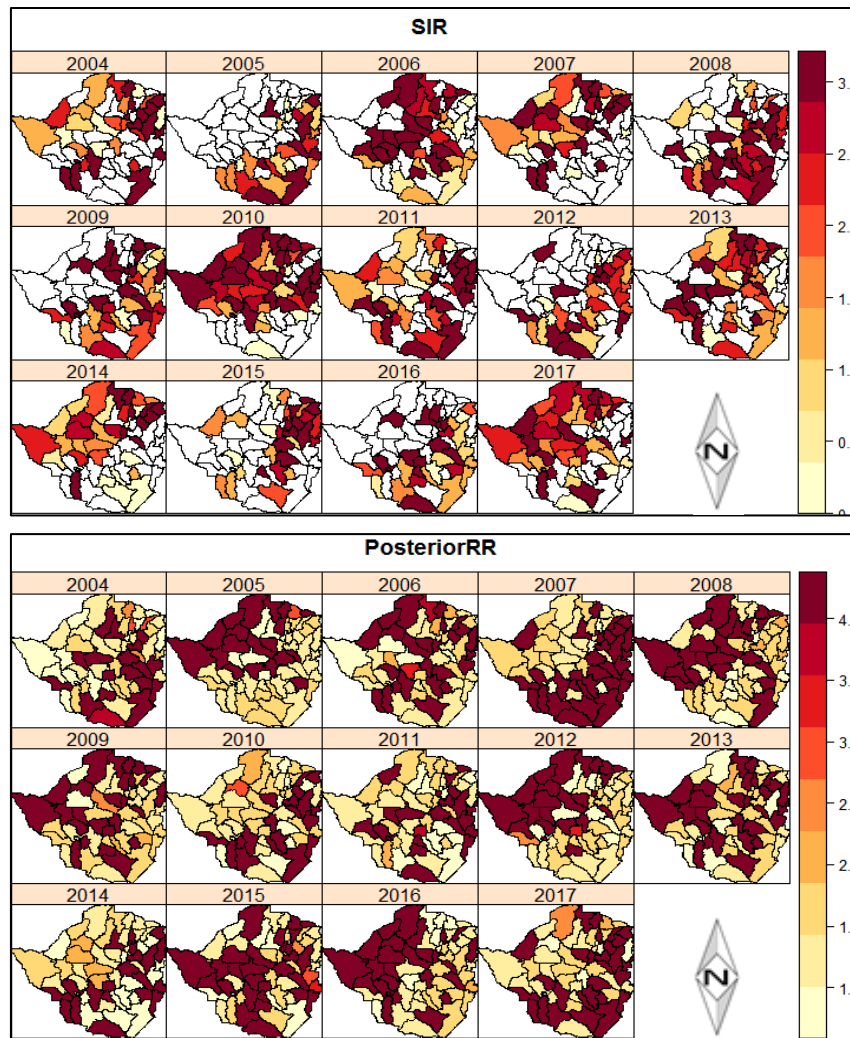


Figure 3-5: Spatio-temporal distribution of the standardised incidence ratios (SIRs) and posterior relative risk (pRR) for the ART drop-out count at the district level

3.4.5. The unstructured, structured and convolutional spatial-temporal random effects at the district level

The maps in **Figure 3-6** depict the structured and unstructured spatial random effects at the district level as estimated by the spatial adjusted models. Generally, the unstructured effects contributed significantly to the overall spatial effects. The unstructured spatial random effects model had exponentiated spatial effects values ranging from 0.197 to 4.909 while the structured spatial random effects model had exponentiated spatial effects from 0.556 to 1.451.

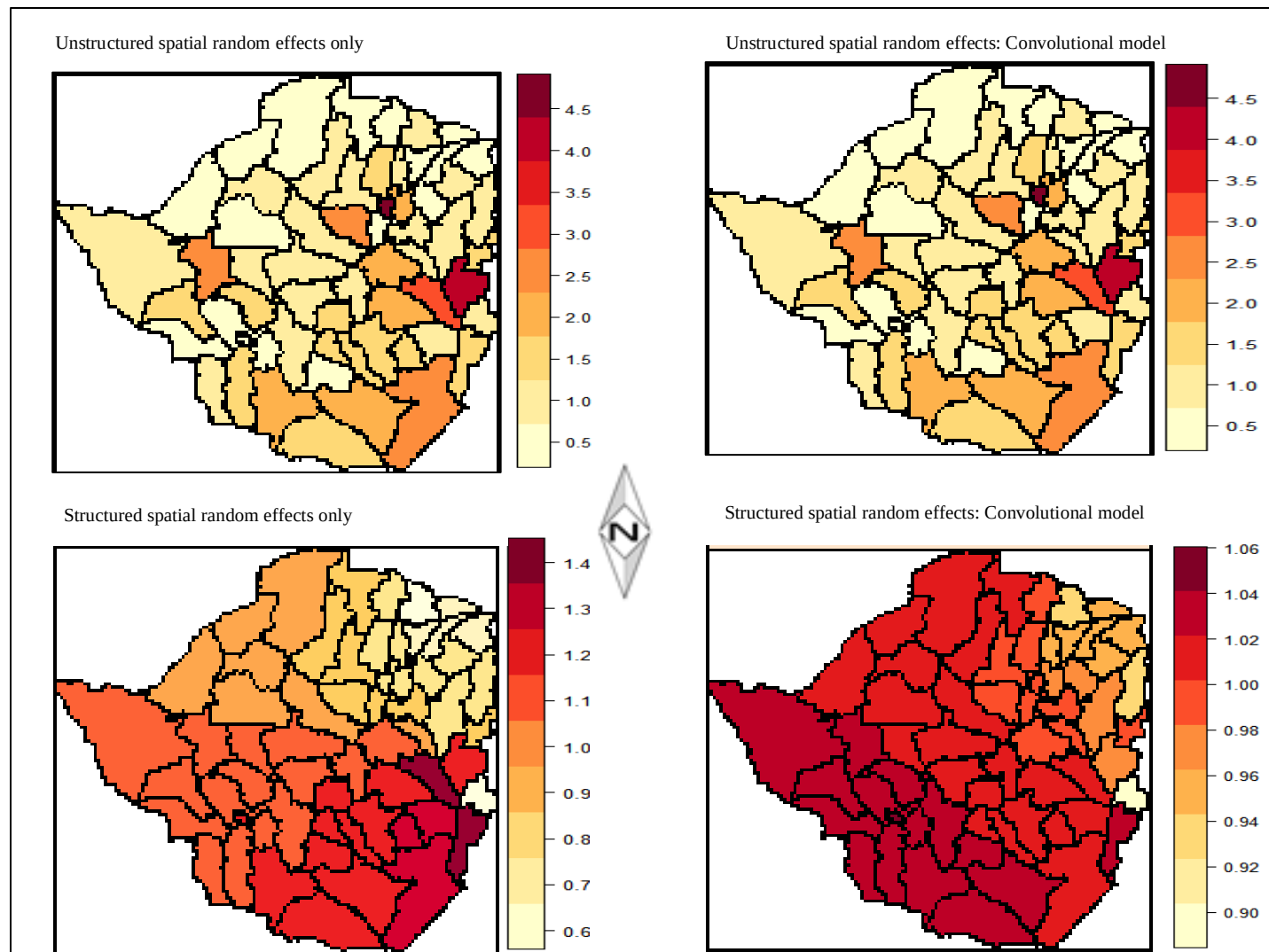


Figure 3-6: Structured and unstructured spatial random effects for the ART drop-out at the district level

In the convolutional model, the unstructured spatial effects remained unchanged while the exponentiated structured spatial effects changed to a range of 0.884-1.061. The two partitioned spatial random effects were mapped directly on the district polygons. The spatial patterns confirm the presence of spatial variation of ART drop-out in Zimbabwe. The unstructured spatial random effects showed highest ART drop-out risk in one metropolitan region and those towards the eastern to the southern parts bordering Mozambique. Though the structured spatial random effects were relatively small, these were more pronounced in the southern parts to the northern parts of the country. In the structured spatial random-effects model, the southern districts were more burdened with ART drop-out while in the convolutional model; districts stretching from the south to the north bordering Botswana were more at risk of ART drop-out.

3.5. Discussion

The main aim of this study was to describe the spatio-temporal patterns of ART drop-out count data in Zimbabwe among adult HIV patients aged 15 years at district and health facility level. A hierarchical Bayesian spatio-temporal Poisson regression model was used assuming CAR priors for the structured spatial random effects at the district level, GMRF prior for the unstructured spatial random effects at the health facility level and first-order random walk Gaussian prior for the temporal random effects. Fixed effects covariates associated the ART drop-out counts were also considered in the analysis. Inferential models were fitted in R-INLA while ArcMap was used to obtain the spatial smoothing effects using aerial interpolation and ordinary kriging of the spatial ART drop-out risk estimates.

In general, the time series plot of the ART drop-out over time showed a general steady decrease in the effects of ART drop-out over time with some fluctuations between 2005 and 2010 which

varied between different models. The temporal decrease in the ART drop-out effects over time, particularly from 2010/2011 may be explained by the introduction of differential monitoring mechanism which aimed to increase ART uptake and access to all HIV-infected individuals. Moreover, study period covers different years in which the ART guidelines have been changing; changes in ART; therefore, the constant update of ART treatment might have positively influenced ART retention and minimised ART drop-out over time. Besides the ART treatment dose also changed over time from two doses per day to a single dose which might have influenced patients' retention.

The identified factors associated with increased risk of ART drop-out were the health facility type, degree of urbanisation and average age while mean duration on ART was protective. The identified factors are consistent with findings from previous studies (27,98–101); however, most of these studies did not account for the spatio-temporal random effects. The high risk of ART drop-out at higher levels of care (secondary and tertiary) may be explained by the introduction of ART decentralisation 2010/2011 whereby individuals “self-transferred” to nearby health facilities to cut transport cost since most of these health facilities are in the urban areas. However, for years before ART decentralisation, the increased risk of ART drop-out in higher levels of care can be explained by transport cost to the health facility considering that most secondary and tertiary health centres are in urban areas. The ART drop-out risk in urban and rural areas varied between district and health facility spatial units. Urban areas were protective at district level at the same time having an increased risk of ART drop-out at health facility level. This variation could be explained by some districts having overlapping rural and urban areas such that the degree of urbanisation effects are neutralised. Since staying longer on ART was protective against ART drop-out, interventions which strengthen ART adherence such as

community-based interventions, smooth transition of adolescence into adult care and manufacturing potent and less toxic drugs are important to strengthen ART retention.

Comparing the maximum likelihood and the Bayesian estimation methods, the Bayesian method gave smoothed out pRR estimates compared to the SIR estimates. The spatio-temporal pRR trellis plots showered that most of the regions along the southern and northern parts of the country had a high risk of ART drop-out over time. Regarding the spatial random effects trellis plots, the unstructured random effects estimates were higher than the structured random effects estimates meaning the unstructured random effects contributed more to the total spatial effects of ART drop-out in Zimbabwe. The structured spatial random effects were more pronounced in the southern and northern parts of the country and these regions were more at risk of ART drop-out in this study. The spatial patterns of the structured random effects are comparable to the national prevalence of HIV in Zimbabwe from the 2015/16 Zimbabwe Population-based HIV Impact Assessment (ZIMPHIA) survey in that, the regions with highest HIV prevalence are same regions with highest structured effects estimates (10). To be more explicit, the spatial patterns confirmed a high risk of ART drop-out in the southern and northern parts of Zimbabwe. This means a majority of the HIV individuals in these regions are more likely to have poor viral suppression (76) which can be attributed to high HIV transmission in the general population; hence, high HIV prevalence in these regions. Such regions require area-specific interventions which minimise ART drop-out and retain patients on care. Possibly strengthening community-based approaches, continual health education addressing beliefs and misconceptions over ART treatments benefits (89).

The strengths of this study include the use of separable space-time hierarchical Bayesian spatio-temporal Poisson regression to determine the spatio-temporal pattern of ART drop-out at district

and health facility level (81). This study is one of the few studies which have used geospatial modelling in HIV monitoring to effectively describe epidemiological spatio-temporal data in Zimbabwe at low administrative spatial units which allow targeted interventions to be implemented. This modelling approach uses probability to measure uncertainty in estimates inferences and has a straightforward way of incorporating spatio-temporal random effects and prior information from either preceding studies (informative priors) or flat priors(non-informative priors); hence, it is a robust method. This study also addressed the spatio-temporal patterns of ART drop-out among HIV patients which is a threat to the overall viral suppression to guide policy and further research formulation.

Nonetheless, there are aerial data structure issues associated with aggregated spatial data. Generally, spatial analysis of aggregated data is subject to Misaligned Data Problem (MIDP), which transpires when spatial data is analysed based on a spatial unit scale different from what they were originally collected. This limitation fits well in our district-level models; however, sometimes it is important to understand the spatial distribution of an outcome of interest at a higher spatial level to formulate hypotheses for further research(102). Another major drawback in using aggregated data is the issue of ecological fallacy (103) which can be considered as a special case of MAUP. Ecological fallacy happens when aggregated data inferences lead to a different conclusion at individual-level using the same underlying data. This ecological bias can be partitioned into aggregation bias which occurs due to the grouping of individuals and specification bias which occurs due to differential distribution of confounding variables. Modifiable Areal Unit Problem (MAUP) (104) is also a drawback in aggregated data analysis, whereby conclusions may vary between different spatial units using the same underlying data. This spatial unit or aggregation inferred effect occurred, for instance, if the same data is

grouped into an increasingly large region like re-aggregating health facility level data into district-level data as we did in this study. Spatial units alternation approach may provide variation in results. Another limitation of this study is the use of aggregated count data from the ePMS database which is a fraction of the total population on ART in Zimbabwe. There is a possibility of selection bias which may affect the generalizability of our findings; however, the health facilities used reflects a national sites distribution in Zimbabwe.

3.6. Conclusion

A separable space-time hierarchical Bayesian spatio-temporal Poisson regression model was used to describe the epidemiological spatio-temporal patterns of ART drop-out in Zimbabwe. We found out that ART drop-out persists in HIV programmes. In Zimbabwe, the regions more at risk were the southern and northern regions of Zimbabwe and these findings were comparable to the nations HIV prevalence geographical distribution. Our analysis puts forward the need for targeted interventions to minimise ART drop-out in high-risk areas, particularly, southern and northern regions which have shown to have a high risk of ART drop-out, policy formulation. Besides, the gained knowledge helps in the formulation of hypothesis for further research and guide surveillance in high-risk regions. In the quest to mitigate ART drop-out, which is a major threat toward achieving the UNAIDS 90-90-90 fast track targets; there is need to implementing targeted interventions in resources constrained countries to sustain the current HIV interventions. Once the ART drop-out has been minimised, viral suppression can be attained and sustained, and HIV transmission is reduced to negligible rates. Interventions and programmes which strengthen ART adherence remain essential in the global HIV control campaign to improve health and prolong survival among HIV infected patients.

3.6.1. Author's contribution

ZMZ and **EM** were responsible for the conceptualization of this paper, **ZMZ** performed all the data management, cleaning and analyzing. **EM** oversaw the statistical analysis process. **ZMZ**, **EM**, **JT** and **TC** contributed to the analysis of the results. **ZMZ** drafted the manuscript. **JT**, **TC** and **EM** reviewed the manuscript for intellectual content. All authors reviewed the final version for submission.

Conflict of interest statement

None declared.

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3.7. Chapter 3 Appendix Section

A: Posterior derivation the hierarchical Bayesian spatio-temporal Poisson regression model for ART drop-out

The Bayesian inference requires the specification of the likelihood function and the prior distributions to define the posterior distribution as

$$P(\text{parameters} | \text{data}) \propto \text{Likelihood} \times \text{Priors}.$$

Likelihood specification

To estimate the ART drop-out risk and quantify the risk associated between ART drop-out and selected covariates in Zimbabwe, we fitted a fully hierarchical Bayesian spatio-temporal Poisson regression model. The ART drop-out counts were modelled based on the Poisson distribution function with the following probability density function:

$$P(Y_{it}) = \frac{\mu_{it}^{Y_{it}}}{Y_{it}!} \exp(-\mu_{it}) ; i = 1, 2, \dots, n \text{ and } t = 1, 2, \dots, Z \quad (\text{C.15})$$

where Y_{it} defines the observed ART drop-out counts at region i in time t measured in years (2004-2017) and the mean of the observed ART drop-out counts $\mu_{it} = \lambda_{it} E_{it}$. The parameter E_{it} defines the total number of drop-out counts expected at region i in time t compared to the standard population and λ_{it} is the unknown relative ART drop-out risk at region i in time t . The known expected (E_{it}) ART drop-out counts for the study regions (538 health facilities or 60 districts) were calculated using direct standardization, that is, $E_{it} = R(P_{it})$, where R is the overall ART drop-out rate of the standard population, and P_{it} is the number of ART patients at risk in region (health facility or district) i at time t . To summarise the distribution of the count data:

$$Y_{it} \sim Po(\mu_{it}) = Po(\lambda_{it}E_{it}) \quad i = 1, 2, \dots, n \text{ and } t = 1, 2, \dots, Z \quad (C.16)$$

The likelihood of the data is defined as:

$$\begin{aligned} P(\mathbf{Y}_{it} | \boldsymbol{\theta}_{it}) &= P(Y_{1t}, Y_{2t}, \dots, Y_{nt} | \lambda_{1t}, \lambda_{2t}, \dots, \lambda_{nt}) \\ &= \prod_{t=1}^Z \prod_{i=1}^n \left[\frac{\mu_{it}^{Y_{it}}}{Y_{it}!} \exp(-\mu_{it}) \right] = \prod_{t=1}^Z \prod_{i=1}^n \left[\frac{(\lambda_{it}E_{it})^{Y_{it}}}{Y_{it}!} \exp(-\lambda_{it}E_{it}) \right] \end{aligned} \quad (C.17)$$

Taking the log-likelihood of equation (C.17), differentiation with respect to λ_{it} and setting the derivative to zero gives a maximum likelihood estimate of the rate

$$\frac{Y_{it}}{\lambda_{it}} - E_{it} = 0 \quad ; \quad \text{SIR}_{it} = \hat{\lambda}_{it} = \frac{Y_{it}}{E_{it}} \quad (C.18)$$

which defines the crude yearly Standardised Incidence Ratio of the ART drop-out counts for a specific region. The use of SIRs is the standard maximum likelihood approach which can be used to describe spatial heterogeneity of the outcome; however, in instances where very extreme values occur in regions with small populations due to the small sample sizes are involved; this may result in the overestimation or underestimation of the associated outcome risk. Moreover, if the likelihood is complex and the number of parameters is large, this approach may become difficult to implement. To overcome this limitation, Bayesian inferential models are preferred to obtain the outcome risk estimates accounting for confounding factors; adjusting for the neighbouring areas random effects and parameter estimates can be smoothed or shrunk to improve the precision (95).

The likelihood function linear predictor in Bayesian inference can handle additional components.

If we consider the log function of the Poisson mean parameter and let $\log(\lambda_{it}) = \psi_{it}$:

$$\log(\mu_{it}) = \log(\lambda_{it}E_{it}) = \log(E_{it}) + \log(\lambda_{it}) = \log(E_{it}) + \psi_{it} \quad (C.19)$$

This shows that $\lambda_{it} = \exp(\psi_{it})$ where ψ_{it} can be assumed to be a random-effects parameter. This random effect component can be split into more additional components to have a convolutional regression model:

$$\log(\mu_{it}) = \log(E_{it}) + \alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t \quad (\text{C.20})$$

where α is the mean log overall risk ART drop-out risk over all areas, $\mathbf{X}_{it}^T \boldsymbol{\beta}$ denotes the fixed effects regression coefficients $\boldsymbol{\beta} = (\beta_1, \beta_2, \dots, \beta_m)$ associated with explanatory variables $(\mathbf{X}_{it}^T = X_{1t}, X_{2t}, \dots, X_{mt})$, $\boldsymbol{\phi} = \phi_1, \phi_2, \dots, \phi_n$ and $\boldsymbol{\eta}_i = \eta_1, \eta_2, \dots, \eta_n$ components define the decomposed structured and unstructured spatial random effects for region i respectively. In other words, spatial random effects S_i are partitioned into two components $(S_i = \boldsymbol{\phi} + \boldsymbol{\eta}_i)$. These spatial random effects accounted for the extra-Poisson variability in the observed ART drop-out counts data(95). The component $\boldsymbol{\varphi}_t = \varphi_1, \varphi_2, \dots, \varphi_p$ defines the overall temporal random effects common to all regions. The spatio-temporal posterior relative risks $(\mathbf{RR}_{it})$ are defined as:

$$\mathbf{RR}_{it} = \mu_{it} = E_{it} \exp(\alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t) \quad (\text{C.21})$$

Therefore, substituting the relative risk expression (equation C.21) into equation (C.17) gives

$$\begin{aligned} L(\mathbf{Y}_{it} | \boldsymbol{\theta}_{it} \equiv \{\boldsymbol{\beta}, \alpha, \boldsymbol{\phi}, \boldsymbol{\eta}_i, \boldsymbol{\varphi}_t\}) &= \prod_{t=1}^Z \prod_{i=1}^n \left[\frac{\mu_{it}^{Y_{it}}}{Y_{it}!} \exp(-\mu_{it}) \right] \\ &\propto \prod_{t=1}^Z \prod_{i=1}^n \left[\left(E_{it} \exp(\alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t) \right)^{Y_{it}} \exp(-E_{it} \exp(\alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t)) \right] \quad (\text{C.22}) \\ &= \left(E_{it} \exp(\alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t) \right)^{\sum_{t=1}^Z \sum_{i=1}^n Y_{it}} \exp(-Zn [E_{it} \exp(\alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t)]) \end{aligned}$$

Prior specification

All unknown parameters and hyper-priors were assigned some prior information.

The model constant or intercept parameter: The α parameter was $\alpha \sim U(-\infty, +\infty)$ to have a “sum to zero” constraint for the structured spatial parameter.

The regression coefficients: The $\beta = (\beta_1, \beta_2, \dots, \beta_m)$ were assumed to follow a non-informative Gaussian distribution with a mean ($\mu_\beta = 0$) and a wide variance, that is, $\beta_m \sim iid N(\mu_\beta, \sigma_\beta^2)$

$$P(\beta_m) = \frac{1}{\sqrt{2\pi\sigma_\beta^2}} \exp \left[-\frac{1}{2} \left(\frac{\beta_m - \mu_\beta}{\sigma_\beta} \right)^2 \right] \quad (C.23)$$

The temporal random effects: The temporal components of the model $\varphi_t = \varphi_1, \varphi_2, \dots, \varphi_p$ were assumed first-order random walk priors $\varphi_t \sim N(\mu_\varphi, \sigma_\varphi^2) \quad t = 2, \dots, Z$.

$$P(\varphi_t | \sigma_\varphi^2) = P(\varphi_t - \varphi_{t-1}) = \frac{1}{\sqrt{2\pi\sigma_\varphi^2}} \exp \left[-\frac{1}{2} \left(\frac{\varphi_t - \mu_\varphi}{\sigma_\varphi} \right)^2 \right] \quad t=2,3,\dots,Z$$

$$P(\varphi_t | \tau_\varphi) = P(\varphi_t - \varphi_{t-1}) = \frac{1}{\sqrt{2\pi/\tau_\varphi}} \exp \left[-\frac{1}{2} \left(\frac{\varphi_t - \mu_\varphi}{1/\sqrt{\tau_\varphi}} \right)^2 \right] \quad t=2,3,\dots,Z \quad ; \mu_\varphi = 0 \quad (C.24)$$

The precision $\tau_\varphi = 1/\sigma_\varphi^2$ parameters were assigned conjugate hyper-priors with a Gamma distribution ($\tau_\varphi \sim Gamma(\alpha_\varphi, \beta_\varphi)$) with $\alpha_\varphi = 0.01$ and $\beta_\varphi = 0.001$. Therefore, the probability density function of the precision hyper-prior for the unstructured effects is:

$$P(\tau_\varphi) = \frac{(\beta_\varphi)^{\alpha_\varphi}}{\Gamma(\alpha_\varphi)} \times \tau_\varphi^{\alpha_\varphi-1} \times \exp(-\beta_\varphi \tau_\varphi) \quad (C.25)$$

Therefore, for $\mu_\varphi = 0$,

$$\begin{aligned}
P(\varphi_i | \tau_\varphi) P(\tau_\varphi) &= \frac{1}{\sqrt{2\pi/\tau_\varphi}} \exp \left[-\frac{1}{2} \left(\frac{\varphi_i - \mu_\varphi}{1/\sqrt{\tau_\varphi}} \right)^2 \right] \times \frac{(\beta_\varphi)^{\alpha_\varphi}}{\Gamma(\alpha_\varphi)} \times \tau_\varphi^{\alpha_\varphi-1} \times \exp(-\beta_\varphi \tau_\varphi) \\
&\propto \tau_\varphi^{\alpha_\varphi-1} \exp \left[-\frac{1}{2} \left(\frac{\varphi_i}{1/\sqrt{\tau_\varphi}} \right)^2 - \beta_\varphi \tau_\varphi \right]
\end{aligned} \tag{C.26}$$

The unstructured spatial random effects: The uncorrelated spatial random effects were assumed Gaussian priors, that is, $\eta_i \sim \text{idd } N(\mu_\eta, \sigma_\eta^2)$.

$$\begin{aligned}
P(\eta_i | \sigma_\eta^2) &= \frac{1}{\sqrt{2\pi\sigma_\eta^2}} \exp \left[-\frac{1}{2} \left(\frac{\eta_i - \mu_\eta}{\sigma_\eta} \right)^2 \right] \\
P(\eta_i | \tau_\eta) &= \frac{1}{\sqrt{2\pi/\tau_\eta}} \exp \left[-\frac{1}{2} \left(\frac{\eta_i - \mu_\eta}{1/\sqrt{\tau_\eta}} \right)^2 \right]; \text{ for } \mu_\eta = 0
\end{aligned} \tag{C.27}$$

where σ_η^2 is the variance component specified as a precision $\tau_\eta = 1/\sigma_\eta^2$ assumed to follow a

$(\tau_\eta \sim \text{Gamma}(\alpha_\eta, \beta_\eta))$ with $\alpha_\eta = 0.01$ and $\beta_\eta = 0.001$. Therefore;

$$P(\eta_i | \tau_\eta) P(\tau_\eta) \propto \tau_\eta^{\alpha_\eta-1} \exp \left[-\frac{1}{2} \left(\frac{\eta_i}{1/\sqrt{\tau_\eta}} \right)^2 - \beta_\eta \tau_\eta \right] \tag{C.28}$$

The structured spatial polygon random effects: Structured spatial polygon random effects were modelled using the intrinsic conditional autocorrelated (CAR) normal prior proposed by Besag-York-Mollie` (81) which assumes spatial dependence between neighbouring spatial polygons.

The CAR prior is expressed as:

$$\phi_i | \phi_{-i} \sim N \left(\frac{\phi_i}{\phi_i}, \frac{\sigma_\phi^2}{N_i} \right) = N \left(\frac{\phi_i}{\phi_i}, \frac{1}{\tau_\phi N_i} \right) \tag{C.29}$$

where N_i defines the number of neighbours of region i and a Gamma hyper-prior for the precision parameter $\left(\tau_\phi = 1/\sigma_\phi^2\right)$.

$$P(\phi_i | \sigma_\phi^2) = \frac{1}{\sqrt{2\pi \left(\sigma_\phi^2 / N_i\right)}} \exp \left[-\frac{1}{2} \left(\frac{\phi_i - \left(\phi_i / \bar{\phi}_i\right)}{\sigma_\phi / \sqrt{N_i}} \right)^2 \right]$$

$$P(\phi_i | \tau_\eta) = \frac{1}{\sqrt{2\pi / N_i \tau_\eta}} \exp \left[-\frac{1}{2} \left(\frac{\phi_i - \left(\phi_i / \bar{\phi}_i\right)}{1 / \sqrt{N_i \tau_\eta}} \right)^2 \right]$$
(C.30)

The precision $\tau_\phi = 1/\sigma_\phi^2$ parameters were assigned conjugate hyper-priors with a Gamma distribution $(\tau_\phi \sim \text{Gamma}(\alpha_\phi, \beta_\phi))$ with $\alpha_\phi = 0.01$ and $\beta_\phi = 0.001$. Therefore,

$$P(\phi_i | \tau_\phi) P(\tau_\phi) \propto \tau_\phi^{\alpha_\phi - 1} \exp \left[-\frac{1}{2} \left(\frac{\phi_i - \left(\phi_i / \bar{\phi}_i\right)}{1 / \sqrt{N_i \tau_\eta}} \right)^2 - \beta_\phi \tau_\phi \right]$$
(C.31)

The structured spatial geo-coordinates random effects: The stationary Gaussian Random Field (GRF) prior was considered for the geographical locations of health facilities (centroid data), Let $\phi = (s_{ix}, s_{iy})$ defines the health facility coordinates and $f(\phi_i) = \kappa_\phi$ be the structured spatial component which follows a zero-mean stationary GRF with variance τ_ϕ and isotropic correlation function $\text{Cov}(\kappa_\phi, \kappa_{\phi+h}) = C(\|\bar{h}\|)$. Therefore:

$$\begin{aligned}
P(\phi_i | \sigma_\phi^2) &= \frac{1}{\sqrt{2\pi\sigma_\phi^2}} \exp\left[-\frac{1}{2}\left(\frac{\phi_i - \mu_\phi}{\sigma_\phi}\right)^2\right] \\
P(\phi_i | \tau_\phi) &= \frac{1}{\sqrt{2\pi/\tau_\phi}} \exp\left[-\frac{1}{2}\left(\frac{\phi_i}{1/\sqrt{\tau_\phi}}\right)^2\right]
\end{aligned} \tag{C.32}$$

Gamma priors for $\boldsymbol{\kappa}_\phi = (\kappa_1, \kappa_2, \dots, \kappa_S)$ were considered Gaussian with the following parameters:

$$P(\boldsymbol{\kappa} | \tau_\phi) \propto \frac{1}{(\tau_\phi)^{\text{rank}(\mathbf{Q})/2}} \exp\left(-\frac{1}{2\tau_\phi} \boldsymbol{\kappa}'_\phi \mathbf{Q}_\phi \boldsymbol{\kappa}_\phi\right) \tag{C.33}$$

where $\mathbf{Q}$ is the penalty matrix. The variance components were assigned Gamma priors $(\tau_\phi \sim \text{Gamma}(\alpha_\phi, \beta_\phi))$ with $\alpha_\phi = 0.01$ and $\beta_\phi = 0.001$. Therefore,

$$\begin{aligned}
P(\phi_i | \tau_\phi) &\equiv P(\boldsymbol{\kappa} | \tau_\phi) \propto \frac{1}{(\tau_\phi)^{\text{rank}(\mathbf{Q})/2}} \exp\left(-\frac{1}{2\tau_\phi} \boldsymbol{\kappa}'_\phi \mathbf{Q}_\phi \boldsymbol{\kappa}_\phi\right) \\
P(\boldsymbol{\kappa} | \tau_\phi) P(\tau_\phi) &\propto \frac{1}{(\tau_\phi)^{\text{rank}(\mathbf{Q})/2}} \exp\left(-\frac{1}{2\tau_\phi} \boldsymbol{\kappa}'_\phi \mathbf{Q}_\phi \boldsymbol{\kappa}_\phi\right) \times \frac{(\beta_\phi)^{\alpha_\phi}}{\Gamma(\alpha_\phi)} \times \tau_\phi^{\alpha_\phi-1} \times \exp(-\beta_\phi \tau_\phi) \tag{C.34} \\
&\propto \tau_\phi^{\alpha_\phi-1} \exp\left(-\frac{1}{2\tau_\phi} \boldsymbol{\kappa}'_\phi \mathbf{Q}_\phi \boldsymbol{\kappa}_\phi - \beta_\phi \tau_\phi\right)
\end{aligned}$$

The posterior estimates

The posterior estimates were obtained through the marginal distribution of each parameter to be estimated. In other words, the posterior estimates are obtained by multiplying the likelihood and the prior distributions. The posterior distribution on which the parameter estimates is based is approximated by a product of the likelihood and prior distribution.

$$\begin{aligned}
P(\Omega \equiv \alpha, \boldsymbol{\beta}, \boldsymbol{\phi}, \boldsymbol{\varphi}_t, \boldsymbol{\eta}_i, \tau_\phi, \tau_\eta, \tau_\varphi | Y_{it}) &\propto L(Y_{it} | \alpha, \boldsymbol{\beta}, \boldsymbol{\phi}, \boldsymbol{\eta}_i, \boldsymbol{\varphi}_t) \times P(\boldsymbol{\beta}_m) \times P(\boldsymbol{\varphi}_i | \tau_\varphi) P(\tau_\varphi) \\
&\times P(\boldsymbol{\eta}_i | \tau_\eta) P(\tau_\eta) \times P(\boldsymbol{\phi}_i | \tau_\phi) P(\tau_\phi) \\
&\propto \left[\left(E_{it} \exp(\alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t) \right)^{\sum_{t=1}^Z \sum_{i=1}^n Y_{it}} \right. \\
&\quad \left. \exp(-Zn [E_{it} \exp(\alpha + \mathbf{X}_{it}^T \boldsymbol{\beta} + \boldsymbol{\phi} + \boldsymbol{\eta}_i + \boldsymbol{\varphi}_t)]) \right] \\
&\times \frac{1}{\sqrt{2\pi\sigma_\beta^2}} \exp\left[-\frac{1}{2} \left(\frac{\beta_m - \mu_\beta}{\sigma_\beta} \right)^2\right] \\
&\times \tau_\phi^{\alpha_\phi - 1} \exp\left[-\frac{1}{2} \left(\frac{\phi_i}{1/\sqrt{\tau_\phi}} \right)^2 - \beta_\phi \tau_\phi\right] \\
&\times \tau_\eta^{\alpha_\eta - 1} \exp\left[-\frac{1}{2} \left(\frac{\eta_i}{1/\sqrt{\tau_\eta}} \right)^2 - \beta_\eta \tau_\eta\right] \\
&\times \tau_\phi^{\alpha_\phi - 1} \exp\left[-\frac{1}{2} \left(\frac{\phi_i - \left(\frac{\phi_i}{\bar{\phi}_i} \right)}{1/\sqrt{N_i \tau_\eta}} \right)^2 - \beta_\phi \tau_\phi\right]
\end{aligned} \tag{C.35}$$

Equation (C.35) represents a model with the structured polygon shapefile. The same concept for the posterior estimates is applied for the geo-coordinate model; however, the $P(\boldsymbol{\varphi}_i | \tau_\varphi) P(\tau_\varphi)$ is replaced with $\tau_\varphi^{\alpha_\varphi - 1} \exp\left(-\frac{1}{2\tau_\varphi} \boldsymbol{\kappa}_\phi' \mathbf{Q}_\phi \boldsymbol{\kappa}_\phi - \beta_\varphi \tau_\varphi\right)$.

Since this posterior function has no closed-form, we used the using R Integrated Nested Laplace Approximation (INLA) package, which is less computationally intensive compared to the Markov Chain Monte Carlo (MCMC) methods (84).

Appendix B: The INLA code

Y=ART drop-out counts

X1=Proportion of secondary health facilities

X2= Proportion of tertiary health facilities

X4= Proportion of health facilities in urban areas

X5= Proportion of male patients

X6= Proportion of patients whoever missed an appointment

X7= Proportion of patients with tuberculosis infection

X8= Average time duration on ART

X9= Proportion of patients taking AZT+3TC+NVP combination therapy

Expected=expected Y as defined in the manuscript using indirect standardisation

District/ID_2= is the variable with district unique codes

ZimG= is a spatial polygon file compatible with INLA

Year= is the temporal variable

#Model without spatial random effects

```
Model4<- inla(Y~ X1+X2+X3+X4+X5+ X6+X7+X8+X9+  
  f(Year, model = "rw1",hyper = prec.prior)  
  data = DataDist, family = "poisson", E =Expected,control.results=  
  list(return.marginals.random=TRUE,return.marginals.predictor=TRUE),  
  control.compute=list(dic=TRUE,cpo=TRUE))
```

#Model with unstructured spatial random effects

```
Model2<- inla(Y~ X1+X2+X3+X4+X5+ X6+X7+X8+X9+  
  f(Year, model = "rw1",hyper = prec.prior)+  
  f(District, model = "iid")+  
  data = DataDist, family = "poisson", E =Expected,control.results=  
  list(return.marginals.random=TRUE,return.marginals.predictor=TRUE),  
  control.compute=list(dic=TRUE,cpo=TRUE))
```

#Model with structured spatial random effects

```
Model3<- inla(Y~ X1+X2+X3+X4+X5+ X6+X7+X8+X9+  
  f(Year, model = "rw1",hyper = prec.prior)+  
  f(as.numeric(ID2), model = "besag", graph = ZimADM2adj.mat,hyper = prec.prior),  
  data = DataDist, family = "poisson", E =Expected,control.results=  
  list(return.marginals.random=TRUE,return.marginals.predictor=TRUE),  
  control.compute=list(dic=TRUE,cpo=TRUE))
```

#Convolutional spatial model

```
Model4<- inla(Y~ X1+X2+X3+X4+X5+ X6+X7+X8+X9+  
  f(Year, model = "rw1",hyper = prec.prior)+  
  f(District, model = "iid")+  
  f(as.numeric(ID2), model = "besag", graph = ZimADM2adj.mat,hyper = prec.prior),  
  data = DataDist, family = "poisson", E =Expected,control.results=  
  list(return.marginals.random=TRUE,return.marginals.predictor=TRUE),  
  control.compute=list(dic=TRUE,cpo=TRUE))
```

CHAPTER 4

This study has so far identified high-risk region of ART outcomes and observed a risk variation in becoming LTFU and mortality by gender, health facility type and age. However, the modelling approach relaxes the time since ART initiation of individuals. Therefore, this chapter introduces the parametric, semi-parametric, Bayesian and maximum likelihood models which handle time to event longitudinal history data which include the simple multistate model and the competing risk multistate model of LTFU with mortality as a competing event. Moreover, this chapter deals with missing observations in the explanatory covariates through multiple imputations (MI) using the Rubin approach. The estimates from a complete case model are compared to the estimates from the MI data. One of the challenges faced was that the laboratory markers (CD4 cell counts and viral load) had more than 65% missing; hence, MI was not feasible. These covariates were excluded in the analysis to maintain the power of the study.

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4. COMPETING RISK OF MORTALITY ON LOSS TO FOLLOW-UP OUTCOME AMONG HIV PATIENTS ON ART: A RETROSPECTIVE COHORT STUDY FROM THE ZIMBABWE NATIONAL ART PROGRAMME

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4.1. Abstract

Objective: To determine the loss to follow-up (LTFU) rates at different health care levels after ART services decentralisation among ART patients who initiated ART between 2004 and 2017 using the competing risk model in addition to the Kaplan-Meier and Cox regressions analysis.

Design: A retrospective cohort study

Setting: The study was done in Zimbabwe using a nationwide routinely collected HIV patient-level data from various health levels of care facilities compiled through the electronic patient management system (ePMS).

Participants: We analysed 390,771 participants aged 15years and above from 538 health facilities.

Outcomes: The primary endpoint was LTFU defined as a failure of a patient to report for drug refill for at least 90 days from last appointment date or if the patient missed the next scheduled visit date and never showed up again. Mortality was considered a secondary outcome if a patient was reported to have died.

Results: The total exposure time contributed was 1,544,468 person-years. LTFU rate was 5.75 (95% confidence interval (CI): 5.71-5.78) per 100 person-years. Adjustment for the competing event independently increased LTFU rate ratio in provincial and referral (adjusted sub-hazard ratios (AsHR) 1.24; 95%CI: 1.20-1.28) and district and mission (AsHR 1.47; 95%CI: 1.45-1.45) hospitals (reference: primary health care); in urban sites (AsHR 1.58; 95%CI: 1.55-1.60) (reference: rural); and among adolescence and young adults (15-24years) group (AsHR 1.17; 95%CI: 1.15-1.19) (reference: 35-44years). We also detected overwhelming association between

LTFU and tuberculosis infected patients (AsHR 1.55; 95%CI: 1.47-1.64) (reference: no tuberculosis).

Conclusions: We have observed considerable findings that “leakages” (LTFU) within the ART treatment cascade persist even after the decentralisation of health services. Risk factors for LTFU reflect those found in sub-Saharan Africa studies. Interventions which retain patients in care by minimising any “leakages” along the treatment cascade are essential in attaining the UNAIDS 90-90-90 fast track targets.

Keywords: Antiretroviral therapy, Competing risk analysis, Loss to follow-up, Mortality, Retention, Risk factors,

4.2. Article Summary: Strength and Limitations of the Study

- The analysis is based on a huge national routinely collected individual-level dataset which has a long follow-up period making our findings generalisable to the HIV patients on ART in Zimbabwe.
- This study fitted a competing risk model based on the cumulative incidence function (CIF) to explore the association between selected covariates and the absolute risk which is an essential modelling approach for medical decision-making so that appropriate sub-population interventions can be implemented.
- Variable selection of the numerous independent factors was performed using the regularisation (shrinkage) lasso regression technique alongside the stepwise selection methods.

- Important factors known to influence LTFU like CD4 cell counts and viral load were not accounted for in the model due to the high percentage of missingness, and the independent factors adjusted for were not time-dependent.
- This study has a possibility of participant selection bias since only participants enrolled in health facilities linked to the electronic patients' management database were used in the sample for analysis.

4.3. Introduction

Globally, remarkable progress has been made on the treatment of HIV-infected people using antiretroviral therapy(ART), particularly in sub-Saharan Africa(SSA)(105). In Zimbabwe, the ART programme is a comprehensive care and support package aiming to slow disease progression(12), improve survival and quality of life (13); and minimise HIV transmission by reducing the viral load. Therefore, it is imperative to monitor individuals on ART to ensure treatment efficacy, support adherence; and identify treatment failure and resistance.

At the national level, aggregated health facility data is usually used for monitoring the ART programme. However, there is an inherent difficulty in using aggregated data to make statistical inferences about individual-level outcomes. This promoted the increasing use of patient-level data worldwide to assess the impact of the ART programme (27,106–109). With efforts to achieve zero HIV incidences by 2030, the 90-90-90 UNAIDS targets were launched, whereby 90% of the people living with HIV (PLWHIV) should know their status, 90% of those diagnosed should be initiated on ART, and 90% of those on ART should achieve viral suppression(1). In Zimbabwe, strides have been made towards achieving these targets; however, limitations exist. For instance, in Zimbabwe, only 73% of PLWHIV who are on ART have achieved viral

suppression (8). To improve the proportion of those who achieve viral suppression, it is crucial to come up with broad efforts which minimise long-term ART attrition due to loss to follow-up (LTFU), mortality, drop-outs and withdrawals.

In Zimbabwe, the health service delivery can be categorised into four levels of care, namely the primary, secondary, tertiary and quaternary(110). The primary care consists of clinics and facilities offering basic preventive and curative services. Majority of these primary health care facilities are in the rural areas, and health problems beyond the scope of these facilities are referred to the secondary health care centres, which are mainly the district and mission hospitals. In the secondary care category, private and company health facilities may fit in if they can handle emergency services as the district hospitals. The tertiary care consists of the provincial hospitals which received referral patients from the district hospitals(111). The quaternary care is the last referral care level which received patients from provincial hospitals. These facilities are mainly in the two largest cities in Zimbabwe(111). The quaternary health care offers much more advanced health care; hence, there is modern equipment, medical specialists and pharmaceutical, which could be missing in the lower levels of care(110).

The ART services were initially centralised at the higher levels of care – quaternary and tertiary health care facilities- normally situated in urban areas. This means rural residents and poorer people were less likely to access HIV testing, care and treatment due to transport cost. In 2010/11, one of the strategies to mitigate the transport barrier was the decentralisation of ART services to lower levels of care (16). These devolved care models were implemented in Zimbabwe to improve patients' access to HIV care, ART adherence and retention in care of PLWHIV. The impact of HIV care and ART decentralisation has been well documented in the SSA region(89). Understanding ART retention patterns after the implementation of decentralised

care is vital to guide the ART programme and policy as well as reflecting on the gaps which may contribute to the poor viral suppression. Loss to follow up (LTFU) is one of the main threats to patient retention and may persist even after the decentralisation of ART services. This may be due to social (stigmatization, social deprivation and health literacy issues) and individual factors (perception and misconceptions over ART benefits) which still hinder retention in care (112).

This study aims to determine LTFU rates at different health care levels after ART services decentralisation among ART patients who initiated ART between 2004 and 2017. The study period covers the pre- and post-ART decentralisation period to get an overall picture of the LTFU patterns over time. The LTFU rates were compared between the different health care facility types (primary health care (PHC), district/mission and provincial/referral hospitals) in Zimbabwe using routinely collected patients-level data from the Zimbabwe National ART database. We further adjusted for the individual-level demographic and clinical characteristics as predisposing or independent factors for LTFU using a statistical model that adjusted for the competing risk of mortality on the LTFU outcome.

4.4. Methods

4.4.1. Study population

This study was conducted in Zimbabwe, a landlocked country in SSA with roughly 1.4 million PLWHIV. The HIV prevalence dropped from 25% in 2004 to 13.7% in 2017 among adults (8,113). Individual patients aged 15 years and above, who initiated ART between 1 January 2004 and 31 December 2017, were eligible for this analysis. A full description of how the final sample size was achieved is illustrated in **Figure 4-1**.

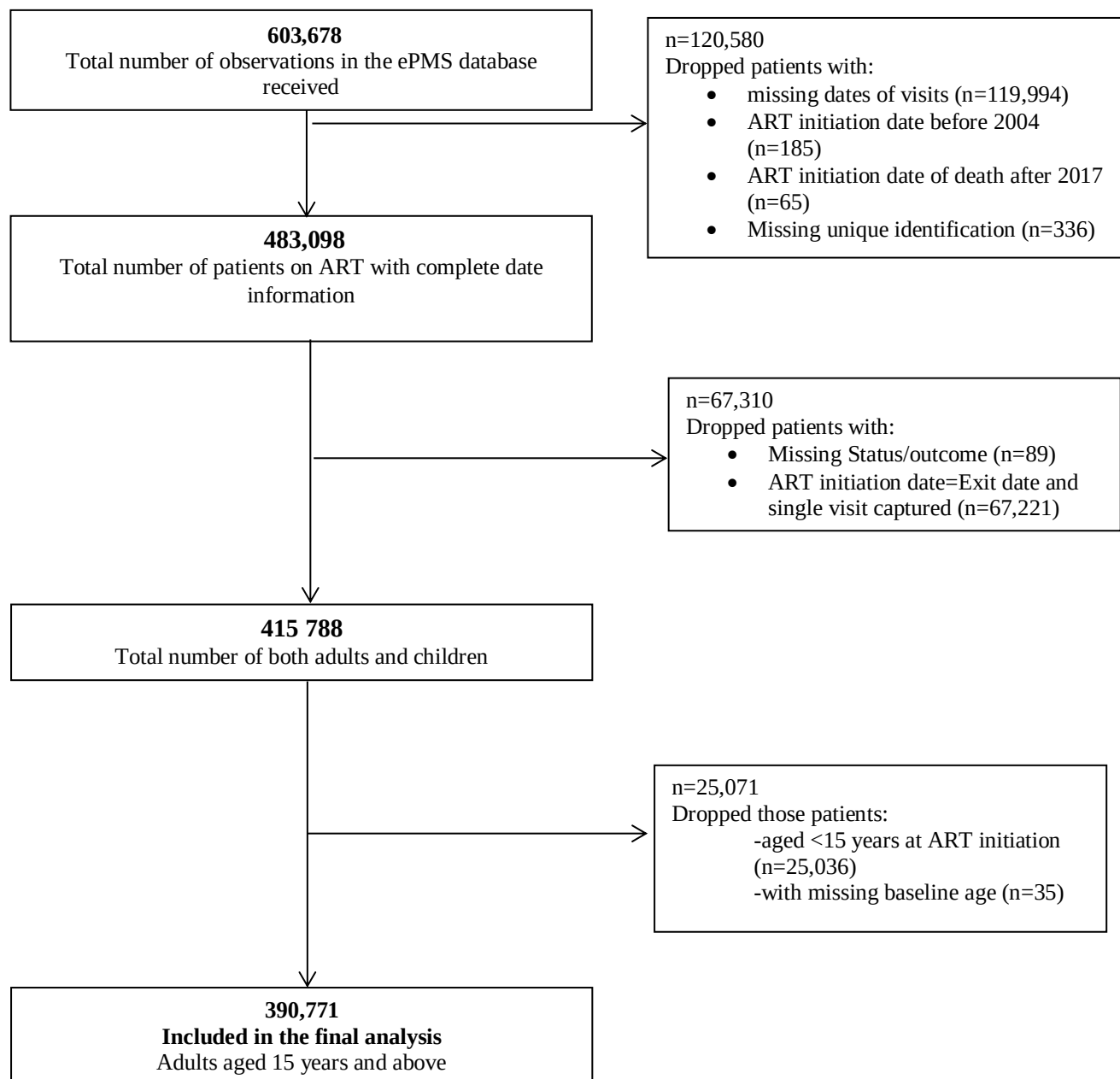


Figure 4-1: Flowchart of the inclusion criteria for analyses of adult ART patients' enrolled in Zimbabwe ART programme followed-up between 2004 and 2017

4.4.2. Study design and data sources

This study was a secondary data analysis from a retrospective cohort study of routinely collected patient data from the Zimbabwe nation ART programme. The data came from the national ART programme, which started in 2004. The ART sites expanded from 5 health facilities in 2004 to 1,566 by 2017(8,11). Treatment guidelines followed WHO recommendations; hence, the ART eligibility criteria and treatment regimens changed over time. The initial regimen for an ART naïve patient is the first-line ART, a combination of two nucleoside reverse transcriptase inhibitors(NRTI), the first drug which can be Zidovudine (AZT), Tenofovir (TDF) (the most common) or Stavudine (D4T) and the second drug is mainly Lamivudine (3TC); and one non-NRTI which can either be Nevirapine (NVP) or Efavirenz (EFV). Majority of the participants were receiving three-drug combination therapy of TDF+3TC+EFV therapy as the first-line treatment. Once the patient experienced treatment failure or intolerance, switch to second-line ART (a three-drug combination of protease inhibitor and two NRTIs) can be made(114).

4.4.3. Monitoring and evaluation system in Zimbabwe

The monitoring and evaluation system of the ART programme in Zimbabwe has been described elsewhere(49). Briefly, since the inception of ART, all patient monitoring records (PMR) had been collected manually using a paper-based system and kept at the health facility where the patient is registered. Since 2012 the paper-based system was no longer functioning properly due to high volumes of ART patients (8). This upsurge in patients' volumes began to affect the accurate ART monitoring and reporting process as the paper-based system could not cope. Moreover, the paper-based system translated into huge workloads and became strenuous to the already over-burdened health workers. As a result, the electronic patient management system (ePMS) was launched in 2012. The ePMS increased efficiency and effective management of

ART patients through improving follow-ups to subsequently increase ART adherence(49). The ePMS provided a platform to compile quality patient-level data to accurately make forecast and evaluate the ART intervention, enabling a more effective program (8).

The ePMS was rolled out in systematic phased approach with priority given to those HIV sites with high volumes of HIV patients at the same time maintaining a good representation of the four health care levels in the country (49). From the ePMS Strategic Plan document, the first phase target was 83 sites in 2013 comprising of central, provincial and district hospitals which covered approximately 61% of ART patients nationwide. Additional 267 city polyclinics, rural/large mission hospitals sites were included to make a total of 350 sites by the end of 2014(49). The last phase included 184 static ART follow up sites to bring the total to 534 sites by the end of 2017. By the end of 2018, there were 622 sites with a functional ePMS with the inclusion of private hospitals which meant that approximately 95% of all patients receiving ART were linked to the ePMS database (8).

The final database of the ePMS has patients' information from all levels of care (quaternary, tertiary, secondary and primary health care levels). It, therefore, reflects the overall ART management services in the country, although the database includes all HIV-related data. At enrolment, the patient's demographic data are captured. At each subsequent clinic visit, information on ART regimen type, clinical information, laboratory investigations and physical examination is captured. Outcomes are assessed and captured as death, LTFU, transfer-out to another health facility or alive and active on treatment. Already existing patient's information prior to 2012 from the paper-based system was retrospectively transcribed into the electronic database at each clinic, and all subsequent clinic visits were recorded prospectively with a real-time entry of patient records.

The introduction of the ePMS for monitoring HIV patients in 2012 has provided a platform for huge data repository in the country which may be used to answer some of the public health questions on the HIV aspects using statistical models. Moreover, the ePMS platform provides readily available data archiving for robust statistical analysis approaches to guide evidence-based decision-making and programme interventions planning at patients-level while eliminating the aggregated data. Therefore, this rich, huge patient-level database was of preference and suitable to answer our study objective.

4.4.4. Study endpoints

The primary endpoint was LTFU defined as a failure of a patient to report for drug replenishment within 90 days from last appointment date or if the patient missed the next scheduled visit date and never showed up again. Patients, who returned after having been LTFU, were classified as alive and active on treatment. We also consider the mortality outcome as a competing event of LTFU if a patient was reported to have died.

4.4.5. Data analysis methods

Descriptive summaries were reported as frequencies and proportions stratified by health facility type. The pattern of LTFU was explored by calendar year. Incidence rates were calculated from the ART initiation date to outcome occurrence date on a quarterly time scale. Kaplan-Meier non-parametric curves (Equations A.1-A.4 in chapter 4 Appendix) were used to describe the probability of LTFU over time stratified by selected covariates. The log-rank test was used to assess the equality of these patient retention probabilities. Estimated hazard rates (HRs) (Equation A.5-A.9 in chapter 4 Appendix) were reported as per 100 person-years.

Important variable selection was done using the lasso regression regularisation technique. Variable selection sensitivity analysis was done using the subset selection techniques (best subset selection, stepwise forward variable selection and stepwise backward variable selection methods). All these methods yield the same independent factors considered in the seven different multiple adjusted time-to-event models fitted, **Figure 4-2**. The baseline predictors used for adjustment, were all categorical, namely: health facility type, degree of urbanisation of the health facility (rural/urban), age groups (15-24, 25-34, 35-44, 45 and above), tuberculosis status (positive/ negative), body functional status-which is the patient's ability to perform normal daily activities expected for the well-being of an individual-(working body, ambulatory body, bed-ridden body), WHO clinical stages (stage 1, II, III and IV), ART enrolment calendar period (2004-2007; 2008-2011; 2012-2014; 2015-2017) and regimen type (Stavudine, Zidovudine or Tenofovir based combination therapy).

The stratification of the health facility type into primary health care, district/mission hospitals, and provincial/referral hospitals was based on the level of care classification of the corresponding health facility an individual was enrolled in, and the grouping of the health facilities was based on the patients' care similarities. For those individuals who had moved from one health facility to the other during the study period covered, the last recorded health facility site was considered for this analysis. Therefore, the health level of care classification was mutually exclusive as one individual was assigned to the last captured health facility.

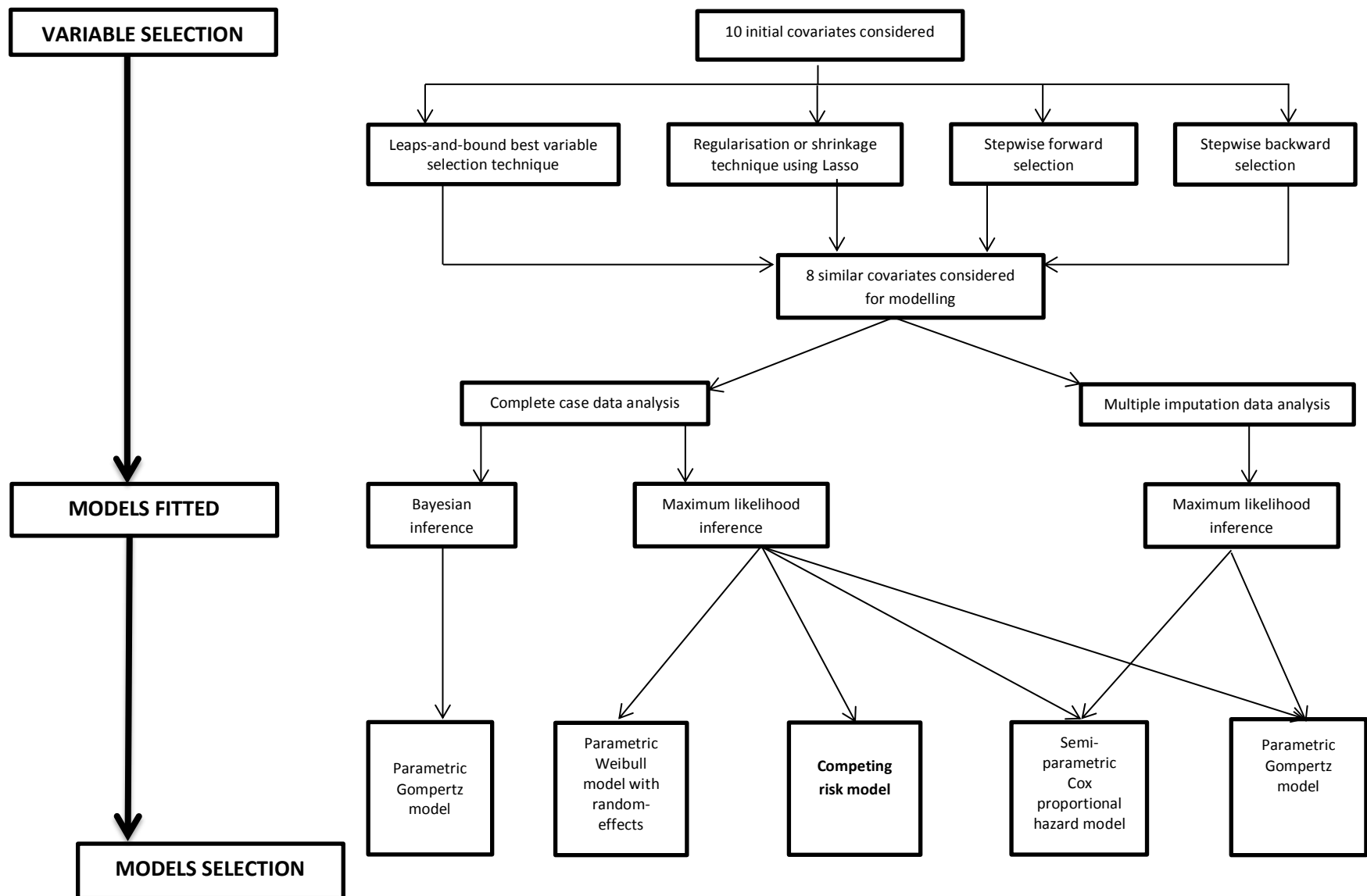


Figure 4-2: Schematic illustration of the variable of importance selection steps and subsequent models fitted for sensitivity analysis of the result

The standard Cox regression model defined in Equation (A.10-A.12) in chapter 4 Appendix is normally used for a time to event analysis; however, this method may give biased estimates in the presence of competing events. We fitted the competing risk (CR) model of mortality on LTFU through the cumulative incidence function (CIF) define in Equation (A.13-A.18) in chapter Appendix) (55). CR analysis assumes that patients are exposed to at least two risks (mortality and LTFU). One of the events is of interest (LTFU) while the other is a competing event (mortality) which inhibits the outcome of interest from occurring. The competing events may not be independent, and the baseline hazard may differ between them. The covariates used were time-independent; however, we adjusted for time to take into account the period the country experienced an economic turmoil around 2008 which resulted in a mass withdrawal of health personnel in the public sectors and an increased scarcity of vital medical supplies in health system including HIV medication (115,116). The adjusted sub-hazard ratios (AsHR) for covariates on LTFU were reported with 95% confidence intervals (95% CI). We censored on 31 December 2017 for those who had not experienced the event of interest and at the last observed date for those who had transferred to other health facilities.

We performed a sensitivity analysis of our key findings through multiple imputations of the missing explanatory covariates using Rubin's method, which assumes that the data are missing at random (MAR) (72). We compared imputed data and the complete case data estimates based on the maximum likelihood estimation (MLE) perspective for both the Cox proportional hazard and Gombertz parametric models. Within the Gombertz parametric models, estimates from the Bayesian estimation (BE) and MLE were compared (117). We assumed non-informative normal priors for all unknown parameters to be estimated with a mean of zero and variance of 100 or precision of 0.001 for the parametric Bayesian model. We fitted a parametric Weibull model

with random effects to account for any individual-heterogeneity(54). Model comparison between BE and MLE was done using the Akaike's information criterion (AIC), Bayesian information criterion (BIC) and Deviance information criterion (DIC). In contrast, model comparison between complete case analysis and imputed data analysis was done using the precision of the confidence interval for the estimates. All data management and analysis were performed using Stata 15.1 (StataCorp, 2017, Stata Statistical Software: Release 15.1, College Station, TX: StataCorp LLC)(118).

4.4.6. Patient and public involvement

This study acknowledges the importance of patients and public involvement in research studies; however, this research was done without patient involvement in all research stages since it was secondary data analysis.

4.4.7. Ethical approval

Ethics approval for this study was granted by The University of Witwatersrand's Human Research Ethics Committee (Medical) (Clearance Certificate No. M170673). Data approval was obtained from the Ministry of Health and Child Care in Zimbabwe, who are the custodians of the countrywide database. Since this study was secondary data analysis, we did not have direct contact with the participants. We received only anonymised data for analyses.

4.5. Results

4.5.1.Descriptive Analysis

At the end of study 268,896 (68.81%) patients were alive, 18,328(4.7%) had died, 88,744 (22.71%) were LTFU, and 14,803(3.79%) had transferred out from the initial health facility

another health facility. Over 1,544,468 person-years of ART, mortality and LTFU rates were 1.19 (95%CI: 1.17-1.20) and 5.75(95%CI: 5.71-5.78) per 100 person-years, respectively. The quarterly trend analysis graph of LTFU over time showed a general increase in LTFU over time with significant peaks in 2012, 2014 and 2016 (**Figure 4-3**).

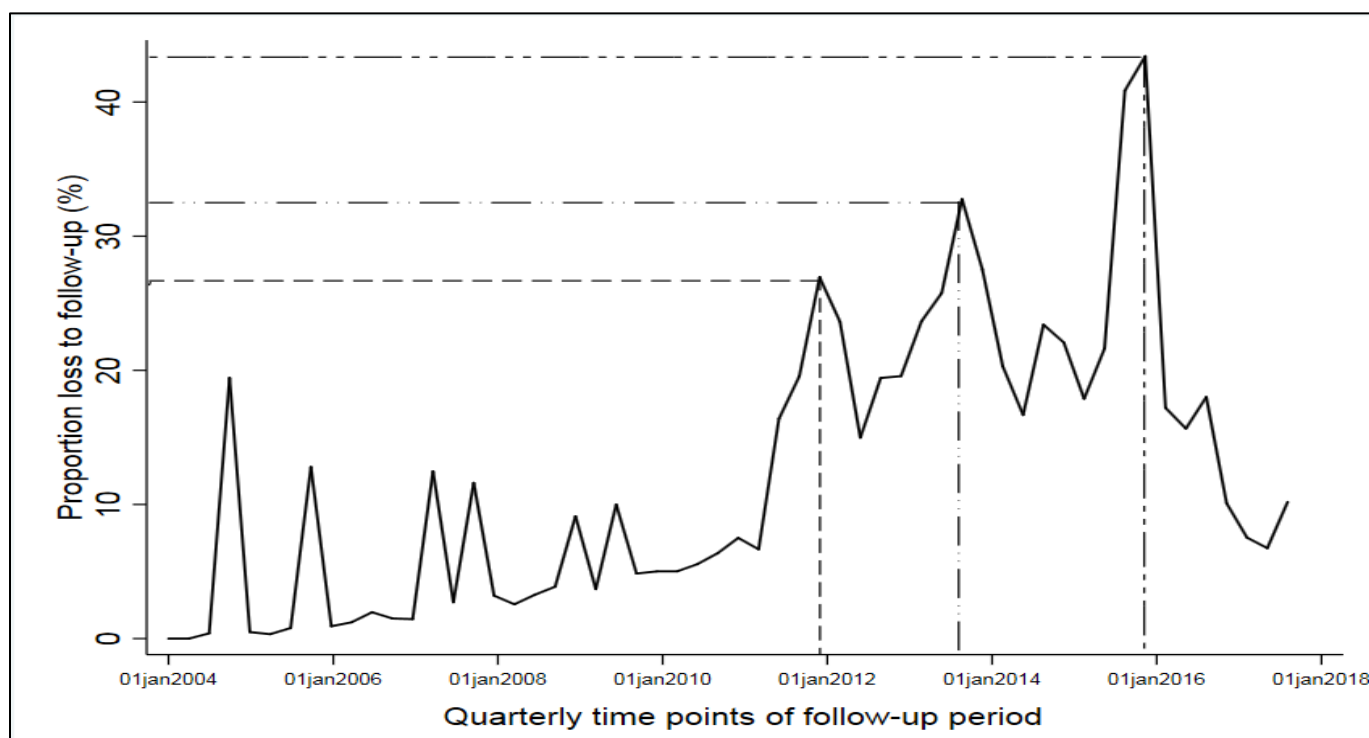


Figure 4-3: Trend analysis of loss to follow-up outcome among patients receiving ART in Zimbabwe National ART Programme, 2004 to 2017

The descriptive characteristics of 390,771 patients from 538 health facilities are presented in **Table 4-1** above. The study participants were enrolled at PHC (45.1%), districts/mission (49.2%) or provincial/referral (5.7%) hospitals. Most patients were enrolled in rural health facilities (66.82%). At ART initiation, the majority of the patients were female 117,567(66.7%), the mean (standard deviation) age was 37.5 (10.2) years and only 6.44% patients had either an ambulatory (n=25) or a bed-ridden (n=143) body functional status.

Table 4-1: Patients sociodemographic and clinical characteristics at ART initiation in Zimbabwe national ART programme, 2004-2017

Characteristics	Categories	Primary health care (PHC) n=176 253 (45.1%)	District/Mission hospitals n=192 238(49.2%)	Provincial/Referral hospitals n=22 280 (5.7%)	Totals N=390 771 (100%)
Patient Demographics					
Age (years) at ART initiation	15-24	20 314 (11.53%)	21 057 (10.95%)	2 601 (11.67%)	43 972 (11.25%)
	25-34	54 416 (30.87%)	58 874 (30.63%)	6 979 (31.32%)	120 269 (30.78%)
	35-44	59 284 (33.64%)	66 418 (34.55%)	7 875 (35.35%)	133 577 (34.18%)
	45+	42 239 (23.96%)	45 889 (23.87%)	4 825 (21.66%)	92 953 (23.79%)
Degree of urbanization	Rural	113 738 (66.92%)	137 380 (73.57%)	432 (2.01%)	251 550 (66.52%)
	Urban	56 223 (33.08%)	49 348 (26.43%)	21 055 (97.99%)	126 626 (33.48%)
Sex	Females	117 567 (66.70%)	124 141 (64.58%)	14 136 (63.45%)	255 844 (65.47%)
	Male	58 686 (33.30%)	68 097 (35.42%)	8 144 (36.55%)	134 927 (34.53%)
Education status at ART initiation	None	3 854 (2.19%)	4 136 (2.15%)	227 (1.02%)	8 217 (2.10%)
	Primary	33 735 (19.14%)	34 062 (17.72%)	2 248 (10.09%)	70 045 (17.92%)
	Secondary	59 181(33.58%)	58 349 (30.35)	6 593 (29.59%)	124 123 (31.76%)
	Tertiary	2 921(1.66%)	4 423(2.30%)	1 177(5.28%)	8 521 (2.18%)
	Missing	76 562(43.44%)	91 268 (47.48%)	12 035(54.02)	179 865 (46.03%)
Marital status at ART initiation	Single	24 438 (13.87%)	24 489 (12.74%)	3 530 (15.84%)	52 457 (13.42%)
	Married	105 504 (59.86%)	113 953 (59.28%)	12 935 (58.06%)	232 392 (59.47%)
	Widowed	25 798 (14.64%)	30 994 (16.12%)	3 523 (15.81%)	3 523 (15.81%)
	Divorced	13 429 (7.62%)	14 732 (7.66%)	1 677 (7.53%)	29 838 (7.64%)
	Missing	7 084(4.02%)	8 070 (4.20%)	615 (2.76%)	15 769 (4.04%)
Calendar time of starting ART	2004-2007	6 635 (3.76%)	8 942 (4.65%)	2 962 (13.29%)	18539 (4.74%)
	2008-2011	38 990 (22.12%)	61 321 (31.85%)	7 899 (35.45%)	108120 (27.67%)
	2012-2014	67 759 (38.44%)	90 582 (47.12%)	9 472 (42.51%)	167 813 (42.94%)
	2015-2017	62 869 (35.67%)	31 483 (16.38%)	1 947 (8.74%)	96 299 (24.64%)
Clinical factors					
WHO staging at ART initiation	I/II	82 203 (46.64%)	69 629 (36.22%)	7 690 (34.52%)	159 519 (40.82%)
	III/IV	79 279 (44.98%)	118 113 (61.44%)	14 425 (64.74%)	211 817 (54.20%)
	Missing	14 771 (8.38%)	4 499 (2.34%)	165 (0.74%)	19 435 (4.97%)
Baseline CD4 (cell/uL) at ART initiation	Above 500	4 783 (2.71%)	4 950 (2.57%)	601 (2.70%)	10 334 (2.64%)
	351-500	8 227 (4.67%)	8 790 (4.57%)	940 (4.22%)	17 957 (4.60%)
	200-350	17 908 (10.16%)	24 895 (12.95%)	2 866 (12.86%)	45 669 (11.69%)
	Below 200	23 796 (13.50%)	35 020 (18.22%)	4 982 (22.36%)	63 798 (16.33%)
	Missing	121 539 (68.96%)	118 583 (61.69%)	12 891 (57.86%)	253 013 (64.75%)
Treatment regimen at the time of data extraction	First-line	170 662 (98.29%)	184 321 (97.37%)	20 724 (94.32%)	375 704 (97.65%)
	D4T(30)+3TC+NVP	625 (0.35%)	2 942 (1.53%)	629 (2.82%)	4 196 (1.07%)
	D4T(30)+ 3TC+EFV	42 (0.02%)	155 (0.08%)	20 (0.09)	217(0.06%)
	AZT+3TC+NVP	1 349 (0.77%)	1 933 (1.01%)	349 (1.57%)	3 631(0.93%)
	AZT+3TC+EFV	212 (0.12%)	425 (0.22%)	56 (0.25 %)	693 (0.18%)
	TDF+3TC+NVP	6 541 (3.71%)	16 334 (8.50%)	2 923 (13.12%)	25 798 (6.60%)
	TDF+3TC+EFV	161 288 (91.51%)	162 006 (84.27%)	16 628 (4.63%)	339 922 (86.99%)
	Other first lines	3 236 (1.84%)	3 474 (1.81%)	428 (1.92%)	7 138 (1.83%)
	Second line	2 960 (1.68%)	4 969 (2.58%)	1 247(5.60%)	9 176 (2.35%)
Tuberculosis status at ART initiation	Negative	156 072 (88.55%)	170 869 (88.88%)	20 218 (90.75%)	347 159 (88.84%)
	Positive	2 092 (1.19%)	2 423 (1.26%)	301 (1.35%)	4 816 (1.23%)
	Not assessed	15 743 (8.93%)	16 387 (8.52%)	1 347 (6.05%)	33 477 (8.57%)
	Missing	2 346 (1.33%)	2 559 (1.33%)	414 (1.86%)	5 319 (1.36%)
Functional status at ART initiation	Working	162 710 (92.32%)	180 417 (93.85%)	20 024 (89.87%)	363 151 (92.93%)
	Ambulatory	11 789 (6.69%)	10 454 (5.44%)	2 089 (9.38%)	24 332 (6.23%)
	Bedridden	331 (0.19%)	452 (0.24 %)	28(0.13%)	811 (0.21%)
	Missing	1 423 (0.81%)	915 (0.48%)	139(0.62%)	2 477 (0.63%)

Missing category refers to information that is unavailable in the dataset for that particular variable

Most patients were married (59.5%) with secondary education (31.8%) while 54.2% were classified in WHO stage III or IV and 34.18% were in the 35-44 years age group. The majority of the participants were on first-line ART treatment (97.7%), and only a few had confirmed tuberculosis infection (1.2%). There were missing data on some covariates, including baseline CD4 cell counts recorded for only 35.3% of the study participants.

The time to event rates for LTFU stratified by baseline characteristics is shown in **Table 4-2**. LTFU rate per 100-person-years was 5.92 for patients enrolled at district and mission hospitals; 6.60 amongst patients from rural health facilities and 17.09 among patients diagnosed with tuberculosis.

Table 4-2: Rates per 100 person-years of loss to follow-up and log rank tests for ART patients' baseline characteristics in Zimbabwe national ART programme, 2004-2017

Characteristics	Category	LTFU cases	Person-years	Rate per 100 person-years	95% CI of rate	Log-rank p-value
Health facility level	Primary health care	34 958	6 200	5.6502	5.5913 to 5.7097	<0.001*
	District/mission hospitals	48 188	8 100	5.9169	5.8643 to 5.9700	
	Provincial/referral hospitals	5 598	1 100	5.0273	4.8973 to 5.1608	
Age (years) at ART initiation	15-24	32 790	4 500	7.3252	7.2463 to 7.4049	<0.001*
	25-34	12 617	1 500	8.4301	8.2843 to 8.5785	
	35-44	27 504	5 500	4.9671	4.9087 to 5.0261	
	45+	15 833	3 900	4.0242	3.9620 to 4.0874	
Degree of urbanization	Rural	52 629	10 000	5.2756	5.2307 to 5.3209	<0.001*
	Urban	36 115	5 500	6.6039	6.5362 to 6.6724	
Sex	Females	59 695	10 000	5.8703	5.8234 to 5.9175	<0.001*
	Male	29 049	5 300	5.5063	5.4433 to 5.5700	
Education status at ART initiation	None	1 470	354	4.1582	3.9509 to 4.3762	<0.001*
	Primary	14 786	2 800	5.3558	5.2702 to 5.4429	
	Secondary	32 629	4 700	6.9961	6.9206 to 7.0725	
	Tertiary	1 803	409	4.4097	4.2108 to 4.6180	
	Missing	38 056	7 300	5.2435	5.1911 to 5.2965	
Marital status at ART initiation	Single	13 078	1 900	6.9036	6.7863 to 7.0230	<0.001*
	Married	7 548	1 100	6.6112	6.4637 to 6.7620	
	Widowed	9 375	2 900	3.1872	3.1233 to 3.2524	
	Divorced	55 985	8 800	6.3313	6.2790 to 6.3839	
	Missing	2 758	625	4.4160	4.2543 to 4.5840	
Calendar time of starting ART	2004-2007	790	1 900	0.4255	0.3968 to 0.4562	<0.001*
	2008-2011	4 572	6 900	0.6593	0.6405 to 0.6787	
	2012-2014	43 565	5 300	8.1802	8.1038 to 8.2574	
	2015-2017	39 817	1 300	29.9903	29.6972 to 30.2863	
WHO staging at ART initiation	I/II	47 410	5 100	9.2080	9.1255 to 9.2912	<0.001*
	III/IV	38 919	9 500	4.0957	4.0552 to 4.1366	

	Missing	2 415	794	3.0432	2.9242 to 3.1671	
Baseline CD4 (cell/uL) at ART initiation	Above 500	4 341	257	16.9190	16.4231 to 17.4299	
	351-500	7 614	455	16.7362	16.3645 to 17.1164	
	200-350	11 556	1 700	6.7428	6.6210 to 6.8669	<0.001*
	Below 200	15 271	2 700	5.7338	5.6436 to 5.8254	
	Missing	49 962	10 000	4.8245	4.7823 to 4.8669	
Treatment regimen at the time of data extraction	First line	88 050	15 000	5.9066	5.8677 to 5.9457	
	D4T(30)+ 3TC+NVP	2 685	167.9730	15.9847	15.3914 to 16.6009	
	D4T(30)+ 3TC+EFV	141	10	14.7353	12.4932 to 17.3797	
	AZT+3TC+NVP	448	184	2.4374	2.2218 to 2.6738	
	AZT+3TC+EFT	158	30	5.3159	4.5484 to 6.2129	<0.001*
	TDF+3TC+NVP	9 652	1 100	9.1737	8.9925 to 9.3586	
	TDF+3TC+EFV	71 378	13 000	5.3710	5.3318 to 5.4106	
	Other first lines	3 588	175	20.5590	19.8972 to 21.2429	
	Second line	694	538	1.2900	1.1985 to 1.3908	
Tuberculosis status at ART initiation	Negative	81 119	14 000	5.9418	5.9010 to 5.9828	
	Positive	2 235	131	17.0906	16.3966 to 17.8141	
	Not assessed	4 188	1 400	2.9328	2.8453 to 3.0230	<0.001*
	Missing	1 202	234	5.1455	4.8627 to 5.4447	
Functional status at ART initiation	Working	81 122	14 000	5.6445	5.6057 to 5.6834	
	Ambulatory	7 059	930	7.5897	7.4147 to 7.7688	
	Bedridden	215	26	8.4201	7.3666 to 9.6243	<0.001*
	Missing	348	117	2.9723	2.6758 to 3.3015	

*Significant at 5%

The cumulative incidence probability (CIP) curve for mortality outcome was lower compared to the LTFU outcome (**Figure 4-4 A**). The LTFU CIP curve increased in the first three years on ART and became steady after that. We observed overwhelmingly significant variation between LTFU and selected covariates, log-rank p-value<0.001. Higher risk of LTFU was observed amongst 15-24 years patients (**Figure 4-4 B**), females (**Figure 4-4 C**), patients enrolled at urban health facilities (**Figure 4-4 D**); tuberculosis-infected patients (**Figure 4-4 E**) and WHO stage I/II patients (**Figure 4-4 F**).

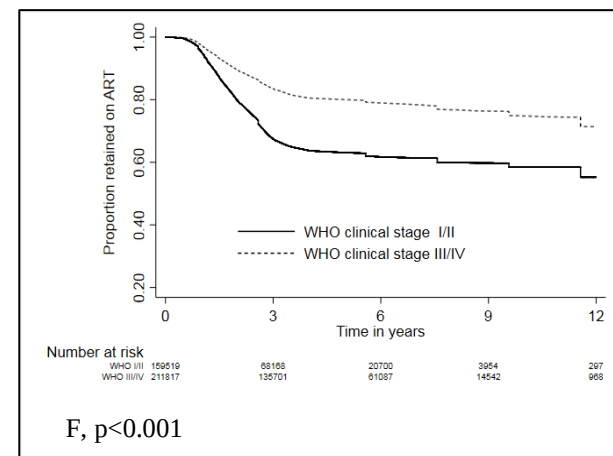
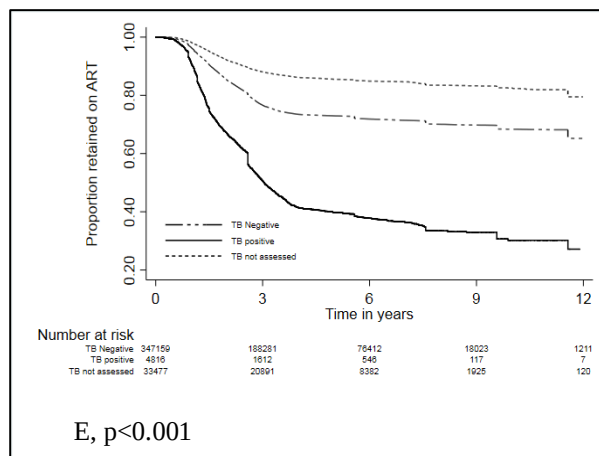
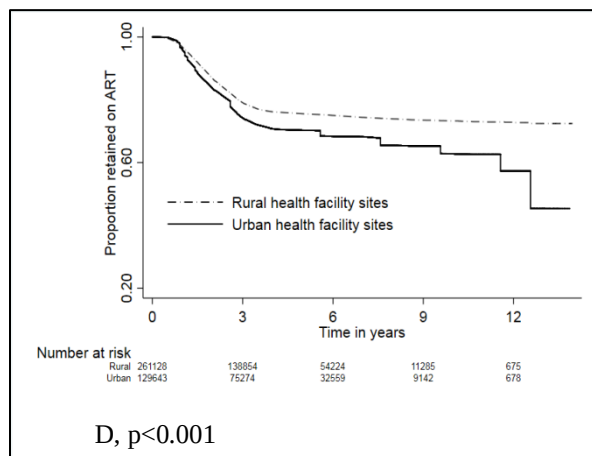
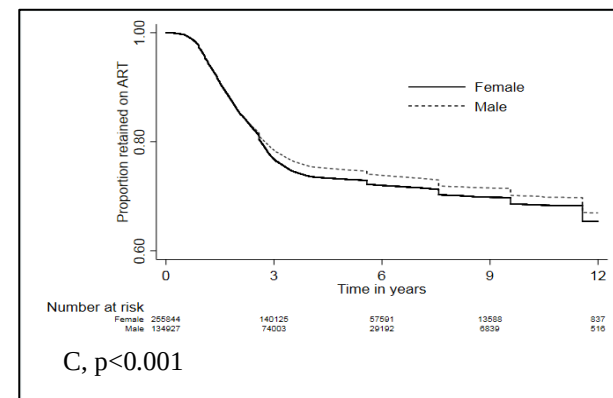
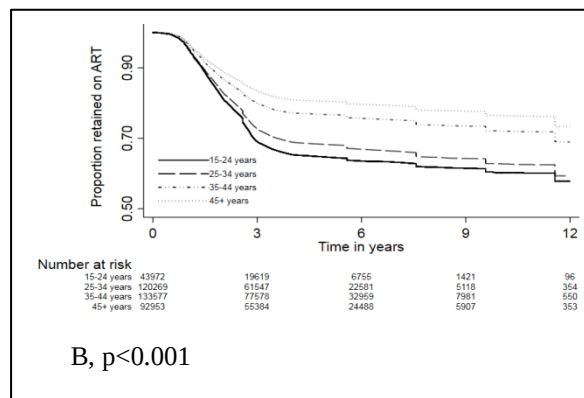
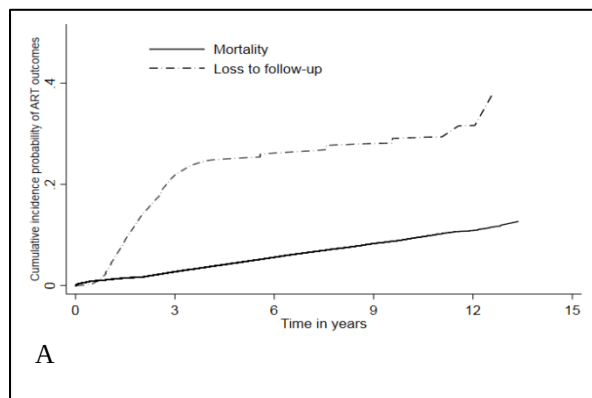


Figure 4-4: The cumulative incidence probability of mortality and loss to follow-up (A); and Kaplan-Meier curves for loss to follow-up stratified by baseline age categories (B), gender (C), level of urbanisation of the health facilities (D), baseline tuberculosis infection status (E) and baseline World Health Organization clinical stages for ART patients from the Zimbabwe national ART Programme electronic patient monitoring data, 2004 to 2017

4.5.2. The sensitivity analysis

To determine the possible independent risk factors associated with LTFU, seven models were fitted as a sensitivity approach, and the results are shown in **Table 4-3**. An additional pictorial view of the estimates is provided in chapter 4 Appendix A7 section (Figure A1) to compare the different model estimates.

The data had approximately 10% of missing information in the explanatory covariates. There was no difference in the model estimates between imputed data and complete case data (model 1 vs model 2 and model 4 vs model 5). The reason behind doing MI was to get unbiased estimates with smaller interval estimates and an improved power since the sample size is increased. Comparing the MLE (model 3) and the BE (model 4) models, the estimates were almost similar for most regression parameters. In survival models, hazard rates can be estimated either assuming a specific parametric form of the baseline distribution function (Gompertz, exponential or Weibull parametric models) or the baseline hazard function might be left unspecified (Cox proportional hazard model). In most studies, the Cox proportional hazard model is preferred as it is easier to fit and less complicated; however, this model might not adequately describe the survival process of the data. We considered the Gompertz model and Weibull parametric models; however, the inclusion of the individual random effects did not improve the model estimates (model 4 vs model 6). Lastly, adjusting for the competing effects of mortality on LTFU showed some significant improvement to the model based on the reduced AIC and BIC values compared to the Cox proportional hazard model. Hence, the competing risk model was considered a better fit compared to other models; and the interpretation of the results will be based on this model.

Table 4-3: Multiple regression models results of LTFU amongst ART patients in Zimbabwe national ART programme, 2004-2017 for different models

Characteristics	Category	Cox proportional hazard			Parametric Gompertz model		Weibull model with random effects	Competing risk model of mortality on LTFU
		CC + MLE (model 1)	MI+ MLE (model 2)	CC+BE (model 3)	CC+MLE (model 4)	MI+MLE (model 5)	CC+MLE (model 6)	CC+MLE (model 7)
Health facility level	Primary health care	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)
	Secondary hospitals ^a	1.48(1.46-1.50)	1.51(1.49-1.53)	1.53(1.51-1.54)	1.53(1.51-1.55)	1.57(1.54-1.59)	1.48(1.45-1.51)	1.47(1.45-1.50)
	Tertiary hospitals ^b	1.17(1.14-1.21)	1.23(1.20-1.27)	1.23(1.21-1.25)	1.23(1.20-1.27)	1.30(1.26-1.34)	1.10(1.06-1.14)	1.22(1.18-1.26)
Age (years) at ART initiation	15-24	1.16(1.13-1.19)	1.17(1.14-1.19)	1.12(1.11-1.14)	1.13(1.10-1.15)	1.14(1.12-1.17)	1.23(1.20-1.27)	1.19(1.16-1.21)
	25-34	1.18(1.17-1.20)	1.19(1.17-1.21)	1.18(1.16-1.19)	1.18(1.16-1.20)	1.19(1.17-1.20)	1.24(1.21-1.27)	1.19(1.17-1.21)
	35-44	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)
	45+	0.88(0.87-0.89)	0.87(0.86-0.89)	0.88(0.87-0.89)	0.88(0.86-0.90)	0.87(0.85-0.88)	0.86(0.84-0.88)	0.87(0.85-0.89)
Degree of urbanisation	Rural	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)
	Urban	1.70(1.68-1.72)	1.67(1.65-1.27)	1.67(1.65-1.69)	1.67(1.65-1.70)	1.64(1.61-1.66)	2.06(2.01-2.10)	1.61(1.59-1.63)
Calendar time of starting ART	2004-2007	0.04(0.04-0.05)	0.04(0.04-0.05)	0.02(0.02-2.02)	0.02(0.01-0.02)	0.02(0.01-0.02)	0.01(0.01-0.01)	0.09(0.09-0.10)
	2008-2011	0.07(0.7-0.08)	0.07(0.07-0.08)	0.04(0.04-0.04)	0.04(0.04-0.04)	0.05(0.04-0.05)	0.02(0.02-0.02)	0.11(0.10-0.11)
	2012-2014	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)
	2015-2017	8.48(8.34-8.63)	8.40(8.26-8.54)	5.95(5.90-6.00)	5.97(5.88-6.06)	5.90(5.81-5.99)	16.09(15.56-16.63)	6.02(5.91-6.12)
WHO staging at ART initiation	I/II	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)
	III/IV	0.73(0.72-0.74)	0.74(0.73-0.75)	0.73(0.73-0.74)	0.73(0.72-0.75)	0.74(0.73-0.75)	0.67(0.65-0.68)	0.74(0.73-0.75)
Treatment regimen at the time of data extraction	D4T(30)+ 3TC+NVP	5.96(5.72-6.21)	6.00(5.77-6.25)	6.06(5.92-6.22)	6.09(5.84-6.34)	6.06(5.82-6.30)	15.05(13.98-16.21)	5.47(5.52-5.75)
	D4T(30)+ 3TC+EFV	8.55(7.21-10.12)	8.34(7.09-9.90)	8.71(8.21-9.20)	8.47(7.16-10.03)	8.29(7.01-9.79)	19.88(15.23-25.87)	7.98(6.41-9.94)
	AZT+3TC+NVP	0.73(0.67-0.80)	0.72(0.66-0.79)	0.74(0.71-0.78)	0.74(0.67-0.81)	0.72(0.65-0.79)	0.74(0.66-0.83)	0.75(0.68-0.83)
	AZT+3TC+EFV	1.19(1.02-1.40)	1.19(1.01-1.39)	1.19(1.16-1.23)	1.21(1.03-1.42)	1.21(1.03-1.40)	1.27(1.03-1.56)	1.09(0.91-1.30)
	TDF+3TC+NVP	2.41(2.36-2.47)	2.46(2.40-2.51)	2.46(2.42-2.50)	2.45(2.40-2.51)	2.50(2.44-2.55)	3.58(3.45-3.70)	2.29(2.23-2.34)
	TDF+3TC+EFV	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)
	Other first lines	1.97(1.90-2.04)	1.97(1.91-2.04)	1.88(1.83-1.93)	1.89(1.82-1.95)	1.89(1.83-1.96)	2.44(2.32-2.57)	1.61(1.54-1.68)
	Second line	0.46(0.42-0.49)	0.45(0.42-0.49)	0.45(0.43-0.47)	0.44(0.41-0.48)	0.44(0.41-0.47)	0.39(0.36-0.42)	0.48(0.44-0.52)
Tuberculosis status at ART initiation	Negative	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)
	Positive	2.14(2.05-2.24)	2.13(2.04-2.23)	2.03(1.99-2.09)	2.02(1.94-2.11)	2.01(1.93-2.10)	2.66(2.50-2.83)	1.53(1.45-1.62)
	Not assessed	0.58(0.56-0.59)	0.59(0.57-0.61)	0.60(0.59-0.60)	0.60(0.58-0.62)	0.61(0.59-0.63)	0.51(0.49-0.53)	0.60(0.58-0.62)
Body functional status at ART initiation	Working	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)	1(reference)
	Ambulatory	1.22(1.19-1.24)	1.23(1.20-1.26)	1.23(1.21-1.26)	1.23(1.20-1.27)	1.25(1.22-1.28)	1.28(1.23-1.32)	1.08(1.05-1.11)
	Bed-ridden	1.34(1.17-1.53)	1.33(1.16-1.52)	1.32(1.29-1.35)	1.34(1.16-1.53)	1.32(1.15-1.51)	1.42(1.18-1.72)	0.64(0.54-0.75)
	AIC	196416.4			379948.9		445559.7	195708.7
	BIC	196439.1			380197.6		445819.3	195731.4
	DIC			379925.9				

CC=complete case, MI=multiple imputation, BE=Bayesian estimation, MLE=maximum likelihood estimation, Bold face= low values of the information criterion

^aDistrict and mission hospitals; ^bProvincial and referral hospitals

4.5.3. The loss to follow-up outcome estimates for the competing risk model

The multivariable competing risk model revealed that patient factors predicting LTFU included: being enrolled at a provincial/referral (AsHR 1.22; 95%CI: 1.18-1.26) or district/mission (AsHR 1.47; 95%CI: 1.45-1.50) hospitals (reference: PHC), urban sites (AsHR 1.61; 95%CI:1.59-1.63) (reference: rural) and 15-24 years group (AsHR 1.19; 95%CI: 1.16-1.21) (reference: 35-44 years). We also detected an overwhelming association between LTFU and tuberculosis-infected patients (AsHR 1.53; 95%CI: 1.45-1.62) (reference: no tuberculosis) and a protective effect of LTFU for patients classified in WHO stage III or IV (AsHR 0.74; 95%CI: 0.73-0.75) (reference: WHO I/II). Patients who were taking stavudine-combination therapy as a first-line ART treatment had an increased risk of becoming LTFU relative to patients taking TDF+3TC+EFV first-line combination therapy, that is, D4T(30)+3TC+NVP (AsHR 5.47; 95%CI:5.52-5.75) and D4T(30)+3TC+EFV (AsHR 7.98; 95%CI: 6.41-9.94). We also observed that patients who initiated ART between 2015 and 2017 had a pronounced risk of becoming LTFU compared to patients who enrolled between 2012 and 2014 (AsHR 6.02; 95%CI: 5.91-6.12).

4.6. Discussion

This study aims to determine the loss to follow-up (LTFU) rates at different health care levels after ART services decentralisation among ART patients who initiated ART between 2004 and 2017 and determine other potential independent factors using the competing risk model approach. Our study followed similar studies adjusting for the competing effect of mortality on LTFU, recognising that those who die are no longer at risk of LTFU (119,120). We found the LTFU rate of 5.7 per 100- person-years, which was lower than that reported in Ethiopia of 8.2 per 100 person-years (98). The lower LTFU rates in our study put forward the positive impact of

the decentralised models implemented in Zimbabwe to increase patients' retention in HIV care. However, there is still a considerable magnitude of LTFU outcome in ART programs contributing to the “leakages” or attrition of patients within the continuum of care cascade in Zimbabwe. This requires continual upscaling of interventions which minimise the LTFU rates and retain patients in care since patients who are LTFU are associated with increased treatment interruptions which can trigger ART treatment defaulting, treatment non-adherence, treatment failure or treatment resistance (121,122).

Similar to other studies, LTFU independently increased at higher levels of care (provincial and referral (AsHR 1.22; 95%CI: 1.18-1.26) and district and mission (AsHR 1.47; 95%CI: 1.45-1.50) hospitals) relative to PHC in this study (106). This finding supports the fact that decentralisation is associated with better patients' retention in care as there are high risks of LTFU rate in higher levels of care compared to the PHC facilities. This finding supports the assumption that if patients seek care from health facilities closer to their homes with cheaper transport cost and less congested hospital environments, there is improved patient retention as compared to seeking care to faraway health facilities (123). Moreover, the high rates of LTFU in secondary and tertiary/quaternary levels of care could be explained by “silent transfers” whereby patients self-transfer themselves to these decentralised PHC facilities based on individual preferences of where to seek care, and the system fails to track it. These “silent transfers” could be a good indication of the upsurge of the decentralisation of services (123). However, such “silent transfers” may result in inflated LTFU rates in higher levels of care as most these patients would be classified as LTFU when in fact they might have self-transferred and the patient tracking system is not efficient enough to pick such scenarios due to significantly high patients' volumes persisting at these health facilities (106). Similarly, the quarterly trend analysis of LTFU rates

showed an increase over time, peaking in the period when decentralised models were implemented. The same issue of “silent transfers” of patients to nearer health facilities can also explain this trend pattern finding.

On the contrary, not everyone would prefer to seek care from these decentralised health facilities. Some may intentionally avoid these nearby health facilities to conceal their HIV status from the community. These individuals remain enrolled in faraway health facilities and most probably the higher levels of care. These individuals may contribute to the observed high rate of LTFU in this cohort as they may still face transport cost challenges to replenish their ART supplies(124). Moreover, tertiary and quaternary levels of care may receive much sicker patients with a high risk of death, hoping to get better treatment through the health care referral system (125). This means some of these much ill patients are more likely to become LTFU eventually as severe immune deterioration hinders one to keep up to date with their treatment replenishments. Earlier studies have also reported that much sicker patients with severe immune deterioration are more likely to become LTFU compared to those with no significant immunodeficiency (126). Other studies have also shown that a significant portion of these severely ill patients who eventually become LTFU from higher levels of care health facilities, if tracked, could be found dead (127). Our findings put forward that though the decentralisation uptake might have been taken up by the majority of the ART patients and improved patient’s retention in the ART program in overall; those groups of individuals who still seek health care from the higher levels of care are still more at risk of becoming LTFU; hence, interventions which may retain patients in the higher levels of care facilities are a priority.

Patients enrolled at urban health facilities had increased risk to become LTFU compared to those at rural sites. This finding contradicts a study done in Ethiopia whereby rural residents had an

increased risk of LTFU due to availability of transport costs, long distances to ART health facilities, social stigma as well as low levels of HIV knowledge in these communities(112). However, our study finding can be explained by the decentralisation of health facilities to walkable distances in favour of rural residents (27,128). Mobility of residents in urban areas is disproportionate relative to rural residents; hence, most of these LTFU in urban areas could be part of the silent transfers to other nearer ART health facilities in their relocated areas.

Another interesting finding was high LTFU among the 15-24 years group. The adolescent's group is known to be associated with additional intricacy in their HIV management due to different types of chronic comorbidities, and this whole complexity may impact on their ART outcomes including LTFU (129,130). The high risk of becoming LTFU among adolescents can be attributed to structural deprivation due to medical and psychological reasons which contribute to poor adherence in this subpopulation group as a result of becoming LTFU (131). The most common medical barrier which has been found to affect ART adherence include treatment side effects, multiple doses and health system dissatisfaction. Research has found that ART has improved perinatal HIV infection into a controllable disease through optimal ART adherence. This opens up an additional challenge among adolescents who were prenatally or perinatally infected in the transition stage to adults care to experience ART adherence lapses and develop worse clinical outcomes as they become LTFU (131). The transition from the paediatric care to adult care would mean changing care providers, absence of youth-friendly facilities, tight and hectic schedules, new responsibilities and deprivation of caregiver support for some of these adolescents. Some of the social deprivation issues among adolescents include inadequate financial support to cover transport costs to health facilities for treatment refill since this group heavily depends on their caregivers (132). Some of the social deprivations faced by adolescents

include lack of family support as some adolescents come from disrupted family structures with depraved caregiver-child relationships; fear perceived HIV-related stigma and discrimination to disclose their status (100,112,132).

Therefore, this study recommends that policymakers strengthen the social protection support to address the complex vulnerability, disadvantages and risks faced by HIV positive adolescents to foster resilience among the HIV positive adolescent population. The social protection support can interrupt some of the social deprivations faced by adolescents through poverty reduction and economic development, improved access to health care, access to health services, reduced stigma and discrimination and improved caregiver psychosocial and physical well-being. Another recommendation is the use of health facility-based peer-supporters programmes for adolescents to improve ART adherence and ultimately, viral suppression(133,134). The peer support activities involve peer-to-peer counselling, peer support groups and treatment buddy programmes among adolescents with the aim of ART adherence and ultimately achieving viral suppression, reducing the HIV-related illnesses among adolescents. As adolescents may exit the HIV care through becoming LTFU or withdrawals due to transition adjustments challenges from paediatric care to adult care; an early multidisciplinary and developmentally suitable transition preparedness mechanism is an alternative. The mechanism should be a comprehensive package addressing inherent adolescents' health issues like cognitive health, ART adherence, stigma, disclosure and socioeconomic issues (129,134). Besides, a simple regimen, directly observed therapy and technological interventions like cell phone reminders have been found to increase ART adherence in adolescents.

We observed an overwhelming association of tuberculosis infection and becoming LTFU which concurs with an earlier study which reported that the risk of becoming LTFU was two times

more likely in HIV patients with tuberculosis infection compared to those who did not have tuberculosis (98). This finding can be explained by overlapping toxicity of HIV and tuberculosis drugs, leading to adverse reactions which have a direct consequence of becoming LTFU (98). Therefore, a push towards integrated care of HIV and tuberculosis service delivery would elevate HIV uptake and tuberculosis screening and reduce travel inconveniences on patients (125,135). Also, tuberculosis treatment before ART initiation reduces the risk to LTFU (100); hence, it is profound to increase efforts in tuberculosis screening and treatment of HIV patients. However, issues around tuberculosis drug resistance cannot be ignored. Nowadays, HIV studies also consider information on non-communicable diseases like cancer, diabetes and hypertension; however, this information was missing from this current study database.

We also detected that patients classified in WHO stage III or IV were less likely to become LTFU relative to those classified in WHO stage I or II. However, our finding contradicts with earlier studies which have reported that experiencing a severe AIDS-defining ailment was associated with reduced risk of becoming LTFU(119,136). Our study finding may put forward the fact that there could have been an upsurge of health-seeking behaviour amongst patients with advanced WHO clinical stages in this database cohort or this finding could be attributed to expansions of community awareness through health promotion in these health facilities communities.

4.6.1. Strengths and weaknesses of this study

This study highlights several strengths. A regularisation variable selection technique was used to identify important covariates. The lasso model shrinks the variable coefficient to zero and produces a simpler model which can be interpreted easily. For the survival analysis, the standard

Cox regression model overestimated the risk in the presence of competing risks, and we used the Fine and Gray competing risk model instead (56). Ignoring competing risks alter the probabilities of occurrence of the outcome giving biased estimates. Standard survival methods normally used in many studies censor the competing risk; however, this is improper because those who have died can no longer become LTFU. Such analysis will either overestimate or underestimate the risk ratios. We also used individual data which enabled exploration and adjustment for patient-level covariates associated with the outcome to get robust information on the ART outcome patterns as compared to aggregated data(99,124). The study follow-up period was relatively long (13years), and the data came from all the ten provinces in Zimbabwe without restriction to specific geographical areas. The data represented quaternary, tertiary, secondary and primary health facilities from private and public sectors. This makes our results generalisable to the whole of Zimbabwe since the data reflect a true representation of all PLWHIV in the country. To the best of our knowledge, this study has used one of the largest datasets to analyse adult ART outcomes at the patient-level.

Our study results should be inferred in light of some limitations. Missing data was of concern, particularly to those variables that influence LTFU like viral load and CD4 cell count in addition to non-communicable diseases comorbidities. The presence of missing data could be explained by poor documentation of information (125) or limited access to the point of care machines for viral load, and CD4 cell counts measurements (27,137,138). The missing patterns for some covariates like viral load and CD4 cell count measurements were likely to be informative and missing not at random (MNAR) since differentiated care monitoring approach was used in some years covered by this study(139). Therefore, to maintain sufficient power, covariates with a high percentage of missing observations were excluded at the multivariable analysis stage. In future,

we recommend that the data clerks should be trained on the importance of capturing full information and to the programme managers to consider expanding the HIV routine data collection tool to capture non-communication diseases conditions of the HIV patients. The socio-demographic and clinical characteristics in the database were only taken at baseline or last observed at the time of data extraction; hence, we could not incorporate the time dependency of some covariates. We also acknowledge that there could be differential misclassification of the LTFU outcome in this study in the sense that some of those recorded as LTFU may be “silent transfers” who have enrolled in a different health facility as a result of ART decentralisation and have been given a different unique identifier number; hence, this might have biased our LTFU estimates in this study. There is also a possibility of participant selection bias since we only considered patients whose information was captured through the ePMS; as a result, the reported findings could be systematically different from those patients not included. However, it is of paramount importance to note that the dataset used was huge, and representation of the health facilities in Zimbabwe was reflected; hence, our findings could be generalised to all ART services health facilities in Zimbabwe.

While our findings for the common predictors of LTFU may be comparable to earlier studies conducted in Sub-Saharan Africa region, we had also hypothesised that those ART patients’ who enrolled around 2008 would have a higher risk of becoming LTFU. This was done taking note of the hyperinflation that occurred in Zimbabwe during the part of the study period under review. The economic turmoil was allied to the increased mass departure of qualified health professionals and scarcities of vital medical supplies in health facilities (115,116). Despite this situation, we detected a protective effect of becoming LTFU between 2008 and 2011 in this study. This could be explained by the support the country received through Global Fund (27),

and ART sites increased from 282 sites in 2008 to 1,006 in 2012 (128). For further studies, we recommend the use of time-varying covariates like regimen type, CD4 cell counts, WHO stages and viral load measurements; and the use of spatial analysis of ART outcome to identify high burdened regions which the policymakers may use to allocate resources, especially in resource-constrained settings.

4.7. Conclusion

The results from this current study using the data spanning over 13 years agree with the evident decline of the HIV incidence and prevalence in Zimbabwe; and the findings are comparable to similar HIV studies' findings, even from Demographic Health Survey (140). Our results indicate that patient retention in care is still a drawback in HIV prevention and control.

Policymakers and program managers should come up with strategies to retain patients on ART. These strategies may include increased patient surveillance and strengthened patient tracing mechanisms to reduce LTFU at health facilities, strengthened community-based caregiver and peer support (89), and nutritional aid support especially for adolescents and young adults (15-34years). Besides, interventions which minimise “leakages” in the HIV treatment cascade including the use of ART adherence clubs to reduce ART resistance (141) and advice on sexual abstinence should remain the cornerstone of HIV prevention and control. As much as most of the observed LTFU outcome at higher levels of care (district, provincial and central hospitals) could be “silent transfers”, most patients who become LTFU are likely to have poor ART adherence if not dead. Poor ART adherence leads to poor viral suppression which affects achieving the third 90% UNAIDS targets, which state that 90% of those patients on ART should be virally suppressed. Clinicians should provide continual educational support on the importance of ART

adherence to increase life expectancy among the HIV population and other benefits of ART. More important than not meeting the UNAIDS targets is the impact that poor viral suppression has on patients' health.

4.7.1. Authors' contributions

ZMZ conceptualized the concept, cleaned and analysed the data and wrote the initial draft of the manuscript. **JT** and **TFC** advised on analysis, **EM** guided and oversaw the analysis and reviewed the manuscript. **ZMZ, JT, TC and EM** contributed to the interpretation of the results. All authors reviewed the final manuscript for submission.

4.8. Chapter 4 Appendices:

4.8.1. A1: Additional theoretical aspects of survival models-Cox proportional hazard

Traditionally for time-to-event analysis, researchers tend to fit the semi-parametric cause-specific proportional hazard model which was proposed by Cox (1972) because of its less stringent assumption on the hazard form and survival function (54). For the conventional cause-specific proportion hazard, we did a non-informative censoring of LTFU and transfer-out. We assumed that the hazard function is an arbitrary, unspecified, non-negative function of time (54).

4.8.2. A2: Survival Function

Let T be a non-negative random variable denoting the survival time of an individual. The survival function $[S(t)]$ is used to represent the probability that an individual survives from time origin to time beyond t

$$S(t) = P(T \geq t) \quad (\text{A.1})$$

If we assume that T is a continuous random variable [$P(T \geq t) = P(T > t)$], the different values that T can take have an underlying probability density function (pdf) given by:

$$S(t) = P(T > t) = \int_0^t f(x)dx = 1 - F(t) \quad (\text{A.2})$$

Where $F(t)$ is the cumulative distribution function. The cumulative distribution function can be expressed as:

$$F(t) = P(T < t) = \int_0^t f(x)dx \quad (\text{A.3})$$

Given a survival function, we can calculate the density function by differentiating the cumulative distribution function as:

$$f(t) = -\frac{dF(t)}{dt} \quad (\text{A.4})$$

4.8.3. A3: The Hazard function

The hazard function is the probability that an individual dies at time t conditional on having survived to that time. The hazard function, therefore, represents an instantaneous death (failure) rate for an individual who survived to that time. In other words, the hazard function considers the probability that a random variable is associated with an individual's survival time lies between t and $t + \delta t$ conditional on T is greater than or equal to t :

$$\begin{aligned} h(t) &= P(t < T < t + \delta t \mid T \geq t) \\ &= \frac{F(t + \delta t) - F(t)}{S(t)} \end{aligned} \quad (\text{A.5})$$

where $F(t)$ is the cumulative distribution function. The hazard function is the limiting value of the above probability in Equation (A.5) divided by the time interval δt , as δt tends to zero.

This can be re-written as:

$$\begin{aligned}
 h(t) = \mu(t) &= \lim_{\delta t \rightarrow 0} \frac{P[t \leq T < t + \delta t \mid T \geq t]}{\delta t} \\
 &= \lim_{\delta t \rightarrow 0} \frac{P[t \leq T < t + \delta t]}{\delta t P(T > t)} \\
 &= \lim_{\delta t \rightarrow 0} \frac{F[t + \delta t - F(t)]}{\delta t S(t)} \\
 &= \frac{1}{S(t)} \left\{ \lim_{\delta t \rightarrow 0} \frac{F[t + \delta t - F(t)]}{\delta t} \right\}
 \end{aligned} \tag{A.6}$$

But $\left\{ \lim_{\delta t \rightarrow 0} \frac{F[t + \delta t - F(t)]}{\delta t} \right\} = f(t)$ and since T is a continuous random variable, then

$$h(t) = \frac{f(t)}{S(t)} = -\frac{d}{dt} \log[S(t)] \tag{A.7}$$

The cumulative hazard is

$$H(t) = \int_0^t h(u) du = -\log[S(x)] \tag{A.8}$$

Thus for a continuous lifetimes

$$\begin{aligned}
 S(t) &= \exp\{-H(t)\} \\
 &= \exp\left[-\int_0^t h(u) du\right]
 \end{aligned} \tag{A.9}$$

4.8.4. A4: The Cox regression model

This model is also known as the Proportional hazard regression model, which models the incidence or hazard rate (mortality rate in our case). This model assumes independence of

survival times between distinct individuals in a sample and a constant hazard ratio regardless of time. The model can be written as:

$$\begin{aligned}\log\left(\frac{h(t)}{h_0(t)}\right) &= \beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k \\ \left(\frac{h(t)}{h_0(t)}\right) &= \exp(\beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k) \\ h(t) &= h_0(t) \exp(\beta_1 X_1 + \beta_2 X_2 + \dots + \beta_k X_k)\end{aligned}\tag{A.10}$$

This model can be simplified in a matrix form as:

$$h(t / \mathbf{Z}) = h_0(t) \exp(\boldsymbol{\beta} \mathbf{Z}^T)$$

where $h(t / \mathbf{Z})$ is the expected hazard at time t conditional to the covariate matrix $\mathbf{Z}$. The expected hazard is a product of the baseline hazard ($h_0(t)$) (which is a function of duration time only) and the exponential function of the regressors ($\boldsymbol{\beta} = (\beta_1, \beta_2, \dots, \beta_k)$; a $1 \times k$ parameter vector) for k covariates. Then the explanatory variables for n persons, $\mathbf{Z}$ matrix, will be:

$$\mathbf{Z} = \begin{bmatrix} X_{11}, & X_{12}, & \cdot & \cdot & \cdot, & X_{1n} \\ X_{21}, & X_{22}, & \cdot & \cdot & \cdot, & X_{2n} \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot & \cdot & \cdot \\ X_{k1}, & X_{k2}, & \cdot & \cdot & \cdot, & X_{kn} \end{bmatrix}$$

Thus for the individual's covariates $Z_i = (X_{i1}, \dots, X_{ik})^T$, the baseline hazard ($h_0(t)$) is equal to $h(t)$ when all the regressors are equal to zero, the function of the regressors will be equal to 1. The Cox model is termed semi-parametric because it is made up of the parametric part for the covariates adjustment and the non-parametric baseline hazard as there are no assumptions for the underlying hazard function.

4.8.5. A5: Likelihood function of the Cox regression

The Cox model parameters are estimated by maximizing the partial log-likelihood function. Letting the minimum censoring time C_j and survival time T_j be denoted by $t_{(j)}$. The censoring time is right censored at C after observing that $T_j > C_j$. Let $R(t_j)$ denotes the set of lives which are at risk before the j th observed lifetime. Then the partial likelihood is a product of the event times of a quotient that compares the hazard of individuals with the event at a time $t_{(j)}$ to all the hazard of all individuals at risk at a time $t_{(j)}$ can be derived in terms of these censoring times. If we observe $\{(T_j, \delta_j)\}_{j=1}^n$ where T_j is still the observed time and δ_j the censoring indicator taking values one if the failure time is observed for individuals $j=1, 2, \dots, n$ where n is the total number of observations and zero if right censoring, then the likelihood can be easily expressed as a product of the probability density function (pdf) and the cumulative survival function expressed as $LH \propto \prod_{j=1}^n f(t_j)^{\delta_j} S(t_j +)^{1-\delta_j}$. This function can be expressed as well as a partial likelihood function in terms of covariates and regression coefficients matrices, as shown below:

$$L_p(\beta | D_{obs}) = \prod_{j=1}^n \left[\frac{\exp(\mathbf{Z}_j^T \beta)}{\sum_{k \in R(t_j)} \exp(\mathbf{Z}_k^T \beta)} \right]^{\delta_j}, \quad (\text{A.11})$$

where $D_{obs} = \{(t_j, \delta_j, \mathbf{Z}) : j=1, 2, \dots, n\}$ is the observed univariate right-censored survival data.

Considering the Breslow concept when ties are present, the partial likelihood may be expressed

as:

$$L_{pt}(\beta | D_{obs}) = \prod_{j=1}^d \frac{\exp(\mathbf{Z}_j^T \beta)}{\left[\sum_{k \in R(t_j)} \exp(\mathbf{Z}_k^T \beta) \right]^{d_j}},$$

where $d = \sum_{j=1}^n \delta_j$, $\mathbf{z}_j = \sum_{k \in D_j} \mathbf{x}_k$, $d_j =$ the number of events at $t_{(j)}$ and $R(t_j)$ is a set of all individuals who have the event at the defined time $t_{(j)}$. Thus, this can be written as

$$L_{pt}(\beta | D_{obs}) = \prod_{j=1}^n \frac{\exp(\delta_j \mathbf{Z}_j^T \beta)}{\left[\sum_{k \in R(t_j)} \exp(\mathbf{Z}_k^T \beta) \right]^{\delta_j}},$$

Expanding the Breslow equation gives:

$$\log L(\beta | D_{obs}) = \sum_{j=1}^D \left[\sum_{i \in D_j} \mathbf{Z}_i^T \beta - d_j \log \left\{ \sum_{k \in R_j} \exp(\mathbf{Z}_k^T \beta) \right\} \right] \quad (\text{A.12})$$

where j indexes the ordered failure times $t_{(j)}$, $j = 1, \dots, D$; D_j is the set of d_j observations that fail at a time $t_{(j)}$; d_j is the number of failures at a time $t_{(j)}$; and R_j is the set of observations k that are at risk at a time $t_{(j)}$ (that is, all k such that $t_{0k} < t_{(j)} \leq t_k$). This can be simplified in set notation form as $k \in R_j$ and $d_j \in D_j$.

4.8.6. A6: Competing risk model specification

In epidemiological studies, more than one cause of failure is possible, hence the estimates of the targeted outcome probabilities are either over-estimated with the Cox model (142); hence, the drive for the competing risk analysis to get marginal probabilities of mortality as proposed by Fine and Gray (55). Competing risk is when we have more than one cause of failure outcomes, and we are only interested in one of them. In this case, mortality was the competing event to LTFU. The Kaplan-Meier estimate is normally used, where the competing risk events are treated as censored observations, but this is biased since the independence assumption is violated. An individual who is censored because of the competing event will certainly not experience the

outcome of interest; hence the Kaplan-Meier may overestimate the probability of failure, especially if completion is high. Hence, using the Kaplan-Meier estimate in this situation would result in the biased estimates.

The competing risk inference is the joint distribution of time of death or failure (T) and failure outcome, in our case death (D) conditional to some covariates, X. The cause-specific hazard (q cause of death) function will be

$$h_q(t) = \lim_{\delta t \rightarrow 0} \frac{P(t \leq T < t + \delta t, D = q | T \geq t)}{\delta t} \quad (\text{A.13})$$

The cumulative cause-specific hazard is written as:

$$H_q(t) = \int_0^t h_q(u) du \quad (\text{A.14})$$

And define

$$S_q(t) = \exp(-H_q(t)) \quad (\text{A.15})$$

The cumulative incidence function or the sub-distribution function for death is defined as:

$$I_q(t) = P(T \leq t, D = q) = \int_0^t h_q(u) S_q(u) du \quad (\text{A.16})$$

This function is sub-distribution since the cumulative probability of death is always below one, that is, $I_q(\infty) = P(D = q) < 1$. The model specification would be:

$$h_q(t) = \frac{d \log(1 - I_q(t))}{dt}$$

is considered the sub-distribution hazard and the model is expressed as

$$h_q(t / \mathbf{Z}) = h_{q,0}(t) \exp(\boldsymbol{\beta}_q \mathbf{Z}^T) \quad (\text{A.17})$$

where $h_{q,0}$ defines the baseline sub-distribution hazard of a cause q , and the vector $\boldsymbol{\beta}_q$ represents the effects of the covariate of cause q . To estimate the unknown $\boldsymbol{\beta}_q$ parameters, we maximize the following log-pseudo likelihood function:

$$\log L(\beta | D_{obs}) = \sum_{i=1}^n \delta_i w_i \left[\mathbf{Z}_i^T \beta + \text{offset}_i - \log \left\{ \sum_{k \in R_i} w_i \alpha_{ik} \exp(\mathbf{Z}_k^T \beta + \text{offset}_k) \right\} \right] \quad (\text{A.18})$$

where δ_i is death for an i th individual, R_i is the set of observations, q at risk at time t_i . The only difference with the Cox is the α_{ik} weights. These weights keep individuals who experience the competing event to be in subsequent risk sets and to reduce their weight over time; hence, their likelihood of being censored increases.

4.8.7. A7: Hazard ratio plots for the different survival models fitted on complete case data and imputed time to LTFU data

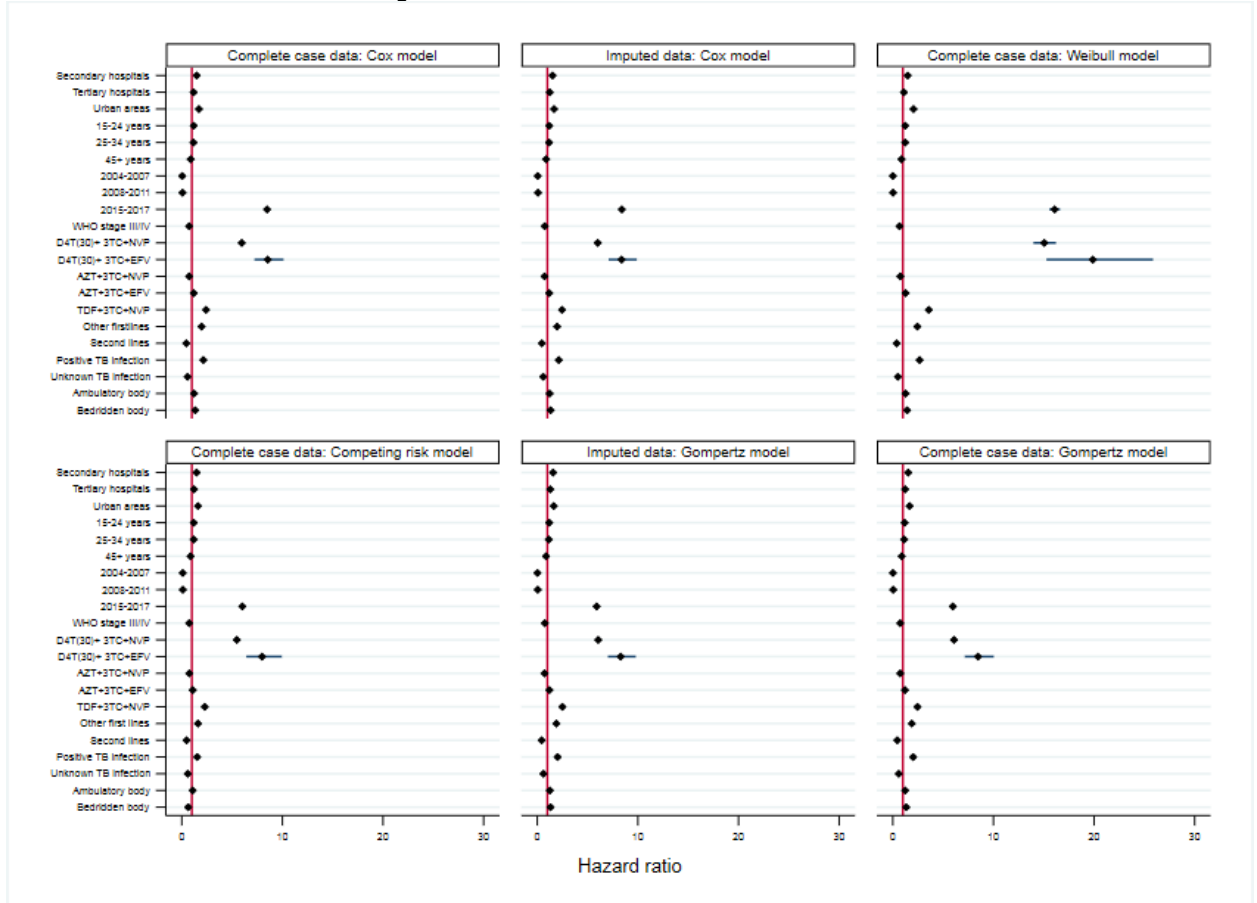


Figure A1: Hazard ratio plots for the different survival models fitted on the complete case data and imputed time to becoming LTFU data among ART patients.

CHAPTER 5

In HIV disease monitoring, quantifying the time to occurrence of ART outcomes like becoming LTFU which is a significant contributor of ART attrition is important in addition to knowing the ART spatial distribution patterns. HIV-related death also contributes to patients' attrition within an ART program; therefore, it is imperative to have an in-depth understanding of the patients' disease progression patterns before the occurrence of an adverse event which could be death. This chapter presents findings on the HIV disease progression patterns among ART patients using maximum likelihood multistate models. The intermediate states of the 5-staged multistate model were defined based on CD4 cell counts, one of the prognostic markers commonly used in low and middle-income countries in HIV monitoring. The implemented model helps to identify the most occurring transition process; the CD4 cell counts level most likely to result in immune deterioration or death, the subpopulation group most at risk of death or immune deterioration defined by gender, age and health facility type. This chapter only considered those patients who had repeated CD4 cell counts measurements.

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5. HIV DISEASE PROGRESSION AMONG ART PATIENTS IN ZIMBABWE: A MULTISTATE MARKOV MODEL

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5.1. Abstract

Background: Antiretroviral therapy (ART) impact has prolonged survival of people living with HIV. We evaluated HIV disease progression among ART patients using routinely collected patient-level data between 2004 and 2017 in Zimbabwe.

Methods: We partitioned HIV disease progression into four transient CD4 cell counts states: State 1($CD4 \geq 500 \text{ cells/uL}$), State 2($350 \text{ cells/uL} \leq CD4 < 500 \text{ cells/uL}$), State 3($200 \text{ cells/uL} \leq CD4 < 350 \text{ cells/uL}$), State 4($CD4 < 200 \text{ cells/uL}$) and the absorbing state death (State 5). We proposed a semi-parametric time-homogeneous Multistate Markov model to estimate bidirectional transition rates. Covariate effects (age, gender, ART initiation period and health facility level) on the transition rates were assessed.

Results: We analysed 204,289 clinic visits by 63,422 patients. There were 24,325 (38.4%) patients in State 4($CD4 < 200$) at ART initiation and 7,995 (12.6%) deaths occurred by December 2017. The overall mortality rate was 3.9 per 100 person-years. The highest mortality rate of 5.7 per 100 person-years (4,541 deaths) was from State 4($CD4 < 200$) compared to other states. Mortality rates decreased with increase in the time since ART initiation. Health facility type was the strongest predictor for immune recovery. Provincial or central hospital patients showed a diminishing dose-response effect on immune recovery by state from a hazard ratio(HR) of 8.30 (95%CI: 6.64-10.36) [State 4 to 3] to HR 3.12(95%CI: 2.54-4.36) [State 2 to 1] compared to primary health care (PHC) facilities. The immune system for males was more likely to deteriorate, and they had a 32% increased mortality risk [HR 1.32; 95%CI: 1.23-1.42] compared to females. Elderly patients (45+ years) were more likely to immune deteriorate compared to 25-

34 years age-group: HR 1.35; 95%CI: 1.18-1.54, HR 1.56; 95%CI: 1.34-1.81 and HR 1.53; 95%CI: 1.32-1.79 for State 1 to 2, State 2 to 3 and State 3 to 4, respectively.

Conclusion: Immune recovery was pronounced among provincial or central hospitals. Male patients with lower CD4 cell counts were at a higher risk of immune deterioration and mortality, while elderly patients were more likely to immune deteriorate. Early therapeutic interventions when the immune system is relatively stable across gender and age may contain mortality and increase survival outcomes. Interventions which strengthen ART services in PHC facilities are essential.

Keywords: ART, disease progression, HIV, mortality, Multistate Markov models, Zimbabwe

5.2. Introduction

Over the last 15years, remarkable strides have been made to tackle the Human Immunodeficiency Virus (HIV) pandemic globally. Sub-Saharan Africa (SSA) region is disproportionately affected by the epidemic accounting for more than 50% of people living with HIV (PLHIV) (143,144). Antiretroviral therapy (ART) treatment remains the backbone of HIV treatment and prevention. Globally, it was estimated that 59% of PLHIV were receiving ART in 2017(144).

Zimbabwe is one of the countries in SSA affected by HIV infection. The country had an estimated 1.3 million PLHIV and an adult prevalence of 13.3% in 2017 (8). The country's ART coverage was estimated at 84% for adult patients in the same year (8). There has been a reduction in the number of new HIV infections and HIV related deaths between 2010 to 2016 (145), and this can be attributed to ART as the main driver. ART drugs help boost the immune

system of the PLHIV (146), which leads to viral load suppression, and an increase in CD4 cell counts. Both CD4 cell counts and viral load are key prognostic markers in measuring HIV disease progression (119). World Health Organization (WHO) recommends the use of viral load in monitoring HIV disease progression amongst ART patients. Viral load suppression has been incorporated as one of the ultimate indicators in the UNAIDS 90-90-90 fast track targets (1). However, over the years, CD4 cell counts have been extensively used as a marker for HIV disease progression.

Disease progression and immune recovery can be evaluated using either time homogeneous or time inhomogeneous semi-parametric multistate Markov models using CD4 cell counts (147). Application of these models in the assessment of HIV progression has been used in the past decades (38), and many studies have recently employed them (38,40,41,77,88,148). The use of CD4 cell counts as a prognostic marker for HIV disease progression has been well documented (41,43,45,64,148). However, across studies, there is variation in terms of the number of discrete multistate model states, the cut-off points defining each state, the type of transitions which can either be reversible or irreversible and the number of transitions to be estimated.

In this new era of “test and treat all” regardless of CD4 cell counts, HIV patients are initiated on ART as soon as they are tested positive. However, this does not rule out the possibility of having patients who present late for HIV diagnosis with an advanced immune deterioration. This put forward the importance of understanding the HIV disease progression across all possible disease states since patients are initiated on ART with different immune stages. Once the HIV-infected patients are started on ART, they are still exposed to different factors which may even affect their ART adherence. Therefore, it is important to understand the different trajectories patients follow in HIV disease progression to inform policymakers on possible interventions to be done

and encourage the patients on the need to adhere on ART for their improved health outcomes, all in the quest to achieve zero HIV incidences by 2030 (26).

Zimbabwe adopted the WHO recommendation on the decentralization of ART services from higher levels of care to primary health care (PHC) facilities to increase ART coverage, access and uptake to those in need; and increase ART patients retention. This approach resulted in lessening the work burden in the higher levels of care (17) through task shifting of HIV management and ART service cascading down to PHC facilities (16,27,149,150). As a result, the ART sites in Zimbabwe increased from 282 in 2008 to 1556 in 2017 (8). However, in primary health care, patient turn-around time is increased, there is a lack of resources and skilled personnel, which may compromise the quality of service delivery; consequently, ART outcomes are compromised. Therefore, there is a gap to understand HIV progression patterns amongst ART patients after ART decentralization since the health facility type a patient is enrolled in may influence their progression or recovery patterns.

This study aims to describe HIV disease progression and immune recovery implementing the multistate model approach based on CD4 cell counts intermediate states amongst adult patients on ART in Zimbabwe using patient-level data adjusting for the health facility type. The multistate model provides an in-depth understanding of the general immune deterioration (decrease in CD4 cell count) patterns, immune recovery (increase in CD4 cell count) patterns and death outcome. Unique to this study is the inclusion of the health facility type in the analysis to account for ART services decentralization effect on transition rates.

5.3. Materials and Methods

The study was carried out in Zimbabwe, a country with eight provinces and two metropolitans. The country is land-locked bordered by South Africa, Botswana, Mozambique and Zambia. We conducted a retrospective analysis of cohort data from a sample of PLHIV receiving ART under the Zimbabwe national ART programme. We used individual records from 538 health facilities linked to the electronic patient management system (ePMS) (8). From patients attending these health facilities, all routine clinic visits with CD4 count data were used from 1st January 2004 to 31st December 2017 in this analysis.

We included patients aged 15years and above at ART initiation (baseline) with complete ART initiation dates, gender and subsequent follow-up information from the dataset. We excluded patients with no information on CD4 cell counts and patients with baseline CD4 measurements only. We also excluded patients who were classified as lost to follow-up or who transferred to other health facilities to reduce the complexity of the multistate model. The patients who were alive at the end of the study were right censored at their last clinic visit before 31st December 2017.

We extracted demographic characteristics such as age (15-24 years, 25-34 years, 35-44 years and 45+years), gender and education level (none, primary, secondary, tertiary). We also extracted data on health facility type (primary health care, district, provincial or central hospitals) and time of ART initiation (2004-2007, 2008-2012 and 2013-2017). Clinical characteristics included for analysis were regimen type (first line, second line), WHO clinical staging (WHO I/II, WHO III/IV), tuberculosis status (negative, positive, not assessed) from the routine monitoring records of each visit to the clinic by the patients. HIV disease progression was defined using WHO based

CD4 cell counts bands of HIV-related immunodeficiency: the no significant immunodeficiency ($CD4 \geq 500 \text{ cells/uL}$) as State 1, the mild immunodeficiency ($350 \text{ cells/uL} \leq CD4 < 500 \text{ cells/uL}$) as State 2, the advanced immunodeficiency ($200 \text{ cells/uL} \leq CD4 < 350 \text{ cells/uL}$) as State 3, the severe immunodeficiency ($CD4 < 200 \text{ cells/uL}$) as State 4 and the absorbing state death as State 5.

5.3.1. Statistical analysis

The patient's retrieved data were cleaned and managed in Stata 15.1 (151). All the preliminary analyses were conducted in Stata software. After data argumentation, the 5-staged semi-parametric time-homogeneous multistate Markov model was fitted in R software (152) using the *msm* package. We fitted a model with reversible transitions (39); therefore, State 1, 2, 3 and 4 were transient states while State 5 was non-transient as depicted in **Figure 5-1**.

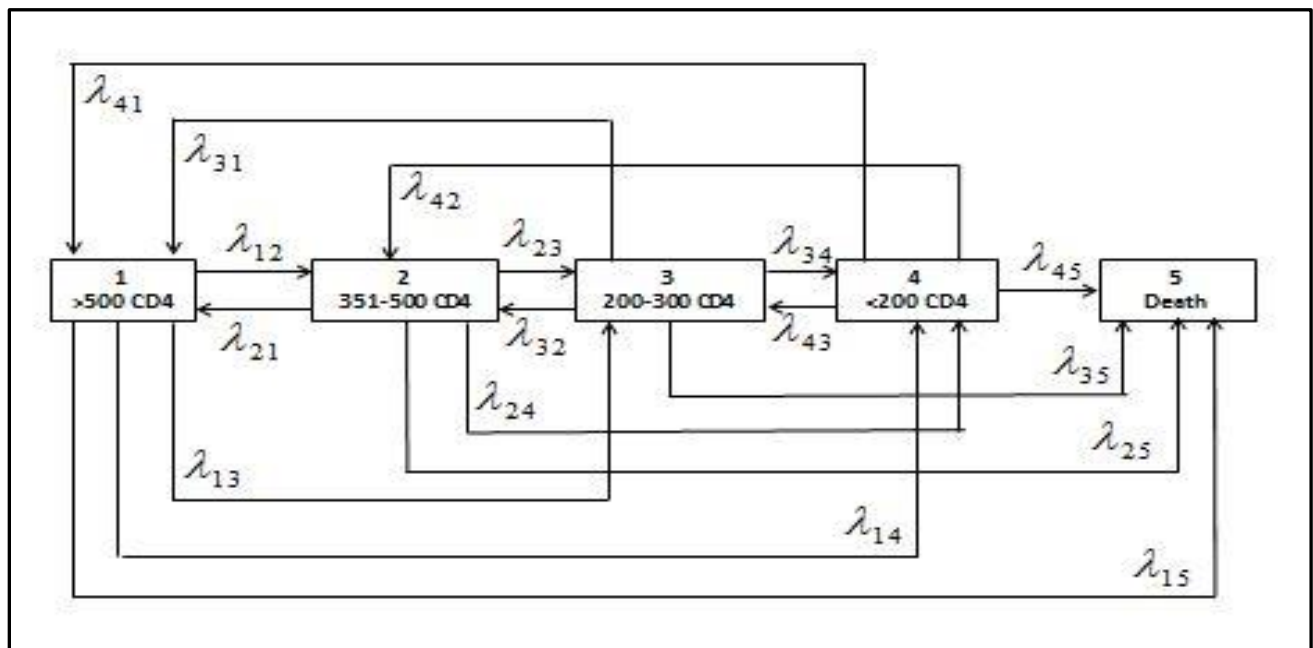


Figure 5-1: Schematic presentation of the 5-staged reversible multistate Markov model with the states of HIV defined as the ranges of CD4 cell counts (cells/uL) and the corresponding individual transition intensities (where $j=1,2,3,4$ and $k=1,2,3,4,5$)

The fitted model was adjusted for demographic factors (sex, health facility type and ART initiation period). The semi-parametric time-homogeneous multistate Markov estimated transition intensities (transition rates or hazard rates), transition probabilities (survival function) between the defined CD4 cell count states, mean sojourn time and the total length of stay in states before making any transitions. Time-varying mortality rates were estimated using the inhomogeneous time model, which assumes that the transitions change with time, and this reflects the reality in infectious disease progression models; hence, this usually is the preferred model. These models generally assume the Markovian process that the transition intensity depends only on the current time and state occupied, i.e. it is independent of the previous transitions. In other terms, these models were assumed to have “memory loss”. We used the *markovchain* library in R to test if the Markov assumption is satisfied. The null hypothesis of this test is that the Markov property holds. We randomly selected patients’ sequences to be tested, and we obtained p-values above 0.05; therefore, we failed to reject the null hypothesis that the sequences are Markovian.

5.3.2. The multistate Markov model

A multistate process is a stochastic process $(X(t), t \in T)$ with finite state space $S = \{1, 2, 3, 4, 5\}$ where $T = [0, \tau]$ $\tau < \infty$ is the period of observation(50). These models can either be discrete-time Markov chains (transitions occur at fixed points in time) or continuous-time Markov chains (transitions occur at any point in time) (61). For a continuous-time Markovian process, the transition intensity (instantaneous incidence rate), $\lambda_{jk}(t)$, of a patient from the state $X(t) = j$ at a time t to state k at the time $t + \delta t$ is defined as:

$$\lambda_{jk}(t) = \frac{d}{dt} p_{jk} \Big|_{t=0} = \lim_{\delta t \rightarrow 0} \frac{p_{jk}(t, t + \delta t) - p_{jk}(t)}{\delta t} = \lim_{\delta t \rightarrow 0} \frac{p_{jk}\{X(t + \delta t) = k \mid X(t) = j\} - p_{jk}(t)}{\delta t} \quad (5.1)$$

where p_{jk} is the probability from state j to k , δt is the change in time. For example, in our case, the transition intensities in Equation (5.1) form the (j, k) transition entry of the transition rate matrix, denoted by $Q(t)$ is given by:

$$Q(t) = \begin{pmatrix} -\lambda_{1\bullet} & \lambda_{12} & \lambda_{13} & \lambda_{14} & \lambda_{15} \\ \lambda_{21} & -\lambda_{2\bullet} & \lambda_{23} & \lambda_{24} & \lambda_{25} \\ \lambda_{31} & \lambda_{32} & -\lambda_{3\bullet} & \lambda_{34} & \lambda_{35} \\ \lambda_{41} & \lambda_{42} & \lambda_{43} & -\lambda_{4\bullet} & \lambda_{45} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

whose rows sum to 0, that is $\sum_{k \in S} \lambda_{jk} = 0$ for all j , and the diagonal entries (interpreted as changes in transition probability) are defined by convention as $\lambda_{jj}(t) = \lambda_{j\bullet} = -\sum_{j \neq k} \lambda_{jk}(t)$ for all $j \in S$.

These transition intensities under the Markov process can be calculated as the product of the flow rate μ_j and the conditional probability of a transition to state k , given a transition is made $j \neq k$ (ρ_{jk}). From the $Q(t)$ values, we can calculate the probability that the next state after state j is state k , for each j and k calculated as $(p_{jk} = -\lambda_{jk} / \lambda_{j\bullet})$. Once the transition intensity matrix is obtained, the transition probability matrix can be obtained using the Chapman-Kolmogorov forward differential equations. The detailed explanation is provided in chapter 5 Appendix section. The probability matrix can be computed from the estimated transition intensities using $P(t) = \exp(Q(t))$ where $(P(t))$ is the transition probability matrix defined as:

$$P(t) = \exp(Q(t)) = \begin{pmatrix} \pi_{11} & \pi_{12} & \pi_{14} & \pi_{14} & \pi_{15} \\ \pi_{21} & \pi_{22} & \pi_{23} & \pi_{24} & \pi_{25} \\ \pi_{31} & \pi_{32} & \pi_{33} & \pi_{34} & \pi_{35} \\ \pi_{41} & \pi_{42} & \pi_{43} & \pi_{44} & \pi_{45} \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

The probability (π_{jk}) that a patient in state j at a time t will be in state k at the time $t + \delta t$ is given by:

$$\pi_{jk}(s, t) = P(X(t + \delta t) = k | X(s) = j) \quad (5.2)$$

where $s, t \in T$ and $s \leq t$. These transition probabilities satisfy the following conditions:

$$(i) \pi_{jk}(t + s) = \sum_{r \in S} \pi_{jr}(t) \pi_{rk}(s) \text{ for all } t \geq 0, s \geq 0 \text{ and } j, k \in S;$$

$$(ii) \sum_{k \in S} \pi_{jk}(t) = 1 \text{ for all } j \in S \text{ and } t \geq 0 \text{ and}$$

$$(iii) \pi_{jk}(t) \geq 0 \text{ for all } j, k \in S \text{ and } t \geq 0.$$

The maximum likelihood procedures (147,153) can be used to estimate these transition intensities as a product of probabilities of transition between observed states, overall individuals $i = 1, 2, \dots, M$ and observation times r which are observed n times, as shown below:

$$L(Q) = \prod_{i=1}^M \prod_{r=1}^{n_i-1} L_{i,j} = \prod_{i,r} \pi_{s(t_{ir})s(t_{i,r+1})}(t_{i,r+1} - t_{ir}) \quad (5.3)$$

Each component $L_{i,r}$ is the entry of the transition probability matrix and the $s(t_{ir})^{th}$ row and the $s(t_{i,r+1})^{th}$ column, evaluated at a pair of consecutive observed state at times t_r and t_{r+1} . This likelihood function, $L(Q)$, is maximum in terms of $\log(\lambda_{jk})$ to compute the estimates of λ_{jk} ,

using the standard optimization algorithms which make use of the derivatives of the likelihood. This likelihood assumes that the sampling times are ignorable (non-informative).

5.3.3. The total length of stay and mean sojourn time

The mean sojourn time is defined as the mean expected holding-time or the average time a patient spends in each state in a single stay before making any transition to other states. The average length of stay in the same state before making any transitions to either lower or higher CD4 cell count states is estimated by a negative inverse of the j^{th} diagonal entry of $Q(t)$, that is $(-1/\lambda_{jj})$. The total length of stay, L_k , in each of the four states excluding death is defined as the anticipated exposure time spent by an individual in each state during the study period before death. This time is estimated as time spent in state k between two successive time points (t_1, t_2) given by:

$$L_k = \int_{t_1}^{t_2} P_{jk}(t) dt \quad (5.4)$$

where j is the initial state which usually is equal to one and is useful in the presence of reversible transitions.

5.3.4. Semi-parametric regression model

To adjust for the effects of the covariates on the transition rates, we proposed a semi-parametric Cox proportional hazard regression model. The transition rates depend on the covariates vector-matrix $\mathbf{Z}$, that is,

$$\lambda_{jk}(t | \mathbf{Z}(t)) = \lambda_{jk0} \exp(\boldsymbol{\beta}_{jk}^T \mathbf{Z}(t)) \quad (5.5)$$

where $\boldsymbol{\beta}_{jk} = (\beta_{jk1}, \beta_{jk2}, \dots, \beta_{jkz})^T$ is a vector of the regression coefficients associated with vector $\mathbf{Z}(t)$ for the transition from state j to state k . The baseline hazard function is denoted by λ_{jk0} . In this study, we assumed time-independent covariates. Parameter estimation was based on the maximization of the hazard function (the transitional intensities). We fitted eight models in total (starting with a no covariates (unadjusted) model, followed by four univariate models and three with at least two covariates). The additional covariates after the univariate models were added sequentially and only covariates without missing information were considered in the adjusted model.

5.3.5. Model diagnostics

Selection of model of best fit with covariates was done using a likelihood ratio test (LRT) defined as $-2\ln(L_s(\hat{\theta}) / L_g(\hat{\theta}))$; where $L_s(\hat{\theta})$ is the likelihood of the reduced (no covariate) model $L_g(\hat{\theta})$ and is the likelihood of the full (with covariates) model which follows a Chi-square distribution with n degrees of freedom. Significance was set at 5% level of significance. The aim was to get a parsimonious model that explains best the model.

5.3.6. Ethical considerations

We used data with no personal identification; however, we used the individual unique identifier for the analysis. We sort permission to use the dataset from the Ministry of Health and Child Care, Zimbabwe and this study was granted ethical approval by the University of Witwatersrand's Human Research Ethics Committee (Medical) (Clearance Certificate No. M170673).

5.4. Results

5.4.1. Descriptive characteristics of patients and total transitions observed

From the 538 clinics, a total of 390,771 patients were seen between 1st January 2004 and 31st December 2017. Of these total patients, we excluded 197,618(50.6%) patients with no CD4 cell counts and 129,731(33.2%) patients with one CD4 cell count measurement. The remaining 63,422 patients of whom 65.4% were females contributed 205,711 years of total analysis time at risk and under observation from 491 health facilities form part of the analysis. The descriptive characteristics are shown in **Table 5-1**. Most patients were enrolled in district or mission hospitals (45.7 %) and from facilities in the rural areas (74.7 %). There was an overwhelming significant difference in the baseline characteristics by CD4 count states in this cohort, P-value<0.05. The median follow-up time was 2.63(interquartile range (IQR) 1.14-4.94) years, median duration between visits was 0.63 (IQR 0.25-1.88) years, and the median number of the visit was 3 (IQR 2-4) visits. Most patients were classified in WHO clinical stage III/IV (58.6%, n=36,626).

Table 5-1: Sociodemographic and clinical baseline characteristics at ART initiation of all study participants from the Zimbabwe national ART program, 2004-2017

Variables	Total (%)	Baseline CD4 states for patients				Chi-square p-value
		<200	200≤CD4<350	350≤CD4<500	≥500	
Health facility type						
Primary Health Care	31 150(49.1)	4 989(44.4)	4 801(51.0)	9 223(50.0)	12 137(49.9)	<0.0001
District /Mission hospital	28 971(45.7)	5 465(48.6)	4 141(44.0)	8 401(45.6)	10 964(45.1)	
Provincial/Central hospital	3 301(5.2)	790(7.0)	474(5.0)	813 (4.4)	1 224(50.3)	
Health facility site						
Rural	47 348(74.7)	8 401(74.7)	7 256(77.1)	14 109(76.5)	17 582(72.3)	<0.0001
Urban	16 074(25.3)	2 843(25.3)	2 160(22.9)	4 328(23.5)	6 743(27.7)	
Age categories (years)						
15-24	3 960 (6.2)	933 (8.3)	671 (7.1)	1 162 (6.3)	1 194 (4.9)	<0.0001
25-34	17 352(27.4)	3 347(29.8)	2 757(29.3)	5 158(28.0)	6 090(25.0)	
35-44	4 060(36.1)	3,447(36.6)	6 843(37.1)	9 842(40.5)	24 192(38.1)	
45 and above	17 918(28.3)	2 904(25.8)	2 541(27.0)	5 274(28.6)	7 199(29.6)	
Sex						
Female	41 505(65.4)	9 068(80.7)	6 508(69.1)	12 027(65.2)	13 902(57.2)	<0.0001

Male	21 917(34.6)	2 176(19.3)	2 908(30.9)	6 410(34.8)	10 423(42.8)	
Educational level*						
None	1 499 (4.4)	266 (4.7)	250 (4.9)	445 (4.5)	538 (4.1)	
Primary	11 804(34.9)	1 996(35.2)	1 782(34.9)	3 501(35.3)	4 525(34.4)	
Secondary	18 956(56.0)	3 124(55.0)	2 843(55.6)	5 552 (56.0)	7 437(56.5)	<0.027
Tertiary	1 598(4.7)	290 (5.1)	263 (4.6)	419 (4.2)	653 (5.0)	
Marital status**						
Single	7 604 (12.4)	1 276 (11.8)	1 144 (12.5)	2 095 (11.7)	3 089 (13.1)	
Married	37 993(62.0)	6 580 (60.7)	5 680 (62.3)	11 460 (64.2)	14 273(60.7)	
Widowed	11 243(18.3)	2 250(20.7)	1 643(18.0)	3 083(17.3)	4 267(18.2)	<0.0001
Divorced	4 494(7.3)	741(6.8)	655(7.1)	1 216(6.8)	1 882(8.0)	
Functional status***						
Working	59 519(94.5)	10 685(95.5)	8 963(94.7)	17 373(94.9)	22 598(93.6)	
Ambulatory	3 270 (5.2)	494 (4.4)	477 (5.1)	877 (4.8)	1 422 (5.9)	<0.0001
Bedridden	193 (0.3)	11 (0.1)	21 (0.2)	43 (0.2)	118 (0.5)	
First line regimen	61 654(97.2)	11 056(98.3)	9 264(98.4)	18 082(98.1)	23 252(95.6)	
D4T(30)+ 3TC+ NVP	389 (0.6)	11(0.0)	18 (0.2)	91 (0.5)	269 (1.1)	
D4T(30)+ #TC+EFV	11 (0.0)	1 (0.0)	1 (0.0)	3 (0.0)	6 (0.0)	
AZT+3TC+NVP	486 (0.8)	91 (0.8)	59 (0.6)	150 (0.8)	186 (0.8)	
AZT+3TC+EFT	82 (0.1)	13 (0.1)	10 (0.1)	17 (0.1)	42 (0.2)	<0.0001
TDF+3TC+NVP	2 919 (4.6)	303 (2.7)	255 (2.7)	907 (4.9)	1 454 (6.0)	
TDF+3TC+EFV	57 085(90.0)	10 358(92.1)	8 841(93.9)	16 807(91.2)	21 079(86.7)	
Other first lines	682(1.1)	279 (2.5)	80 (0.9)	107 (0.6)	216 (0.9)	
Second line regimen	1 768 (2.8)	188 (1.7)	152 (1.6)	355 (1.9)	1 073 (4.4)	
AZT+3TC+ATV/r	560 (0.9)	374 (1.5)	107 (0.6)	41 (0.4)	38 (0.3)	
AZT+3TC+LPV/r	84 (0.1)	48 (0.2)	15 (0.1)	7 (0.1)	14 (0.1)	
TDF+3TC+ATV/r	563 (0.9)	275 (1.1)	131 (0.7)	70 (0.7)	87 (0.8)	
TDF+3TC+LPV/r	89 (0.1)	49 (0.2)	21 (0.1)	7 (0.1)	12 (0.1)	
ABC+DDI+ATV/r	73 (1)	50 (0.2)	13 (0.1)	7 (0.1)	3 (0.0)	
ABC+DDI+LPV/r	389 (0.6)	273 (1.1)	69 (0.4)	19 (0.2)	37 (0.3)	
Other second line	683 (1.1)	220 (0.9)	106 (0.6)	81 (0.9)	276 (2.5)	
Tuberculosis status****						
Negative	54 474(87.0)	9 869(88.6)	8 172(87.7)	15 830(86.9)	20 603(86.0)	
Positive	618 (1.0)	48 (0.4)	56 (0.6)	140 (0.8)	374 (1.6)	<0.0001
Not assessed	7 524 (12.0)	1 220 (11.0)	1 090 (11.7)	2 240 (12.3)	2 974 (12.4)	
WHO clinical staging*****						
I/II	25 891(41.4)	4 680(42.0)	4 277(46.0)	8 322(45.9)	8 612(36.0)	
III/IV	36 626(58.6)	6 460(58.0)	5 012(54.0)	9 826(54.1)	15 328(63.0)	<0.0001

* The denominator of the proportions for this variable is 33,857; **The denominator of the proportions for this variable is 61,334; ***The denominator of the proportions for this variable is 62,982; ****The denominator of the proportions for this variable is 62,616; *****The denominator of the proportions for this variable is 62,517

5.4.2. Observed transitions between states

As displayed in **Table 5-2**, the 63,422 patients contributed 140,867 transitions between the follow-up period, of which 12.6% (n=7,995) were mortalities. The highest contribution of the observed transitions of 114,561(81.3%) came from those patients who remained in the same state over time without making any transition to other states.

Table 5-2: Number of the total observed patients' transitions between the five states, the total number of patients at ART initiation ("beginning state") and the total number of patients at 31st Dec 2017 (and the "end state") among ART patients in Zimbabwe

A summary of the total observed patients’ transition between the five states							
	To	State 1 (>500 cell/uL)	State 2 (351-500 cells/uL)	State 3 (200-350cells/uL)	State 4 (<200 cells/uL)	State 5 (Death)	Total Transitions
From							
State 1 (>500 cell/uL)		24 709	1 971	1 639	1 396	606	30 321
State 2 (351-500 cells/uL)		2 493	17 169	1 691	1 134	640	23 127
State 3 (200-350cells/uL)		3 459	2 606	28 645	1 763	2 208	38 681
State 4 (<200 cells/uL)		2 879	2 343	2 932	36 043	4 541	48 738
Total		33 540	24 089	34 907	40 336	7 995	140 867
Total number of patients by CD4 state at ART initiation and the end of follow-up (Denominator=63 422)							
Beginning state n (%)		11 244 (17.7)	9 416 (14.9)	18 437(29.1)	24 325 (38.4)	-----	63 422
End state n (%)		14 463 (22.8)	10 378 (16.4)	14 663 (23.1)	15 923 (25.1)	7 995 (12.61)	55 427 (Alive) 7 995 (Dead)

At baseline, majority of the patients were in State 4($CD4 < 200$) (38.4%, $n=24,325$) and State 3($200 \leq CD4 < 350$) (29.1%, $n=18,437$). Similarly, this was the picture at the end of the study; however, relative to baseline numbers, there was a non-significant decline in the total number of patients in State 3($200 \leq CD4 < 350$) (P-value=0.2621) while a significant decline was observed in State 4(P-value=0.0478). Majority of the deaths at the end of the study came from State 4($CD4 < 200$) and State 3($200 \leq CD4 < 350$) which accounted for 27.6% ($n=2,208$) and 56.8% ($n=4,541$), respectively.

Immune recovery is observed when a patient makes a transition from lower CD4 cell counts states to higher CD4 cell counts states (particularly $350 \leq CD4 < 500$ State to $CD4 \geq 500$ State, $200 \leq CD4 < 350$ State to $350 \leq CD4 < 500$ State and $CD4 < 200$ State 4 to $200 \leq CD4 < 350$ State) while immune deterioration is experienced if a patient makes a transition from higher CD4 cell count states to lower CD4 cell count states (particularly $CD4 \geq 500$ State to $350 \leq CD4 < 500$ State, $350 \leq CD4 < 500$ State to $200 \leq CD4 < 350$ State and $200 \leq CD4 < 350$ State to $CD4 < 200$ State). There were more transitions ($n=8,031$) from lower CD4 cell counts states to higher CD4 cell counts states (State 2 to 1=2,493, State 3 to 2=2,606 and State 4 to 3=2,932) as compared to higher CD4 cell counts states to lower CD4 cell count states transitions of the corresponding reversible transitions ($n=5,425$). This result is an indication of immune recovery in this cohort.

5.4.3. Time homogeneous transition rates and probabilities

The transition rates and probabilities were estimated using the time-homogeneous multistate Markov model incorporating the semiparametric Cox survival function, and results are displayed in **Table 5-3**.

Table 5-3: Estimates of transition rates (intensities) per person-years and probability matrices and 95% confidence intervals (CI) for the time-homogeneous multistate Markov model among ART patients in Zimbabwe national ART from 2004 to 2017

Transitions	Crude transition intensity (95% CI)	Covariates adjusted transition intensity (95% CI)	Transition probabilities (95% CI)	The probability that each state is next
1 → 1	-0.26548 (-0.273 to -0.258)	-0.26950 (-0.278 to -0.261)	0.779 (0.772,0.784)	0
1 → 2	0.10928 (0.104 to 0.115)	0.10783 (0.102 to 0.114)	0.083 (0.08 to 0.086)	0.41162 (0.397 to 0.427)
1 → 3	0.07823 (0.074 to 0.083)	0.08184 (0.0772 to 0.087)	0.067 (0.063 to 0.070)	0.29468 (0.280 to 0.309)
1 → 4	0.05980 (0.056 to 0.063)	0.06313 (0.059 to 0.067)	0.052 (0.050 to 0.055)	0.22526 (0.214 to 0.238)
1 → 5	0.01817 (0.016 to 0.021)	0.01669 (0.014 to 0.019)	0.020 (0.018 to 0.022)	0.06844 (0.061 to 0.077)
2 → 1	0.18073 (0.173 to 0.189)	0.16085 (0.153 to 0.169)	0.136 (0.132 to 0.142)	0.45731 (0.443 to 0.472)
2 → 2	-0.39520 (-0.406 to -0.384)	-0.37098 (-0.382 to -0.360)	0.686 (0.679 to 0.692)	0
2 → 3	0.11767 (0.112 to 0.124)	0.11264 (0.106 to 0.119)	0.092 (0.088 to 0.096)	0.29775 (0.285 to 0.312)
2 → 4	0.06960 (0.065 to 0.074)	0.07160 (0.067 to 0.077)	0.058 (0.055 to 0.061)	0.17613 (0.165 to 0.186)
2 → 5	0.02719 (0.024 to 0.031)	0.02589 (0.023 to 0.029)	0.027 (0.025 to 0.030)	0.06881 (0.061 to 0.077)
3 → 1	0.09501 (0.091 to 0.099)	0.08428 (0.080 to 0.088)	0.080 (0.077 to 0.083)	0.35266 (0.340 to 0.365)
3 → 2	0.08723 (0.083 to 0.091)	0.08188 (0.078 to 0.086)	0.068 (0.065 to 0.071)	0.32376 (0.312 to 0.336)
3 → 3	-0.26942 (-0.276 to -0.263)	-0.24886 (-0.256 to -0.243)	0.772 (0.768 to 0.776)	0
3 → 4	0.05397 (0.051 to 0.057)	0.05147 (0.049 to 0.055)	0.047 (0.045 to 0.045)	0.20032 (0.190 to 0.210)
3 → 5	0.03321 (0.031 to 0.035)	0.03122 (0.029 to 0.034)	0.032 (0.031 to 0.034)	0.12325 (0.116 to 0.131)
4 → 1	0.04814 (0.046 to 0.051)	0.04363 (0.041 to 0.046)	0.044 (0.042 to 0.045)	0.22794 (0.218 to 0.238)
4 → 2	0.04584 (0.044 to 0.048)	0.04360 (0.041 to 0.046)	0.038 (0.036 to 0.040)	0.21708 (0.207 to 0.228)
4 → 3	0.05793 (0.055 to 0.061)	0.05261 (0.050 to 0.055)	0.049 (0.048 to 0.051)	0.27430 (0.263 to 0.285)
4 → 4	-0.21118 (-0.215 to -0.207)	-0.19535 (-0.200 to -0.191)	0.814 (0.810 to 0.817)	0
4 → 5	0.05928 (0.057 to 0.061)	0.05551 (0.053 to 0.058)	0.055 (0.053 to 0.057)	0.28069 (0.272 to 0.290)

Generally, there were higher transition rates from lower CD4 cell count states to lower CD4 cell counts states compared to the corresponding reversible transitions. Results show that moving from State 2($350 \leq \text{CD4} < 500$) to State 1($\text{CD4} \geq 500$) was 1.49(0.16085/0.10783) times more likely

than moving from State 1($CD4 \geq 500$) to 2($350 \leq CD4 < 500$); hence, a high probability of immune recovery. Patients in State 2($350 \leq CD4 < 500$) were 1.38(0.11264/0.08188) times more likely to move to State 3($200 \leq CD4 < 350$) compared to moving from State 3($200 \leq CD4 < 350$) to State 2($350 \leq CD4 < 500$). This finding was a clear indication of immune deterioration between the two states. Transition rate from State 4($CD4 < 200$) to State 3($200 \leq CD4 < 350$) was 1.02(0.05261/0.05147) times more likely compared to the transition from State 3($200 \leq CD4 < 350$) to State 4($CD4 < 200$) indicating immune recovery from State 4($CD4 < 200$), but this was not statistically significant.

We estimated the probabilities for which state is next after the currently occupied state. The results show that an individual in State 1($CD4 \geq 500$) had a probability of 41.2% to move to State 2($350 \leq CD4 < 500$); an individual in State 2($350 \leq CD4 < 500$) had a 45.7% probability of moving to State 1($CD4 \geq 500$); an individual in State 3($200 \leq CD4 < 350$) had 35.3% probability of moving to State 1($CD4 \geq 500$); and an individual in State 4($CD4 < 200$) had 28.1% probability of death. The cumulative probability of moving from higher CD4 cell counts states to lower CD4 cell counts states increased over time.

The probability of moving from State 1($CD4 \geq 500$) to State 2($350 \leq CD4 < 500$) changed from 8.3% at 1year to 16.2% at 6years; State 2($350 \leq CD4 < 500$) to State 3($200 \leq CD4 < 350$) transition changed from 9.2% at 1year to 20.2% at 6years and State 3($200 \leq CD4 < 350$) to State 4($CD4 < 200$) transition changed from 4.7% at 1year to 15.3% at 6years. Similarly, the probabilities of moving from lower CD4 cell counts states to higher CD4 cell counts states increased over time. The probability of moving from State 2($350 \leq CD4 < 500$) to State 1($CD4 \geq 500$) changed from 13.6% at 1year to 26.2% at 6years; State 3($200 \leq CD4 < 350$) to State 2($350 \leq CD4 < 500$) transition changed from 6.8% at 1year to 14.7% at 6years and State

4(CD4<200) to State 3(200≤CD4<350) transition changed from 4.5% at 1year to 14.5% at 6years.

5.4.4. Time inhomogeneous mortality rates

The transition rates for mortality were also estimated, and results are shown in **Table 5-4**. The overall mortality rate in this cohort was 3.9 (95%CI: 3.8-4.0) per 100 person-year. Stratifying by the CD4 states, the mortality rates per 100 person-years increased with a decrease in CD4 cell counts: State 1(CD4≥500) (rate=1.8, 95%CI: 1.1-2.1), State 2(350≤CD4<500) (rate= 2.7, 95%CI: 2.4-3.1), State 3(200≤CD4<350) (rate=3.3, 95%CI: 3.1-3.8) and State 4(CD4<200) (rate=5.9, 95%CI: 5.7-6.1). Hence, the mortality burden was highest in State 4(CD4<200) compared to other states, and these mortality rates were significantly different (Log-rank test P-value<0.001).

Table 5-4: Estimated time-varying mortality rates per person-years and 95% confidence intervals for the time-inhomogeneous multistate Markov model among ART patients in Zimbabwe national ART from 2004 to 2017

Time	Time-varying transition rates (95% confidence interval)					
	Overall Mortality rate	State 1to5	State 2to5	State 3to5	State 4to5	Log-rank p-value
0<time≤1	0.3512 (0.3368- 0.3661)	0.1006 (0.0863- 0.1172)	0.1490 (0.1292-0.1719)	0.2790 (0.2534- 0.3071)	0.7609 (0.7225- 0.8013)	<0.0001
1<time≤2	0.0505 (0.0472- 0.0540)	0.0186 (0.0147- 0.0234)	0.0291 (0.0239- 0.0355)	0.0383 (0.0330- 0.0444)	0.1010 (0.0925- 0.1102)	<0.0001
2<time≤3	0.0591 (0.0563- 0.0621)	0.0245 (0.0206- 0.0290)	0.0287 (0.0244- 0.0338)	0.0687 (0.0632- 0.0747)	0.0885 (0.0825- 0.0950)	<0.0001
3<time≤4	0.0416 (0.0392-0.0441)	0.0200 (0.0162- 0.0247)	0.0186 (0.0148- 0.0233)	0.0441 (0.0400- 0.0486)	0.0581 (0.0535- 0.0631)	<0.0001
4<time≤5	0.0312 (0.0291-0.0334)	0.0135 (0.010-0.0179)	0.0162 (0.0121-0.0217)	0.0312 (0.0277-0.0351)	0.0412 (0.0375-0.0453)	<0.0001
5<time≤6	0.0221 (0.0204-0.0240)	0.0076 (0.0053-0.0109)	0.0133 (0.0099-0.0180)	0.0214 (0.0185-0.0247)	0.0310 (0.0278-0.0346)	<0.0001
6<time≤7	0.0160 (0.0145-0.0178)	0.0079 (0.0057-0.0111)	0.0092 (0.0061-0.0137)	0.0160 (0.0133-0.0193)	0.0215 (0.0188-0.0247)	<0.0001

7<time≤8	0.0112 (0.0097-0.0128)	0.0041 (0.0025-0.0066)	0.0052 (0.0029-0.0095)	0.0117 (0.0088-0.0155)	0.0159 (0.0134-0.0189)	<0.0001
8<time≤9	0.0108 (0.0092-0.0128)	0.0050 (0.0030-0.0083)	0.0044 (0.0021-0.0093)	0.0132 (0.0094-0.0186)	0.0142 (0.0116-0.0175)	<0.0001
9<time≤10	0.0070 (0.0055-0.0089)	0.0014 (0.0005-0.0044)	0.0019 (0.0048-0.0076)	0.0082 (0.0049-0.0136)	0.0103 (0.0077-0.0138)	0.0001
10<time≤11	0.0066 (0.0050-0.0088)	0.0021 (0.0008-0.0056)	0.0021 (0.0005-0.0084)	0.0072 (0.0036-0.0145)	0.0104 (0.0074-0.0147)	0.0005
11<time≤12	0.0034 (0.0020-0.0058)	0.0015 (0.0004-0.0061)	0.0046 (0.0012-0.0184)	0.0066 (0.0025-0.0176)	0.0033 (0.0014-0.0080)	0.2154
12<time≤13	0.0030 (0.0011-0.0081)	0.0058 (0.0014-0.0230)	0	0.0031 (0.0004-0.0220)	0.0021 (0.0003-0.0151)	0.7305

The Kaplan-Meier curve further confirmed the survival probabilities of this cohort stratified by state, that mortality risk increase with a decrease in CD4 cell count, **Figure 5-2**. However, the fundamental difference was between the mortality in State 3($200 \leq \text{CD4} < 350$) and State 4($\text{CD4} < 200$) versus the mortality in State 1($\text{CD4} \geq 500$); and State 2($350 \leq \text{CD4} < 500$).

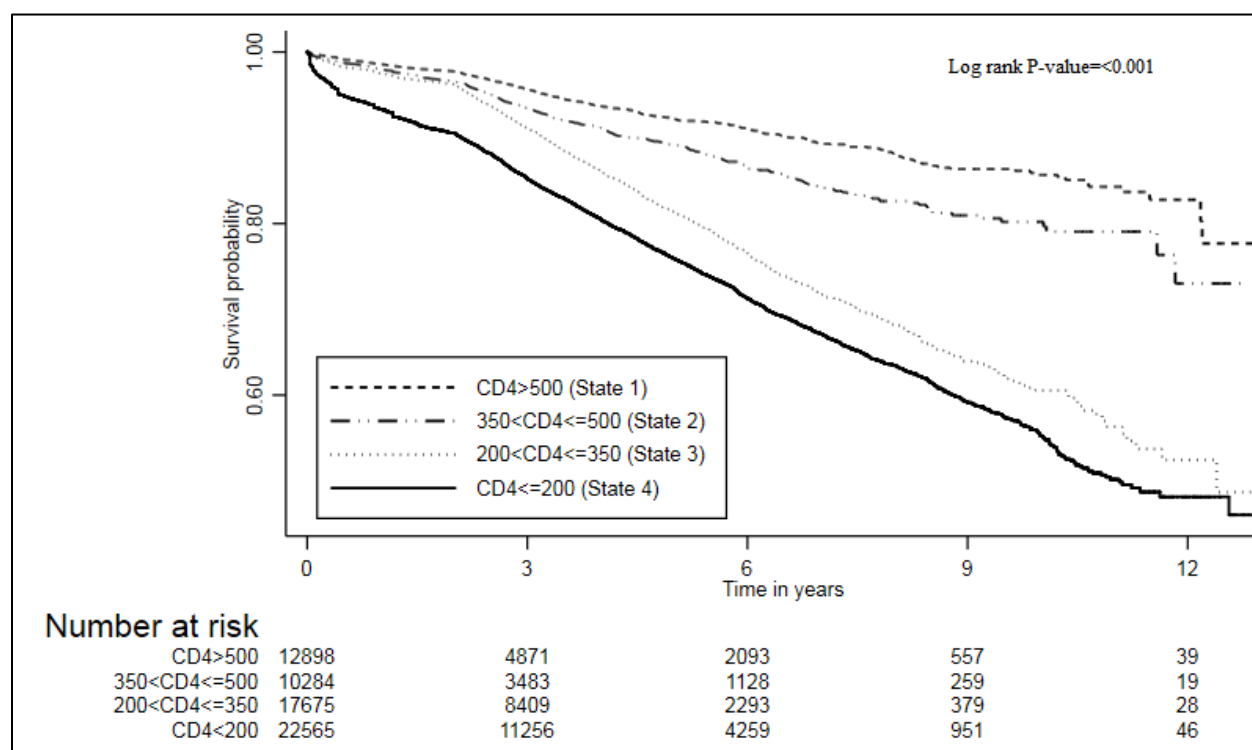


Figure 5-2: The survival plot of ART patients from the Zimbabwe national ART programme stratified by CD4 cell counts states, 2004 -2017

In general, the time-varying mortality rates decrease with an increase in the time since ART. The cohort experienced high mortality rates in the first year of ART initiation averaging at 3.5 (95%CI: 3.4-3.7) per 100 person-years. There was a sharp drop (7 folds) in mortality rate from first to the second year (hazard ratio (HR)=6.95[0.3512/0.0505], 95%CI 6.78-7.14). Gradually, the mortality rates further decrease over time by the end of the follow-up period. Mortality patterns across states followed this similar trend to the overall pattern. In the first 3years, mortality rates had an inverse relationship with the CD4 cell counts, and there was an overwhelming difference in these rates between the states.

This study forecasted the total length spent in each of the CD4 states by HIV patients on ART before death and estimated the mean sojourn (holding) time for each state, as shown in **Table 5-5**.

Table 5-5: Estimates of mean sojourn time and the total length of stay for the time-homogeneous multistate Markov model among ART patients in Zimbabwe national ART from 2004 to 2017

States	Mean sojourn time		The total length of stay (years)
	Estimate (95% CI)(years)	Standard error	
State 1 (>500 cell/uL)	3.77 (3.66 to 3.88)	0.054	11.33
State 2 (351-500 cells/uL)	2.53 (2.46 to 2.60)	0.036	5.51
State 3 (200-350cells/uL)	3.71 (3.63 to 3.80)	0.042	7.17
State 4 (<200 cells/uL)	4.74 (4.64 to 4.82)	0.047	6.86

The results show that when an individual enters State 4($CD4 < 200$), the time he or she spends in this state for a single stay before moving to another state was estimated to be 4.74(4.64 -4.83) years on average. This result could be linked to the time taken by a patient in this state to respond to ART and subsequently boost immunity since this is the worst state in our HIV progression model. Since the holding times for all states are relatively long; therefore, HIV disease progression in this cohort was relatively slow.

It was also of interest to forecast the total length of stay for State 1, 2, 3 and 4 before death which is and quite informative in the presence of reversible transitions. The results show that an individual will stay 11.3years in State 1($CD4 \geq 500$), 5.5years in State 2($350 \leq CD4 < 500$), 7.2years in State 3($200 \leq CD4 < 350$) and 6.9 years in State 4($CD4 < 200$) before death. In general, these results reflected that an HIV patient on ART is expected to spend more time in the highest CD4 cell counts state compared to other states.

5.4.5. Covariates effects on immune recovery and deterioration transition rates

We further included time-independent covariates (health facility level, ART initiation period and sex) and age in the multistate Cox proportional hazard model, and the results are displayed in **Table 5-6**. This model was a better fit using an LRT compared to the model without covariates ($P\text{-value} < 0.001$). Adjusting for other covariates, the higher levels of health facility are more likely to have patients moved from lower to higher CD4 cell count states. Provincial or central hospital individuals were predominantly more likely to move from State 4($CD4 < 200$) to State 3($200 \leq CD4 < 350$) ($HR=8.30$; 95%CI: 6.64-10.36) followed by the State 3($200 \leq CD4 < 350$) to State 2($350 \leq CD4 < 500$) transition ($HR=8.04$; 95%CI: 6.41-10.10) compared to PHC.

Table 5-6: Multiple variable estimates of the hazard ratios and 95% confidence intervals from the time-homogeneous multistate Cox proportional hazard model among ART patients in Zimbabwe national ART from 2004 to 2017

Transitions	Health facility type*		Age categories in years**			Sex ***	ART initiation period****	
	District/Mission	Provincial/Central	15-24	35-44	45 +	Males	2008-2012	2013-2017
1 → 2	2.36 (2.12-2.62)	2.10 (1.69-2.62)	0.78 (0.61-0.99)	1.25 (1.10-1.41)	1.35 (1.18-1.54)	1.15 (1.01-1.28)	0.78 (0.67-0.93)	0.90 (0.76-1.07)
1 → 3	1.28 (1.14-1.43)	0.58 (0.39-0.85)	0.80 (0.62-1.04)	1.11 (0.96-1.27)	1.32 (1.14-1.53)	1.04 (0.91-1.19)	1.65 (1.31-2.10)	1.62 (1.27-2.07)
1 → 4	1.01 (0.90-1.14)	0.33 (0.22-0.50)	0.90 (0.68-1.21)	1.05 (0.91-1.22)	1.32 (1.13-1.54)	0.91 (0.78-1.05)	0.35 (0.30-0.42)	0.25 (0.21-0.31)
1 → 5	1.48 (1.19-1.84)	1.89 (1.32-2.67)	3.71 (2.90-4.76)	0.68 (0.51-0.91)	0.94 (0.70-1.24)	1.56 (1.26-1.92)	3.26 (2.07-5.14)	3.02 (1.87-4.89)
2 → 1	2.84 (2.57-3.13)	3.12 (2.54-4.36)	0.98 (0.80-1.19)	1.05 (0.94-1.18)	1.06 (0.93-1.20)	0.57 (0.51-0.64)	0.56 (0.47-0.67)	0.54 (0.45-0.64)
2 → 3	3.18 (2.83-3.58)	3.33 (2.54-4.36)	0.74 (0.54-1.00)	1.31 (1.14-1.51)	1.56 (1.34-1.81)	1.23 (1.10-1.38)	0.88 (0.71-1.08)	0.39 (0.30-0.52)
2 → 4	1.27 (1.11-1.46)	1.20 (0.83-1.73)	0.76 (0.52-1.10)	1.25 (1.05-1.48)	1.33 (1.11-1.60)	1.10 (0.96-1.27)	0.64 (0.49-0.83)	0.54 (0.43-0.67)
2 → 5	1.51 (1.17-1.95)	3.36 (2.05-5.52)	1.66 (1.09-2.53)	0.87 (0.63-1.20)	1.37 (1.01-1.86)	0.89 (0.69-1.15)	2.67 (1.20-5.95)	4.89 (2.22-10.79)
3 → 1	2.54 (2.32-2.79)	4.28 (3.45-5.30)	1.12 (0.94-1.36)	0.91 (0.81-1.01)	0.92 (0.81-1.03)	0.46 (0.41-0.52)	1.11 (0.87-1.43)	1.11 (0.86-1.44)
3 → 2	4.41 (3.96-4.87)	8.04 (6.41-10.10)	0.79 (0.61-1.03)	1.24 (1.10-1.40)	1.35 (1.18-1.54)	0.96 (0.87-1.06)	0.70 (0.57-0.87)	0.66 (0.53-0.82)
3 → 4	2.62 (2.34-2.93)	2.28 (1.59-3.28)	0.98 (0.73-1.32)	1.29 (1.12-1.50)	1.53 (1.32-1.79)	1.67 (1.49-1.86)	0.43 (0.35-0.54)	0.51 (0.40-0.63)
3 → 5	1.16 (0.99-1.13)	1.25 (0.73-2.16)	1.71 (1.32-2.21)	0.93 (0.77-1.08)	1.18 (0.99-1.42)	1.32 (1.15-1.51)	1.69 (0.99-2.85)	4.14 (2.47-6.96)
4 → 1	2.29 (2.05-2.55)	0.63 (0.34-1.17)	1.39 (1.09-1.77)	1.01 (0.89-1.16)	1.20 (1.04-1.38)	0.36 (0.31-0.41)	0.28 (0.24-0.34)	0.18 (0.15-0.22)
4 → 2	2.70 (2.41-3.03)	4.88 (3.55-6.71)	0.82 (0.60-1.11)	1.07 (0.94-1.24)	1.20 (1.04-1.40)	0.72 (0.64-0.81)	1.01 (0.77-1.33)	0.89 (0.67-1.18)
4 → 3	3.97 (3.61-4.37)	8.30 (6.64-10.36)	0.84 (0.64-1.09)	1.11 (0.99-1.25)	1.25 (1.10-1.42)	1.28 (1.17-1.41)	0.95 (0.76-1.19)	1.42 (1.13-1.78)
4 → 5	1.60 (1.49-1.73)	2.23 (1.80-2.74)	1.71 (1.47-1.98)	0.95 (0.86-1.04)	1.08 (0.98-1.20)	1.32 (1.23-1.42)	2.18 (1.69-2.82)	9.15 (7.12-11.79)

Note: The covariates included in the adjusted model were those with complete observation information and considered possible risk factors for the individual transitions

*Reference: Primary health care facilities

**Reference: 25-34 years age group

***Reference: female patients

****Reference: 2004-2007 time period

Boldface values are significant at 5%

This means patients at the provincial or central hospital had a high probability of immune deterioration once they are on ART compared to PHC patients. For district or mission hospital patients, State 3($200 \leq \text{CD4} < 350$) to State 2($350 \leq \text{CD4} < 500$) was the predominant transition, (HR=4.41: 95%CI: 3.96-4.87) followed by the State 4($\text{CD4} < 200$) to State 3($200 \leq \text{CD4} < 350$) transition (HR=3.97: 95%CI: 3.61-4.37), compared to PHC patients. Similarly, this was a positive indication of immune recovery for patients in district or mission hospital compared to PHC patients.

Adjusting for other covariates, age was generally associated with immune deterioration transitions ($\text{CD4} \geq 500$ State to $350 \leq \text{CD4} < 500$ State, $350 \leq \text{CD4} < 500$ State to $200 \leq \text{CD4} < 350$ State and $200 \leq \text{CD4} < 350$ State to $\text{CD4} < 200$ State). Compared to the 25-34 years age group, there was no significant difference in immune deterioration transitions. However, the results showed that the older the patient, the more likely he or she is to become immune deteriorated. This result was observed in elderly patients (45+ years) with a pronounced risk of immune deterioration across age groups. With reference to 25-34 years age group, both the 35-44 years and the 45+ years age groups were predominantly more likely to move from State 2($350 \leq \text{CD4} < 500$) to State 3($200 \leq \text{CD4} < 350$) transition, (HR=1.31: 95%CI: 1.14-1.51) and (HR=1.56: 95%CI: 1.34-1.81), respectively. Holding other covariates constant, sex was significantly associated with immune deterioration transitions. Male patients had an increased risk of immune deterioration compared to female patients: State 1($\text{CD4} \geq 500$) to State 2 ($350 \leq \text{CD4} < 500$) (HR=1.15: 95%CI: 1.01-1.28), State 2($350 \leq \text{CD4} < 500$) to State 3($200 \leq \text{CD4} < 350$) (HR=1.23: 95%CI: 1.10-1.38) and State 3($200 \leq \text{CD4} < 350$) to State 4($\text{CD4} < 200$) (HR=1.67: 95%CI: 1.49-1.86). Moving from State 3($200 \leq \text{CD4} < 350$) to State 4($\text{CD4} < 200$) was predominant in males compared to females.

5.4.6. Covariates effects on mortality rates

In overall, mortality was high amongst patients in State 4($CD4 < 200$) in this cohort, as shown in **Table 5-6**. The mortality risk was pronounced amongst patients in provincial or central hospitals than those in district hospitals if in State 1($CD4 \geq 500$) (HR=1.89: 95%CI: 1.32-2.67), State 2($350 \leq CD4 < 500$) (HR=3.36: 95%CI: 2.05-5.52), State 3($200 \leq CD4 < 350$) (HR=1.25: 95%CI: 0.73-2.16 and State 4($CD4 < 200$) (HR=2.23: 95%CI: 1.80-2.74). State 2($350 \leq CD4 < 500$) mortality risk was predominant in the provincial or central hospitals. This means PHC facilities had a low risk of mortality in this cohort compared to both a higher level of care facilities. Interestingly, the mortality risk was much more pronounced amongst the 15-25 years age groups than other age groups. The mortality risk for State 1($CD4 \geq 500$) was 3.71(95%CI: 2.90-4.76), State 2($350 \leq CD4 < 500$) (HR=1.66: 95%CI: 1.09-2.53), State 3($200 \leq CD4 < 350$) (HR=1.71: 95%CI: 1.32-2.21 and State 4($CD4 < 200$) (HR=1.71: 95%CI: 1.47-1.98). Patients who were aged 45 years and above were more likely to immune deteriorate compared to 25-34 years age-group: HR 1.35; 95%CI: 1.18-1.54, HR 1.56: 95%CI: 1.34-1.81 and HR 1.53: 95%CI: 1.32-1.79 for State 1 to 2, State 2 to 3 and State 3 to 4, respectively. Males were more likely to die compared to females: State 1 to 5 (HR=1.56: 95%CI: 1.26-1.92), State 3 to 5 (HR=1.32: 95%CI: 1.15-1.51 and State 4 to 5 (HR=1.32: 95%CI: 1.23-1.42). Considering the ART initiation period, mortality risks were pronounced amongst patients who initiated ART in 2013-2017: State 2($350 \leq CD4 < 500$) (HR=4.89: 95%CI: 2.22-10.79), State 3($200 \leq CD4 < 350$) (HR=4.14: 95%CI: 2.47-6.96) and State 4($CD4 < 200$) (HR=9.15: 95%CI: 7.12-11.79).

5.5. Discussion

This study's objective was to describe HIV disease progression (immune deterioration) and immune recovery amongst adult patients on ART in Zimbabwe using patient-level data after ART decentralization. This study made use of semi-parametric time-homogeneous and time inhomogeneous multistate Markov models based on four CD4 cell counts intermediate transient states and mortality as the absorbing state. This study was a quantitative secondary data analysis of the routinely collected patient-level data through ePMS among HIV- infected patients on ART in Zimbabwe between 2004 and 2017. The study findings were comparable to other earlier studies and indicated a poor immune recovery in PHC facilities compared to higher levels of care facilities.

This study observed significant findings to evaluate HIV disease progression and immune recovery based on CD4 cell counts amongst ART patients between 2004 and 2017 in Zimbabwe after the decentralization of ART services. The estimated mortality rate of 3.9 per 100 person-years is low and patients in State 4(CD4 < 200) had the highest risk of death (5.9 per 100 person-years on average) compared to other states. This finding was evident throughout in the time-varying analysis of rates. The high rates in State 4(CD4 < 200) were consistent over time; however, there was a sharp drop by 7 folds from 1year to 2years since ART initiation. There finding of high rates in lower CD4 cell count states is comparable to finding from previous work in India and South Africa (13,14). Immune deterioration pronounced in patients aged 45years and above, provincial or central hospital levels of care and male patients. However, immune recovery was also observed in this cohort since there were higher transitions and transition rates from lower CD4 cell counts states to higher CD4 cell counts states. Moreover, patients in the high levels of care (district and provincial or central hospitals) had an increased probability of

immune recovery compared to PHC facilities; however, mortality was high in the high levels of care. Male patients had an increased risk of mortality compared to female patients in this cohort.

Generally, there was a gradual improvement in CD4 cell count after ART initiation. This result was evident by the higher immune recovery rates compared to immune deterioration rates. This is an indication of effective ART treatment to HIV-infected individuals and that if ART is initiated at early phases of HIV infection (with baseline CD4 cell count at least 350), immune recovery and reduced progression can be achieved since the immune system is intact. This matches the findings reported in South Africa in a similar population (45). This study also found out that a patient in State 1($CD4 \geq 500$) is estimated to spent 11.3 years in higher CD4 cell count state before death, which is similar to other findings (41). This means that if individuals have a good immunity which can be attributed to the ART regimen efficacy, they tend to live longer than those with weak immunity.

This study further found that the probability of mortality increases with a decrease in CD4 cell count, which concurs with findings from similar settings(42,45). This is explained by the fact that being in an AIDS-defining stage leads to the highest probability of mortality. The highest mean sojourn time was in State 4($CD4 < 200$) compared to other states. This finding can be explained by the fact that patients with deteriorated immunity (low CD4 cell count) take a longer time to respond to treatment and boost their immunity before moving to lower states (154). Research has shown that CD4 cell count may remain unchanged despite the suppressed viral load due to weak CD4 cell recovery in other patients (155). This is the limitation of using CD4 cell count; hence, the use of viral load in monitoring the efficacy of ART treatment is recommended (156).

We found that the higher the level of care, the better the probability of immune recovery. Patients enrolled in either provincial or central hospitals, and district facilities had an increased probability of immune recovery relative to those in PHC. The risk of immune recovery increased with an increase in care regardless of the immune status of the patient. This result can be supported by tremendous resources through government channels or donor-funded and skilled personnel at the high levels of care (27). As much as patients prefer PHC facility for ART services because of reduced transport cost, easy to access (16), they are most likely understaffed. Also, PHC facilities are at times over-burdened resulting in a high patient care turn-around time(98,112,157,158). Surprisingly, we observed relatively high mortality rates among patients enrolled in higher levels of care since one would anticipate the opposite to occur. However, this finding could be explained by either the referral system of patients within the patient care cascade or “silent-transfer” of patients from one health facility to another seeking better care (123,125,159). This means the tertiary health facilities were more likely to receive patients who are more seriously ill and with a greater likelihood of death (125,137,160).

As we accounted for inter-individual variability effects to get an in-depth insight on HIV disease progression in this cohort, we found that HIV patients who were aged 15-24years at ART initiation tend to have higher mortality than patients aged 25-34years and the progression to death was much more pronounced if a patient was coming from State 1($CD4 \geq 500$) or State 2($350 \leq CD4 < 500$). This finding supports other earlier studies which showed that adolescents are heavily burdened by chronic complications; hence, require a high level of patients management (130). Also, this group is prone to stigma, vulnerable and prone to various chronic comorbidities as well as being and the transitional stage of becoming independent without much parental care. Intensifying community-based support for caregivers can help reduce poor health

outcomes in adolescence (89). However, more research is required to confirm this observed association in our study further.

Patients aged 45years and above showed a higher risk of immune deterioration compared to younger patients (25-34 years) which were similar to other studies which reported that younger people have a higher probability of immune recovery than the elderly (41,148). Also, this could be explained by the immune response in older patients is weak compared to young people, that is, the capacity to generate CD4 cell counts and suppress viral load is reduced in elderly patients (161). Moreover, this could be explained by the fact that this age group is highly associated with non-communicable diseases like hypertension and diabetes. Managing an HIV patient with multiple comorbidities is known to be complex. Also, the intake of different drugs results in overlapping drug toxicity and the lowering of the ART drug effect (98). As a result, most patients with comorbidities (communicable or non-communicable diseases) may either default ART treatment or ART drug becomes less effective due to the presents of other medications an individual is on; therefore, these patients subsequently get worse. These results confirm the need for “test and treat” for all regardless of disease stage and age, which have much positive influence in patients aged 45years and above(162,163).

In our study, we found that males had higher rates of immune deterioration. This was quite pronounced on the transition from State 3($200 \leq \text{CD4} < 350$) to State 4($\text{CD4} < 200$). In addition to this, we also observed poor survival outcomes among males. This finding is consistent with other results from Shoko and Chikobvu (45) who found out that men were 6 times more likely to move to higher CD4 cell count state. Another study which supports this result reported that males gain fewer CD4 cell counts as compared to females, and they have an increased immunological non-response than females (164). However, this finding contradicts other earlier

studies which documented that gender difference does not exhibit any significant differences in HIV disease progression (41,148). The participants in this study were predominantly females, and this could mirror the fact that females have better involvement in HIV issues and their health-seeking behaviour compared to males. Females have multiple entry points in HIV care like efficient linkage of ART treatment in antenatal clinics, and prevention-of-mother-to-child programmes which results are better immune recovery than males (164). Male involvement in HIV care strategies needs to be enhanced to complement the female role in HIV prevention (165–169). Therefore, there is a need to scale up HIV testing rate among men and intensify repeated testing and increasing acceptance of HIV care linkages. With the critical societal role played by men, they improve decision making within a household and society at large if they are fully involved in HIV programmes (170). There is need to intensify existing strategies like male circumcision, self-testing, HIV programmes at workplaces and recreational places and also come up with flexible clinic hours and conditions which accommodate males like shortening clinic turn-around time and increase privacy (164).

Our results should be viewed in light of some limitations. The dataset used had incomplete information, especially in the clinical parameters, which resulted in dropping off a considerable portion of the data. Also, this study could not adjust for ART adherence which is an important issue in HIV disease progression since it directly associated with the probability of moving to a lower CD4 cell count state if a patient fails to adhere to treatment. This study also considered patients from ART centres linked to the ePMS; this might have caused overestimation or underestimation of the transition intensities reported in this study. The analysis was solely based on the time homogenous assumption, which is much more useful in the presence of heavy right censoring. Earlier studies have shown that, if a patient on ART is virally suppressed, if there is

no treatment uptake violation, that patient is likely to continue recovering well. However, this violates the Markov and memory loss properties of these models, and this limitation affects the time-homogeneous Markov process models. Other assumptions like non-Markovian, semi-Markovian or hidden Markovian can be explored incorporating interval censoring and assuming time-varying effects. This model could not account for frailty terms to explain unobserved individual heterogeneity and spatial effects to show regions with an increased likelihood for a particular transition.

Moreover, this study covers the period in which ART initiation guidelines were changed three times; hence there could be some bias in the estimates. Also, the period covered is mainly when the country was conducting targeted differential monitoring, whereby most of the patients who had their CD4 measurement taken were mostly those done on the discretion of the physician. Authors acknowledge the measurement error (25) associated with CD4 cell counts in ART monitoring since a patient's measurement may indicate a lower CD4 when, in fact, the patients had recovered. Hence, the switch to using the viral load in ART monitoring.

There could be possible participant inclusion bias in this study since we excluded those who were loss to follow-up (LTFU) ending up with a sub-sample. The exclusion of this group was to have a less complicated model with fewer states since this group would be a stand-alone compartment. However, this may have impacted in the generalizability of our research findings in that the model used is not a complete picture of the transition patterns in an ART programme as some of the exits points have been excluded. Majority of the patients who became LTFU were mainly those who were very sick (with a $CD4 < 200$) and if tracked there could be a possibility that some of them would have died(171). The implications of such an LTFU pattern normally lead to data missing not at random (MNAR) in longitudinal time to event studies. Had we

included the LTFU group and right-censored them in their last observed states; this would have caused an upward bias of the Kaplan-Meier curve which at times may affect the generalizability of the findings (57). In future studies, it would be essential to include the LTFU and withdrawals states in the model to have detailed transition patterns of these outcomes in an ART programme. Our data could not allow us to estimate transitions to AIDS since the information was not available and exhaustively adjust for comorbidities which might be linked to the observed transition patterns in this cohort other than tuberculosis. However, tuberculosis was not included as a covariate because of the high computational intensive of this huge dataset if many covariates are added. Hence, we restricted our analysis to demographic covariate so that we attain convergence. A notable limitation in this study is the low mortality rate of which most deaths were for those patients who initiated ART in the 2013-2017 year period. The plausible explanation for this could be an issue of a biased dataset in terms of capturing patient's information. It is most likely that the majority of the deaths which occurred earlier may have been lost during data capturing from patients files to the electronic database since this was a retrospective exercise. So we are most likely to have the long term survivors from the early period.

5.6. Conclusion

Multistate models are crucial in providing the general disease trajectories through intermediates states to alert programme response before an adverse event occurs. Our findings have significant implication in the continuum of HIV care. It is prudent to target early ART treatment initiation to prevent subsequent immune deterioration. Once this is achieved, survival outcomes and quality of life can be improved with the subsequent reduction in opportunistic infections. Strengthening of PHC facilities in ART is imperative in decentralization environment. More aggressive male

involvement strategies should be enhanced to strengthen male involvement in HIV care, and adolescents/young adult management has to be upscaled to prevent ART defaulting and avert poor health outcomes.

5.6.1. Author's Contribution

ZMZ cleaned and analysed the data and drafted the manuscript, **JT** and **TC** reviewed the manuscript and advised on analysis, **EM** guided and oversaw the analysis and reviewed the manuscript. All authors reviewed the final manuscript before submission.

5.6.2. Data availability Statement

The dataset used for this study can be found through an application process from the Ministry of Health and Child Care in Zimbabwe which is the custodian of the ePMS data through the AIDS/TB Unit who manages and oversees the ePMS data collection process.

5.7. Chapter 5 Appendix: The Chapman-Kolmogorov Example of computing probabilities

The transition intensities, $\lambda_{jk}(t)$, often termed the rates or force of transmission for infectious diseases, from state j to k is defined as

$$\lambda_{jk}(t) = \lim_{\delta t \rightarrow 0} \frac{p_{jk}(t, t + \delta t)}{\delta t} = \frac{d}{dt} \lambda_{jk}(t) \Big|_{t=0} \quad (\text{E.1})$$

where the time interval is defined by $(t, t + \delta t)$, and the transition states take the values

$j = 1, 2, 3, 4, 5$ $k = 1, 2, 3, 4, 5$ and which satisfies these conditions: $\sum_{k \in S} \lambda_{jk} = 0$ for all j and the

diagonal entries are defined by convention as $\lambda_{jj}(t) = -\sum_{j \neq k} \lambda_{jk}(t)$ for all $j \in S$. The probability

from state j to k is defined by p_{jk} . Once the transition intensity matrix, $P_{jk}(t)$, is known, transition probabilities can be estimated by simplifying a set of the differential equation known as the Kolmogorov-Chapman differential equations defined as:

$$\frac{d}{dt} P_{jk}(t) = \sum_{\forall z} P_{jz}(t) \lambda_{zk} \quad \forall j, k \quad (\text{E.2})$$

where z is the pass-through state for a transition j to k , that is $j < z < k$. For this current study, a five-state time the homogenous model was assumed of which the states were defined based on WHO clinical cut off points for ART initiation. At any given time point, the individual state is defined by four CD4 cell counts states or whether the patient is dead (fifth state) as illustrated in **Figure 5.1** in the main chapter. The four CD4 states are bidirectional, meaning a patient can make a backward or forward movement from these states while the fifth state is absorbing. Also, an individual can be in any of these states making movements, or some may not make any transitions from these states; hence they remain in the same state over time.

To understand the model formulation, we assumed that between two-time points $(t, t + \delta t)$, a transition occurs from state j to state k . Secondly, if a patient makes a transition with a rate of λ_{jk} where $k = j - 1$ the patients would have indicated a positive movement as he/she would have moved from a bad to a good state. Practically, regarding ART uptake, such transitions can be explained by treatment efficacy; hence a patient would have shown immune recovery. This is termed backward transition, and it is a good sign for ART efficacy. Reversely, a patient can make a transition with a rate of λ_{jk} where $k = j + 1$. This forward movement is alarming in ART since it is a sign of immune deterioration. This can be a result of ART defaulting, adherence issues and treatment failure in some cases. Patients would have moved to a lower CD4 cell

count, and it is a cause of concern when monitoring ART patients. Not all model states are bidirectional, the transition from any of the four states (1, 2, 3, 4) to State 5 (absorbing) at a rate of λ_{jk} where $k = 5$ can occur as well. Lastly, an individual can remain in the same state overtime at a rate of $\lambda_{jj} = -\lambda_j$. From these background assumptions, the transition rate matrix ($Q(t)$) for the proposed model displayed in Figure 5.1 can be written as:

$$Q(t) = \begin{bmatrix} -(\lambda_{12} + \lambda_{13} + \lambda_{14} + \lambda_{15}) & \lambda_{12} & \lambda_{13} & \lambda_{14} & \lambda_{15} \\ \lambda_{21} & -(\lambda_{21} + \lambda_{23} + \lambda_{24} + \lambda_{25}) & \lambda_{23} & \lambda_{24} & \lambda_{25} \\ \lambda_{31} & \lambda_{32} & -(\lambda_{31} + \lambda_{32} + \lambda_{34} + \lambda_{35}) & \lambda_{34} & \lambda_{35} \\ \lambda_{41} & \lambda_{42} & \lambda_{43} & -(\lambda_{41} + \lambda_{42} + \lambda_{43} + \lambda_{45}) & \lambda_{45} \\ 0 & 0 & 0 & 0 & 0 \end{bmatrix}$$

Once there is a complete transition intensity matrix, as shown above, the transition probabilities matrix can be estimated using the Chapman-Kolmogorov forward differential equations. These equations generally link the relationship between the transition intensities and the transition probabilities. Employing this technique, yield the following set of equations:

$$\frac{d}{dt} P_{j1}(t) = -(\lambda_{12} + \lambda_{13} + \lambda_{14} + \lambda_{15}) P_{j1}(t) + \lambda_{21} P_{j2}(t) + \lambda_{31} P_{j3}(t) + \lambda_{41} P_{j4}(t) \quad \text{for } j = 1, 2, 3, 4 \quad (E.3)$$

$$\frac{d}{dt} P_{j2}(t) = \lambda_{12} P_{j1}(t) - (\lambda_{21} + \lambda_{23} + \lambda_{24} + \lambda_{25}) P_{j2}(t) + \lambda_{32} P_{j3}(t) + \lambda_{42} P_{j4}(t) \quad \text{for } j = 1, 2, 3, 4 \quad (E.4)$$

$$\frac{d}{dt} P_{j3}(t) = \lambda_{13} P_{j1}(t) + \lambda_{23} P_{j2}(t) - (\lambda_{31} + \lambda_{32} + \lambda_{34} + \lambda_{35}) P_{j3}(t) + \lambda_{43} P_{j4}(t) \quad \text{for } j = 1, 2, 3, 4 \quad (E.5)$$

$$\frac{d}{dt} P_{j4}(t) = \lambda_{14} P_{j1}(t) + \lambda_{24} P_{j2}(t) + \lambda_{34} P_{j3}(t) - (\lambda_{41} + \lambda_{42} + \lambda_{43} + \lambda_{45}) P_{j4}(t) \quad \text{for } j = 1, 2, 3, 4 \quad (E.6)$$

$$\frac{d}{dt} P_{j5}(t) = \lambda_{15} P_{j1}(t) + \lambda_{25} P_{j2}(t) + \lambda_{35} P_{j3}(t) + \lambda_{45} P_{j4}(t) = \sum_{z=1}^4 P_{jz}(t) \lambda_{z5} \quad \text{for } j = 1, 2, 3, 4 \quad (E.7)$$

These displayed Equations (E.3 to E.7), represent the transition probabilities and affirm the transition scenarios of bidirectional for State 1, 2, 3 and 4 and absorbing for state 5.

An example of the Chapman –Kolmogorov equation in relation to this study for a unique solution which can be recovered from the transition intensities through the product integration, to determine the probability to move from State 1 to State 5, i.e. dying from State 1 will be:

$({}_tP_x^{15})$ at a given age x will be:

$${}_{dt+t}P_x^{15} = ({}_tP_x^{11} \cdot {}_{dt}P_{x+t}^{15}) + ({}_tP_x^{12} \cdot {}_{dt}P_{x+t}^{25}) + ({}_tP_x^{13} \cdot {}_{dt}P_{x+t}^{35}) + ({}_tP_x^{14} \cdot {}_{dt}P_{x+t}^{45}) + ({}_tP_x^{15} \cdot {}_{dt}P_{x+t}^{55}) \quad (E.8)$$

Using $\lambda_{x+t}^{jk} = \mu_{x+t}^{jk}$ from Figure 5- 1 shown, then ${}_{dt}P_{x+t}^{jk} = \mu_{x+t}^{jk} \cdot dt + o(dt)$ and ${}_{dt}P_{x+t}^{55} = 1$ since a dead person stays as such, substituting these into Equation (E.8) above gives:

$${}_{dt+t}P_x^{15} = {}_tP_x^{11} \cdot \mu_{x+t}^{15} \cdot dt + {}_tP_x^{12} \cdot \mu_{x+t}^{25} \cdot dt + {}_tP_x^{13} \cdot \mu_{x+t}^{35} \cdot dt + {}_tP_x^{14} \cdot \mu_{x+t}^{45} \cdot dt + {}_tP_x^{15} \cdot 1 + o(dt) \quad (E.9)$$

Taking the ${}_tP_x^{15}$ term and dividing through by dt and then taking limits of Equation (E.9) as

Taking the ${}_tP_x^{15}$ term and dividing through by dt and then taking limits of Equation (E.9) as

$dt \rightarrow 0$ using $\lim_{dt \rightarrow 0} \frac{0(dt)}{dt} = 0$, we get the expression below:

$$\begin{aligned} \lim_{dt \rightarrow 0} \left(\frac{{}_{dt+t}P_x^{15} - {}_tP_x^{15}}{dt} \right) &= \frac{\partial}{\partial t} ({}_tP_x^{15}) \\ &= {}_tP_x^{11} \cdot \mu_{x+t}^{15} + {}_tP_x^{12} \cdot \mu_{x+t}^{25} + {}_tP_x^{13} \cdot \mu_{x+t}^{35} + {}_tP_x^{14} \cdot \mu_{x+t}^{45} \end{aligned} \quad (E.10)$$

Therefore,

$${}_tP_x^{15} = \int {}_tP_x^{11} \cdot \mu_{x+t}^{15} + {}_tP_x^{12} \cdot \mu_{x+t}^{25} + {}_tP_x^{13} \cdot \mu_{x+t}^{35} + {}_tP_x^{14} \cdot \mu_{x+t}^{45} dt \quad (E.11)$$

can be solved by a separate method and integration factor method and can be simplified in Bayesian WinBUGS software. However, using some properties of occupancy and that exit from a state is the negation of that, this expression can be shown to be:

$${}_tP_x^{15} = \frac{e^{-\int_0^t \left(\sum_{k=2}^5 \mu_{x+t}^{1k} \right) dt} \left(\mu_{x+t}^{15} \right)}{\sum_{k=2}^5 \mu_{x+t}^{1k}} + \frac{1 - e^{-\int_0^t \left(\sum_{k=2}^5 \mu_{x+t}^{2k} \right) dt} \left(\mu_{x+t}^{25} \right)}{\sum_{k=2}^5 \mu_{x+t}^{2k}} + \frac{1 - e^{-\int_0^t \left(\sum_{k=3}^5 \mu_{x+t}^{3k} \right) dt} \left(\mu_{x+t}^{35} \right)}{\sum_{k=3}^5 \mu_{x+t}^{3k}} + \frac{1 - e^{-\int_0^t \left(\sum_{k=4}^5 \mu_{x+t}^{4k} \right) dt} \left(\mu_{x+t}^{45} \right)}{\sum_{k=4}^5 \mu_{x+t}^{4k}} + C \quad (E.12)$$

CHAPTER 6

In previous chapters, the HIV continuum of care "leakages" have been identified and quantified using spatial models to show the heavily burdened areas, survival and competing risk models (types of multistate models) to estimate time to occurrence of becoming LTFU and multistate disease progression models (illness-death models) to determine the transition patterns as defined by CD4 cell counts intermediate states. In all the previous analysis, covariate influence on the outcome of interest was assessed, and age of an individual, gender and health level type remains significant risk factors associated with ART outcomes. However, WHO recommends the use of the viral load as a primary prognostic marker to monitor HIV disease progression as it is much more sensitive compared to CD4 cell counts. Moreover, the MLE multistate model cannot account for nonlinear effects of continuous covariates and frailty terms which may contribute to biased inferences. In this chapter, the viral suppression and viral rebound patterns were described using BE multistate models. The model accounted for frailty terms (individual heterogeneity and nonlinear effects of continuous covariates (age). Furthermore, the BE multistate model accounted for the spatial effects to explain unobserved heterogeneity, which make it the first BE multistate model to incorporate the geostatistical information. A sub-sample of the ART database was used, and only those patients with repeated measurements of viral load were considered.

6. SPATIAL HETEROGENEITY OF VIRAL SUPPRESSION AND VIRAL REBOUND PATTERNS AMONG ART PATIENTS IN ZIMBABWE FROM 2004 TO 2017: A BAYESIAN MIXED EFFECTS MULTISTATE MODEL

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6.1. Abstract

Augmenting the global efforts towards HIV control and prevention, spatial modelling helps identify areas with poor viral suppression to inform programme planning. This study aims to describe spatial viral suppression and viral rebound trajectories among ART patients. This study provides the first application of the fully Bayesian geospatial semiparametric multistate Markov models to account for unobserved geographical heterogeneity. Time-varying log-baseline effects of the transition intensities and nonlinear effects of continuous covariates were estimated as smoothed functions of time using penalised splines. Non-parametric effects of fixed covariates and frailty effects to account for individual variability were also considered. Viral load was the preferred markers for better prediction of HIV/AIDS disease progression; therefore, a three-staged model was proposed based on two viral load transient states defined by undetectable viral cut-off limits and death as the third absorbing state. The model application was based on the routinely collected individual-level data of ART patients from the Zimbabwe national ART programme. Amongst 18,150 participants, both the log-baseline transition rates of attaining undetectable viral suppression and attaining a viral rebound increased with increase in ART duration. Viral rebound transition was significantly prevalent among patients living on the long-distance truck route region (Matabeleland North province) which borders with Botswana and Zambia. Interventions which address health literacy and beliefs barriers on the potent and

effectiveness of ART and the gravity of attaining and sustaining viral suppression are a priority in the fight of HIV to increase patients' life expectancy and lower HIV transmission.

Keywords: Bayesian estimation, multistate Markov models, spatial heterogeneity, viral suppression, viral rebound

6.2. Introduction

Multistate models are useful in the management of chronic diseases since intermediate transitions give quick insights into the complex pathways patients experience before the final event, death, occurs(57). With reference to Human immune-deficiency virus (HIV) infections, multistate models can be used to evaluate the performance of ART programmes and identify patients who are at a high risk of immune deterioration so that appropriate interventions can be implemented.

Numerous studies have used a frequentist approach for multistate models of HIV disease progression (41,43,45). Most of these studies have implemented the multistate models developed by Jackson (2011)(147,172). However, there are limitations associated with the use of frequentist multistate models. Firstly they are unable to account for unexplained individual heterogeneity in transition rates which may be represented by the random-effects model. Accounting for individual variation is crucial in infectious disease modelling since individuals respond to treatment differently(147). Secondly, frequentist multi-state models are restrictive on the types of covariates they can handle, as the functional form of the effects of the predictive factors is assumed to be linear (or log-linear). As a result, these effects may be poorly estimated, and penalized splines (P-splines) may better estimate nonlinear functions for these covariates. These errors may lead to inaccurate statistical conclusions, the increased bias in estimates and

decreased statistical power for statistical significance tests (147). Besides, most of the studies done to assess HIV disease progression have used CD4 cell count measurement to define the finite number of states which is known to have measurement error; hence, may not be sensitive enough to assess HIV disease progression (25). A recent study by Shoko and Chikobvu (2019) have reported the superiority of the use of viral load measurements compared to CD4 cell counts in predicting ART outcomes(44).

The work by Kneib and Hennerfeind (2008) on the use of Bayesian inference in multistate models (46) forms the basis of this study analysis. The transition hazard rates are estimated in a multiplicative Cox-type way whereby the nonparametric effects of the log-baseline hazard are simultaneously estimated with other predictor components and assumed to be time-varying. The flexible linear predictor of the model can handle nonlinear effects of continuous covariates modelled using penalized splines (173). Additional components may include covariates with time-varying effects; nonlinear effects of a continuous covariate modelled non-parametrically with a smoothing function, parametric fixed effects and frailty terms (46). However, there are no reports of the inclusion of spatial random effects into the flexible predictor using a Bayesian semiparametric multistate model. This current study aims to incorporate such frailty terms in multistate models.

The World Health Organization (WHO) now encourages the use of viral load measurement in monitoring HIV, and this has been supported in the UNAIDS 90-90-90 fast track targets whereby 90% of all people living with HIV know their status, 90% of those who know their status receive ART and 90% of those on ART achieve viral suppression(1). In Zimbabwe, only 73% of ART patients were estimated to be virally suppressed in 2018, which is a concern for HIV prevention and control in the country (8). With the global quest to achieve zero new HIV

infections by 2030, the current goal is attaining an undetectable viral load among HIV-infected population, as it is now evident that undetectable HIV results in un-transmittable virus (U=U) (26). The use of viral load monitoring in HIV disease progression is important to enhance understanding of HIV infection to the various stakeholders and motivates the need for ART adherence. Therefore, it is imperative to understand the HIV disease progression and attaining undetectable viral suppression patterns among HIV patients. With the scarce resources in low-middle income countries like Zimbabwe, it was also of interest to be able to link these transition trajectories to the geographical regions to pinpoint high burdened areas to guide resource allocation and to inform policy on targeted interventions.

This manuscript aimed to describe the spatial heterogeneity of viral suppression to undetectable levels and viral rebound to detectable levels trajectories among antiretroviral therapy (ART) patients using the Bayesian semi-parametric geosadditive multistate model. The model was fitted on patient-level data from the Zimbabwe national ART programme for patients who initiated ART between 2004 and 2017. In addition to the nonlinear continuous covariates, the model accounted for time-varying transition rates and individual heterogeneity which reflects the reality of HIV in Zimbabwe. The spatial component assumes that the viral load transitions are likely to be induced characteristics of geographical units, which may depend on neighbouring regions but may as well be heterogenic. We hypothesized that there is spatial heterogeneity of viral suppression and rebound in this cohort, and these transition rates change with time. Findings from this study may provide additional information on HIV disease progression and give a proxy on how well the ART patients are adhering to ART to achieve un-transmittable virus levels. The knowledge gained from this analysis may also be used to encourage HIV patients to understand the importance of ART adherence.

Data management and preliminary analyses were handled in Stata Statistical Software Version 15.1 (118). Inference procedures were implemented in free BayesX software package Version 3.0.2 (75) using Markov chain Monte Carlo (MCMC) simulation technique. Results visualization were performed in R (174). The rest of the chapter is structured as follows: **Section 6.3** describes the fully Bayesian multistate model formulation (likelihood, prior, posterior), MCMC inference, model validation and diagnostics; **Section 6.4**, we apply the proposed model to the Zimbabwe national ART programme data to describe the HIV transition trajectories in patients between 2004 and 2017; and **Section 6.5**, we discuss the advantages of these models and highlight the Public Health and statistical implications of our findings. Chapter 6 Appendix provides additional detail to Section 6.3.

6.3. Multistate Geoadditive Model

6.3.1. Description of the multistate model

In this study, we considered a time-continuous Markov process $\{X(t), t \geq 0\}$ with two reversible transient states and one absorbing (death) stage defining the finite states ($S = 1, 2, 3$) as depicted in Figure 6-1. The viral load cut-off points were based on guidelines for undetectable viral load (26), that is, “undetectable viral suppression (<50 copies/mL)” state as state 1, “detectable viral rebound (≥ 50 copies/mL)” state as state 2 and the absorbing state, death, as state 3. The multistate model is described by a group of individual-specific hazard rates $\lambda_{jk,i}(t)$, where jk , ($j = 1, 2, \dots, J$ and $k = 1, 2, \dots, K$), indexes the type of transition from state j to k and $i = 1, 2, 3, \dots, n$ indexes the individuals.

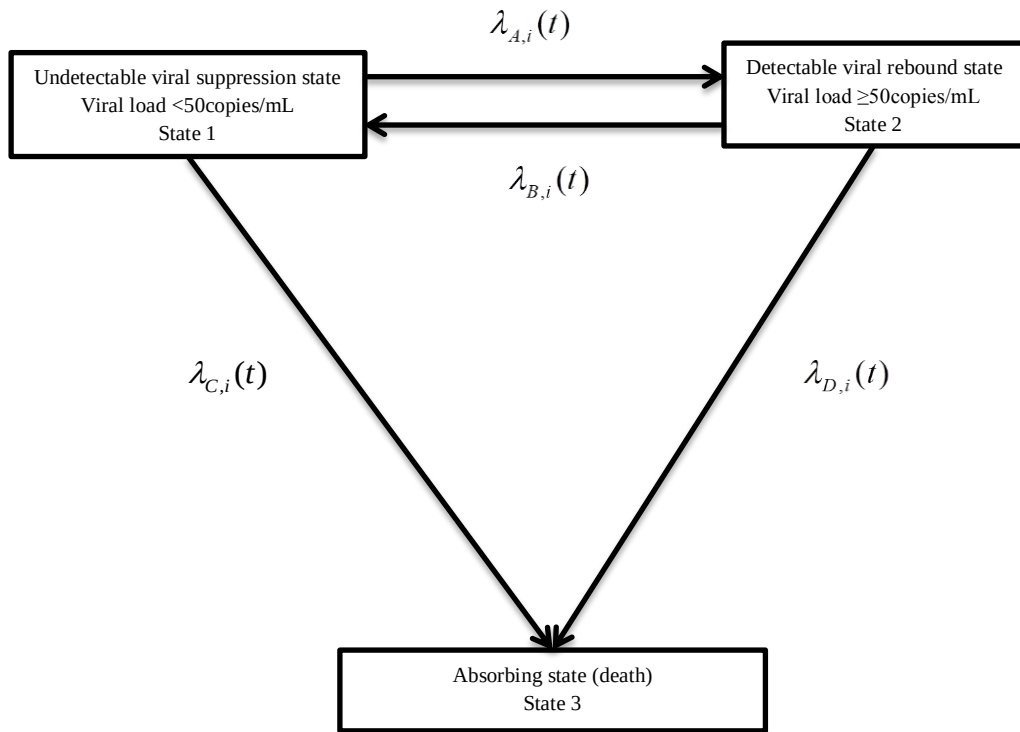


Figure 6-1: The schematic presentation of HIV disease progression stages multistate model and the corresponding individual-specific transition intensities.

These hazard rates are specified in analogy to hazard rates for continuous-time survival analysis (detailed information provided in Appendix A1- A4) in a multiplicative semi-parametric regression model way:

$$\lambda_{jk,i}(t) = \exp(\eta_{jk,i}(t)) \quad (6.1)$$

where $\eta_{jk,i}(t)$ is a flexible additive predictor expressed as

$$\eta_{jk,i}(t) = g_{jk,0}(t) + \sum_{r=1}^L g_{jk,r}(t)u_{r,i}(t) + \sum_{r=1}^R f_{jk,r}(t)x_{r,i}(t) + \mathbf{v}_i(t)' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} . \quad (6.2)$$

This flexible predictor's components are defined as:

- i. A time-varying, nonparametric baseline effect $g_{jk,0}(t)$ mutual for all observations. Generally, in the conventional Cox approach, the baseline hazard $\lambda_{jk,0}(t)$ remained unspecified; however, in this model, the baseline hazard is re-parameterised through $g_{jk,0}(t) = \log(\lambda_{jk,0}(t))$ function (detailed information is provided in Appendix A3). Instead of modelling the hazard rates through a piecewise exponential model assuming that all-time depended values are piecewise constant (175), this study estimated nonlinear shape the log-baseline effect by a P-spline prior of arbitrary degree with a second-order penalty (80).
- ii. Covariates $u_{r,i}(t)$ with time-varying effects $g_{jk,r}(t)$. However, in this study, time-varying effects were not included in the analysis.
- iii. Nonlinear effects $f_{jk,r}(t)x_{r,i}(t)$ of a continuous covariate $x_{r,i}(t)$. In this study, we considered individual age in years. Age was modelled non-parametrically with a smoothing function $f_{jk,r}(t)$ as it is directly proportional to time. Similarly, these nonlinear effects were modelled by the P-spline prior.
- iv. Parametric fixed effects γ_{jk} of covariates $v_i(t)$. The vector of the regression coefficients $\gamma_{jk,c}$ contains the usual linear effects the vector of fixed effects $\mathbf{v}_i(t)$ which were WHO clinical stages (I/II or III/IV) and gender (male or female) in this study.
- v. The spatial structural effects $f_{jk,spat}(t)(s_i)$ which form the unique part of our multistate model, where $s = 1, 2, \dots, S$ is a spatial index, with $S_i = S$ if an individual i is from region or site S to account for spatial heterogeneity assuming a Gaussian Markov random field (GMRF) prior. The spatial effects in this study were split into two components, that is,

$f_{jk,spat}(t)(s_i) = f_{jk,str}(t)(s_i) + f_{jk,unstr}(t)(s_i)$ where $f_{jk,str}(t)(s_i)$ to define the structured (correlated) part and $f_{jk,unstr}(t)(s_i)$ represents the unstructured (uncorrelated) part.

- vi. Random effects (frailty) term $b_{jk,i}$ was included to account for individual-specific unobserved heterogeneity.

Additional information is provided in chapter 6 Appendix section A5. To estimate viral suppression to undetectable levels, viral rebound and mortality transition rates; and determine the associated spatial heterogeneity amongst ART patients, the model in Figure 6-1 assumed that: a patient-initiated on potent and effective ART treatment may become virally suppressed to undetectable virus levels, may have viral rebound to detectable levels due to poor adherence to treatment or treatment failure, ART defaulting or treatment failure; or may die from any of the states. Baseline characteristics effects (WHO clinical stage at ART initiation and gender) were adjusted for in addition to the spatial and individual frailty terms. Therefore, the four transitions to be estimated were:

$$\begin{aligned}
 \lambda_{A,i}(t) &= \exp(\eta_{A,i}(t) = g_{A,0}(t) + f_{A,age_i}(t) + \gamma_{A,1}(WHOstage) + \gamma_{A,2}(sex) + f_{A,spat}(t)(province_i) + b_{A,i}) \\
 \lambda_{B,i}(t) &= \exp(\eta_{B,i}(t) = g_{B,0}(t) + f_{B,age_i}(t) + \gamma_{B,1}(WHOstage) + \gamma_{B,2}(sex) + f_{B,spat}(t)(province_i) + b_{B,i}) \\
 \lambda_{C,i}(t) &= \exp(\eta_{C,i}(t) = g_{C,0}(t) + f_{C,age_i}(t) + \gamma_{C,1}(WHOstage) + \gamma_{C,2}(sex) + f_{C,spat}(t)(province_i) + b_{C,i}) \\
 \lambda_{D,i}(t) &= \exp(\eta_{D,i}(t) = g_{D,0}(t) + f_{D,age_i}(t) + \gamma_{D,1}(WHOstage) + \gamma_{D,2}(sex) + f_{D,spat}(t)(province_i) + b_{D,i})
 \end{aligned} \tag{6.3}$$

where A defines the viral rebound transition, B defines the undetectable viral suppression transition, C and D defines the mortality transition from undetectable virally suppressed and viral rebound states, respectively.

6.3.2. The likelihood function

The likelihood contribution in a multistate model for each individual $i = 1, 2, 3, \dots, n$ is derived from a counting process $N_{jk,i}(t)$, counting j to k transitions for an individual i . If we consider $S_{iz}, z = 1, 2, \dots, m_i$ as the individual transition times corresponding to a transition process under the non-informative censoring, the intensity process of the counting process is defined as $\alpha_{jk,i} = I_{jk,i}(t) \lambda_{jk,i}(t)$ where $I_{jk,i}(t)$ is the predictable at-risk indicator process and the hazard rate $\lambda_{jk,i}(t)$ defined as in Equation (6.1). Therefore, the individual log-likelihood function is given by:

$$\log L_i(\gamma, \beta, \tau^2) = \sum_{jk=1}^{JK} \left[\int_0^{S_{i,m_i}} \log(\lambda_{jk,i}(t)) dN_{jk,i}(t) - \int_0^{S_{i,m_i}} \lambda_{jk,i}(t) I_{jk,i}(t) dt \right] \quad (6.4)$$

where $\gamma = (\gamma'_{jk,1}, \gamma'_{jk,2}, \dots, \gamma'_{jk,d})'$ for $c = 1, 2, \dots, d$ is a vector of all fixed effects parameters,

$\beta = (\beta_{jk,1}, \beta_{jk,2}, \dots, \beta_{jk,p})'$ is a vector of (regression) coefficients,

$\tau^2 = (\tau^2_{jk,1}, \tau^2_{jk,2}, \dots, \tau^2_{jk,y})'$ for $q = 1, 2, \dots, y$ is a vector of all variance components under

consideration and S_{i,m_i} denotes the time until an individual i has been observed. In survival models, the first term can be viewed as the log-hazard for uncensored data while the second term reflects the cumulative intensities.

Alternatively, the likelihood can be defined in terms of each individual contributions defined in terms of transition censoring indicators $\delta_{jk,i}(t)$ by which is equal to one if a jk transition occurs before time (t) and zero otherwise. The observed transition times $S_{iz}, z = 0, 1, \dots, m_i$

defined by the time an individual experience the transition. The alternative log-likelihood formula is given by:

$$\log L_i(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) = \sum_{z=1}^m \sum_{j,k=1}^{JK} \left[\delta_{jk,i}(S_{iz}) \log(\lambda_{jk,i}(S_{iz})) - I_{jk,i}(S_{iz}) \int_{S_{i,z=1}}^{S_{iz}} \lambda_{jk,i}(t) dt \right] \quad (6.5)$$

where $\lambda_{jk,i}(t)$ is defined by Equation (6.1) and this whole expression reflects the commonly known hazard rate models fitted for continuous survival times. If the P-spline prior degree for the log-baseline hazard function is greater than one, then the likelihood integral can no longer be solved in a closed-form. Detailed steps of the log-likelihood are provided in chapter 6 Appendix A6 section.

6.3.3. The prior specifications

We performed a fully Bayesian inference in that all unknown parameters were assigned prior information. We assigned non-informative diffuse prior, $P(\boldsymbol{\gamma}) \propto \text{const}$ to the *fixed-effects parameters*; alternatively, a weak (large variance) normal prior can be used. The *individual random effects* $b_{jk,i}$ were assumed to be independent and identically distributed (iid) Gaussian distributed with a transition specific precision, $b_{jk,i} \sim N(0, \tau_{jk,b}^2)$. Priors for the *random effects (regression) coefficients parameter vector* $\boldsymbol{\beta}_{jk,r}$ for $r = 0, 1, \dots, p$, was assumed to follow a Gaussian distribution which could be computed as a product of conditional densities defined by the random walk smoothness priors. The general form of the prior for $\boldsymbol{\beta}_{jk,r}$ is given by:

$$P(\boldsymbol{\beta}_{jk,r} / \tau_{jk,r}^2) \propto \exp\left(-\frac{\boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,r}^2}\right) \quad (6.6)$$

where $\mathbf{W}_{jk,r} \geq 0$ is a precision or penalty matrix of rank $(\mathbf{W}_{jk,r}) = h_{jk,r}$. The variance $\tau_{jk,r}^2$ acts as an inverse smoothness hyper-parameter controlling for the trade-off between smoothness and flexibility. That is a small value of $\tau_{jk,r}^2$ corresponds to an increase of the penalty or shrinkage (error) or vice-versa.

Unknown *nonparametric effects* $f_{jk,r}(t)$ of continuous smooth covariate x_r are estimated using Bayesian P-splines (173) as a linear combination of a larger number of B-splines basic functions

B_d , that is, $f_{jk,r}(x_r) = \sum_{d=1}^{D_r} \beta_{jk,rd} B_d(x_r)$. The basic functions B_d are the B-splines of a

known degree l on a set of equally spaced knots $x_r(\max) = \varsigma_0 < \varsigma_1 < \varsigma_2 < \dots < \varsigma_{s-1} < \varsigma_s = x_r(\max)$

within the main domain of x_r , $D_r = l + s$. The Bayesian analogue is the second-order random walk smoothness priors of the form:

$$\beta_{jk,rd} = 2\beta_{jk,r,d-1} - \beta_{jk,r,d-2} + \varepsilon_{jk,rd}, d = 3, 4, \dots, D \quad (6.7)$$

with iid Gaussian errors $(\varepsilon_{jk,rd} \sim N(0, \tau_{jk,\varepsilon}^2))$ where $\tau_{jk,\varepsilon}^2 = 1/\sigma^2$. The linear trend coefficients' initial values of the random walk were assigned diffuse priors, $P(\beta_{jk,r1}) \propto \text{const}$ and $P(\beta_{jk,r2}) \propto \text{const}$.

The *spatial effects* were modelled separately to distinguish between the different effects on the outcome, that is, $f_{jk,spat}(t)(s_i) = f_{jk,str}(t)(s_i) + f_{jk,unstr}(t)(s_i)$. For the spatial correlated (structured) effects $(f_{jk,str}(t)(s))$ were assumed a GMRF (81) prior. In this case, we defined areas as neighbours if they share a common boundary and assume that the effect of an area

$s \in \{1, 2, 3, \dots, S\}$ is conditionally Gaussian. The spatial smoothness prior to the spatial function evaluation $f_{jk, str}(s) = \beta_s^{str}$ is given by:

$$f_{jk, str}(s) = \beta_s^{str} = \frac{1}{N_s} \sum_{s' \in \partial_s} \beta_{s'} + u_s, u_s \sim N\left(0, \frac{\tau_{jk, str}^2}{N_s}\right) \quad (6.8)$$

where $s' \in \partial_s$ denotes that province s' is a neighbour of the province s . The conditional mean of β_s is an unweighted average of function evaluations of neighbouring provinces. The number of parameter D equals the number of distinct areas S , and the $n \times S$ design matrix Z_{str} is a 0-1 incidence matrix. Its values on the i^{th} row and s^{th} column is a one if observation one is located in the province s and zero otherwise. The $S \times S$ penalty matrix W_{str} has the form of the adjacency matrix with $rank(W_{str}) = S - 1$. The dimension of the penalty matrix in MRF equals to the number of different spatial regions (provinces in our case) S ; hence the computational burden is less compared to the stationary GRF priors approach. The *unstructured spatial effects* $f_{unstr}(s)$ were assumed to be independent and identically distributed Gaussian priors, that is, $f_{unstr}(s) \sim N(0, \tau_{unstr}^2)$. In real situations, it usually is not known how much spatial variation is explained by both the structured and the unstructured effects; therefore the interpretation of the spatial effects is based on the sum of the two effects.

The variance parameter vector $\tau_{jk, q}^2 = (\tau_{jk, 1}^2, \tau_{jk, 2}^2, \dots, \tau_{jk, y}^2)'$ for $q = 1, 2, \dots, y$ contains variance parameters for the error term $\tau_{jk, \varepsilon}^2$, frailty term $\tau_{jk, b}^2$, structured spatial terms $\tau_{jk, str}^2$, the unstructured spatial terms $\tau_{jk, unstr}^2$ and the generic random effects (regression) coefficients $\tau_{jk, r}^2$.

Routinely, each of these variance hyperparameters is assigned a non-informative inverse Gamma priors with known parameter values $a=b= 0.001$, that is, $(\tau_{jk,q}^2 \sim IG(a_q, b_q))$

$$P(\tau_{jk,q}^2) \propto \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(-\frac{b_q}{\tau_{jk,q}^2}\right), \text{ for } a_q, b_q > 0 \quad (6.9)$$

Supplementary information is given in chapter 6 Appendix section A7.

6.3.4. Posterior distribution

Let full Bayesian inference is based on the entire posterior distribution, and more detail is shown in chapter 6 Appendix A8:

$$P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2 / \text{data}) \propto L(\text{data} / \boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) \quad (6.10)$$

The likelihood, as defined in Section 6.3.2 and the joint prior made up of the individual prior distributions of the specified parameters yield the posterior distribution. Due to conditional independence assumptions, the joint prior factorizes into:

$$P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) = \left\{ \prod_{r=0}^m P(\boldsymbol{\beta}_{jk,r} / \tau_{jk,q}^2) P(\tau_{jk,q}^2) \right\} P(\boldsymbol{\gamma}) \propto \left\{ \prod_{q,r=0}^m \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(-\left(\frac{b_q}{\tau_{jk,q}^2} - \frac{\boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,q}^2}\right)\right) \right\} \quad (6.11)$$

The component $P(\boldsymbol{\gamma})$ can be omitted since it represents fixed effects prior. The posterior distribution $P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2 / \text{data})$ is then an approximation of the product of Equation (6. 5) and Equation (6. 12).

6.3.5. Markov Chain Monte Carlo inference

Since this posterior distribution is not in a closed form, we, therefore, used the Markov Chain Monte Carlo (MCMC) simulation method based on updating full conditionals of single parameters or blocks of parameters (for the same transition rate), given the rest of parameters and data. For updating the parameter vector $\boldsymbol{\beta}_{jk,r}$, which corresponds to the time-independent functions, spatial effects, fixed effects and random effects, we use the Metropolis-Hastings (MH) algorithm based on iteratively weighted least squares (IWLS) proposals for fixed random effects (176) and adapted to generalized structure additive models (177). Suppose we want to update $\boldsymbol{\beta}_{jk,r}$ with the current value, $\boldsymbol{\beta}_{jk,r}^c$, of the chain. The new value $\boldsymbol{\beta}_{jk,r}^p$ is proposed by drawing a random vector from the high-dimensional multivariate Gaussian proposal distribution $q(\boldsymbol{\beta}_{jk,r}^c, \boldsymbol{\beta}_{jk,r}^p)$ which is attained from the quadratic approximation to the posterior by a second-order Taylor expansion with respect to $\boldsymbol{\beta}_{jk,r}^c$. An explicit illustration is given in the Appendix section A9. For the other parameters corresponding to the log-baseline effects, depending on time functions, a computationally faster MH-algorithm based on conditional prior proposals was adopted. Unlike the Iteratively weighted least square (ILWS) algorithm, which requires derivatives, MH-algorithm involves the evaluation of the log-likelihood since the derivatives are computationally intensive for these parameters due to the additional integrals involved. As the full conditionals of the variance parameters are inverse Gamma distributions, updating the hyper-parameters can be done by simple Gibbs steps.

6.3.6. Model diagnostics and sensitivity analysis

The convergence of the Markov chains to their stationary distributions was assessed by inspecting the sampling paths and autocorrelation functions of the sampled parameters. Trace plots and visual autocorrelation plots were used to evaluate the performance of the model. In

running the MCMC algorithm, 10,000 iterations were made with a burn-in of 2,000 and a thinning parameter of 20. We also performed a sensitivity analysis to ensure that the choice of the priors did not influence the obtained results. In the initial run, default Gamma priors with hyper-parameters ($\alpha = \beta = 0.001$) were used then two more trials using values of $\alpha = \beta = 0.0001$ and $\alpha = 1$ with $\beta = 0.001$. The results reported are those of the model with default prior values.

6.4. Application of the Model to the Adult ART data

6.4.1. The Zimbabwe National ART programme data

The national ART programme was introduced in Zimbabwe in 2004 to provide treatment for people living with HIV (PLHIV) and support the fight against HIV (11). Patients' data are routinely collected at ART initiation, and subsequent follow-up visits, through the electronic patient management system (ePMS) (49). The ePMS was introduced to improve and increase efficiency in patient monitoring compare to the paper-based system and allows analysis at the national level of suitably anonymized patient data.

At baseline, demographic and clinical information is captured including gender, age, and WHO clinical stage, while viral load and CD4 measurements are captured at baseline as well as in subsequent visit. WHO recommends the use of laboratory monitoring to manage HIV patients on ART, using viral load measurements at baseline (6 months after ART initiation) and then every six months to guide patient management. Due to limited resources, for much of the time covered by our study is only targeted, viral load monitoring was done (139). Therefore, a small number of ART patients from the dataset received had at least two subsequent viral load measurements.

6.4.2. Study design and ethics

This study is a secondary data analysis of a retrospective cohort of anonymous HIV positive patients initiated on ART between 2004 and 2017, and whom their routine data was captured through the ePMS system linked with the Zimbabwean Ministry of Health and Child Care (ZMOHCC). Permission to use the data was obtained from ZMOHCC, and ethical clearance was granted by the University of Witwatersrand's Human Research Ethics Committee (Medical) (Clearance Certificate No. M170673).

6.4.3. Results

6.4.3.1. Descriptive analysis of the baseline characteristics

Of the 18,150 participants with two or more viral load measurements following ART initiation: majority of the participants, 64.3% (n=11,671), had detectable viral load (>50copies/mL) while 35.7% (n=6,479) had undetectable viral load (<50copies/mL). There was a significant difference between these baseline proportions of patients with undetectable viral load and those with detectable viral load, p-value<0.001. The mean (standard deviation) age and weight was 39.1(10.2) years and 62.4(13.5) Kgs at ART initiation, respectively. Majority of the patients were females (67.1%), enrolled at the primary health care (PHC) centres (68.2%) within rural areas (52.4%). Patients were mainly on the first-line drug regimen (95.0%), in WHO clinical stage III or IV (53.3%). Most of the transitions observed were those of the patients who did not make any transition out of their initially occupied state, particularly the unsuppressed state (68.74%). A total of 496 patients (2.73%) died within the follow-up period (**Table 6-1**).

Table 6-1: Participants’ baseline characteristics (sociodemographic and clinical) and the observed transitions during the follow-up period in the Zimbabwe national ART programme, 2004-2017

Variable	Category	Frequency	Percentage
Health facility type	Primary Health Care	12 385	68.24
	District /Mission hospital	4 527	24.94
	Provincial/Referral hospital	1 238	6.82
Degree or urbanization of health facilities	Rural	9 700	53.44
	Urban	8 450	46.56
Sex	Female	12 169	67.05
	Male	5 981	32.95
Regimen type	First line	17 234	94.95
	D4T(30)+ 3TC+NVP	9	0.05
	AZT+3TC+NVP	353	1.94
	AZT+3TC+EFT	38	0.21
	TDF+3TC+NVP	280	1.54
	AZT+3TC+EFV	16 554	91.21
	Second line	916	5.05
WHO clinical states	I/II	7 700	42.42
	III/IV	9 679	53.33
	Missing	771	4.25
Baseline viral load states	Suppressed state (State 1)	6 401	35.27
	Unsuppressed state (State 2)	11 749	64.73
Transitions between states	1 $\longrightarrow$ 1	21 645	24.39
	1 $\longrightarrow$ 2	2 803	3.16
	1 $\longrightarrow$ 3	200	0.23
	2 $\longrightarrow$ 1	2 804	3.16
	2 $\longrightarrow$ 2	61 015	68.74
	2 $\longrightarrow$ 3	296	0.33

6.4.3.2. Fully Bayesian time-varying transition intensities pattern results

We fitted an unadjusted (no covariate) and covariate-adjusted models to obtain the time-varying log-baseline hazard plots. The unadjusted model gave unprecise credible intervals for both the viral rebound (undetectable (state 1) to detectable (state 2)) and viral suppression (detectable (state 2) to undetectable (state 1)) transitions as shown in **Figure 6-2** (top panel).

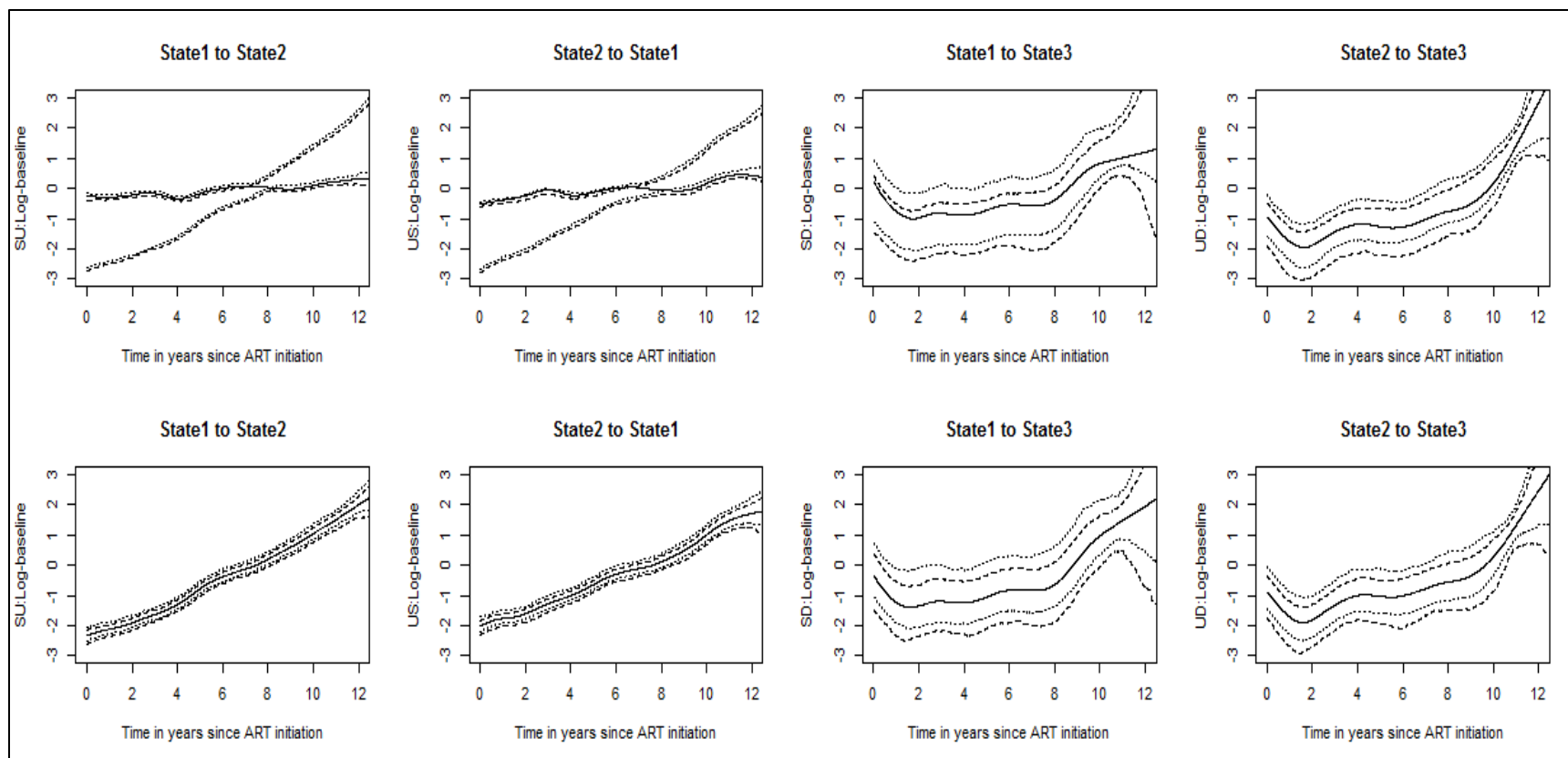


Figure 6-2: Estimated time-varying log-baseline transitions (middle line) and their 95% and 80% credible intervals from the fully Bayesian inference estimation of univariate analysis/no covariates (top panel) and multiple covariate model with nonlinear, fixed and

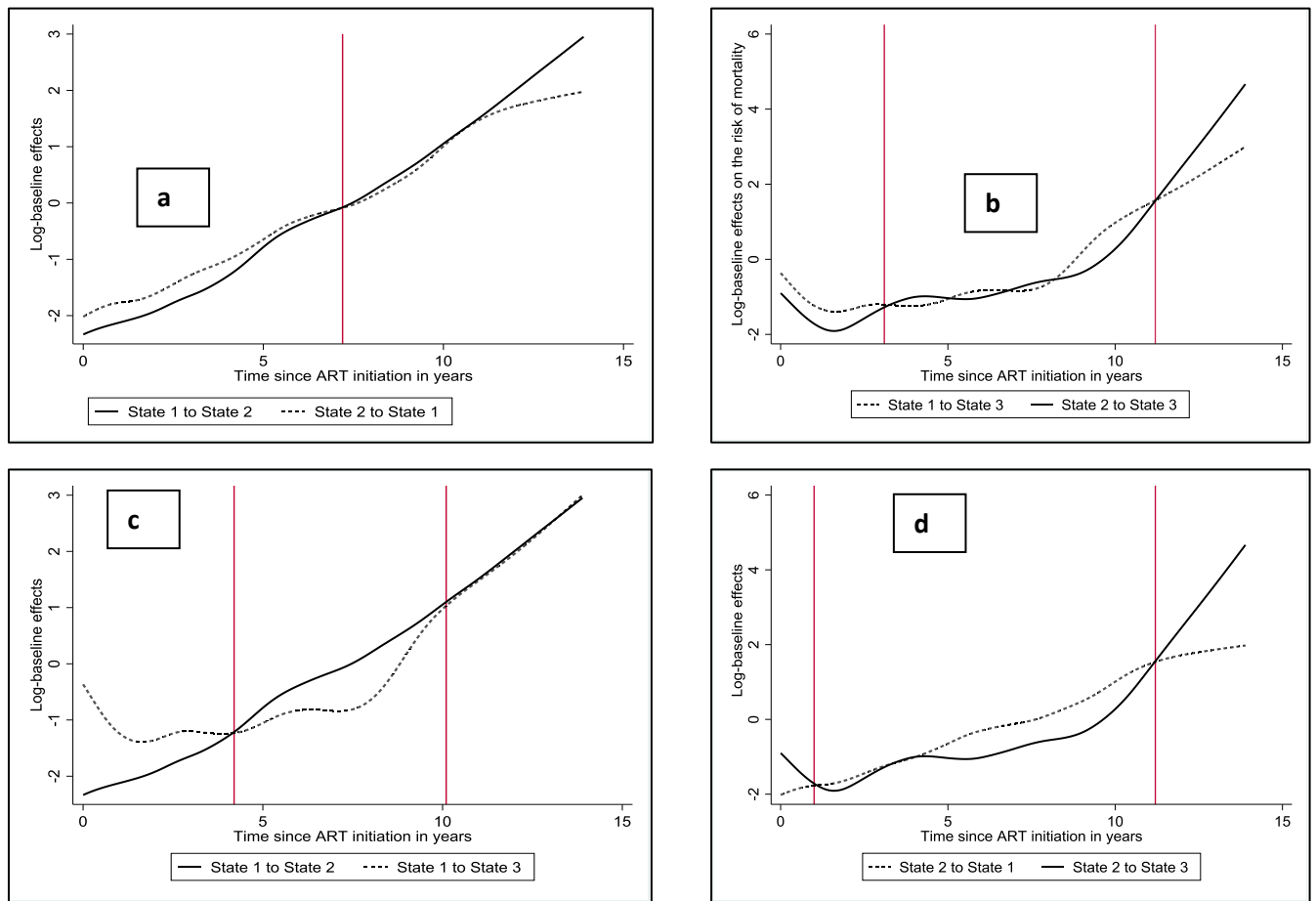


Figure 6-3: Cross comparison of the estimated time-varying log-baseline transitions from the fully adjusted Bayesian multistate model

Adjusting for the other covariates, the time-varying log-baseline credible intervals increased in precision. The results reported in this study will be based on the adjusted model **Figure 6-2** (bottom panel). We observed an increase in the log-baseline hazard rates with time since ART initiation for both the viral suppression (state 2 to state 1) and viral rebound (state 1 to state 2) transitions. The time-varying log-baseline transition rates for death slowly increased with time for both states following a similar pattern. Comparing the viral suppression (state 2 to state 1) and viral rebound (state 1 to state 2) transitions on one plane, we observed that the log-baseline effects of attaining viral suppression (state 2 to state 1) were higher from ART initiation till the

7.2-year mark before going down after that (**Figure 6-3 a**). Comparing the log-baseline hazard rates of mortality from either state, a fluctuating pattern was observed throughout the observed time (**Figure 6-3 b**). Among virally suppressed (state 1) patients, the risk of was higher in the early years of ART initiation compared to the risk of attaining viral rebound; however, after the 10-year mark, there was no difference between the two transitions (**Figure 6-3 c**). Contrary, among the patients who attained viral rebound (state 2), the risk of moving to state 2 was higher than that of death in general (**Figure 6-3 d**).

Table 6-2 presents the results of the effects of the fixed covariates on each of the transition.

Table 6-2: Fixed effect covariates results for the estimated transition intensities coefficients and ratios in the Zimbabwe National ART programme based on viral load measurements, 2004 to 2017

Covariates		WHO III/IV (Reference: WHO I/II) Mean(95% Credible Intervals)	Sex (Reference: Female) Mean(95% Credible Intervals)
Transitions			
Viral rebound (state 1 to 2)	Coefficients	0.23 (0.03 to 0.39)*	-1.02 (-1.24 to -0.79)*
	Exponents	1.26 (1.03 to 1.48)*	0.36 (0.29 to 0.45)*
Viral suppression (state 2 to 1)	Coefficients	-0.12 (-0.29 to 0.04)	0.45 (0.25 to 0.64)*
	Exponents	0.89 (0.75-1.04)	1.57 (1.28-1.90)*
Viral suppression mortality (state 1 to 3)	Coefficients	0.19 (-0.11 to 0.51)	-0.17 (-0.49 to 0.11)
	Exponents	1.21 (0.90-1.67)	0.84 (0.61-1.12)
Viral rebound mortality (state 2 to 3)	Coefficients	-0.43 (-0.53 to 0.17)	0.52 (0.28 to 0.76)*
	Exponents	0.65 (0.59-1.19)	1.68 (1.32-2.05)*

*Significant at 5%

Although the WHO clinical stage effects were not significant for the viral suppression (state 2 to state 1) transition and on the risk of death from any state; patients in WHO clinical stage III/IV had a higher risk of a viral rebound compared to those in WHO I/II (posterior hazard rate (PHR)

=1.26; 95% credible interval (CI): 1.03-1.48). Compared to females, male patients were 64% times less likely to attain a viral rebound (PHR=0.36; 95%CI: 0.29-0.45); 1.57 times (95%CI: 1.28-1.90) more likely to become virally suppressed and 1.68 times (95%CI: 1.32-2.05) more likely to die if they have a viral rebound. However, there was no significant difference in gender on the risk of death if an individual was virally suppressed

The effects of age on the risk of the four transitions are presented in **Figure 6-4**. The age effects on the risk of mortality and viral rebound for an individual with suppressed viral load was high if a patient was either an adolescents/young adult (below 30years) or older (above 60years) as shown by the bath-tub “ $\cup$ ” shaped splines; however, the effects for older patients were not significant due to fewer numbers of participants in this category. Contrarily, the age effects on the risk of viral suppression followed a convex “ $\cap$ ” shape.

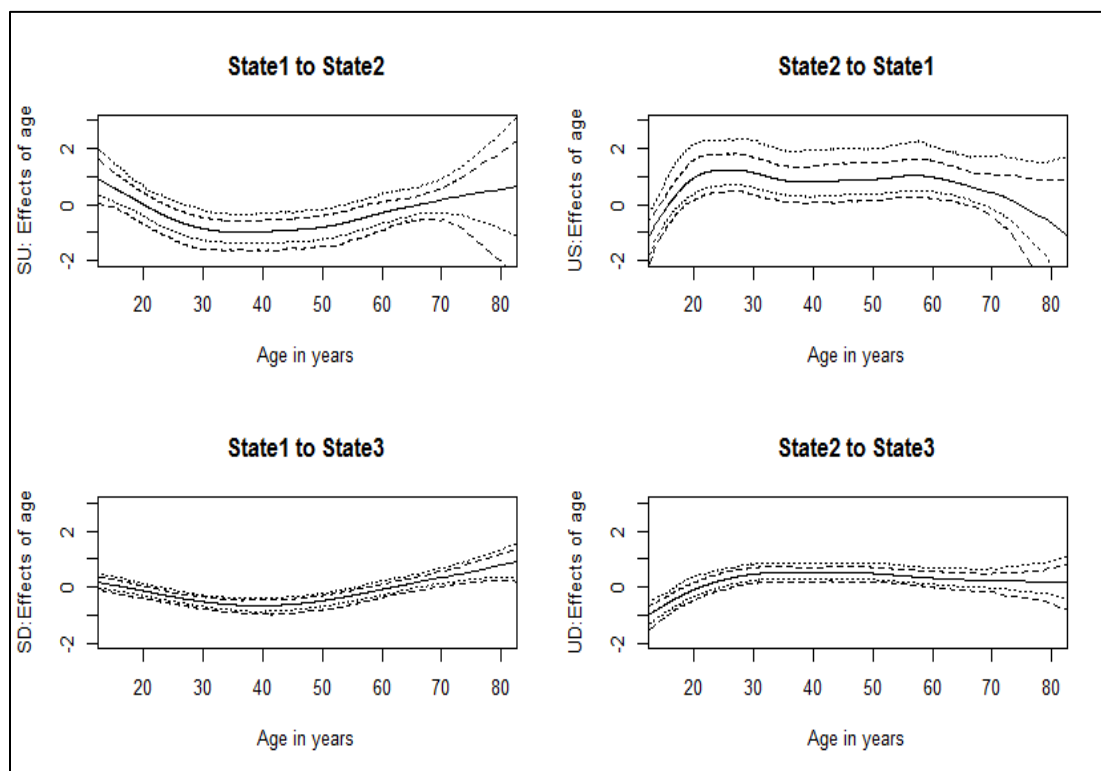


Figure 6-4: Estimated nonparametric effects of the continuous covariate (age) (middle line) and their 95% and 80% credible intervals from the full Bayesian inference for the four transitions

This means individuals aged 30-60 years with viral load rebound had a higher risk of experiencing the reverse transition and subsequently attaining viral suppression. Also, the age effects on the risk of mortality for an individual with viral rebound increased with an increase in age until 30 years before remaining constant after that.

The smooth geographical effects are shown in **Figure 6-5** with their corresponding 95%CI for each transition. The spatial unit of analysis was the ten regions in Zimbabwe. The yellow colour represents regions with non-significant spatial effects for all the transitions. For the risk of viral rebound and the risk of mortalities from either state, the red colour indicates an increased spatial effect while green colour indicates a decreased spatial effect. The region which borders with Botswana and Zambia had the highest likelihood of viral rebound (state 1 to state 2) transition compared to the other regions, and this was significant.

For the risk of viral suppression, the red colour indicates decreased spatial effects while green colour indicates increased spatial effects. The southern region which borders with Botswana, middle regions in the central parts of the country and northern regions bordering Zambia and Mozambique had a low likelihood of the viral suppression (state 2 to state 1) transition. This means that patients in these regions were less likely to attain undetectable viral suppression compared to other regions.

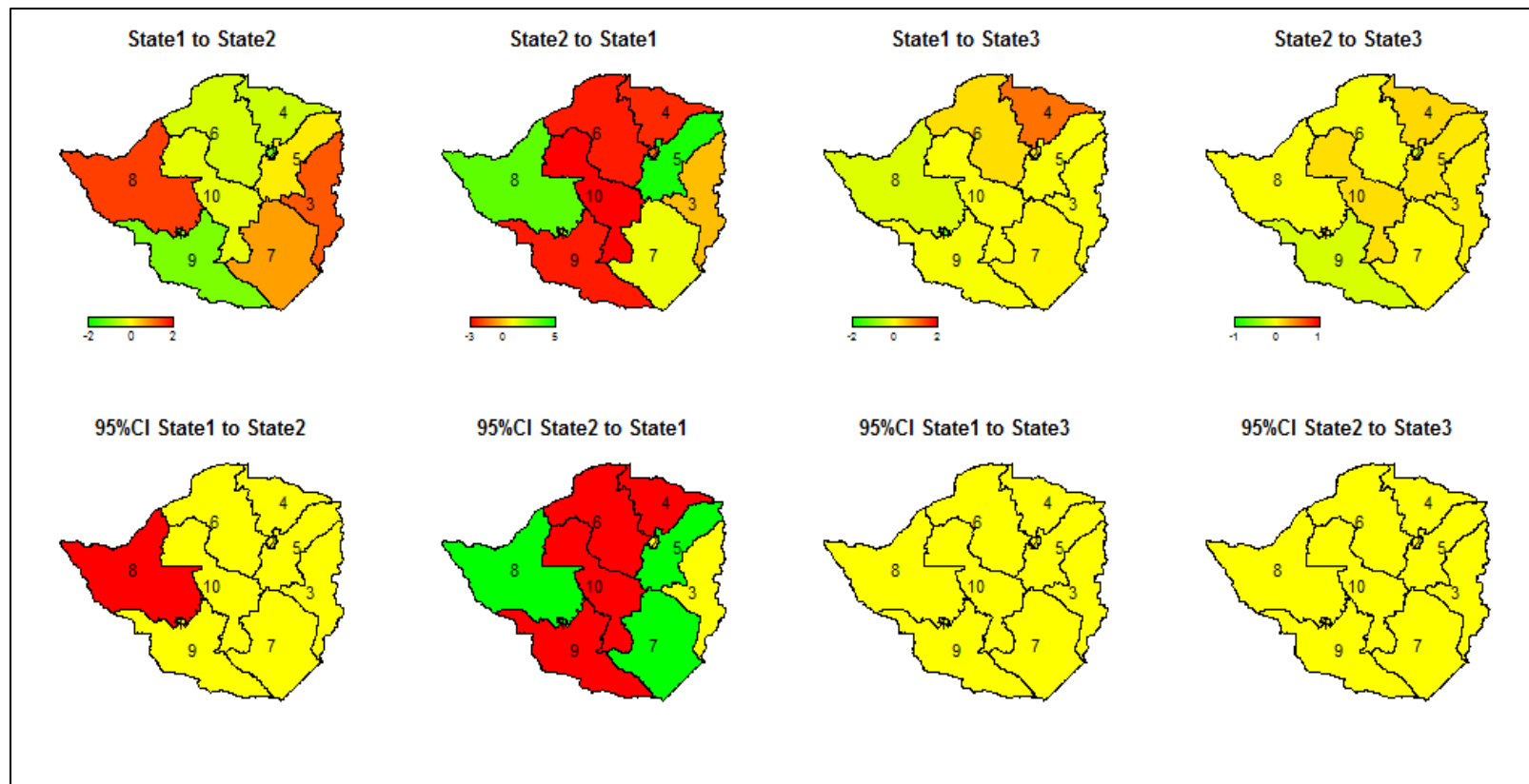


Figure 6-5: Smooth spatial effects posterior means of provinces in Zimbabwe (top panel) and their corresponding 95% credible intervals (bottom panel) from the fully Bayesian inference

6.5. Discussion

The major aim of this study was to determine the spatial heterogeneity of viral suppression and viral rebound trajectories from a subset of the Zimbabwe national ART programme data using a Bayesian geoaddivitive multistate model. To our knowledge, this is the first application of spatial effects within the multistate models' framework since none of the models in the original design has included the spatial random effects. Use of multistate Bayesian models in HIV studies is also scarce in the literature compared to the maximum likelihood multistate models; however, these Bayesian models are equally robust despite being computationally intensive. The fitted model in this study was adjusted for the effects of fixed covariates (gender and WHO status), continuous covariates (age) and individual heterogeneity for unobserved variation were assessed. This study observed that there were variations on the viral transition patterns by geographical region, age, gender and WHO status in the Zimbabwean cohort.

6.5.1. Epidemiological discussion

The study findings showed that the log-baseline hazard rates for the viral load suppression to undetectable levels (state 2 to state 2) transition were as expected. The longer the patient was on ART, the more likely that patient was to attain viral suppression to undetectable levels. This is a good indication of how ART helps one to regress to a better state with time by improving viral suppression. This finding affirms the primary objective of ART which is to sustain viral suppression leading to a dramatic decrease in HIV transmission in the general population and improves survival outcomes of the individuals through immune function reconstitution(178). Moreover, attaining a viral suppression is crucial for people living with HIV so that their life expectancy can be comparable to HIV uninfected population (178). The observed results also put

forward the fact that patients who are initiated on ART while they have advanced illness tend to adhere to their medication anticipating to recover and prolong their lives together with their families (106).

Surprisingly, male patients were more likely to attain viral suppression compared to female patients; however, male patients with high viral load measurements were more likely to die than recover. The higher risk of mortality among males can be explained by the poor immunological response to treatment associated with male patients resulting in deaths (164). Male patients also have poor health-seeking behaviour compared to females which may result in late HIV diagnosis and delayed ART initiation (179). For this subpopulation, interventions which minimize mortality targets high-risk behaviour changes and increase the gravity of ART adherence are crucial to achieving and sustaining viral suppression among males. For instance, rapid roll-out and promotion of self-testing campaigns (31) for people who do not usually go and seek voluntary HIV testing in health facilities should be strengthened to promote community-based testing (29,30). The 30-60 years aged patients showed a higher effect of attaining viral suppression in this study, while adolescents and young adult subpopulations showed lower effects. This finding aligns with previous studies indicating that adolescents and young adult subpopulations experience suboptimal clinical outcomes and face different challenges which may result in treatment non-adherence (178). The adolescence group is also known to be vulnerable as they are in the dynamic life transition of becoming independent (132). Young adults group may not fully understand the gravity of ART adherence; hence, health care and social service providers should compassionately offer continual counselling support to improve retention.

The log-baseline hazard rates for the viral rebound transition also increased with increase in time. Aligning with the ultimate goal of potent and effective ART treatment, one would anticipate a decrease in the viral rebound (state 1 to state 2) transition rates over time; however, since the opposite transition pattern was observed in this cohort, sustaining viral suppression is still a challenge in HIV treatment. The observed viral rebound result can be explained by the fact that once individuals attain viral suppression, they may think they are fully healthy again and no longer needs treatment. This results in treatment interruptions which can trigger treatment defaulting, treatment non-adherence, treatment failure or treatment resistance (121,122,180). Other studies have shown that majority of patients who attain a viral rebound are more likely to experience poor ART outcomes like HIV disease progression, loss to follow-up and mortality resulting in poor patient retention in HIV care(178).

Interestingly, this study observed that adolescence and young adults aged below 30 years were found to have a higher risk of viral rebound. This finding supports previous studies that have shown that adolescence and young adults are less likely to achieve and sustain viral suppression(181), and can be explained by the fact that the below 30 years age group faces different life encounters which may lead to treatment non-adherence putting them at risk of unsustained viral load suppression and consequently viral rebound(132,178). We also observed that older patients age 60 years and above) had a high risk of attaining viral rebound in this cohort. This can be explained by the fact that this group is associated with non-communicable comorbidities like hypertension, diabetes and cancers in addition to communicable illnesses like tuberculosis associated with HIV infection (182). These comorbidities result in multiple drug toxicity which may trigger non-adherence and subsequently viral rebound. Therefore, pharmacological services should aim to continue providing potent and effective ART regimens

with minimum side-effects and less prone to resistance to achieve treatment adherence and viral suppression (8). Not only can viral rebound results in death outcomes but also in an upsurge in vulnerability to opportunistic infections since the immune system becomes weaker; and this is supported by the observed high risk of viral rebound among patients with advanced WHO clinical stages in this study.

The smooth spatial effects show that patients from the region which borders with Botswana and Zambia were at a higher risk of viral rebound. This finding could be supported by the fact that this region has a lot of migration of Zimbabweans visiting neighbouring countries for job seeking, tourism activities which attract diverse people into the country and it has the long truck route connecting into neighbouring countries. As a result, there is a high risk of multiple sex partners (93) and sex for money activities (183) in this region which are a threat to viral suppression and promote viral rebound. Besides, the viral rebound spatial patterns depicted in this region could be due to non-adherence to treatment due to poor provider-patient relationships; hence, professional training of service providers on the proper code of conduct towards HIV patients is also critical. Another reason could be the treatment dispensary period of three months which might be short, especially for people who visit neighbouring countries for jobs; hence, revising these guidelines to cover 6 months can be considered. In this region, individuals may face transport challenges due to the poor road networks and terrain, particularly in rural areas of this region. Interventions like ART adherence clubs(122,141), functional mobile clinics or community-based dispensing points or other optional ART distribution strategies for these communities may be of benefit (89).

The smooth spatial effects for viral suppression show that patients from the regions stretching from the Botswana border to Zambia/Mozambique border were less likely to attain viral

suppression. This finding could be explained by late presentation (138), leading to delayed ART initiation (184); hence, immune recovery becomes slow in most instances. Interventions which were found to be effective include strengthening and intensifying index testing, lay testing, and community mobilization of testing-HIV musical galas campaigns in addition to self-testing campaigns (29,30).

6.5.2. Statistical discussion

Our modelling approach incorporated the spatial random effects in the flexible semiparametric predictor of the multistate model framework. This controlled for unobserved heterogeneity in addition to individual random effects which frequentist models cannot handle (94). Modelling approaches which control unobserved variations in epidemiological studies are of importance to get unbiased estimates and reflect reality. The spatial component was split into spatial correlated (structured) and the spatial uncorrelated (unstructured) components. This convolution modelling approach was preferred since it fully accounts for the spatial heterogeneity (84). This enables one to address essential public health aspects that are beyond the scope of a simple pictorial analysis. Moreover, the transition intensities were assumed to change with time as compared to the time homogenous assumption normally considered in frequentist multistate models.

Our findings should be interpreted cautiously, participants used in this study were conveniently sampled from the Zimbabwe national ART programme ePMS database based on having two consecutive viral load measurements leading to participant selection bias; hence, this small sample might not be a true representation of all ART patients in Zimbabwe over this period in time and may negatively impact on the generalizability and inference of the observed results. In other words, the data should be viewed as a non-random representation from all those who are on

ART in Zimbabwe. Relatively few death outcomes were observed in this study which could be due to under-reporting of the deaths in the ePMS database. This has an effect on the underestimation of the linear predictors of mortality which directly affect the mortality rates estimation. Moreover, the model assumed right censoring of observations since it cannot support interval censoring. However, going forward the statistical analysis approach used provides useful information to epidemiologist, patients and policymakers on the spatial variations of viral load transitions for HIV/AIDS disease progression and death.

This study acknowledges how the data was collected from patients. The WHO recommends that viral load monitoring should be done at baseline and after every six months (185); however, in resource-limited settings, differential monitoring was encouraged and mainly targets those patients with clinical signs which require viral load assessment as recommended by the doctor for patient management. However, most of the time covered by this study is when the Zimbabwean country conducted differential monitoring of CD4 and viral load measurements due to limited resources(139). This means, after achieving viral suppression, most of these patients did not have another viral load measurement taken until they had clinical signs which justify a viral load measurement to be taken; however, since 2016 there have been significant strides towards viral loads measurements monitoring are per WHO recommendations for HIV monitoring (8).

This measurement pattern which was done due to limited resources in the country may give biased inferences of results since ART patients in this analysis are predominantly those with conditional viral load measurements based on the physician discretion. This viral load measurement pattern may have affected the obtained transition trajectories obtained in this study and hence their inferences. We also did not consider ART adherence in this study which is an

important predictor of viral suppression and viral rebound since it was not measured in the data; therefore, future research should take note of these influential variables. The fitted model had only one absorbing state for death and excluded becoming loss to follow-up (LTFU), which is a potential threat to "leakages" within the HIV continuum of care. The reason for excluding this state was to reduce the model complexity as many transition processes may result in non-convergence of the models or the model may take longer (hours or days) to converge. However, a sub-analysis of this ART outcome among these patients considered in this manuscript showed that patients who were likely to become LTFU were those who had a high viral load of above 50copies/uL compared to those with undetectable viral load, $p\text{-value} < 0.05$. This finding shows that much sicker patients leave the programme compared to healthier patients.

Additionally, the difference between the spatial regions in viral suppression or viral rebound may be due to the small sample sizes of participants in these regions which might not completely represent the regional picture had the estimated been weighted or increased in sample size. However, our results for the spatial viral rebound transitions align with the ZIMPHIA 2015/16 national survey in the sense that, this region with the highest likelihood of viral rebound was estimated to have the second-highest HIV above 20% (10). This correlates to the fact that the regions with high viral rebound are prone to have a high risk of viral transmission leading to high HIV infections in the general population.

Moreover, the variances in health facilities which offer ART services in the country could have influenced the observed results in the sense that, regions with fewer health facilities result in poor HIV disease progression outcomes since access to treatment is not as easy as those regions with multiple health facilities. Health facility sites variations may also have brought some differences in that, those health facilities in urban or cities are known to perform better in terms

of ART patients support and service provision compared to rural health facilities. Despite these limitations, important information regarding viral suppression and viral rebound transitions and the associated spatial heterogeneity patterns were determined using the Bayesian geospatial multistate model. The subpopulation groups of people with a high risk of suboptimal viral rebound and mortality were also identified.

6.5.3. Conclusion

This study demonstrated the first inclusion of spatial random effects in Bayesian multistate models' framework implemented in the C++ BayesX free software and we observed that the viral suppression transitions were not static. The inclusion of spatial effects in multistate models is of profound relevance in resource-limited settings in the evolving modelling techniques. Structured maps are useful for policymakers to visually identify high-risk regions and interventions on those areas unveiling eminent outcome risk (36). Further studies need to consider the effects of CD4 cell counts on the viral load suppression and rebound transitions to get improved outcomes from a Bayesian perspective(44).

Suboptimal adherence and poor retention in care increase the risk of viral rebound, particularly among adolescence and young adult subpopulation. Holistic intervention approaches which may be considered include self-monitoring, peer support, patient follow-ups, treatment refill mobile phone reminders, and patient and caregiver educational support. Health literacy and belief are major barriers to ART adherence; hence, interventions which include education sessions on ART addressing the negative effects of beliefs in divine healing, the inclination for traditional medicine and misconceptions over ART benefits and safety are crucial to achieve and sustain viral suppression.

Moreover, models which expedite treatment uptake for the newly diagnosed patients coupled with tailored approaches for adolescence, young adults and males subpopulations should be developed to promote early diagnostics and ART uptake, reduce barriers to care and subsequently to achieve optimal health of these subpopulations. Most promising interventions which improve ART adherence and patient retention in care through minimizing “leakages” in the HIV continuum of care cascade are essential for all patients in care and should be the focus of HIV treatment and prevention in the pursuit of the UNAIDS 90-90-90 fast track targets.

6.5.4. Author’s contribution

ZMZ conceived the idea and performed all the analyses. **EM** guided and oversaw the analysis. **ZMZ**, **EM**, **JT** and **TFC** contributed to the interpretation of the results. **ZMZ** drafted the manuscript. All authors reviewed the manuscript critically for and approved the final version submitted for publication.

6.6. Chapter 6 Appendix section

6.6.1. Introduction

Modelling data with the following characteristics: a dependent variable is a waiting time until the occurrence of an event; observations are censored where the event of interest has not occurred during the observed time, and the data has predictors whose effect on the waiting time is of interest. To be able to tackle this, we make use of survival models, and their basic functions are the survival and hazard functions which are illustrated below.

6.6.2. Appendix 1: The Survival function

Assuming T to be a continuous random variable with a known probability density function $f(t)$; the cumulative distribution function is defined as the probability that the event has occurred by duration time t :

$$F(t) = P(T < t) = 1 - \int_0^t f(s) ds \quad (F.1)$$

Often, much interest is on getting the probability that the event of interest has not occurred by duration time t . This leads to the following expression, which is a compliment of the cumulative distribution function, the *survival function* in convectional survival models:

$$S(t) = P(T \geq t) = 1 - F(t) = \int_t^{\infty} f(x) dx \quad (F.2)$$

6.6.3. Appendix 2: The hazard function

An alternative characterization of T is the *hazard function* $\lambda(t)$ defined as the instantaneous rate of occurrence of the event. In continuous time, $\lambda(t)$ is expressed as:

$$\lambda(t) = \lim_{\delta t \rightarrow 0} \frac{P(t \leq T < (t + \delta t) / T \geq (t))}{\delta t} = \lim_{\delta t \rightarrow 0} \frac{P(t, t + \delta t)}{\delta t} \quad (F.3)$$

The numerator of the Equation (F.3) is the conditional probability that the event will occur in the interval $(t, t + \delta t)$ given that it has not occurred before while the denominator is the width of the interval. This conditional probability may be written as a ratio of a joint probability that T is in the interval $(t, t + \delta t)$ and $T \geq (t)$, to the probability of the condition $T \geq (t)$. In other words, the hazard rate is a quotient of the probability density function $f(t)$ and the survival function $S(t)$. Further expanding Equation (F.3) yields:

$$\lambda(t) = \lim_{\delta t \rightarrow 0} \frac{P(T \geq (t) / t \leq T < (t + \delta t)) P(t \leq T < (t + \delta t))}{P(T \geq (t)) \delta t} \quad (\text{F.4})$$

But $f(t) = \lim_{\delta t \rightarrow 0} \frac{P(t \leq T < (t + \delta t))}{\delta t}$, $P(T \geq (t) / t \leq T < (t + \delta t)) = 1$ and from Equation (F.2) $P(T \geq t) = S(t)$. Substituting these into Equation (F.4) yields:

$$\lambda(t) = \frac{f(t)}{S(t)} \quad (\text{F.5})$$

From Equation (F.5) above, $-f(t)$ is the derivative of $S(t)$, explicitly expressed as $f(t) = \frac{d}{dt} F(t) = \frac{d}{dt} P(T < t) = \frac{d}{dt} (1 - S(t)) = -\frac{d}{dt} S(t)$. Therefore, Equation (F.5) becomes

$$\lambda(t) = \frac{f(t)}{S(t)} = \frac{-\frac{d}{dt} S(t)}{S(t)} = \frac{-S'(t)}{S(t)}. \quad (\text{F.6})$$

Integrating both sides of this latest expression: $\int_0^t \lambda(t) dt = \int_0^t -\frac{d}{dt} S(t) \times \frac{1}{S(t)} dt$ and simplifying the right-hand side (RHS) using integration by parts, $u = -\frac{d}{dt} S(t)$ and $v = \frac{1}{S(t)}$ yields:

$$\int_0^t \lambda(t) dt = -\frac{d}{dt} S(t) \left(\frac{1}{S(t)} \right) - \int_0^t \frac{1}{S(v)} dv = -[\log S(t) - \log S(0)] \quad (\text{F.7})$$

If we differentiate both sides, $\frac{d}{dt} \int_0^t \lambda(t) dt = \frac{d}{dt} -\log S(t)$, we get the hazard rate expressed in terms of the derivative of log survival function:

$$\lambda(t) = \frac{d}{dt} -\log S(t) \quad (\text{F.8})$$

To obtain the expression of the survival function, we integrate both sides of Equation (F.8):

$$\int_0^t \lambda(t) dt = \int_0^t \frac{d}{dt} -\log S(t) dt = -\log S(t)$$

Re-arranging this expression above gives the survival function as an exponential distribution with a parameter $\lambda(t)$ as:

$$S(t) = \exp \left[- \int_0^t \lambda(t) dt \right] \quad (F.9)$$

The integral expression is called the *cumulative hazard* (or cumulative risk) $\Lambda(t)$, which is a sum of all risks from duration 0 to t , denoted by:

$$\Lambda(t) = \int_0^t \lambda(t) dt \quad (F.10)$$

In summary, these results show that the survival function and the hazard function give an equivalent characterization of the distribution of the random variable T . If provided with $S(t)$, we differentiate to obtain $f(t)$ and estimate $\lambda(t)$ using Equation (F.5). Alternatively, starting with $\lambda(t)$, we can integrate and obtain $\Lambda(t)$ and exponentiate to get $S(t)$ using Equation (F.9).

In time-to-event modelling, the probability density function $f(t)$ plays a central role. Similarly, we can obtain the density as follows, using Equation (F.5), we integrate both sides

$$\int_0^t \lambda(t) dt = \int_0^t \left(\frac{f(t)}{S(t)} \right) dt = \int_0^t \left(\frac{f(t)}{1 - F(t)} \right) dt = \int_0^t \left(\frac{f(s)}{1 - \int_0^t f(s) ds} \right) ds. \text{ If we integrate the RHS by}$$

parts, $u = f(s), v = \frac{1}{1 - \int_0^t f(s) ds}$ this gives:

$$\begin{aligned} \int_0^t \left(\frac{f(s)}{1 - \int_0^t f(s) ds} \right) ds &= \frac{f(s)}{1 - \int_0^t f(s) ds} - \int_0^t \left(\frac{1}{1 - \int_0^t f(v) dv} \right) dv \\ &= \frac{-\frac{d}{dt} S(t)}{[1 - F(t) = S(t)]} - \log \left[1 - \int_0^t f(v) dv \right]_0^t \\ &= -\log \left[1 - \int_0^t f(t) dt \right] \end{aligned} \quad (F.11)$$

With this expression, $\int_0^t \lambda(t) dt = -\log \left[1 - \int_0^t f(t) dt \right]$ can be rearranged as:

$$S(t) = \exp \left(- \int_0^t \lambda(t) dt \right) = 1 - \int_0^t f(t) dt, \quad (F.12)$$

and if we differentiate both sides of Equation (F.12), we get:

$$\begin{aligned}\frac{d}{dt} \exp\left(-\int_0^t \lambda(t) dt\right) &= \frac{d}{dt} \left(1 - \int_0^t f(t) dt\right) \\ \frac{d}{dt} \exp\left(-\int_0^t \lambda(t) dt\right) &= \frac{d}{dt} (1 - F(t)) \\ -\lambda(t) \exp\left(-\int_0^t \lambda(t) dt\right) &= -f(t)\end{aligned}\tag{F.13}$$

This solution leads to the probability density function, which is fundamental in time to event analysis:

$$f(t) = \lambda(t) \exp\left(-\int_0^t \lambda(t) dt\right)\tag{F.14}$$

From Equation (F.14), we can see that the probability density function is a product of transition (hazard) rate and the survival function.

6.6.4. Appendix 3: Likelihood function

The likelihood function of the survival model is just a product of the probability density function, Equation (F.14).

$$L = \prod_{i=1}^n \lambda_i(t_i)^{\delta_i} \exp\left(-\int_0^t \lambda_i(t) dt\right) = \prod_{i=1}^n \lambda_i(t_i)^{\delta_i} S(t_i)\tag{F.15}$$

where $i = 1, 2, \dots, n$ individuals and δ is the censoring indicator for the process. Taking the logs, and recalling the link between $S(t)$ and $\Lambda(t)$, we obtain the log-likelihood function of the censored survival data. Simplifying the product sign:

$$\begin{aligned}L &= \prod_{i=1}^n \lambda(t_i)^{\delta_i} \exp\left(-\int_0^t \lambda(t) dt\right) \\ L &= \lambda(t_i)^{\sum_{i=1}^n \delta_i} \exp\left(\sum_{i=1}^n -\int_0^t \lambda(t) dt\right)\end{aligned}\tag{F.16}$$

Taking logs both sides:

$$\begin{aligned}\log L &= \log \lambda(t_i)^{\sum_{i=1}^n \delta_i} \left(\sum_{i=1}^n - \int_0^t \lambda(t_i) dt \right) \\ \log L &= \sum_{i=1}^n \delta_i \log \lambda(t_i) - \left(\sum_{i=1}^n \Lambda(t_i) \right)\end{aligned}\tag{F.17}$$

Hence, the final expression for the log-likelihood would be:

$$\log L = \sum_{i=1}^n (\delta_i \log \lambda(t_i) - \Lambda(t_i))\tag{F.18}$$

From this expression, we can get the maximum likelihood estimator as follows: Let $D = \sum_{i=1}^n \delta_i$ be

the total observed outcomes during the period under observation, $T = \sum_{i=1}^n t_i$ be the total

observation/exposure time and $\lambda(t_i) = \lambda$ for all t and the cumulative risk is the integral of a constant; hence, is equal to $\lambda(t)$. If we differentiate with respect to λ we get:

$$\log L = D \log \lambda(t) - \lambda T, \text{ ie, } \frac{d \log L}{d \lambda} = D \lambda - T = 0$$

Therefore, the maximum likelihood estimator will be:

$$\hat{\lambda} = \frac{D}{T}\tag{F.19}$$

6.6.5. Appendix 4: The Cox proportional Hazard

A conventional method for analysing the effects of covariates on right-censored survival data defined by observed lifetimes t_i with censoring indicators for individuals $i = 1, 2, 3, \dots, n$ and additional covariate observations $\mathbf{v}_i$ is the semi-parametric Cox proportional hazard model (1972). The model focuses directly on the hazard function, where the hazard at a time t for an individual with a vector of covariates $\mathbf{V}$ is assumed to be:

$$\lambda_i(t) = \lambda_i(t/\mathbf{v}) = \lambda_0(t) \exp(\mathbf{v}'_i \boldsymbol{\gamma}) \quad (\text{F.20})$$

where $\lambda_0(t)$ is the baseline hazard function. Taking logs, the proportional hazard model becomes a simple additive model for the log of the hazard and separates the effects of time from the covariates, i.e.,

$$\log \lambda_i(t) = \log \lambda_i(t/\mathbf{v}) = \log \lambda_0(t) + \mathbf{v}'_i \boldsymbol{\gamma} \quad (\text{F.21})$$

The cumulative hazards are obtained by integrating Equation (F.21):

$$\int_0^t \lambda_i(t/\mathbf{v}) dt = \exp(\mathbf{v}'_i \boldsymbol{\gamma}) \int_0^t \lambda_0(t) dt, \text{ i.e., } \Lambda_i(t/\mathbf{v}) = \Lambda_0(t) \exp(\mathbf{v}'_i \boldsymbol{\gamma}) \quad (\text{F.22})$$

The survival function is obtained by multiplying Equation (F.22) by a negative sign and exponentiating both sides. This gives:

$$\exp \int_0^t -\lambda_i(t/\mathbf{v}) dt = \exp \left(\int_0^t -\lambda_0(t) \exp(\mathbf{v}'_i \boldsymbol{\gamma}) dt \right), \text{ i.e., } S_i(t/\mathbf{v}) = S_0(t) \exp(\mathbf{v}'_i \boldsymbol{\gamma}) \quad (\text{F.23})$$

6.6.6. Appendix 5: The description of the multistate model

When an individual is observed longitudinally, he/she is likely to experience multiple outcomes in the course of the follow-up period. In such a scenario, Cox proportional hazards are not appropriate since there will be multiple outcomes; hence, multiple possible transitions. In this regard, the multistate models are preferred to estimate the transition rates/intensities of these individuals simultaneously.

A multistate process is a stochastic process $(X(t), t \in T)$ with finite state space $S = \{1, 2, \dots, R\}$ where $T = [0, \tau]$ is a non-negative, continuous random variable denoting the survival time of an individual and $X(t)$ is the state occupied by an individual at a time $t > 0, X(t) \in S$ (50). The standard functions governing the multistate models are the transition intensities (hazard rates)

and transition probabilities (survival function). The individual-specific transition intensity for the transition j to k , i.e., $\lambda_{jk,i}(t)$, with covariates $\mathbf{v}_i(t)$ and parametric effects γ_{jk} is estimated in a multiplicative proportional hazard model way define in Equation (F.20) as:

$$\lambda_{jk,i}(t) = \lambda_{jk,i}(t / \mathbf{v}) = \lambda_{jk,0}(t) \exp(\mathbf{v}_i'(t) \gamma_{jk}) \quad (\text{F.24})$$

This semiparametric model hazard rate can be calculated in two ways, either through a piecewise exponential model assuming that all time-dependent values are piecewise constant (175) or through estimating the log-baseline effect by a P-spline prior of arbitrary degree with a second-order penalty (80). The latter is a more general way to model the nonlinear shape of the baseline effect. The log-baseline is defined as $\lambda_{jk,0}(t) = \exp[\log\{\lambda_{jk,0}(t)\}]$ this updates Equation (F.24) to

$$\lambda_{jk,i}(t) = \exp(\eta_{jk,i}(t)) \quad (\text{F.25})$$

where

$$\eta_{jk,i}(t) = \exp(\log \lambda_{jk,0}(t) + \mathbf{v}_i'(t) \gamma_{jk}) = \exp(g_{jk,0}(t) + \mathbf{v}_i'(t) \gamma_{jk}) \quad (\text{F.26})$$

and the log-baseline hazard rate is reparametrized to $g_{jk,0}(t) = \log(\lambda_{jk,0}(t))$ which is the nonparametric baseline effects uniform for all individuals. The linear predictor $\eta_{jk,i}(t)$ is flexible and different types of covariates can be added, including continuous covariates with nonparametric effects, spatial terms and random effects in addition to the fixed parametric effects. Including such covariates use in this study, we have:

$$\eta_{jk,i}(t) = g_{jk,0}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + \mathbf{v}_i(t)' \gamma_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \quad (\text{F.27})$$

where $f_{jk,r}(t) x_{r,i}(t)$ are nonlinear effects of a continuous covariate $x_{r,i}(t)$ (age; parametric fixed effects γ_{jk} of covariates $\mathbf{v}_i(t)$ we had WHO clinical stages (I/II or III/IV) and gender (male or female; the

function $f_{jk,spat}(t)(s_i)$ is a structured spatial effect, where $s, s = 1, 2, \dots, S$, is a spatial index with $s_i = s$ if an individual i is from province S to account for spatial heterogeneity. The spatial effect can be split into structured (correlated) and unstructured (uncorrelated), that is, $f_{jk,spat}(t)(s_i) = f_{jk,str}(t)(s_i) + f_{jk,unstr}(t)(s_i)$. The parameter $b_{jk,i}$ is a subject or group-specific frailty or random effect.

6.6.7. Appendix 6: Likelihood specification in multistate models

Similarly, the likelihood in the multistate model is the product of the probability density function within the survival data which is generally exponentially distributed, as defined in Equation (F.14); however, we specify the transition as:

$$f_{jk,i}(t) = \lambda_{jk,i}(t_i) \exp\left(-\int_0^{t_i} \lambda_{jk,i}(t) dt\right) \quad (F.28)$$

In this case, the integral evaluates or sum all transitions the corresponding individual is at risk for the period under observation. We assume that a full transition path occurs for each individual of the following parts: A set of ordered time points $0 = S_{i0} < S_{i1} < \dots < S_{iz} < \dots < S_{im_i}$ indicating the transition times for an individual i , the state $Y_i(S_{iz}), z = 0, \dots, m_i$, the individual moves to at the end of the time interval and where each individual contributions is defined in terms of transition indicators $\delta_{jk,i}(t)$ which is equal to one if a jk transition before time (t) and zero. We can deduce the duration time in the z^{th} state as $T_{iz} = S_{iz} - S_{i,z-1}, z = 1, \dots, m_i$.

Rewriting the observation model (Equation F.27) in generic matrix notation, we define some matrices. Let $\boldsymbol{\eta}_{jk} = (\eta_{jk,1}, \eta_{jk,2}, \dots, \eta_{jk,n})'$ be a predictor vector, where $\eta_{jk,i} = \eta_{jk,i}(t_i)$ is the predictor value (Equation F.27) at the observed time $t_i, i = 1, 2, \dots, n$. Correspondingly, let

$\mathbf{f}_{jk,r} = (f_{jk,r}(x_{1r}), f_{jk,r}(x_{2r}), \dots, f_{jk,r}(x_{nr}))'$ denotes the vector of functions $f_{jk,r}(x_r), r=1,2,\dots,R$;

$\mathbf{f}_{jk,spat} = (f_{jk,spat}(s_1), f_{jk,spat}(s_2), \dots, f_{jk,spat}(s_n))'$ denotes the vector of spatial effects and

$\mathbf{b}_{jk,i} = (b_{jk,1}, b_{jk,2}, \dots, b_{jk,n})'$ denote a vector of uncorrelated spatial and individual-specific random

effects. The predictor components $\mathbf{f}_{jk,r}$, $\mathbf{f}_{jk,spat}$ and $\mathbf{b}_{jk,i}$ can be expressed as the matrix product of

a defined design matrix $\mathbf{Z}$ and a (high dimensional) vector of random effects

$\boldsymbol{\beta} = (\boldsymbol{\beta}_{jk,1}, \boldsymbol{\beta}_{jk,2}, \dots, \boldsymbol{\beta}_{jk,p})'$ of (regression) coefficients parameters for $r=1,2,\dots,p$; for instance,

$(\mathbf{f}_{jk,r} = \mathbf{Z}_{jk,r} \boldsymbol{\beta}_{jk,r})$. After re-indexing the observable transitions in the multistate model, we can

represent the predictor vector $\boldsymbol{\eta}_{jk}$ in a generic notation as:

$$\boldsymbol{\eta}_{jk} = \mathbf{V}\boldsymbol{\gamma} + \mathbf{Z}_{jk,1}\boldsymbol{\beta}_{jk,1} + \mathbf{Z}_{jk,2}\boldsymbol{\beta}_{jk,2} + \dots + \mathbf{Z}_{jk,p}\boldsymbol{\beta}_{jk,p} \quad (\text{F.29})$$

With reference to this current study, the generic notation becomes

$$\boldsymbol{\eta}_{jk} = \mathbf{V}\boldsymbol{\gamma} + \mathbf{Z}_{jk,1}\boldsymbol{\beta}_{jk,1} + \mathbf{Z}_{jk,2}\boldsymbol{\beta}_{jk,2} + \mathbf{Z}_{jk,3}\boldsymbol{\beta}_{jk,3} \quad \text{for } 1=\text{nonlinear continuous effects, } 2=\text{spatial effects}$$

and 3= random effects accounting for heterogeneity. The individual likelihood for continuous

survival data assumes non-informative censoring, given the parameters

$$\boldsymbol{\gamma}_{jk,c} = (\gamma'_{jk,1}, \gamma'_{jk,2})', \boldsymbol{\tau}_{jk,q}^2 = (\tau_{jk,r}^2, \tau_{jk,gi}^2, \tau_{jk,spat}^2)' \text{ and } \boldsymbol{\beta}_{jk,r} = (\beta'_{jk,1}, \beta'_{jk,2}, \beta'_{jk,3})', \text{ the probability density}$$

function with specified transition expressed as:

$$L(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\tau}^2) = \prod_{i=1}^{JK} \lambda_i(t_i)^{\delta_{jk,i}(t_i)} \exp\left(-\int_0^{t_i} \lambda_i(t) dt\right) \quad (\text{F.30})$$

Considering the individual transition times $S_{zi}, z=1,2,\dots,m_i$ corresponding to a transition process yields:

$$L(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\tau}^2) = \prod_{z=1}^{m_i} \prod_{i=1}^{JK} \lambda_i(S_{zi})^{\delta_{jk,i}(S_{zi})} \exp \left(- \int_{S_{i,z-1}}^{S_{zi}} \lambda_i(t) dt \right) \quad (\text{F.31})$$

If we take logs both sides and simplify the product, we get:

$$\log L(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\tau}^2) = (\log \lambda_i(S_{zi})) \sum_{i=1}^{m_i} \sum_{i=1}^{JK} \delta_{jk,i}(S_{zi}) - \sum_{z=1}^{m_i} \sum_{i=1}^{JK} \left(\int_{S_{i,z-1}}^{S_{zi}} \lambda_i(t) dt \right) \quad (\text{F.32})$$

From the classical counting process theory, the intensity processes $\alpha_{jk,i}(t)$ are a product of the hazard rate for a specified transition $(\lambda_{jk,i}(t))$ constructed in terms covariates as shown in Equation (F.27); and a predictable at-risk indicator process $(I_{jk,i}(t))$ which is equal to one if an individual is at risk of a jk transition before time (t) and zero otherwise, that is,

$$\alpha_{jk,i}(t) = \lambda_{jk,i}(t) \times I_{jk,i}(t) \quad (\text{F.33})$$

Considering the log-likelihood formula for the same data by including the risk indicator process $(I_{jk,i}(t))$ yields:

$$\log L(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\tau}^2) = (\log \lambda_i(S_{zi}) \times I_{jk,i}(S_{zi})) \sum_{i=1}^{m_i} \sum_{i=1}^{JK} \delta_{jk,i}(S_{zi}) - \sum_{z=1}^{m_i} \sum_{i=1}^{JK} \left(\int_{S_{i,z-1}}^{S_{zi}} (I_{jk,i}(S_{zi})) \lambda_i(t) dt \right) \quad (\text{F.34})$$

which simplifies to

$$\begin{aligned} \log L(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\tau}^2) &= \left(\sum_{i=1}^{m_i} \sum_{i=1}^{JK} \delta_{jk,i}(S_{zi}) \log \lambda_i(S_{zi}) \times I_{jk,i}(S_{zi}) \right) - \sum_{z=1}^{m_i} \sum_{i=1}^{JK} \left(\int_{S_{i,z-1}}^{S_{zi}} (I_{jk,i}(S_{zi})) \lambda_i(t) dt \right) \\ &= \sum_{i=1}^{m_i} \sum_{i=1}^{JK} \left[(\delta_{jk,i}(S_{zi}) \log \lambda_i(S_{zi}) \times I_{jk,i}(S_{zi})) - \left(I_{jk,i}(S_{zi}) \int_{S_{i,z-1}}^{S_{zi}} \lambda_i(t) dt \right) \right] \end{aligned} \quad (\text{F.35})$$

where $\lambda_i(S_{zi})$ is defined by Equation (F.27) to give the final expression as:

$$\log L(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\tau}^2) = \sum_{i=1}^{m_i} \sum_{j=1}^{JK} \left[\delta_{jk,i}(S_{zi}) \times I_{jk,i}(S_{zi}) \times \log \left(g_{jk,0}(S_{zi}) + \sum_{r=1}^R f_{jk,r}(S_{zi}) x_{r,i}(S_{zi}) + \mathbf{v}_i(S_{zi})' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(S_{zi})(s_i) + b_{jk,i} \right) - (I_{jk,i}(S_{zi})) \times \int_{S_{i,z-1}}^{S_{zi}} \left(g_{jk,0}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + \mathbf{v}_i(t)' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \right) dt \right] \quad (\text{F.36})$$

Let $\boldsymbol{\delta}_{jk,i} = (\delta_{jk,1}, \delta_{jk,2}, \dots, \delta_{jk,n})'$ be a vector of censoring indicators and $\boldsymbol{\Lambda}_{jk,i} = (\Lambda_{jk,1}(t), \Lambda_{jk,2}(t), \dots, \Lambda_{jk,n}(t))'$ the vector of cumulative hazard rates $\Lambda_{jk,i}(t_i) = \int_0^{t_i} \lambda_{jk,i}(t) dt$. Then the log-likelihood can be expressed in terms of cumulative hazard function as:

$$\log L(\boldsymbol{\gamma}, \boldsymbol{\beta}, \boldsymbol{\tau}^2) = \boldsymbol{\delta}_{jk,n}' \boldsymbol{\eta}_{jk,n} - \mathbf{1}' \boldsymbol{\Lambda}_{jk,n} \quad (\text{F.37})$$

If the degree of the P-spline prior for the log-baseline hazard function is greater than one, then the likelihood integral can no longer be solved in a closed-form.

6.6.8. Appendix 7: The prior specifications

(1) Priors for functions and spatial components (*random effects (regression) coefficients parameter vector $\boldsymbol{\beta}_{jk,r}$*) are defined by a suitable design matrix $\mathbf{Z}_{jk,r}$ for $r = 0, 1, \dots, p$ and a joint prior of the parameter vector $\boldsymbol{\beta}_{jk,r}$ in Equation (F.29) is Gaussian expressed as:

$$P(\boldsymbol{\beta}_{jk,r} / \tau_{jk,r}^2) \propto \exp \left(- \frac{\boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,r}^2} \right) \quad (\text{F.38})$$

where $\mathbf{W}_{jk,r} \geq 0$ is a precision or penalty matrix of rank $(\mathbf{W}_{jk,r}) = h_{jk,r}$ with a band structure that is very useful for computationally efficient Markov Chain Monte Carlo (MCMC) updating schemes.

(2) Unknown *nonparametric effects* $f_{jk,r}(t)$ of continuous smooth covariate x_r are estimated using Bayesian penalized splines (P-spline) (173) as a linear combination of a larger number of B-splines basic functions B_d , that is,

$$f_{jk,r}(x_r) = \sum_{d=1}^{D_r} \beta_{jk,rd} B_d(x_r) \quad (\text{F.39})$$

The Bayesian analogue is the second-order random walk smoothness priors of the form:

$$\beta_{jk,rd} = 2\beta_{jk,r,d-1} - \beta_{jk,r,d-2} + \varepsilon_{jk,rd}, d = 3, 4, \dots, D \quad (\text{F.40})$$

The error terms of the smoothing term $(\varepsilon_{jk,rd})$ identically and independently distributed assuming a normal distribution prior with mean zero and variance in the form of precision $(1/\sigma^2 = \tau_{jk,\varepsilon}^2)$, that is $(\varepsilon_{jk,rd} \sim N(0, \tau_{jk,\varepsilon}^2))$. The linear trend coefficients' initial values of the random walk were assigned diffuse/ vague priors, that is, $P(\beta_{jk,r1}) \propto \text{const}$ and $P(\beta_{jk,r2}) \propto \text{const}$.

(3) For *fixed effects parameters* $\gamma_{jk,c}$, we assigned non-informative diffuse prior, $P(\gamma) \propto \text{const}$.

Alternatively, a weak (large variance) normal prior would be another choice.

(4) For the *spatial effects*, we assumed the Gaussian Markov Random Field (GMRF) (81)

priors expressed as:

$$f_{jk,str}(s) = \beta_s^{str} = \frac{1}{N_s} \sum_{s' \in \partial_s} \beta_{s'} + u_s, u_s \sim N\left(0, \frac{\tau_{jk,str}^2}{N_s}\right) \quad (\text{F.41})$$

where $s' \in \partial_s$ denotes that province s' is a neighbour of the province s . The unstructured spatial effects

$f_{unstr}(s)$ were assumed to be independent and identically distributed Gaussian priors, that is,

$$f_{unstr}(s) \sim N(0, \tau_{unstr}^2).$$

(5) The individual *random effects and uncorrelated (unstructured) area-specific spatial effects*

$b_{jk,i}$ were assumed identically and independently distributed Gaussian priors with transition specific variances to the frailty terms:

$$b_{jk,i} \sim N(0, \tau_{jk,b}^2) \quad (F.42)$$

(6) The *variance parameter vector* $\tau_{jk,q}^2 = (\tau_{jk,1}^2, \tau_{jk,2}^2, \dots, \tau_{jk,y}^2)'$ for $q=1, 2, \dots, y$ contains a variance

parameter for the error term $\tau_{jk,\varepsilon}^2$, frailty term $\tau_{jk,b}^2$, spatial terms, $\tau_{jk,Str}^2$ and $\tau_{jk,unstr}^2$, and the

generic regression coefficients $\tau_{jk,r}^2$. These variance parameters are normally assigned weakly

informative inverse Gamma hyper-priors in fully Bayesian inference, that is, the vector

$(\tau_{jk,q}^2 \sim IG(a_q, b_q))$ with the following probability density function:

$$P(\tau_{jk,q}^2) \propto \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(-\frac{b_q}{\tau_{jk,q}^2}\right), \text{ for } a_q, b_q > 0 \quad (F.43)$$

Updating $\tau_{jk,q}^2$ is done using Gibbs Sampler by sampling from an inverse Gamma distribution.

The Bayesian model specification is complete by assuming that all priors for parameters are conditionally independent, and all priors are mutually independent. All the priors for the parameters are assumed, independent. Estimation is based on MCMC simulation technique.

6.6.9. Appendix 8: Posterior distribution

Let full Bayesian inference is based on the entire posterior distribution:

$$P(\beta, \gamma, \tau^2 / \text{data}) \propto L(\text{data} / \beta, \gamma, \tau^2) P(\beta, \gamma, \tau^2) \quad (F.44)$$

The likelihood is:

$$L(data / \beta, \gamma, \tau^2) = \prod_{z=1}^{m_i} \prod_{i=1}^{JK} \left\{ \left[\left(g_{jk,0}(S_{zi}) + \sum_{r=1}^R f_{jk,r}(S_{zi}) x_{r,i}(S_{zi}) + \mathbf{v}_i(S_{zi})' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(S_{zi})(s_i) + b_{jk,i} \right) (S_{zi}) \right]^{\delta_{jk,i}(S_{zi})} \right. \\ \left. \times \exp \left(- \int_{S_{i,z-1}}^{S_{zi}} \left(g_{jk,0}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + \mathbf{v}_i(t)' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \right) (t) dt \right) \right\} \quad (F.45)$$

The joint prior is made up of the individual prior distributions for the parameters. With particular reference to this current study, $\beta_{jk,r} = (\beta'_{jk, fixed\_effects}, \beta'_{jk, non\_linear\_effects}, \beta'_{jk, frailty\_term})'$ is a vector of all coefficients parameters from the generic formulation equation, and $\gamma_{jk,c} = (\gamma_{jk,WHO}, \gamma_{jk,sex})'$ is the vector of fixed effects and $\tau_{jk,q}^2 = (\tau_{jk,\varepsilon}^2, \tau_{jk,r}^2, \tau_{jk,spat}^2, \tau_{jk,b}^2)'$ the vector of all variance parameters, that is,

- a) the variance parameter of the error terms in the second random walk for non-parametric effects of continuous covariates $(\tau_{jk,\varepsilon}^2)$
- b) the variance parameter of the individual ad spatial uncorrelated random effects $(\tau_{jk,b}^2)$
- c) the variance parameter of the correlated (structured) random effects $(\tau_{jk,spat}^2)$
- d) variance parameter for the regression coefficients parameters $(\tau_{jk,r}^2)$

This means the variance vector $\tau_{jk,q}^2 = (\tau_{jk,\varepsilon}^2, \tau_{jk,r}^2, \tau_{jk,spat}^2, \tau_{jk,b}^2)'$ also follow an inverse Gamma

distribution as follows: $P(\tau_{jk,q}^2) \propto \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(-\frac{b_q}{\tau_{jk,q}^2}\right)$, for $a_q, b_q > 0$. Due to conditional

independence assumptions, the joint prior factorizes into taking into consideration that

$\tau_{jk,r}^2$ is same as $\tau_{jk,q}^2$, therefore :

$$\begin{aligned}
P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) &= \left\{ \prod_{q,r=0}^m P(\boldsymbol{\beta}_{jk,r} / \tau_{jk,q}^2) P(\tau_{jk,q}^2) \right\} P(\boldsymbol{\gamma}) \\
&= \left\{ \prod_{q,r=0}^m \exp\left(-\frac{\boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,q}^2}\right) \times \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(\frac{b_q}{\tau_{jk,q}^2}\right) \right\} P(\boldsymbol{\gamma}) \\
&= \left\{ \prod_{q,r=0}^m \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(\left(\frac{b_q}{\tau_{jk,q}^2}\right) - \frac{\boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,q}^2}\right) \right\} P(\boldsymbol{\gamma})
\end{aligned} \tag{F.46}$$

The last component $P(\boldsymbol{\gamma})$ can be omitted since it represents fixed effects prior; the expression can be further simplified to:

$$\begin{aligned}
P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) &\propto \prod_{q,r=0}^m \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(\left(\frac{b_q}{\tau_{jk,q}^2}\right) - \frac{\boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,q}^2}\right) \\
&= \frac{1}{(\tau_{jk,q}^2)^{m(a_q+1)}} \exp\left(\sum_{r=0}^m \left(\left(\frac{b_q}{\tau_{jk,q}^2}\right) - \frac{\boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,q}^2}\right)\right) \\
&= \left(\frac{1}{\tau_{jk,q}^{2m(a_q+1)}}\right) \exp\left(b_q m - \frac{1}{2} \sum_{r=0}^m \boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}\right)
\end{aligned} \tag{F.47}$$

The posterior distribution $P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2 / \text{data})$ will be an approximation of the product of Equation (F.45) and (F.47) as shown below:

$$\begin{aligned}
P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2 / \text{data}) &\propto \prod_{z=1}^{m_i} \prod_{i=1}^{JK} \left\{ \left[\left(g_{jk,0}(S_{zi}) + \sum_{r=1}^R f_{jk,r}(S_{zi}) x_{r,i}(S_{zi}) + \mathbf{v}_i(S_{zi})' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(S_{zi})(s_i) + b_{jk,i} \right) (S_{zi}) \right]^{\delta_{jk,i}(S_{zi})} \right. \\
&\quad \times \exp\left(-\int_{S_{i,z-1}}^{S_{i,z}} \left(g_{jk,0}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + \mathbf{v}_i(t)' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \right) (t) dt \right) \Big\} \\
&\quad \times \left(\frac{1}{\tau_{jk,q}^{2m(a_q+1)}} \right) \exp\left(b_q m - \frac{1}{2} \sum_{r=0}^m \boldsymbol{\beta}_{jk,r}' \mathbf{W}_{jk,r} \boldsymbol{\beta}_{jk,r}\right)
\end{aligned} \tag{F.48}$$

Since this posterior distribution is not in a closed form, we, therefore, update the full conditionals of single parameters or blocks of parameters, given the rest of the data. For updating the parameter vector $\boldsymbol{\beta}_{jk,r}$, which corresponds to the time-dependent functions, spatial effects, fixed

effects and random effects, we use the MH algorithm based on iteratively weighted least squares (IWLS) proposals.

6.6.10. Appendix 9: Iteratively weighted least square (IWLS): The Taylor expansion

For updating the parameter vector $\beta_{jk,r}$, we use the Metropolis-Hastings (MH) algorithm based on iteratively weighted least squares (IWLS) proposals. For instance, we want to update $\beta_{jk,r}$ with the current value, $\beta_{jk,r}^c$, of the chain. The new value $\beta_{jk,r}^p$ is proposed by drawing a random vector from the high-dimensional multivariate Gaussian proposal distribution $q(\beta_{jk,r}^c, \beta_{jk,r}^p)$ which is attained from the quadratic approximation to the posterior by a second-order Taylor expansion with respect to $\beta_{jk,r}^c$.

To explicitly illustrate of the Taylor expansion, the primary goal is to approximate the posterior by Gaussian distribution obtained by accomplishing one IWLS step in each of the iterations of the sampler. Then random samples have to be drawn from a high dimensional multivariate Gaussian distribution with the precision matrix and mean:

$$\tilde{\mathbf{P}}_{jk,r} = \mathbf{Z}'_{jk,r} \mathbf{K}(\beta_{jk,r}^c) \mathbf{Z}_{jk,r} + \mathbf{W}_{jk,r} \tau_{jk,r}^{-2}, \tilde{\mathbf{m}}_{jk,r} = \tilde{\mathbf{P}}_{jk,r}^{-1} \mathbf{Z}'_{jk,r} \mathbf{K}(\beta_{jk,r}^c) (\tilde{\mathbf{y}} - \tilde{\boldsymbol{\eta}}) \quad (\text{F.49})$$

where $\tilde{\eta}_{jk,i} = \eta_{jk,i}(t_i) - f_{jk,r}(x_{ir})$ and $\mathbf{K}(\beta_{jk,r}^c) = \text{diag}(k_{jk,1}, k_{jk,2}, \dots, k_{jk,n})$ with the weight matrix for IWLS with weights

$$k_{jk,i} = \exp \left(\sum_{r=1}^R f_{jk,r}(S_{iz}) x_{r,i}(S_{iz}) + \mathbf{v}_i(S_{iz})' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(S_{iz})(s_i) + b_{jk,gi} \right) \cdot I_{jk,i} \quad (\text{F.50})$$

obtained from the current state $\beta_{jk,r}^c$. The working observations are: $\tilde{y}_{jk,i} = \eta_{jk,i}(t_{jk,i}) + \frac{\delta_{jk,i}}{k_{jk,i}} - 1$.

The proposed vector $\beta_{jk,r}^p$ is accepted as the new state of the chain with probability:

$$\alpha(\beta_{jk,r}^c, \beta_{jk,r}^p) = \min \left(1, \frac{p(\beta_{jk,r}^p / \cdot) q(\beta_{jk,r}^p, \beta_{jk,r}^c)}{p(\beta_{jk,r}^c / \cdot) q(\beta_{jk,r}^c, \beta_{jk,r}^p)} \right) \quad (\text{F.51})$$

where $p(\beta_{jk,r} / \cdot)$ is the full conditional for $\beta_{jk,r}$ (that is, the conditional distribution of $\beta_{jk,r}$ given all other parameters and the data).

6.6.11. Appendix 10: BayesX code used to fit the Bayesian geoaditive multistate model

Warnings: - The computations are time-consuming. The models took 6 days to converge

The dataset contains the following variables

ID: unique patient identifier
tsu= transition from undetectable viral load state to viral rebound state
tus= transition from viral rebound state to undetectable viral load state
tsd=transition from undetectable viral load state to death
tud=transition from viral rebound state to death
sex= gender-coded 1 “Males” and 0 “Females”(ref=females)
whoadv=baseline WHO clinical stages 1 “III/IV” and 0 “I/II” (ref WHO stage I/II)
age= the individual baseline age at ART initiation (continuous variable)
end= the last observed time at the exit from a state
start= is the initial time at entry into a state
states= the currently occupied state
Province= spatial unit of analysis present on both the data file and the spatial map file
states=state the process jumps to at the end of the current interval

Create regression objects and reading the data

```
bayesreg sp
map m
dataset d
m.infile using C:\Users\sph-user\Desktop\Zvifadzo\Zimbabwesort.bnd
d.infile using C:\Users\sph-user\Desktop\Zvifadzo\VLdata2.raw
sp.outfile=C:\Users\sph-user\Desktop\Zvifadzo\VLresults9\results
logopen, replace using C:\Users\sph-user\Desktop\Zvifadzo\VLresult\result.log
```

Change the delimiter to allow for line breaks in commands

```
delimiter=;
```

The model code

```
sp.mregress tus = end(baseline, nrknots=40) + ID(random) + sex + whoadv +
age(psplinerw2) + Province(random) + Province(spatial, map=m):
tsd = end(baseline, nrknots=40) + ID(random) + sex + whoadv +
age(psplinerw2) + Province(random) + Province(spatial, map=m):
tsu = end(baseline, nrknots=40) + ID(random) + sex + whoadv +
age(psplinerw2) + Province(random) + Province(spatial, map=m):
tud = end(baseline, nrknots=40) + ID(random) + sex + whoadv +
age(psplinerw2) + Province(random) + Province(spatial, map=m),
family=multistate state=states begin=start noposteriormode iterations=12000
burnin=2000 step=20 predict using d ;
logclose;
sp.autocor;
sp.getsample;
delimiter = return;
```

CHAPTER 7

In the previous chapters, spatial models and survival models, competing risk, illness-death (disease progression) multistate models were fitted. The transition rates, estimated within the multistate HIV disease progression models, were fitted using separate models for time-varying CD4 cell counts and time-varying viral load (VL) measures. This has been a norm in most studies may be due to unavailability of data, especially, VL data. However, where both CD4 cell counts and VL data are available and are representative of the HIV-positive population, joint modelling of these two markers would be important. The joint model will help to account for the effects of the one prognostic marker in a time-varying model of the other marker. For instance, in a CD4 cell count model, the effects of VL are accounted to explain what CD4 cell counts can't explain alone and vice versa. This modelling approach and implemented in this chapter provides a comprehensive understanding of how these two markers can be used in describe HIV disease progression patterns. Moreover, this chapter provides a sub-analysis of the joint mapping of two HIV immune deterioration conditions based on CD4 cell counts and VL. The multivariate intrinsic conditional autoregressive (MCAR) prior model was used to simultaneously describe the interactions between these two HIV immunological conditions and any shared geographical patterns. However, the sub-analysis of all observations with both CD4 cell counts and VL data had few participants; hence, there are limitations to the inference that can be made of the results at a provincial level.

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7. JOINT MODELLING AND MAPPING HIV DISEASE PROGRESSION PATTERNS BASED VIRAL LOAD AND CD4 CELL COUNTS PROGNOSTIC MARKERS IN MONITORING ART PATIENTS

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7.1. Abstract

Background

This study aimed to jointly model HIV disease progression patterns based on viral load (VL) among adult ART patients adjusting for the time-varying “incremental transients states” variable, and the CD4 cell counts orthogonal variable in a single 5-staged time-homogenous multistate Markov model. We further jointly mapped the relative risks of HIV disease progression conditions defined by $VL \geq 50 \text{ copies/uL}$ and $CD4 < 350 \text{ cells/uL}$ at the last observed visit conditional not to have died or become loss to follow-up (LTFU).

Methods

Secondary data analysis was performed on the Zimbabwe national ART programme electronic patients’ database. Adjusted transition intensities, hazard ratios (HR) and regression coefficients were estimated from the joint multistate model with two ART outcome states defining patients’ retention in care (mortality and LTFU). Joint mapping of HIV disease progression conditions was done using the Bayesian intrinsic Multivariate Conditional Autoregressive (MCAR) prior

model. Models were compared using the likelihood ratio test and the Akaike's Information Criterion (AIC).

Results:

The viral rebound (increased VL) from the undetectable state was 1.78 times more likely compared to viral suppression among patients with VL ranging from 50-1000copies/uL. Patients with CD4 cell counts lower than expected had a higher risk of viral increase above 1000copies/uL (state 2 to 3: HR=1.83) and death if their VL was above 1000copies/uL (state 3 to 4: HR=1.42). Regarding the time-varying effects of CD4 cell counts on the VL transition rates, as the VL increased, (λ_{12} and λ_{23}) the transition rates increased with a decrease in the CD4 cell counts over time. Regardless of the VL state, an individual was in, the transition rates to become LTFU decreased with a decrease in CD4 cell counts. Individuals with high CD4 cell counts were more likely to become LTFU in this cohort (λ_{15} , λ_{25} and λ_{35}); however, patients with CD4 ≥ 500 cells/uL and a VL range of 50-1000copies/uL had an increased risk of becoming LTFU. We observed a strong shared geographical pattern of 66% spatial correlation between the relative risks of the two HIV disease progression conditions. High relative risks of VL ≥ 50 copies/uL, and CD4 < 350 cells/uL after ART initiation were observed in Matabeleland North and Mashonaland East provinces.

Conclusion:

With high rates of viral rebound, interventions which encourage ART adherence and continual educational support on the barriers for ART uptake are crucial to achieve and sustain viral suppression. Area-specific interventions which focus on early ART screening through self-

testing, behavioural change campaigns and social support strategies should be strengthened in heavily burdened regions to achieve and sustain viral suppression. This results in lowering HIV transmission in the general population, a step towards achieving zero HIV incidences by 2030.

Keywords: CD4 counts and viral load, joint multistate models, joint spatial maps, multivariate conditional autoregressive prior, HIV disease progression

7.2. Introduction

Antiretroviral therapy (ART) has since been the backbone of HIV prevention and control as it reduces viral load (VL) replication in the human host through blocking the virus life cycle (162). Once the virus replication has been inhibited, the CD4 cell counts increase, and the individual life expectancy is expanded. HIV patients' management involves monitoring VL, and CD4 cell counts prognostic markers through laboratory repeated measurements; hence, they can be utilized in understanding the HIV disease progression patterns among ART patients (185). Of these two prognostic markers, VL is the preferred marker in HIV monitoring due to its high sensitivity, and its implications for transmission of HIV to sexual partners. However, in most developing countries, there is still a challenge to use VL primarily due to higher costs associated with VL testing (186).

Multistate Markov models are mathematical models which have been used to evaluate HIV disease processes (50); however, the number of states, state cuts-off points and the number of transitions vary across studies. This explains the flexibility of the multistate models' implementation, but the model becomes complex as the number of states and transitions increase. Multistate models have been used extensively in HIV disease progression using CD4 cell counts states (45,126) or VL states (44,76) to define the model states (categories) separately.

Low-middle-income countries have traditionally relied on the use of CD4 cell counts in ART monitoring as this has been the readily available laboratory marker; however, if both VL and CD4 cell counts are available, it is imperative to model these prognostic markers jointly to understand better the HIV disease progression patterns. Joint modelling helps to explain those effects which one marker cannot explain alone or in the absence of the other marker.

In this study, we fitted two time-homogeneous multistate Markov models with states defined by CD4 cell counts and VL. In each multistate model, we jointly model these prognostic markers with one marker defining the finite multistate model states and the other marker forming the covariate matrix components of the regression model. The first covariate was an orthogonal variable generated using the principal component analysis (PCA) (187). The second covariate was the time-varying “incremental transient states” variable to estimate the changes in transition rates over time with respect to how the marker changes (44). Uniquely to this study is the inclusion of these two covariates in a single multistate model covariate matrix.

In HIV disease monitoring programmes, Bayesian spatial modelling is an emerging tool to analyse spatially related multidimensional data with an underlying spatial process to guide policy (47,76); however, joint spatial modelling using the Bayesian intrinsic Multivariate Conditional Autoregressive (MCAR) prior has not been fully utilized in this field. The advantage of joint mapping is that it gives an understanding of the HIV dynamics and the spatial overlap between the joint mapped outcomes. In this study, we performed a joint spatial mapping of HIV disease progression processes defined by $VL \geq 50 \text{ copies/uL}$, and $CD4 < 350 \text{ cells/uL}$ at the last observed visit conditional not to have died or become loss to follow-up (LTFU).

The main objective of our study was to perform joint modelling of HIV disease progression using two 5-staged time-homogenous multistate Markov models based on CD4 cell counts and VL. Selection of the best fit model was conducted using the likelihood ratio test (LRT) for nested models and the Akaike's Information Criterion (AIC). We fitted these models in the R statistical package (174) using the “msm library” (147). Lastly, we performed a joint mapping of VL $\geq$ 50copies/uL, and CD4 cell counts $<$ 350cells/uL to describe the immune deterioration spatial overlap using the intrinsic MCAR prior implemented in OpenBUGS.

7.3. Methods

7.3.1. Data source, description and study design

This study was a secondary analysis of data from patients' records compiled for monitoring and guiding programme planning purposes. The data used in this manuscript came from the Zimbabwe National ART programme collected through the electronic patients' management system (ePMS) database described elsewhere (188,189). The electronic system was implemented nationally to improve and increase efficiency in HIV patients' management and monitor their response to ART. Stratified sampling of health facilities offering HIV services was done; hence, a representative sample of primary, secondary, tertiary and quaternary health facilities which provide HIV services was achieved during the ePMS roll out. However, a continual up-scale is currently ongoing, which will ensure that the system covers all health facilities.

We considered individuals aged 15 years and above, with at least two repeated measurements of both CD4 cell counts and VL who initiated ART between 2004 and 2017. However, since this was programme data, the follow-up visits of the patients were intermittent, and there may have been clinical reasons for requesting CD4 count and VL measurements from patients. Each

individual had an average follow-up period of two years, and the majority of the patients (79.2%) in the final sample considered for analysis were enrolled on ART between 2009 and 2015.

7.3.2. The time-homogeneous Markov multistate model formulation

A multistate model is a stochastic continuous-time process $\{X(t), t \in [0, T) \text{ years}\}$ defined as a finite space $X = \{1, 2, 3, 4, 5\}$ based on VL or CD4 cell counts states:

$$\text{Viral load (VL) states (copies/uL)} = \begin{cases} 1; \text{ VL} < 50 \\ 2; 50 \leq \text{VL} < 1000 \\ 3; \text{ VL} \geq 1000 \\ 4; \text{ Dead} \\ 5; \text{ Loss to follow-up} \end{cases} \quad (7.1)$$

$$\text{CD4 cell counts states (cells/uL)} = \begin{cases} 1; \text{ CD4} \geq 500 \\ 2; 350 \leq \text{CD4} < 500 \\ 3; \text{ CD4} < 350 \\ 4; \text{ Dead} \\ 5; \text{ Loss to follow-up} \end{cases} \quad (7.2)$$

where LTFU was defined as a failure of a patient to report for drug refill for at least 90 days from last appointment date or if the patient missed the next scheduled visit date and never showed up again. The schematic presentation of the 5-staged multistate model is shown in **Figure 7-1**.

Based on these possible transitions shown in **Figure 7-1**, the corresponding transition rates are

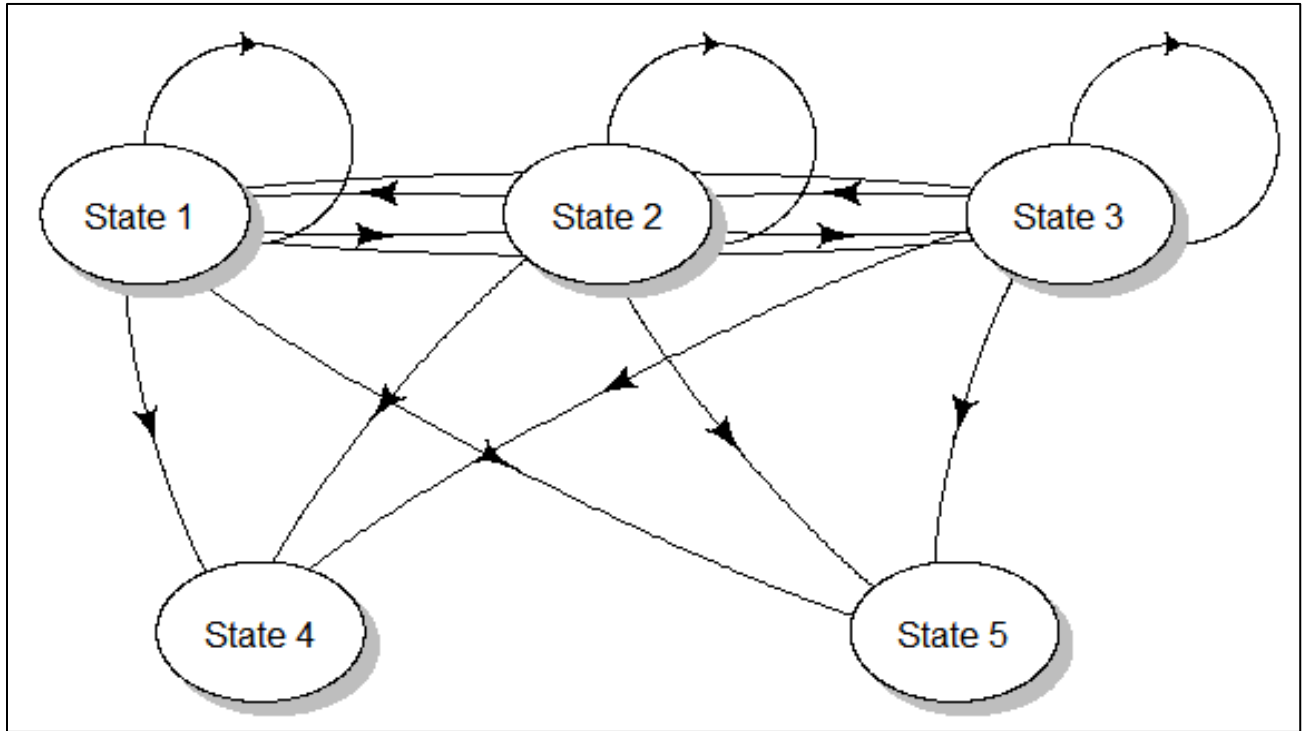
defined by a 5×5 transition matrix $Q(t)$ with λ_{ij} elements defining the movement between state

i and state j with properties $\sum_{j=1}^5 \lambda_{ij} = 0$ and $\lambda_{ii} = -\sum_{i \neq j} \lambda_{ij}$ λ_{ij} is assumed to be time-

homogeneous. In reality, the individuals who become LTFU have a possibility of coming back to the clinic and have VL and CD4 measurements if taken. However, in this study, we could not

ascertain any return of participants after they have become LTFU. This means the λ_{5j} transition rates from the LTFU state were not estimated as the data could not support this.

$$Q(t) = \begin{pmatrix} -(\lambda_{12} + \lambda_{13} + \lambda_{14} + \lambda_{15}) & \lambda_{12} & \lambda_{13} & \lambda_{14} & \lambda_{15} \\ \lambda_{21} & -(\lambda_{21} + \lambda_{23} + \lambda_{24} + \lambda_{25}) & \lambda_{23} & \lambda_{24} & \lambda_{25} \\ \lambda_{31} & \lambda_{32} & -(\lambda_{31} + \lambda_{32} + \lambda_{34} + \lambda_{35}) & \lambda_{34} & \lambda_{35} \\ 0 & 0 & 0 & 0 & 0 \\ \lambda_{51} & \lambda_{52} & \lambda_{53} & \lambda_{54} & -(\lambda_{51} + \lambda_{52} + \lambda_{53} + \lambda_{54}) \end{pmatrix}$$



State 1(VL<50or CD4 $\geq$ 500), State 2 (50 $\leq$ VL<1000 or 350 $\leq$ CD4<500), State 3(VL $\geq$ 1000 or CD4<350), State 4 (dead) and State 5 (Loss to follow-up (LTFU))

Figure 7-1: The schematic diagram for the possible transition between the defined state for both the viral load and the CD4 cell counts models

The effects of the covariates on each model were modelled using the semi-parametric proportionality hazards. The focus at this stage was to account for the effects of one of the prognostic marker, which cannot be explained by the multistate model defining states prognostic

marker. For instance, we aimed to describe how the uncorrelated factor of VL values can explain the component of mortality, LTFU or HIV disease progression transition rates that cannot be explained by the CD4 cell counts values alone (or in the absence of VL values) in the CD4 cell counts multistate model. To achieve this, we generated an orthogonal variable through the PCA technique, which is a data reduction approach used to combine highly correlated variables into uncorrelated components to improve model efficiency as described elsewhere (187).

To describe the PCA approach briefly, let the predictive power of CD4 cell counts and VL values be P_{CD4} and P_{VL} , respectively. If a basic linear regression is fitted to estimate the regression coefficients β_1 and β_2 in the equation between VL and CD4 cell counts variables, i.e.:

$$P_{VL} = \beta_1 + \beta_2 P_{CD4}^* + \varepsilon_{CD4} \quad (7.3)$$

where $P_{CD4}^* = P_{CD4}$ is considered to be the uncorrelated factor, β_1 is the model intercept, β_2 is the slope parameters, and ε_{CD4} is the “error” term. This error term ε_{CD4} , by definition, is independent of the uncorrelated factor $P_{CD4}^* = P_{CD4}$. Rearranging Equation (7.3) above to define the error term ε_{CD4} yields:

$$\varepsilon_{CD4} = P_{VL} - \beta_1 - \beta_2 P_{CD4}^* = P_{VL} - (\beta_1 + \beta_2 P_{CD4}^*) \quad (7.4)$$

which defines ε_{CD4} as a residual term in the equation. If we let $P_{VL}^* = \varepsilon_{CD4}$, then the P_{VL}^* term is uncorrelated with P_{CD4} values by construction. These residual values P_{VL}^* from the fitted model defined in Equation (7.1) are used to generate a categorical orthogonal VL variable coded “1” for negative residual values or “0” otherwise. A negative residual value would mean that the observed VL value is smaller than the expected VL value. This generated orthogonal variable is

then included as a covariate in the proportionality hazard mode mathematically defined by the following equation:

$$\lambda_{ij,k(CD4)}(t) = \lambda_{ij,k(0)} \exp(\beta_{ij} \times P_{VL,k}^*) \text{ for } i \neq j \quad (7.5)$$

where $\lambda_{ij,(CD4)}$ is the transition rate between state i and state j at the time t , $\lambda_{ij(0)}$ is the baseline transition rate for an individual k with a positive residual value for the orthogonal effect of VL values ($P_{VL,(k)}^* = 0$) and β_{ij} is the log-linear effects (coefficients) of the orthogonal covariate. The second covariate is the time-varying VL measurements variable which is categorized into “incremental transient states” to be included in the covariate matrix components. The cut-off points for the time-varying covariate were based on the range defined in Equation (7.2) above, excluding the mortality and the LTFU states. Mathematically, we can show that:

$$\lambda_{ij,k(CD4)}(t) = \lambda_{ij,k(0)} \exp(\beta_{ij} \times VL_{states,k}) \text{ for } i \neq j \quad (7.6)$$

where $VL_{states,k}$ is the categorized “incremental transient states” covariate. These same approaches were repeated for the VL multistate model adjusting for the CD4 cell counts orthogonal values.

What is important to note is that most studies have used either the orthogonal variable or the time-varying covariate only in the joint modelling stage; however, in this study, we further explored if including these two covariates in a single model improves the model. In this study, we consider that given the generic form of the proportional hazard model within a multistate is defined as follows:

$$\lambda_{ij,k} / \mathbf{Z}(t) = \lambda_{ij,k(0)} \exp(\beta'_{ij} \mathbf{Z}_k), \text{ } i \neq j \quad (7.7)$$

where $\mathbf{Z}$ is a m –dimensional vector of the explanatory covariates. In this current study, $m = 2$ and the two multistate Markov models fitted were:

$$\lambda_{ij,k(CD4)} / \mathbf{Z}(t) = \lambda_{ij(CD4,0)} \exp(\beta_{ij,CD4(1)} P_{VL(k)}^* + \beta_{ij,CD4(2)} VL_{states,k}) \quad (7.8)$$

$$\lambda_{ij,k(VL)} / \mathbf{Z}(t) = \lambda_{ij(VL,0)} \exp(\beta_{ij,(VL)1} P_{CD4(k)}^* + \beta_{ij,(VL)2} CD4_{states,k}) \quad (7.9)$$

where Equation (7.8) defines the CD4 cell counts multistate Markov model with $\lambda_{ij(CD4,0)}$ as the baseline transition intensity for an individual k with positive residual values the orthogonal effect of viral load ($P_{VL(k)}^* = 0$) and the time-varying VL transient levels ($VL_{states,k} = 1(VL < 50 \text{ copies} / uL)$). Similarly, Equation (7.9) defines the VL multistate Markov model with $\lambda_{ij(VL,0)}$ representing the baseline transition intensities for an individual k with positive residual values for the orthogonal effect CD4 cell counts ($P_{CD4(k)}^* = 0$) and the time-varying CD4 cell counts levels ($CD4_{states,k} = 1(CD4 \geq 500 \text{ cells} / uL)$). The $\beta_{ij,(CD4)d}$ and $\beta_{ij,(VL)d}$ for $d = 1, 2$ on both the CD4 cell count model and the VL model are the log-linear effects (coefficients) of the corresponding covariates.

Since the analyses were purely based on existing modelling approached within the "msm" R library, additional covariates like baseline CD4 cell counts, baseline VL values, age, sex and WHO staging could be adjusted for in the model; however, in this study, we encountered a convergence warning as more covariates were added. Failure to converge of the multistate Markov model means the optimization criterion could not converge to the maximum likelihood; hence, the standard errors of the estimated parameters were not calculated, and the confidence interval estimates were missing on the printout of results. This modelling challenge is normally faced if there is data sparsity in some cells within the multistate model. Usually, in such instances, the scaling factor is increased to a higher value adjusted to normalize the likelihood and prevent overflow within the optimization process; however, in our case, this was not helpful.

The final model selection was based on the AIC values which are defined as $AIC = -2(\text{Log-likelihood}) + 2q$, where $2q$ represents the variance component, q is the number of parameters to be estimated in the fitted model and the bias is defined by $-2(\text{Log-likelihood})$. The better fitting model is the model with the lowest AIC value. The nested models were assessed using the LRT defined as:

$$LRT = -2 \times \log_e \left(\frac{L_1(\hat{\phi})}{L_2(\hat{\phi})} \right) \quad (7.10)$$

where $L_1(\hat{\phi})$ is the likelihood for the simple (unsaturated) model with few covariates and $L_2(\hat{\phi})$ is the likelihood for the full (saturated) model with additional covariate(s). A significant p-value < 0.05 for the LRT leads to the rejection of the null hypothesis (simple model is better) in favour of the alternative hypothesis (full model is better). To assess how well the final selected models predict HIV disease, mortality and LTFU, percentage prevalence in each state were plotted to compare the observed and the expected frequencies.

7.3.3. Joint mapping of HIV progression based on two prognostic markers

The intrinsic MCAR prior model was used to jointly map the relative risks of HIV disease progression immunological conditions defined by $VL \geq 50 \text{ copies/uL}$, and $CD4 < 350 \text{ cells/uL}$ at the last observed visit conditional not to have died or become LTFU. This model assumes that the occurrence of one condition coincidentally affect the other condition due to shared geographical pattern. The choice of the VL cut-off point was based on the global goal to achieve an undetectable VL to minimize viral transmission in the general population (26) while the choice of the CD4 cell counts cut-off point was based on earlier studies which have shown that

individuals with CD4 cell counts of 200-350cells/uL immune deterioration patterns are not significantly different from those with CD4 cell counts less than 200cells/uL (126).

The model formulation of the MCAR model as proposed by Besag et al. (1991) (81) is a special type of Gaussian Markov random field prior models (GMRF) (81,82) defined as follows: let the number of observed individuals with $VL \geq 50$ copies/uL be $Y_{VL,r}$, and the number of observed individuals with $CD4 < 350$ cells/uL be $Y_{CD4,r}$ at the last observed visit as reported for the region S_r , where the set of regions $\{S_r\}, r=1,2,3,...,R$ represents a finite number of the areas partitioned from the entire study area. In this study, we considered partitioning the Zimbabwe country into 10 provinces, i.e. $R=10$. The geospatial variations are observed through an aerial map partitioned based on administrative spatial units. For each region, the expected number of individuals for each prognostic marker outcome ($E_{VL,r}$ and $E_{CD4,r}$) was calculated using the following the generic formula:

$$E_{r,q} = n_{r,q} \bar{r}_q \equiv n_{r,q} \left(\frac{\sum_r y_{r,q}}{\sum_r n_{r,q}} \right) \text{ for } r = 1, 2, 3, \dots, R \text{ and } q = CD4, VL \quad (7.11)$$

where $\bar{r}_q$ is the overall $VL \geq 50$ copies/uL or $CD4 < 350$ cell/uL rate in the whole study region, $n_{r,q}$ is the at-risk population in the region r and $y_{r,q}$ is the total counts of individuals observed in the region. This approach is commonly referred to as “internal standardization”. The observed frequencies can be considered as the random variables while the expected frequencies are thought of as fixed and known functions of the at-risk population $n_{r,q}$ in the region r . In this study, we assumed that the observed count data follow a Poisson distribution for the two prognostic marker outcomes, i.e.

$$\begin{aligned}
Y_{q,r} &\sim \text{Poisson}(E_{q,r}\theta_{q,r}) \text{ for } r=1,2,3,\dots,R \text{ and } q = CD4, VL \\
\log(\theta_{q,r}) &= \log(E_{q,r}) + \alpha_q + S_{q,r}
\end{aligned}
\tag{7.12}$$

where α_q is an intercept term representing the baseline (log) relative risk of disease progression outcomes q across the study region. We further assumed that the log relative risks are spatially correlated across the regions, and the log relative risks for the two prognostic markers are also correlated within each region r due to shared region-level unmeasured risk factors. These assumptions were supported through the intrinsic bivariate CAR prior of a $2 \times R$ dimensional matrix of $S_{q,r}$ values. The spatial prior is expressed as:

$$S_q | S_{1(-q)}, S_{2(-q)} \sim \text{Bivariate Normal}(\bar{S}_q, \mathbf{V} / n_q) \tag{7.13}$$

where $S_{1(-q)}, S_{2(-q)}$ denotes the elements of the $2 \times R$ matrix, $\bar{S}_r = (\bar{S}_{r,1}, \bar{S}_{r,2})$ and $\bar{S}_{r,p} = \sum_{f \in \sigma_r} S_{fp} / n_r$ where σ_r and n_r denote the set of labels of the "neighbours" of the region r and the number of neighbours, respectively assuming a $p=2$. The matrix $\mathbf{V}$ is a 2×2 covariance matrix with diagonal elements v_{11} and v_{22} denoting the conditional variances of S_1 and S_2 respectively, and off-diagonal element v_{12} denoting the conditional within-area covariance between S_1 and S_2 .

The MCAR model was performed in the OpenBUGS, which is open-source statistical software and the code used is provided in this chapter's appendix section. We ran 10,000 Markov chain Monte Carlo (MCMC) simulations, burn-in of 2,000 and thinning of 10. A prior sensitivity analysis was done through varying prior distributions and parameter values. We ran simultaneously two chains and the results reported are based on the better chain of initial values. Model diagnostics were assessed through trace plots, density plots and autocorrelation plots.

7.4. Results

The total sample used for analysis had 3,896 participants who contributed 8,655 observations. Of these patients, 2,551(65.5%) were females, 1,388(35.6%) aged 35-44 years. At study baseline, 2,557 (65.6%) had VL within the 50-1000 copies/uL range while 1,846 (47.4%) had CD4 cell counts of below 350cells/uL. Most of the patients were on a first-line drug regimen, particularly taking a triple combination therapy of TDF+3TC+EFV while 5% were on second-line drugs. **Table 7-1** the simple regression model results used to generate the orthogonal covariates for both the CD4 cell counts and the VL model. We observed a significant correlation between CD4 cell counts and VL for both models and the slopes were negative as expected.

Table 7-1: Estimated regression coefficients for the simple linear regression model for the viral load on CD4 cell counts and CD4 cell counts on viral load.

	Parameter	Estimate	R-adjusted	P> t	VIF*
Viral load on CD4 cell counts	β_1	333.0816 (321.51- 344.66)	0.5134	<0.001	2.29
	β_2	-0.003955 (-0.008 to -0.0003)		0.035	
	β_1	62.86 (5.19- 120.52)	0.5646	0.033	1.03
CD4 cell counts on viral load	β_2	-0.12 (-0.21 to -0.04)		0.006	

*variance inflation factor

Table 7-2 presents a detailed summary of the log-likelihood values, LRT statistics, LRT p-values and the AIC values. Using the LRT results for the nested models, we assessed a better fit model between the no covariate model $\left[\lambda_{ij}(t) = \lambda_{ij(0)} \exp(\beta'_{ij}), i \neq j \right]$ and the orthogonal adjusted model $\left[\lambda_{ij}(t) = \lambda_{ij(0)} \exp(\beta_{ij} \times P^*) \right]$ for both the CD4 cell counts and VL multistate models.

Table 7-2: Model selection process for the various model fitted for both viral load and CD4 cell counts multistate models

Covariate	-2*LL ^a	AIC ^b	Models compared	LRT ^c statistic	Df ^d	P-value
Viral load multistate model						
Model 1- No covariates	7074.605		-		-	-
Model 2- CD4effects	7014.406	7062.99	Model 1 vs Model 2	59.61457	12	2.65e-08**
Model 3- CD4 states	7007.724	7055.72	Model 1 vs Model 3	66.88163	12	1.22e-09**
Model 4- CD4effects+ CD4 states	6930.714	7002.71	Model 2 vs Model 4	83.69604	12	8.10e-13**
			Model 3 vs Model 4	77.01372	12	1.53e-11**
CD4 cell counts multistate model						
Model 1- No covariates	7334.08		-	-	-	
Model 2- VLeffects	7298.644	7342.64	Model 1 vs Model 2	35.36379	11	2.16e-04**
Model 3- VLstates	7256.166	7344.17	Model 1 vs Model 3	77.84109	33	1.74e-05**
Model 4- VLeffects + VLstates	7227.461	7337.46	Model 2 vs Model 4	71.18325	33	1.28e-04**
			Model 3 vs Model 4	28.70595	11	2.52e-03**

^aLog-likelihood ^bAkaike's information criterion ^cLikelihood ratio test ^ddegrees of freedom **Significant at 5%

Both the CD4 cell count and the viral load multistate models showed that the model with the orthogonal variable (model 2) was a better fit compared to the no variate model (model 1). Similarly, the multistate models which adjusted for the time-varying effects of the other prognostic marker, $\left[\lambda_{ij,VL}(t) = \lambda_{ij(0)} \exp(\beta_{ij} \times CD4_{state}) \right]$ and $\lambda_{ij,CD4}(t) = \lambda_{ij(0)} \exp(\beta_{ij} \times VL_{state})$ (model 3) were better fit compared to the no covariate models (model 1). Simultaneously adjusting for the orthogonal variable and the time-varying effects on the CD4 cell count model

and VL effects (model 4) further improve the model, P-value<0.05; hence, the interpretation of results was based on these models (model 4).

7.4.1. The joint modelling of CD4 cell counts and viral load as a covariate component: Multistate time-homogeneous Markov model

Another time-homogeneous multistate Markov model to evaluate HIV disease progression based on CD4 cell counts. The effects of the orthogonal VL and the time-varying VL effects were regressed in one model. In this model, the movement between state i to state j for $i > j$ defines an increase in CD4 cell counts which indicates immune recovery process while $i < j$ defines a decrease in CD4 cell counts, which means immune deterioration transition.

Table 7-3 results show that the rates of decrease in CD4 cell counts (immune deterioration) among patients in state 2 (CD4 cell count range of 350-500 cells/uL) ($\lambda_{23} = 0.0404$) were 11.25 times higher than the rates of increase in CD4 cell counts (immune recovery) among patients in state 3 (CD4<350cells/uL) ($\lambda_{32} = 0.0036$). Patients in state 2 (CD4 cell count range of 350-500 cells/uL) were more likely to become LTFU ($\lambda_{25} = 0.0551$). The positive VL log-linear effects of ($\beta_{23}P_{VL(k)}^* = 0.4762$) showed an increased risk of immune deterioration for an individual in state 2 (CD4 cell count range of 350-500 cells/uL) to state 3 (CD4< 350cells/uL). Similarly, the log-linear effects of time-varying VL variable showed an increased risk of immune deterioration for the λ_{23} transition ($\beta_{23}VL_{states,k} = 1.0791$). The time-varying VL values and the negative VL (residuals covariate) had an increasing effect on the risk of death in this cohort for individuals with CD4< 350 cell/uL, the hazard ratio (HR) =1.75 and HR=1.67, respectively.

Table 7-3: The joint effects of change over time of viral load levels and orthogonal viral load variable on the CD4 cell counts transition rates Markov model

Transition Rate λ_{ij}	Baseline	Log-linear β_{ij}		Hazard $\exp(\beta_{ij})$		Time-varying viral load (VL) levels $VL_{states,k}$		
	$\lambda_{ij(CD4,0)}$	$VL_{states,k}$	$P_{VL(k)}^*$	$VL_{states,k}$	$P_{VL(k)}^*$	State 1	State 2	State 3
State 1 to 2 λ_{12}	0.0192	0.1678	0.1739	1.0827	1.1899	0.0182	0.0161	0.02763
State 1 to 3 λ_{13}	0.2856	-0.3505	-1.8298	0.7044	0.1604	0.7431	0.4755	1.3939
State 1 to 5 λ_{15}	0.0381	0.5612	0.5131	1.7528	1.6704	0.0245	0.0333	0.0535
State 2 to 1 λ_{21}	0.0114	-0.6837	0.6186	0.5048	0.8563	0.0168	0.0068	0.0088
State 2 to 3 λ_{23}	0.0404	0.4762	1.0791	1.6099	2.9419	0.0239	0.0261	0.0948
State 2 to 4 λ_{24}	0.0086	-1.0434	-0.6853	0.3663	0.5039	0.0283	0.0067	0.0126
State 2 to 5 λ_{25}	0.0551	0.5786	-0.0711	1.7836	0.9314	0.0338	0.0729	0.0416
State 3 to 1 λ_{31}	0.0062	-1.6657	-0.5138	0.1891	0.5982	0.0235	0.0055	0.0077
State 3 to 2 λ_{32}	0.0036	0.2016	-0.3475	1.2233	0.7064	0.0039	0.0032	0.0131
State 3 to 4 λ_{34}	0.0079	0.1820	0.1034	1.1996	1.1089	0.0057	0.0069	0.0421
State 3 to 5 λ_{35}	0.0195	0.2806	-0.1784	1.3239	0.8366	0.0156	0.0217	0.0305

-2*log-likelihood=7227.461; Akaike information criterion=7337.461

Regarding the time-varying effects of VL on the CD4 cell counts transition rates, as the CD4 cell counts increased for an individual with CD4 cell count range of 350-500 cells/uL (λ_{23}), the transition rates increased with an increase in VL levels over time. Similarly, individuals with $CD4 \geq 500$ cells/uL (λ_{15}) and those with $CD4 < 350$ cell/uL (λ_{35}) showed an increased risk of becoming LTFU as their VL increased over time. A comparable trend was observed for individuals with $CD4 < 350$ cell/uL (λ_{34}) who exhibited an increased risk of death with an increase in VL over time.

7.4.2. The joint modelling of viral load and CD4 cell counts as a covariate component: Multistate time-homogeneous Markov model

We fitted a time-homogeneous multistate Markov model to evaluate HIV disease progression based on VL defined states. The effects of the orthogonal CD4 cell counts and the time-varying CD4 cell counts effects were accounted for in a single model. In this model, the movement between state i to state j for $i > j$ defines a VL suppression which indicates immune recovery process while $i < j$ defines VL rebound, which means immune deterioration process. In **Table 7-4**, the rates of viral rebound among patients with $VL < 50$ copies/uL ($\lambda_{12} = 0.0286$) were 1.78 times higher than the rates of VL suppression among patients with VL range of 50-1000 copies/uL ($\lambda_{21} = 0.0161$). However, patients with $VL \geq 1000$ copies/uL were 7.77 times more likely to die ($\lambda_{32} = 0.0035$ vs $\lambda_{34} = 0.0272$) and 9.8 times more likely to become LTFU ($\lambda_{32} = 0.0035$ vs $\lambda_{35} = 0.0343$).

Table 7-4: The joint effects of change over time of CD4 cell counts levels, and orthogonal CD4 cell counts variable on the viral load transition rates Markov model

Transition Rate λ_{ij}	Baseline	Log-linear β_{ij}		Hazard $\exp(\beta_{ij})$		Time-varying CD4 cell counts levels $CD4_{states,k}$		
	$\lambda_{ij(VL,0)}$	$CD4_{states,k}$	$P_{CD4(k)}^*$	$CD4_{states,k}$	$P_{CD4(k)}^*$	State 1	State 2	State 3
State 1 to 2 λ_{12}	0.0286	0.0434	-0.3383	1.0443	0.713	0.0305	0.0321	0.0337
State 1 to 3 λ_{13}	0.0025	-1.0072	-0.3336	0.3652	0.7163	0.0167	0.0059	0.0021
State 1 to 4 λ_{14}	0.0082	0.0288	0.0247	1.0292	1.0243	0.0078	0.0081	0.0083
State 1 to 5 λ_{15}	0.0159	-0.7155	-1.1045	0.4889	0.3312	0.1774	0.0422	0.0206
State 2 to 1 λ_{21}	0.0161	-0.3926	-0.2849	0.6762	0.7521	0.0351	0.0237	0.0161
State 2 to 3 λ_{23}	0.0008	0.2065	0.6052	1.2293	1.8315	0.0004	0.0005	0.0006
State 2 to 4 λ_{24}	0.0057	0.0725	-0.2381	1.0752	0.7881	0.0056	0.0061	0.0066
State 2 to 5 λ_{25}	0.0305	-0.7458	-0.9312	0.4744	0.3941	0.3372	0.0759	0.0361
State 3 to 1 λ_{31}	0.0266	-0.9855	-0.7571	0.3733	0.4691	0.1926	0.0728	0.0275
State 3 to 2 λ_{32}	0.0035	-1.4092	-2.8306	0.2443	0.0589	0.1359	0.0324	0.0077
State 3 to 4 λ_{34}	0.0272	-0.0811	0.3475	0.9221	1.4155	0.0255	0.0237	0.0221
State 3 to 5 λ_{35}	0.0343	-0.5176	0.0947	0.5959	1.0993	0.1273	0.0457	0.0273

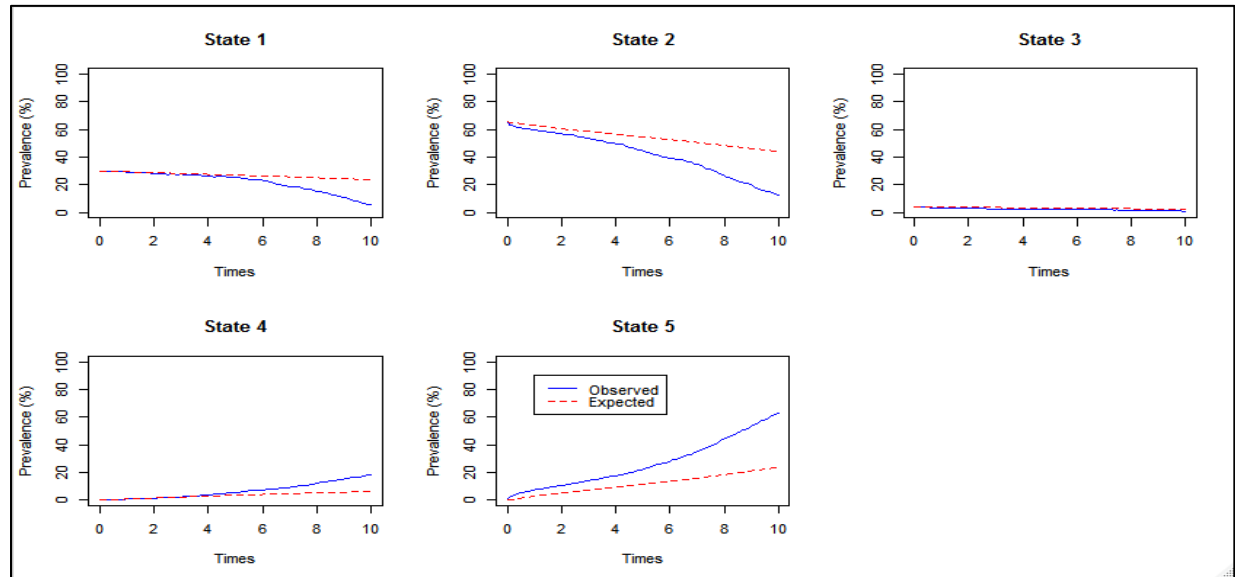
-2*log-likelihood=6930.71; Akaike's information criterion=7002.7

The time-varying CD4 cell counts had an increasing effect on the risk of viral increase from a VL range of 50-1000copies/uL to $VL \geq 1000$ copies/uL in this cohort, HR =1.23. Similarly, the negative CD4 cell count residual was associated with an increased risk of viral increase from a VL range of 50-1000copies/uL to $VL \geq 1000$ copies/uL ($\beta_{23}P_{CD4(k)}^* = 0.6052$; HR=1.83); and increased risk of death among individuals with $VL \geq 1000$ copies/uL ($\beta_{34}P_{CD4(k)}^* = 0.3475$; HR=1.42). Regarding the time-varying effects of CD4 cell counts on the VL transition rates, as the VL increased (λ_{12} and λ_{23}) the transition rates increased with a decrease in the CD4 cell counts over time while as the VL decreased (λ_{21} , λ_{31} and λ_{32}) the transition rates decreased with a reduction in the CD4 cell counts decreased over time. Individuals with $VL < 50$ copies/uL and those with VL range between 50-1000copies/uL had death transition rates increasing over time as CD4 cell count decreases (λ_{14} and λ_{24}). Regardless of the VL state, an individual was in, the transition rates to become LTFU decreased with a decrease in CD4 cell counts. Individuals with high CD4 cell counts were more likely to become LTFU in this cohort (λ_{15} , λ_{25} and λ_{35}); however, patients with $CD4 \geq 500$ cells/uL and a VL range of 50-1000copies/uL had an increased risk of becoming LTFU.

7.4.3. Multistate Markov models assessments

We performed a post-estimation test to assess which of the two multistate models fit better on this data in describing the HIV disease progression, mortality and becoming LTFU. We used the prevalence plot to compare the observed and the expected percentage prevalence for CD4 cell counts and VL multistate models. The VL multistate model showed a perfect fit for state 3 ($VL \geq 1000$ copies/uL) and fair (moderate) fit for state 1 ($VL < 50$ copies/uL) and state 4 (died).

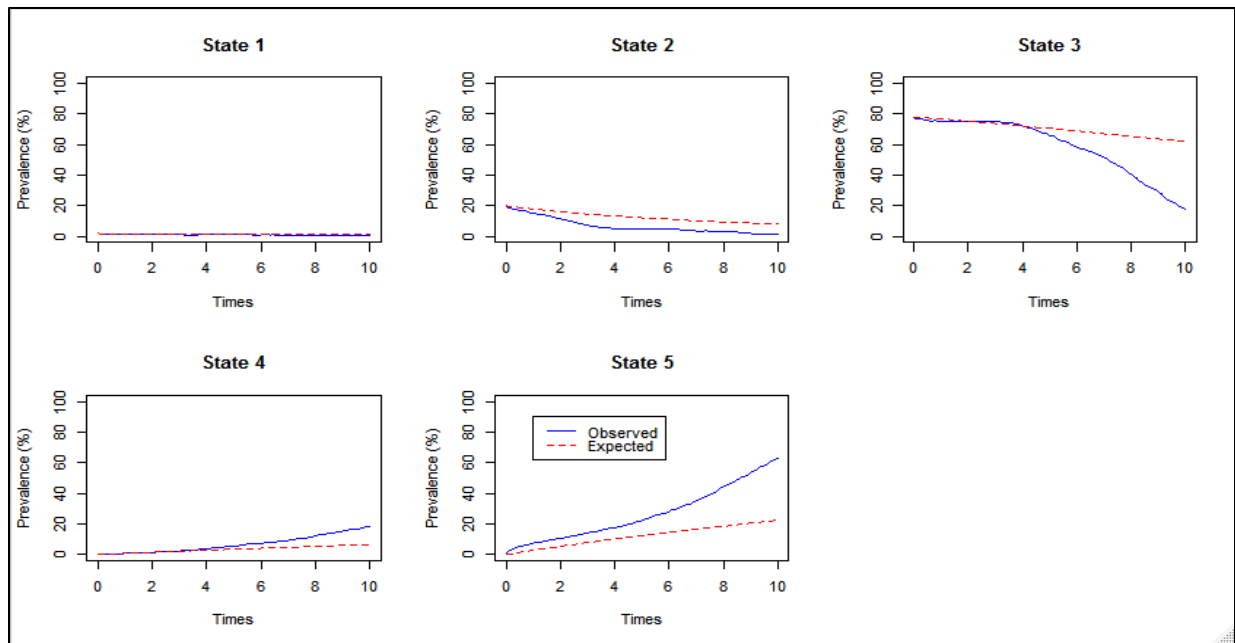
State 3 ($VL \geq 1000$ copies/uL) and state 5 (LTFU) of this model were not perfectly fitted by this model (**Figure 7-2**).



State 1($VL < 50$), State 2 ($50 \leq VL < 1000$), State 3($VL \geq 1000$), State 4 (dead) and State 5 (Loss to follow-up (LTFU))

Figure 7-2: The percentage prevalence plot of orthogonal CD4 cell counts and the time-varying CD4 cell counts values on the HIV disease progression

Regarding the CD4 cell counts multistate model, state 1 ($CD4 \geq 500$ cell/uL) was perfectly fitted while state 2 ($350 \leq CD4 < 500$) and state 4 (died) were fairly fitted. State 3 ($CD4 < 350$ cell/uL) was perfectly fitted between time 0 and time 5 years only while state 5 (LTFU) was not perfectly fitted (**Figure 7-3**). Since the percentage prevalence plots could not give conclusive results on the better model, instead of using the LRT as the models were not nested, we used the AIC values. The VL multistate model was a better fit model with an $AIC=7002.71$ compared to the CD4 cell counts multistate model with an $AIC=7337.46$.



State 1($CD4 \geq 500$), State 2 ($350 \leq CD4 < 500$), State 3 ($CD4 < 350$), State 4 (dead) and State 5 (Loss to follow-up (LTFU))

Figure 7-3: The percentage prevalence plot of orthogonal viral load variable and the time-varying viral load values on the HIV disease progression

7.4.4. Sub-analysis of the spatial covariate (province of ART enrolment) on the multistate models and joint mapping of the two immunological HIV conditions using the Multivariate intrinsic CAR model

We further assessed for the effects if the region variable (province) on the VL and CD4 cell count multistate models to identify any association between the observed transition processes and the region. We estimated the hazard ratio summarised in **Table 7-5**. In general, we observed that there is an association between the transition intensities and the province administrative level. We found that 57.6% of the transition rates for CD4 cell count and VL models adjusting for province covariate were showed the same effect direction (risk or protective effect) of the hazard ratios; however, there were variations in the magnitude of the risk of transitions among provinces.

Table 7-5: The spatial effects (province-level) on the viral load and CD4 cell counts multistate model adjusted for time-varying effects and residual effect of the other prognostic marker with Harare province as a reference category

Province		Transition processes for Viral load (VL) and CD4 cell counts multistate models											
Hazard	Ratio	State 1 to State 2	State 1 to State 3	State 1 to State 4	State 1 to State 5	State 2 to State 1	State 2 to State 3	State 2 to State 4	State 2 to State 5	State 3 to State 1	State 3 to State 2	State 3 to State 4	State 3 to State 5
P1:	VL	0.004	0.405	3.711	0.311	0.327	1.296	26.41	0.089	0.042	0.162	0.047	0.089
	CD4	0.912	0.854	_____	0.794	1.253	0.996	1.001	0.972	1.821	1.181	1.683	1.089
P2:	VL	0.056	0.514	0.001	0.109	5.611	1.834	0.021	0.721	1.729	1.981	0.022	0.071
	CD4	1.705	0.615	_____	1.019	0.831	1.595	0.866	0.614	0.899	0.561	0.347	0.151
P3:	VL	0.342	0.313	6.096	0.001	0.885	1.033	0.778	0.206	0.301	0.704	0.003	0.007
	CD4	0.958	1.861	_____	0.869	0.945	1.364	0.961	0.775	1.493	1.204	1.469	0.854
P4:	VL	3.191	0.208	5.524	2.625	3.933	0.028	3.066	2.082	1.041	2.447	0.043	0.064
	CD4	0.709	9.371	_____	1.664	0.732	6.099	1.019	2.636	2.186	2.279	2.894	2.743
P5:	VL	0.002	0.411	2.101	1.671	0.172	0.974	0.347	2.155	0.537	0.925	0.013	1.759
	CD4	1.216	1.125	_____	1.159	0.974	1.058	0.981	0.844	1.358	1.459	1.114	2.543
P6:	VL	0.256	1.633	0.019	0.379	9.378	2.479	0.081	3.455	2.525	9.423	0.094	0.138
	CD4	0.934	1.263	_____	0.967	1.747	3.451	0.928	1.046	6.262	5.288	1.241	1.439
P7:	VL	1.198	16.68	2.564	0.428	3.145	0.025	2.984	0.568	9.323	0.653	0.225	0.398
	CD4	1.744	0.331	_____	0.712	1.509	0.269	1.519	0.479	0.439	0.851	2.565	0.585
P8:	VL	0.013	0.507	6.321	0.834	0.414	1.677	0.701	0.133	0.705	0.924	0.455	0.029
	CD4	0.968	1.641	_____	0.915	0.975	2.006	1.229	1.047	1.711	1.489	1.766	1.231
P9:	VL	0.001	0.101	0.005	0.087	0.095	0.816	0.177	0.026	0.036	0.153	0.001	0.095
	CD4	0.978	1.249	_____	0.934	0.907	0.652	0.932	0.953	0.618	0.764	0.654	0.355

Bold-faced values are hazard ratios above 1;

CD4 model -2*Log-likelihood=6932.39; CD4 model AIC=7196.39; Viral load model -2*log-likelihood=6429.69; Viral load model AIC=6716.69;

P1=Bulawayo, P2=Manicaland, P3=Mashonaland Central, P4= Mashonaland East, P5= Mashonaland West, P6=Masvingo, P7=Matabeleland North, P8= Matabeleland South, P9=Midland;

_____ indicates no observed transition for that particular multistate model

Immune deterioration (decrease in CD4 cell counts) was evident among patients belonging to Mashonaland East (P4) (state 1 to 3 and state 2 to 3) and Matabeleland North (P7) (state 1 to 2), while the immune recovery was most evident among patients from P6. Becoming LTFU was observed to be highest among patients from Mashonaland East (P4) regardless of their CD4 cell count. We found that the risk of viral rebound to above 50copies/uL was high among patients from Matabeleland North (P7) (state 1 to 2), Mashonaland East (P4) (state 1 to 3) regions. In contrast, viral suppression to undetectable levels ($VL < 50$ copies/uL) were evident among patients from Masvingo (P6) (state 2 to 1) and Matabeleland North (P7) (state 3 to 1). The risk of becoming LTFU was high among patients from Mashonaland East (P4) if their $VL < 50$ copies/uL, Masvingo (P6) if their VL range was between 50-1000copies/uL and Mashonaland West (P5) if their $VL \geq 1000$ copies/uL.

To get a pictorial view of the spatial patterns and correlation between the CD4 cell counts marker and the VL measurements, we fitted the multivariate intrinsic CAR prior model with the province as the spatial unit. We jointly modelled those patients who had a $VL \geq 50$ copies /uL (VL state 2 and 3 combined) at the end of the follow-up to define that group that might not have attained undetectable VL or have a VL rebound to detectable levels, and those patients who had a $CD4 < 350$ cells/uL (CD4 state 3) to define that group that is still in the immune-deterioration phase at the end of the follow-up period.

Table 7-6 shows the posterior estimates after the joint mapping of the two immunological conditions for HIV disease progression among ART patients based on CD4 cell counts and VL. The posterior correlation between the spatially structured risk components of having a $VL \geq 50$ copies/uL and $CD4 < 350$ cells/uL was 61.3% (95% credible interval (CI): 47%-97%). This strong correlation suggests strong shared geographical patterns of the risk of immune deterioration

defined by these two prognostic markers. The baseline (log) relative risk of the HIV disease progression based on $VL \geq 50$ copies/uL was -0.472 while that of CD4 cell counts above 350cells/uL was -0.043.

Table 7-6: The posterior estimates for the multivariate conditional autoregressive model for the two HIV disease progression prognostic markers

Parameter	Estimate	Standard deviation	95% Credible interval
Alpha[VL ≥ 50 copies/uL]	-0.472	0.0628	-0.60 to -0.35
Alpha[CD4 <350 cells /uL]	-0.043	0.0314	-0.11 to 0.02
Correlation	0.613	0.3815	0.47 to 0.97
Sigma[VL ≥ 50 copies/uL]	1.226	0.3505	0.72 to 2.08
Sigma[CD4 <350 cells /uL]	0.147	0.0668	0.06 to 0.31

The joint mapping of the posterior relative risk of the HIV disease progression defined by the VL (RR1) and CD4 cell counts (RR2) under the multivariate conditional autoregressive model is shown in **Figure 7-4**. The dark blues or deep grey colours indicate areas with high relative risk while the light blue or light grey colours show regions with the lowest relative risks of the defined conditions. These maps show a geographical overlap of $VL \geq 50$ copies/uL and $CD4 < 350$ cells/uL in seven provinces. Patients in Matabeleland North province bordering Botswana and Zambia; and Mashonaland East province toward the Mozambique border had higher relative risks of $VL \geq 50$ copies/uL, and $CD4 < 350$ cells/uL conditions in addition to Bulawayo and Harare metropolitan provinces.

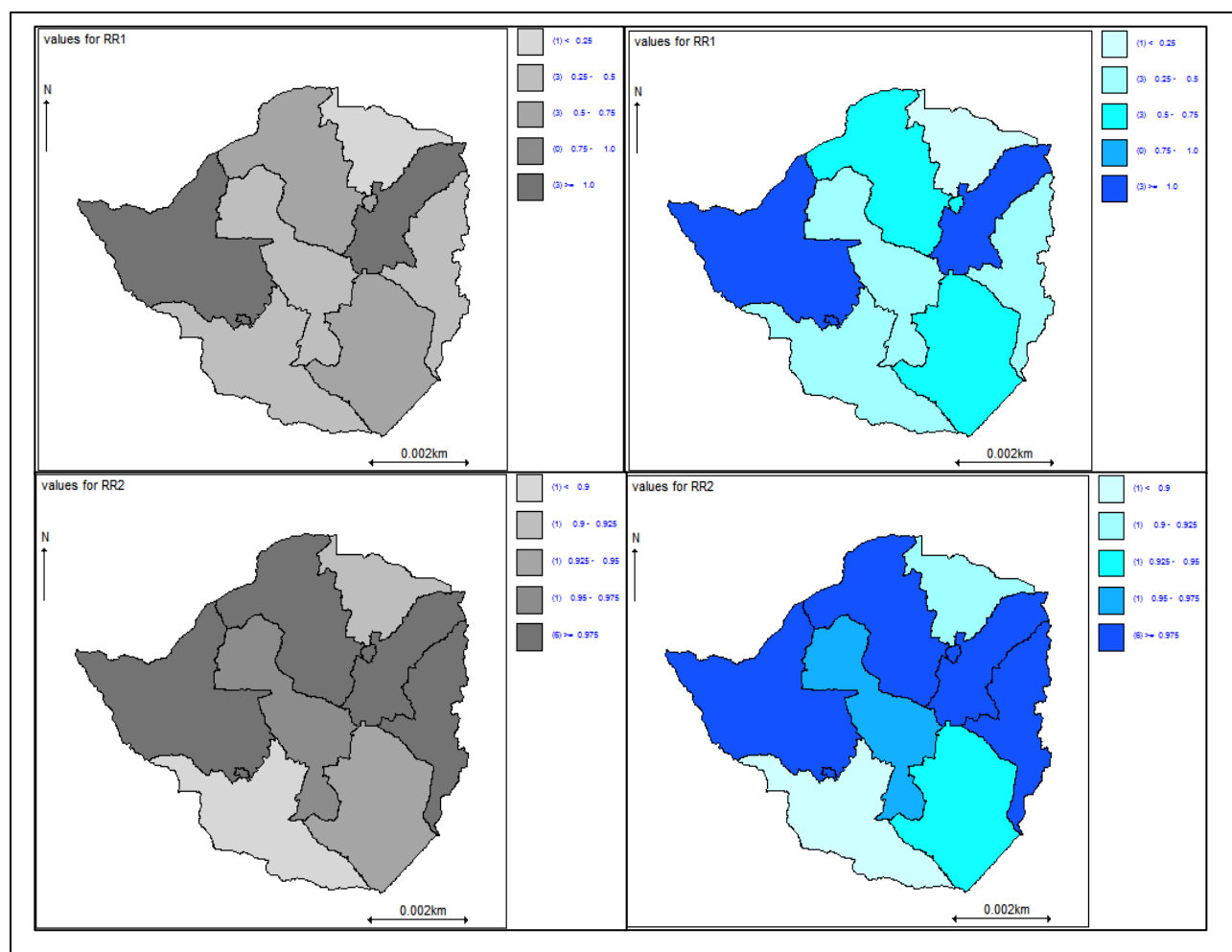


Figure 7-4: The joint mapping of the posterior relative risk of the HIV disease progression defined by the viral load (RR1) and CD4 cell counts (RR2) under the multivariate conditional autoregressive model

7.5. Discussion

The broad aim of this study was to jointly model and map HIV disease progression patterns based on CD4 cell counts and VL measurements among ART patients aged 15 years and above using time-homogeneous multistate Markov models and intrinsic MCAR prior spatial models. The multistate model covariates were generated through the PCA to account for collinearity between CD4 cell counts and VL measurements as orthogonal variables and as “incremental

transient states” variables for the time-varying effects in a single model, unlike most studies which ignore the correlation between these two markers. We also fitted an intrinsic MCAR prior model to jointly map the relative risks of HIV disease progression conditions defined by $VL \geq 50 \text{copies/uL}$ and $CD4 \text{ cell counts} < 350 \text{cells/uL}$ at the last observed visit conditional not to have died or become LTFU.

We fitted different time-homogeneous multistate Markov models based on each prognostic marker and used LRT to compare the best fitting model. We observed that the inclusion of either the orthogonal variable or the time-varying variable as “incremental transient states” in a univariate multistate model strongly improved the model as compared to the unadjusted models. However, the multivariate multistate models with both the orthogonal variable and the time-varying variable were the best fitting models based on the significant LRT and the much-improved $-2 \times (\log - \text{likelihood})$ values. This showed that joint modelling the prognostic markers based on PCA only or time-varying effects only may over- or under-estimate the transition rates. Lastly, we observed multivariate multistate model based on VL states was a superior model and predicted better the HIV disease progression patterns in this cohort compared to the multivariate multistate model based on CD4 cell counts states. These findings reflect what earlier studies have reported on the superiority of VL measurements in modelling HIV disease progression patterns compared to the use of CD4 cell counts (44,190). Our findings support the global guidelines in the use of VL measurements as the primary laboratory marker to monitor HIV disease progression amongst ART patients.

The multivariate multistate model based on VL states with CD4 cell counts in the covariate matrix showed that VL rebound and VL increase transition rates (state 1 to 2; state 1 to 3 and

state 2 to 3) were higher than the VL suppression transition rates (state 2 to 1; state 3 to 2 and state 3 to 1). This finding could be explained by poor ART adherence which remains a challenge among ART patients(191). Moreover, we found that poor ART outcomes were more likely among patients with a $VL \geq 1000$ copies/uL (state 3 to 4 and state 3 to 5) while patients with CD4 cell counts lower than expected (negative orthogonal variable) were associated with viral regaining and subsequently, death if their VL was above 50copies/uL. These findings are consistent with the known relationship between these two prognostic markers. As VL increases, the level of CD4 cell counts decreases. However, in the presence of effective and potent ART without non-adherence, one would expect the reverse to occur. This observed finding brings forward the need to continuously monitor these ART patients throughout to quickly pick treatment failure or side-effects before adverse events occur (190).

We found that as the VL increased (λ_{12} and λ_{23}) the transition rates increased with a decrease in the CD4 cell counts over time while as the VL decreased (λ_{21} , λ_{31} and λ_{32}) the transition rates decreased with a decrease in the CD4 cell counts over time. This finding aligns with the negative correlation which exists between these two prognostic markers that once the CD4 cell count levels are low, the rates of having a low VL decrease. The model results also show that the more the patients are immune deteriorated (high VL), the higher the risk of death. These findings support other earlier studies that once the immune system deteriorates the chances of immune recovery becomes slim and thus when most deaths occur (41–43). The risk of becoming LTFU was high among patients with $VL \geq 50$ copies/uL and $CD4 < 350$ cells/uL. This finding is consistent with previous studies which have shown that more ill patients tend to drop from the ART programme (126). However, some of these patients if tracked, would have died, which may result in misclassification error of the LTFU outcome.

Adjusting for the spatial covariate in the multistate models, we observed that the regions with a high risk of viral rebound transition were also more likely to have a high risk of CD4 cell counts decrease transitions. This was as expected since these two markers negatively correlate. The intrinsic MCAR prior model further confirmed a strong overlapping geographical correlation between individuals with a $VL \geq 50$ copies/uL and those individuals with $CD4 < 350$ cells/uL of 66%. This finding showed that a shared geographical pattern of relative risks between these two conditions exists. High relative risks of the two conditions defining immune deterioration were among the provinces which border with nearby countries (deep blue or deep grey colours).

High risk of immune deterioration conditions was observed in Matabeleland North province, which borders with Botswana and Zambia countries in the northern part of Zimbabwe. This particular province is a busy truck route to neighbouring countries and high mobility of people between countries which result in a high number of sexual partners and subsequently compromising viral suppression among HIV patients (93,183). These findings are consistent with earlier studies looking at spatial heterogeneity of viral suppression in this province and observed poor viral suppression and high HIV burden (10,76). Some of the factor associated with high immune deterioration in this region might be the late presentation for health care (138), resulting in delayed ART initiation (184); hence, immune recovery becomes slow. Therefore, interventions such as self-testing (192), pre-exposure prophylaxis (PrEP) pills for high-risk groups (193) should be intensified in such regions. We observed that having lower CD4 cell counts than expected results in an increased risk of mortality while higher CD4 cell counts were associated with becoming LTFU. This could be explained by the fact that much sicker patients are more likely to be bedridden; hence, they are hospital-bound while healthier patients may become LTFU as a result of "silent-transfers" to nearby health (27,123).

The reported results should be inferred in light of some limitations. Firstly, the dataset used in this study is very small and might not be an accurate representation of the Zimbabwean HIV population since we conveniently consider only those participants whose information was captured through the ePMS with both VL and CD4 cell counts repeated measurements. This sampling approach excluded those individuals whose health facility data was not linked to the ePMS; hence, the selection approach of participants was not a true representative of all people living with HIV in Zimbabwe as there were attached reasons of why the VL and the CD4 measurements were taken. In this regard, the MCAR assumption might not have been fully satisfied. The spatial effects were observed at a higher level (provincial level) which might not precisely pinpoint the marginalised areas to guide policy. This was as a result of our small sample size in this study; however, future studies should consider lower administrative level spatial units. Moreover, the MCAR model only describes the spatial interaction across the error terms to explain spatial autocorrelation; however, this model falls short when a more direct presentation of spatial interaction is desired.

Moreover, this data covers the period when differential monitoring was done due to resource constraints; hence, a biased group of individuals had laboratory information which was taken non-randomly. The estimated transition rates were assumed to be time-homogeneous; however, the HIV care in relation to the treatment of HIV-infected patients has changed many times between 2004 and 2017 which was not accounted for in these models. The limitation of the joint model used was its inability to account for the biological order of the association between VL and CD4 cell counts in this cohort, that is, increasing VL will reduce CD4 cell counts so VL change may precede CD4 changes. This study could not adjust for ART adherence, other comorbidities like diabetes and hypertension; and other demographic factors like age and gender

which have an influence to HIV disease progression due to failure to converge of the fitted model and missing information on some covariates. This may have resulted in biased transition rate estimates either by over-or under-estimation of the rate values.

Despite these limitations, this study managed to jointly model CD4 cell counts and VL measurements in describing HIV disease progression, which most studies ignored in such models. We also managed to simultaneously model the time-varying effects of the CD4 cell counts marker and include the negative residual effects of the CD4 cell counts in the covariate matrix in a single model which has not been done in previous studies. Lastly, spatial mapping of HIV disease progression patterns has not been adequately covered in literature; however, this approach is vital for low-and middle-income countries where resources are minimum.

7.6. Conclusion

In conclusion, the findings from this study provide a foundation on the HIV disease progression patterns in Zimbabwe to guide policy going forward and motivate future statistical modelling to consider such modelling approaches in infectious disease to guide policy and programme management. We found that VL models were much more superior compared to CD4 cell count models in HIV monitoring. We also observed that after joint modelling of CD4 cell counts and VL in a single model, the rates of VL rebound risks are still higher than viral suppression. We observed that being virally immune deteriorated ($VL \geq 1000$ copies/uL) increased the risk of becoming LTFU and death. The spatial overlap between VL and CD4 cell counts indicates the inter-linkages between these two markers in HIV monitoring; however, the VL model was superior compared to the CD4 cell counts model. With the global efforts to achieve zero HIV incidence, interventions which encourage ART adherence and continual educational support on

the barriers for ART uptake is crucial. Region-specific interventions which focus on behavioural change and social support should be strengthened all in the quest to achieve zero HIV incidences by 2030.

7.7. Ethics approval

The permission to use the routinely collected HIV data amongst ART patients was sort and granted from the Zimbabwe Ministry of Health and Child Care through the AIDS/TB Unit who oversees the data collection and storage. Ethical approval was granted by the University of Witwatersrand's Human Research Ethics Committee (Medical) (Clearance Certificate No. M170673).

7.8. Data Availability Statement

The data that supports the findings of this study are available through an application process from the Ministry of Health and Child Care in Zimbabwe which is the custodian of the ePMS data through the AIDS/TB Unit who manages and oversees the ePMS data collection process and are the custodian of the database.

7.9. Author's contribution

ZMZ cleaned and analysed the data and drafted the manuscript, **JT** and **TFC** reviewed the manuscript and advised on analysis, **EM** guided and oversaw the analysis and reviewed the manuscript.

7.10. Chapter 7 Appendix: The Multivariate Conditional Autoregressive (MCAR)

model code

```
model {
  for (i in 1: Nareas)
    {
      for (k in 1 : Ndiseases)
        {
          Y[i, k] ~ dpois(mu[i, k])
          log(mu[i, k]) <- log(E[i, k]) + alpha[k] + S[k, i]
        }
      RR1[i] <- exp(alpha[1] + S[1, i])

      RR2[i] <- exp(alpha[2] + S[2, i])
    }
  S[1:Ndiseases, 1 : Nareas] ~ mv.car(adj[], weights[], num[], omega[ , ])
  for (i in 1:sumNumNeigh)
    {weights[i] <- 1}

  # Other priors
  for (k in 1 : Ndiseases)
    {alpha[k] ~ dflat()}
  omega[1 : Ndiseases, 1 : Ndiseases] ~ dwish(R[ , ], Ndiseases)
  sigma2[1 : Ndiseases, 1 : Ndiseases] <- inverse(omega[ , ])
  sigma[1] <- sqrt(sigma2[1, 1])
  sigma[2] <- sqrt(sigma2[2, 2])
  corr <- sigma2[1, 2] / (sigma[1] * sigma[2])
  mean1 <- mean(S[1,])
  mean2 <- mean(S[2,])
}
```

CHAPTER 8

This chapter knits together the findings from previous chapters, as the research work is concluded. In the last chapters, issues around HIV monitoring among ART patients have been answered and linked to the global goal of attaining zero HIV incidences by 2030. Chapter 3 has highlighted the spatio-temporal variation of ART drop-out in Zimbabwe, which is useful to understand the geographical distribution of the ART drop-out problem, policy formulation and future research hypothesis formulation. In chapter 4, the time to occurrence of becoming LTFU and associated risk factors were determined using the basic multistate model (survival models) and the competing risk model. Chapter 4 focused on the LTFU outcome which is the main contributor of "leakages" within the HIV treatment cascade; hence, a threat to ART adherence and viral suppression which is the ultimate goal of ART. In chapter 4 and 5, the illness-death multistate models were used to describe the HIV disease progression patterns based on separate modelling of CD4 cell counts and viral load, respectively. These two chapters gave an in-depth understanding of the HIV disease progression patterns as these two markers defined the intermediate states the absorbing event (death) occurs. Chapters 4 and 5 help to identify the subpopulation groups of individuals who are likely to experience viral rebound and have low CD4 cell counts. In chapter 6, further clustering effects of the province were assessed for mortality, and viral load (VL) changes spatial patterns. In chapter 7, joint multistate models of CD4 cell counts and VL coupled with a sub-analysis of the simultaneous mapping of HIV immunological conditions after ART initiation using the MCAR model was performed. LTFU outcome was also considered as a stand-alone state in the multistate model instead of censoring the LTFU outcomes as in chapters 4 and 5. Therefore, this current chapter of the thesis presents

the main findings, general study limitations and evens out the "so what" question of this thesis in terms of public health implications and theoretical contribution of the research work. Recommendations are made towards missing data, the benefits of fitting different multistate models in HIV monitoring, the merits of BE compared to the conventional MLE. Lastly, this chapter provided the direction of the future research scope, which may be considered for HIV research as well as statistical methodology.

8. DISCUSSION

Motivated by the epidemiological questions around the need to achieve the HIV global goal of having zero HIV incidence by 2030 spear-headed by the 90-90-90 UNAIDS targets which have an ultimate goal of achieving viral suppression, existing MLE multistate models, extended BE multistate models coupled with geostatistical models were used in this thesis. These models were applied to address crucial epidemiology questions such as 1) quantifying and mapping the ART outcomes (mortality, LTFU and attrition) to characterize possible "leakage" pathways within the HIV continuum of care and treatment cascade at district level; 2) determine the time to occurrence of becoming LTFU among ART patients which are strongly associated with poor ART adherence; 3) to estimate transition rates between CD4 cell counts and VL intermediate states (outcomes) for HIV disease progression among ART patients conditional not to have died or become LTFU; 4) and to determine the shared geographical patterns of CD4 cell counts and VL immunological conditions patterns. The dataset used in these analyses were extracted from the Zimbabwe National ART programme through the ePMS database compiled between 2004 and 2017. In each of the previous results chapters from chapter 3 to 7, a comprehensive

discussion on the research findings was given. This section of the thesis focuses on the main contributions of the research work.

8.1. Theme 1: Risk Factors Associated with ART Outcomes

Theme 1 Key Points

- ART drop-out persist to contribute to the patients' attrition within the HIV continuum of care treatment cascade which are a threat to ART adherence
- Intermediate immunological ART outcomes provide an in-depth understanding of the HIV dynamics through yielding additional linkages
- Higher levels of care are associated with becoming LTFU while PHC is associated with immune deterioration
- Male HIV patients are associated with poor immunological response as they remain a blind spot in HIV prevention and control
- Adolescence and young adults HIV patients are associated with poor ART outcomes attributed to AIDS-related illnesses which are a leading cause of death in this group
- Multi-disease patients management remain a challenge among older HIV patients on ART due to drug toxicity

A successful ART programme is evaluated by the rate at which patients are retained into care. ART outcomes (mortality, LTFU, attrition, withdrawal and dropouts) are the most prominent challenges in HIV control as these results in "leakages" in the HIV continuum of the care pathway, and these outcomes were observed in this research work among the Zimbabwean cohort. As much as the broad objective is to fight and minimize these "leakages" to retain as

many patients as possible, the implementation of strategies has to be systematically guided by evidence-based findings.

One of the essential aspects of epidemiological research is to know the person at risk. Through the different analysis approaches implemented in this research, the most common risk factors which came out firmly were the health facility type, gender, age and comorbidities. The interlinkages of the cofactors to the ART outcomes of interest are illustrated in **Figure 8-1**.

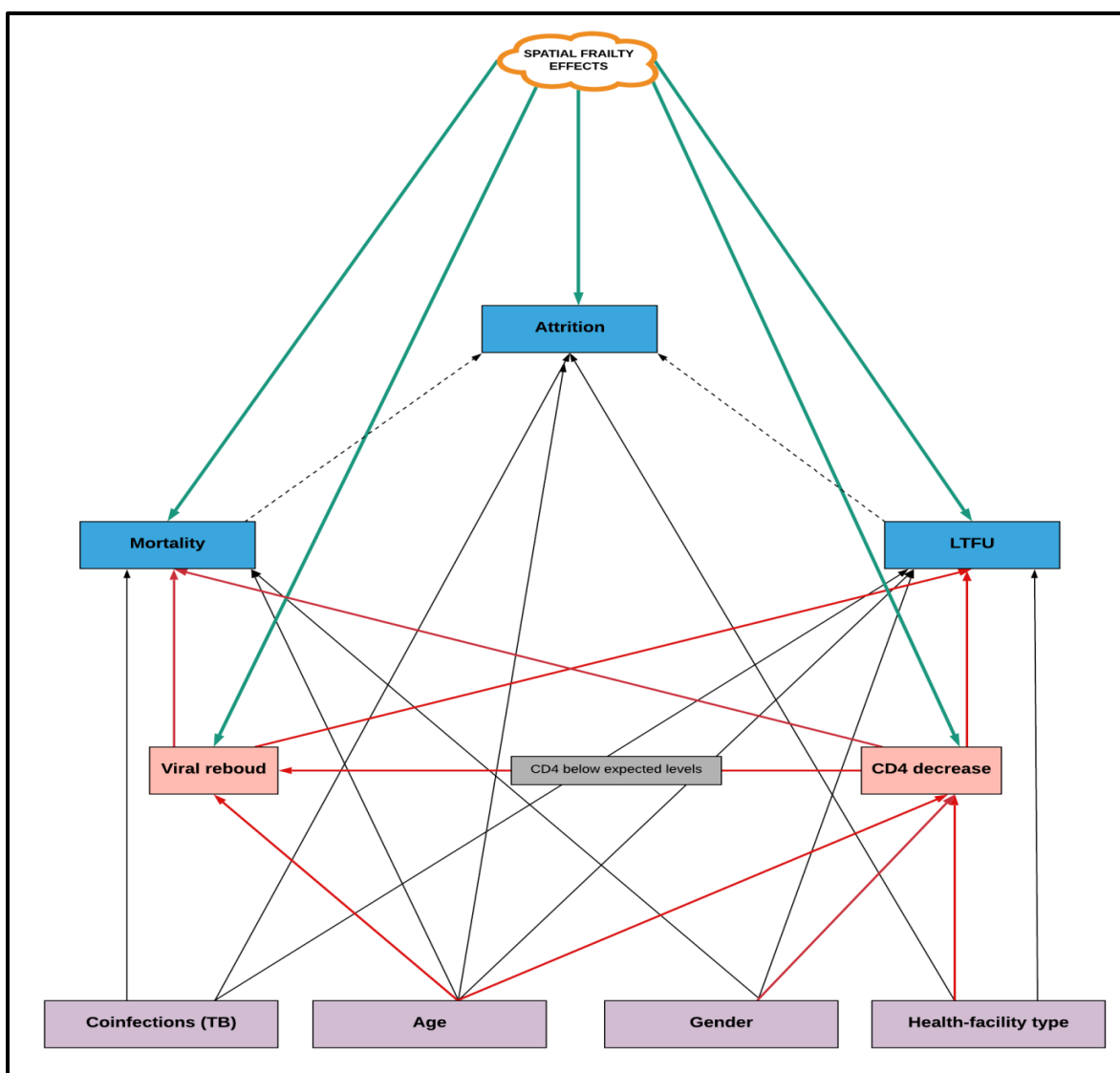


Figure 8-1: The inter-linkage of possible risk factors and ART outcomes in an HIV programme

Regarding black arrows, there was an overwhelming increased risk of associations between high levels of care health facilities and attrition (chapter 3); and becoming LTFU (chapter 3 and 4). Male patients were more likely to become LTFU (chapter 3) and die (chapter 3 and 4) compared to females. Age was also associated with becoming LTFU, mortality and attrition outcomes in this study. The adolescence/young patients (15-24years in chapter 4) and (15-20 years in Chapter 3) were more likely to become LTFU while older patients had an increased risk of mortality (chapter 3). Tuberculosis infection was consistently associated with becoming LTFU (chapter 3 and 4), death and attrition (chapter 3). Although these relationships have been well researched in literature, unique to other studies was the used of individual-level data compared to aggregated data (194), covering all the ten provinces in Zimbabwe, not a restriction to specific geographical areas (195) like other studies which confine to donor-funded sites (100,119) and included quaternary, tertiary, secondary and primary health facilities without restricting ourselves to government-supported health facilities only (196). This study used a huge database with a long follow-up period of 13 years; hence, it could be the first study to handle such huge data.

A further contribution to the knowledge of HIV was the expansion of the risk factor-ART outcomes inter-linkages by including the intermediate immunological outcomes shown by red arrows in **Figure 8-1**. This study established that patients enrolled in PHC, male patients, adolescents/young (15-24 years) age group and older patients above 45 years had an increased risk of immune deterioration (chapter 5). The inclusion of the intermediate immunological outcomes was motivated by the fact that the global focus is on routine monitoring of ART patients through VL primarily. The risk of viral rebound was high among the adolescents (15-20 years) age group and those above 60 years (chapter 6). As expected, those patients with a low

than expected CD4 cell counts had a higher risk of viral rebound in this cohort. Through the immunological ART outcomes, those patients who are at a high risk of experiencing attrition, mortality or LTFU are quickly identified considered under the intensive monitoring strategy to mitigate any fallout. This is supported by the study findings reported in chapters 5, 6 and 7.

8.1.1. ART outcomes- a source of "leakages" in HIV continuum of care

The contributions of these findings are that patients' retention into HIV care remains a challenge in the ART programme even after the decentralization of ART services. Identification and quantification of ART outcomes as sources of "leakages" within the HIV quantum of care cascade is crucial in the fight of HIV, particularly, becoming LTFU outcome which is a considerable threat to attaining viral suppression among ART patients. If patients become LTFU, withdraw from the programme or drop-out, this has a substantial bearing towards ART adherence patterns, and eventually, health outcomes are compromised. Once HIV individual experience poor health outcomes, the risk of death is elevated, and the life expectancy of these patients is reduced. Such processes contradict the main goals of ART which are to slow disease progression (12), improve survival (13), and quality of life (14), and minimize HIV transmission by reducing the viral load.

This study recommends the use of immunological ART outcomes which have been a missing link in HIV monitoring as a proxy to the occurrence of attrition, retention, mortality and LTFU within an HIV programme. Use of the immunological ART outcomes can quickly help in identifying when an adverse ART event is more likely to occur. In this study, patients with low CD4 cell counts than expected and high viral rebound or poor viral suppression were more likely to become LTFU. To avoid LTFU among patients with low CD4 cell counts and high viral load,

an efficient patient monitoring system which can quickly flag these patients for an intensive follow-up and support care before the patients become LTFU is a priority. Through the intensive follow-up and support care, strategies which ensure support ART adherence (197), quick identify ART treatment failure and resistance (180,186) and treatment efficacy (24) among these patients is a priority. In the intensive follow-up and support care, the patients may receive much more frequent reminders to take ART medication as recommended, monthly mobile clinic visits for these patients at their homes and continual education on the benefits of ART. Such intensive support for these patients may reduce the number of people who become LTFU with the perception that ART is not helpful and might instil hope to recover as some deaths will be averted.

8.1.2. Decentralization of ART services-strengthen primary health care facilities

The ART services decentralisation strategy has shown positive results toward HIV care and control through relieving workload from the already heavily burdened clinicians to the nurses, to increase ART access to everyone in need and those hard to reach areas by cutting transport costs. However, in most countries, these primary health care (PHC) facilities are still understaffed compared to the increasing population of the number of people receiving ART, have no specialized personnel, have poor infrastructure to provide routine laboratory monitoring; hence, rely on the referral system for such care and have limited resources. As a result, patients care, and management becomes compromised at PHC facility-level compared to higher levels of care as observed in this study; hence, viral suppression among PHC patients may remain a farfetched achievement.

Therefore, this study recommends policy managers to improve the wellness of HIV patients in PHC through equipping these centres with adequate resources to meet the required need. PHC facilities mostly rely on higher levels of care facilities for advanced patients' care like VL measurements as few sites are offering VL measuring in low-and middle-income countries like Zimbabwe. This process compromise effective patient care at PHC sites as the turn-around time of results is long; results may be misplacements or missing results due to the high workload at the VL referral sites to cope up with the demand. Improvement of PHC capacity for HIV care can be achieved through channelling down of donor funds to PHC levels to be comparable to the higher levels of care clinics.

Moreover, from the patients' perspective, the majority of the PHC sites are in rural areas; hence, their catchment areas are made up of rural residents. These rural patients are subjected to poor health knowledge and belief barriers on the efficiency of ART in treating HIV infections which are barriers to ART adherence resulting in poor immune recovery among these patients. For such, this study recommends the establishment of interventions which include education sessions on ART addressing the negative effects of beliefs in divine healing, the inclination for traditional medicine and misconceptions over ART benefits and safety. Moreover, rural settings are made up of communities which have a high risk of social stigma, which is strongly associated with poor ART adherence (112). Further recommendations are to implement policies which protect HIV patients through minimizing stigma and discrimination and continual education in the rural communities to provide social support towards PLWHIV as there is a chance to live a healthy life after being HIV infected.

8.1.3. Male patients-a “blind spot” in the HIV agenda

Identification of subpopulation groups of PLWHIV is vital to come up with appropriate specific interventions for these groups of people. This study observed that male patients had a higher risk of poor immune recovery, high risk of mortality and high risk of becoming LTFU. The trend of these worse health patterns of males is reflected in their life expectancy estimates which are lower than those of females. The lower life expectancy in males predominantly influenced by their health and lifestyle behavioural patterns. Globally, the ART coverage among men aged 15 years and above was estimated at 55% (41%-68%) compared to 68% (51%-82%) among women in 2018. In the SSA region, the percentage of women who know their HIV status was 20% higher compared to males while the number of men receiving ART was 27% lower than women in the same year (198). The Zimbabwe Demographic Health Survey 2015 (ZDHS 2015) reported that only 36% of men had been tested in the last 12 months compared to 49% women. These variations were also evident in this study which had more female participants (65.5%) compared 34.5% male participants in the ART programme (140). The gender disparities in HIV activities can be attributed to the fact that men have been a blind spot in HIV agenda as they have been left out more often in HIV campaigns.

Numerous researchers have reported that men in a general visit health clinic for check-ups less frequently than women, often diagnosed with life-threatening conditions at late stages than women due to late presentation and have fewer interactions with the health facility compared to women with multiple entry points in HIV care through antenatal clinics, and prevention-of-mother-to-child (PMTCT) programmes which results are better immune recovery compared to males which can be attributed to their improved ART outcomes (164). Moreover, HIV interventions specifically for males like male condom use and voluntary medical male

circumcision (VMMC) have struggled to reach national, regional and global targets in the past years. This brings out the urgent need to reach out to men who are a missing link to HIV care to boost their HIV services uptake to better their ART outcomes, improved survival and life expectancy comparable to women and ultimately for their contribution toward the global viral suppression targets currently trailing at 53% of all PLWHIW.

Issues of concern among men include their poor health-seeking behaviour due to health institutional hindrances and national policy gaps which are more appealing to women than men with regards to HIV response. Most health facilities lack extended opening periods to accommodate workingmen; the health sites are inconveniently located; limited privacy; inefficient appointment system as some just operate through the first come first serve system; long waiting periods from the time of arrival to seeing the physician; hence, the waiting time is often unpredictable. Most health services models and health awareness for HIV care currently in place tend to suit and engage women more than men. For instance, healthy nutrition and HIV testing services interventions have been offered through antenatal clinics mostly before being integrated into reproductive health services which is a positive move towards increasing male involvement.

The rigidity and non-reluctance of these institutional health services drive men away, and they become less willing to seek health assistance. Furthermore, national policies developed for the health-service delivery in a nation are mostly women centred in most SSA countries and lack strong national health policies for men. Therefore, to enhance the men's health-seeking behaviour, their use of health facilities should be boosted by providing a much more male appealing health facility environment. This study recommends the establishment of men's clinics which operate for longer hours with efficient appointments, increased privacy and minimum

waiting period. In such clinics, maternal and child health, sexual reproductive health and HIV services can be integrated to positively boost the health-related attitude and behaviour of men towards HIV care. Moreover, the health service personnel should be more alert to attend, help and understand men's health and behaviour to achieve a smooth provider-client relationship which is attractive to males to increase their retention in care. An additional recommendation for male involvement is integrating HIV testing component in the multi-disease health campaigns for other diseases like diabetes, hepatitis, hypertension and cancer; and full utilization of the VMMC service.

Another drawback among males leading to poor immunological responses is the negative societal perceptions towards them. Men have been negatively portrayed in HIV disclosure as the ones who bring the HIV infection in relationships, infect young women, are the main drivers of sex-for-money activities and are considered as perpetrators of gender-based violence. Such social stereotypes in men may have an influence over them; hence, remaining as the “blind spot” in HIV care resulting in their late presentation in HIV care. Furthermore, the societal masculinity norms for males like indulging in high HIV transmission risk behaviours including alcohol intake, having multiple sexual partners, substance use and gender inequality. These societal masculinity norms have been thought to embolden high-risk HIV transmission leading to an increase in new HIV infections in the general population, and compromise ART adherence leading to the observed poor ART outcomes among men. With the global notion to expand HIV services to achieve the set targets, the male masculinity norms and negative societal perception obscure the optimum ART uptake in men cannot be ignored any further.

For those men who are mostly at home or work, this study recommends improving the HIV services for male patients through implementing HIV campaigns which reach out to men through

their “male spaces”. Interventions which have been found highly appealing to male clients who rarely visit the health sites include the community-based testing and counselling which encompasses home-based testing, door-to-door testing, mobile clinics, HIV testing musical galas and social hubs testing. Community or workplace outreaches have also improved male participation in HIV care coupled with self-testing, which proved to be convenient, affordable, low-cost and subtle approach in HIV screening.

Self-testing strategy requires expansion as it does not only increase HIV screening service but facilitates linkages to care among men (29,30); however, considerations to clinic proximity and follow-up of these patients who tested positive through home-based tests are required as a health facility confirmatory test is required. This strategy has been evident in the Zimbabwe pilot study and the UNITAID-supported HIV Self-Testing Africa (STAR) study which reported that self-testing strategy is useful especially those people who do not usually go and seek voluntary HIV testing in health facilities (31). Couples' testing during pregnancy at homes or health facilities has been found to be more appealing to increase HIV testing among men. These interventions aim at increasing the number of HIV-infected males to know their status and start ART early; hence, fight late presentation issues to achieve a successful viral suppression among males.

Enabling the male patients to link to care, adhere to treatment and achieve and maintain viral suppression has been the main challenge in HIV agenda. To mitigate this gap, "test and treat" strategies that immediately initiate ART after testing positive have been found to be highly associated with high patients' retention and attaining viral suppression among men. Implementation and intensifying such intervention can bring more men on board and reduce the gender disparities, which have resulted in low uptake of HIV interventions among male. Once

men become accountable in the HIV agenda, their risk of HIV transmission is reduced, and the global targets can be achieved.

8.1.4. Adolescence patients-social protection support strengthening

In this study, adolescents were strongly associated with low CD4 cell counts, viral rebound, becoming LTFU, attrition and mortality. This finding aligns to the HIV-related illnesses reported which have become the leading cause of death among adolescents (199). This finding could be explained by the fact that adolescents and young adults are less likely to become linked and retained on care. Several studies have shown improved viral suppression among adults; however, adolescents appear to be far from achieving this goal, as shown by the high transition rates in this study. Several studies have documented that, adolescents with chronic illnesses have intricacy management which results in an increased risk of poor viral suppression (130).

These poor ART outcomes among adolescents can be attributed to structural deprivation due to medical, psychological and logistical reasons, which affect poor adherence in this subpopulation group (131). The most common medical barrier which has been found to affect ART adherence include treatment side effects, multiple doses and health system dissatisfaction. The logistical issues encompassed travelling, forgetting doses resulting in errors, inconsistent and inconvenience routine drug uptake. Research has found that ART has improved perinatal HIV infection into a controllable disease through optimal ART adherence. This opens up an additional challenge among adolescents who were prenatally infected in the transition stage to adults care to experience ART adherence lapses and develop worse clinical outcomes (131). The transition from paediatric care to adult care would mean changing care providers, absence of youth-

friendly facilities, tight and hectic schedules, new responsibilities and deprivation of caregiver support.

Some of the social deprivation issues among adolescents include inadequate financial support to cover transport costs to health facilities for treatment refill since this group heavily depends on their caregivers (132); food insecurities (availability, access, utilization and stability) which compromise their immune system as nutritious food is fundamental for immune recovery as some adolescents belong to child-headed families; lack of family support as some adolescents come from disrupted family structures with depraved caregiver-child relationships; experience psychological distress leading to mental health; generally defiant (136); disposed to peer pressure (112); vulnerable (132); often fear perceived HIV-related stigma and discrimination to disclose their status (100,112,132); depression and anxiety; and caregiver physical illness and emotional challenges contribute to inconsistent HIV care which increases to highly observed poor ART outcomes among adolescence.

Therefore, this study recommends the policymakers to strengthen the social protection support policy which addresses complex vulnerability, disadvantages and risks faced by HIV positive adolescents. This strategy also may foster resiliencies in general, HIV positive adolescents' population. The social protection support can interrupt some of the social deprivations faced by adolescents through poverty reduction and economic development, improved access to health care, access to health services, reduced stigma and discrimination and improved caregiver psychosocial and physical well-being. Another recommendation is the use of health facility-based peer-supporters programmes for adolescents to improve ART adherence and ultimately, viral suppression(133,134). The peer support activities involve peer-to-peer counselling, peer support groups and treatment buddy programmes among adolescents with the aim of ART

adherence and ultimately achieving viral suppression, reducing the HIV-related illnesses among adolescents.

As adolescents may exit the HIV care through becoming LTFU or withdrawals due to transition adjustments challenges from paediatric care to adult care; an early multidisciplinary and developmentally suitable transition preparedness mechanism is an alternative. The mechanism should be a comprehensive package addressing inherent adolescents' health issues like cognitive health, ART adherence, stigma, disclosure and socioeconomic issues (129,134). Besides, a simple regimen, directly observed therapy and technological interventions like cell phone reminders have been found to increase ART adherence in adolescents.

8.1.5. Older patients-multi-disease HIV patients' management

Multi-disease HIV patient management among older patients is an emerging threat to attaining viral suppression among this subpopulation. In this study, older patients had an increased risk of immune deterioration, viral rebound and mortality which could be explained by the weaker immune response in older patients compared to young people as their capacity to generate CD4 cell counts and suppress VL is reduced with an increase in age (161). Furthermore, elderly patients are susceptible to multiple diseases which could either be communicable (e.g. tuberculosis) or non-communicable (e.g. diabetes, hypertension or cancer) in addition to other opportunistic infections. Multiple diseases among HIV-infected patients' results in a much more intricate multi-disease patient management process as multiple drug administration or medication doses may yield overlapping toxicity between drugs leading to adverse reactions (98) which lead to poor ART outcomes.

This study recommends early HIV screening, ART initiation and ART adherence among elderly patients to ease off the multi-disease patient management challenge thereof. Older patients should be screened for other non-communicable diseases as routine care for HIV patients for early detection and treatment before advanced stages. Another recommendation is for the pharmacists to manufacture more potent and effective ART drugs which are non-toxic and have minimum side-effects to encourage adherence.

8.2. Theme 2: Spatial and spatio-temporal variation of ART Outcomes

Theme 2 Key Points

- Spatial modelling is an emerging tool in HIV disease monitoring
- The HIV burden in Zimbabwe varies by province/ districts due to the significant heterogeneity in social, cultural and population dynamics which are mainly influenced by geographical correlation of the epidemic
- Most ART drop-out, poor viral suppression and immune deterioration burdened areas are those bordering neighbouring countries, particularly the southern and northern regions which are the same region with high HIV prevalence in Zimbabwe

In HIV monitoring, problem identification (e.g. ART drop-out burden) and knowing who is affected ("person," e.g. age or gender) are essential aspects for epidemiological studies to come up with possible interventions as discussed earlier. However, these aspects are complete if the affected "place" is known. Such questions are comprehensively answered by spatial and spatio-temporal models which have been intensively used in disease outbreaks to identify the hot-spots where the problem is emerging. These models are starting to creep in in HIV disease monitoring

as they are a useful tool to guide implementation of interventions and this current research study is among the very few early HIV researches which have applied this technique, particularly in Zimbabwe. The usefulness of spatial models is felt more in low-and middle-income countries which have limited resources for public health programmes like HIV. Therefore, spatial models are convenient to help identify high burdened regions so that area-specific interventions can be implemented. Spatial maps are convenient for policymakers to visually identify high-risk areas and cold and hot spots so that they can allocate resources on those areas unveiling eminent outcome risk (36). Moreover, spatial modelling forms the basis of future research hypothesis formulation and planning of surveillance activities in these high-risk regions.

This study implemented the spatial models for ART drop-out as illustrated by the green arrows in **Figure 8-1**. This was motivated by UNAIDS 90-90-90 targets of HIV to attain viral suppression; hence, a statistical approach to pinpoint the high-risk areas for fast implementation of area-specific interventions was an innovative idea. Also, the modelling approach hypothesised that ART outcomes (drop-outs, viral rebound, viral suppression and low CD4 cell counts) vary by provinces, districts or health facility level due to the social, cultural and population dynamics which are mainly influenced by geographical correlation of the epidemic in Zimbabwe.

This study observed substantial geographical variation in the occurrence of ART drop-out and immunological HIV conditions in Zimbabwe, as discussed in detail in chapter 3, 6 and 7. In chapter 3, districts along southern and northern parts of the country had a higher risk of ART drop-out. In chapter 6, a high likelihood of poor VL suppression spatial effects was observed in Matabeleland North province, which borders with Botswana and Zambia. In chapter 7, the intrinsic multivariate conditional autoregressive (MCAR) prior model showed a strong overlapping geographical correlation between individuals with a viral load ≥ 50 copies/uL and

those individuals with CD4 cell counts < 350 cells/uL of 66% after ART initiation which indicated that a shared geographical pattern of relative risks between these two conditions exists. Patients in Matabeleland North province bordering Botswana and Zambia; and Mashonaland East province toward the Mozambique border had higher relative risks of VL above 50 copies/uL, and CD4 cell counts below 350 cells/uL conditions in addition to Bulawayo and Harare metropolitan provinces.

In general, southern and northern regions indicated to be the most at risk province as it was associated with a high risk of immune deterioration conditions and ART drop-out. Regions with busy border entrances from or exits points to neighbouring countries have high mobility of people to nearby countries, an influx of truck drivers which encourage the masculine norms of multiple sexual partners, sex for money activities, drug use, alcohol drinking and smoking. These risk behavioural hype activities become a threat to viral suppression among HIV patients (93,183). This study recommends extending PrEP intervention (193) among these male truck drivers to sex workers in Matabeleland North and other busy border areas to reduce HIV transmission and minimize acquiring new HIV strains to achieve viral suppression. This study also recommends extending the supply period of ART from 3 months to 6 months or a year for those individuals who spent most of their times in neighbouring countries to increase ART adherence since the chapter 3 results showed that the longer individuals are on ART, the less likely they are to drop-out. Automated dispensary machine is another alternative for easy access to ART refill, especially, for people who work far away from their enrolled health centres.

Regarding the geographical location of the patients on ART, provinces along the country boundaries have hard to reach areas with poor road networks; hence, patients residing in these areas have limited transport network to nearby health facilities for treatment refill as some

districts in remote provinces still have dispersed ART sites despite ART services decentralization (35). Patients residing in the hard to reach areas have limited access to current HIV information through radios, televisions or official social media communications due to unavailability of those facilities in those regions or unaffordability of the devices. This creates a knowledge gap which is more likely in rural areas on the benefits of ART over traditional herbs which may result in withdrawals or dropouts of these patients from ART programme increases the risk of immune deterioration. For such geographical locations, this study recommends strengthening mobile clinics; more extended ART supply periods can be introduced for these people, support group programmes whereby individuals collect ART treatment supply on behalf of other group members rotationally which encourage HIV disclosure and minimize stigma; and continual community-based health education addressing false impressions over ART treatments benefits to mitigate poor ART adherence.

8.3. Theme 3: Multistate Models in HIV Disease Monitoring

Theme 3 Key Points

- Multistate models framework is a very powerful, informative tool to analyse time to event analysis
- The multistate model framework provides a variety of model types which can be used holistically to answer epidemiological research questions, e.g. How well are PLWHIV adhering to ART?
- The competing risk model estimates the absolute risk of an event without censoring the competing events which are essential for medical decision-making
- Joint modelling of time-varying VL accounting for CD4 cell counts effects provides additional information which VL cannot explain alone.

In longitudinal studies, patients are follow-up over time and observations are repeatedly collected. In such epidemiological studies, multistate models are the most appropriate models as they account for the time change, and individuals multiple outcomes can be estimated simultaneously. Multistate model is useful in predicting an individual's disease progression trajectories through time which is helpful for programme managers to make informed decisions. A detailed review of multistate models has been provided in chapter 2. Multistate models offer an in-depth understanding of a public health problem if they are implemented holistically answering a broad research question like "*how well are PLWHIV adhering on ART to achieve viral suppression?*" from different perspectives as demonstrated in chapters 4, 5, 6 and 7. The advantage of a holistic analysis approach is that each model answers a different question which when the results are pooled together, they become much more informative.

In chapter 4, two types of multistate models were used, namely the simple multistate model (survival model) and the competing risk model. The survival model is appropriate in estimating a single (or composite) endpoint. The competing risk model was used to quantify the effect of becoming LTFU in an HIV programme to understand the rate at which ART patients "leakages" through LTFU occurs so that interventions which promote patients retention can be implemented. Through the two multistate model approaches implemented chapter 4, this study recommends that in follow-up studies where multiple outcomes occur and other secondary outcomes obscure the occurrence of the primary outcome, the competing risk model is the most appropriate as it estimated the absolute risk (cause-specific) through the cumulative incidence risk function without censoring the competing events which are critical particularly in decision-making and prognostic research work (53,200). In such cases, the Kaplan-Meier estimator's assumption of independence of time to the event and the censoring distribution is violated;

hence, the estimator overestimates the cumulative incidence function in the presence of competing risk (57). However, an apparent distinctive effect of the estimates is observed if the competition between the outcomes is heavy.

In chapter 5, 6 and 7, illness-death multistate models were fitted to describe the HIV disease progression patterns based on CD4 cell counts or VL intermediate states. The CD4 cell counts normally are expected to increase while the VL is expected to be suppressed in the presence of potent and effective ART treatment; however, this is subject to patients' adherence issues among other factors. Inclusion of these intermediates states helps to alert physicians in advance for a cautious action before an adverse event occurs. In chapter 5, there were high transitions rates of progressive depletion of CD4 cell counts among ART patients resulting in immune deterioration which subsequently leads to an increased likelihood of opportunistic infections and poor ART outcomes (21,22). The high risk of mortality was associated with the severely immune-compromised group; however, the mortality hazard rates decreased with an increase in time since ART initiation. Based on the findings in chapter 5, this study affirms the issue of early ART initiation when the immune system is still intact, and the improved survival outcomes associated with a longer stay on ART. In chapter 6, a more sensitive marker was used to estimate the transition rates of viral changes and viral rebound transition rates were higher compared to viral suppression transition rates. In chapter 7, a joint model of VL and CD4 cell counts to accounts for the unobserved error which VL cannot explain on its own showed that patients with CD4 cell counts below the expected levels were more likely to experience a viral rebound.

This study recommends intensifying ART adherence interventions to attain viral suppression; however, since the transition rates for a viral rebound above detectable levels were high in this cohort, the ultimate goal for viral suppression should reinforce the implementation of

interventions to those individuals who would have already attained viral suppression to maintain and sustain viral suppression. This can be done through incentivizing those who would have managed to maintain and sustain viral suppression; dispersing simpler, less toxic, more efficient ART regimen to virally suppressed individuals to enhance continued adherence. Those who may not maintain viral suppression through the routine primary care visits and require special assistance beyond the regular primary care may be supported through direct observed or assisted therapy approach.

8.4. Theme 4: Bayesian Inference in HIV Disease Progression Monitoring

Theme 4 Key Points

- Bayesian methods are on the rise and have undergone an enormous renaissance in public health research
- The direct probability statements in BE inference on hypothesis and data is much more appealing to researchers
- Prior subjectivity is a non-compelling issue since the use of non-informative priors can mimic MLE; prior sensitivity analysis brings the BE rigour
- Bayesian models have shown to outperform MLE models as BE models make assumptions which reflect reality
- Bayesian multistate models can handle aggregated data using Kolmogorov-Chapman differential equations in instances where individual-level data is unavailable

The novel statistical modelling of HIV disease progression based on Bayesian inference has been implemented predominantly in this thesis. In most analysis, additional theoretical details of the model specification and derivations have been provided as supplementary material in each

Chapter. In chapter 4, a Bayesian parametric survival model with a Gompertz distribution was fitted as a sensitivity analysis of the competing risk model while in chapter 6, a BE multistate model was fitted based on VL measurements. Chapter 5 and 7 presented the results from MLE multistate models. In this section, a detailed discussion on the strengths and weaknesses of BE models over MLE will be provided, and some recommendations of the modelling approach appropriate in HIV disease progression studies.

The frequentist (MLE) approach continues to dominate research, particularly in life sciences. This approach relies on the available data defined through the likelihood function; hence, the MLE is generally affected by the sample size (201). The small sample sizes may result in the inferential process to be internally logically inconsistent. Results interpretations of the frequentist approach are customarily based on the repeated sampling property, which may be ambiguous; the probability of the hypothesis is non-applicable; however, this estimation approach tends to be less computationally intensive (117). The MLE provides a natural framework to validate the obtained estimates as it has a proper post-estimation procedure, and this is a constraint in Bayesian inference (117).

In the era of big data and powerful computing machines, Bayesian methods are on the rise. They have undergone an enormous renaissance in public health research, particularly in machine learning and genetics. The BE inference approach is based on the Bayes Theorem, which is logically rigorous as it allows the fitting of the predictive distribution of future observations which is of importance in decision-making programmes (117). The BE approach estimates are based on the mapping of the prior distribution, which constitutes of the existing and new belief information and the likelihood function of the observed data. This yields posterior estimates which are much more coherent compared to the MLE approach. Many different models can be

fitted within the BE framework; however, the result validation is typically done through the prior sensitivity approach as many different priors can be tried; this makes the BE modelling much more rigorous compared to the MLE approach (201). The nuisance priors within the BE modelling are always marginalized out of the joint posterior distributions, which is a straightforward way to deal with such parameters, and this is hardly done in the MLE approach (201). Therefore, in this regard, the BE can be viewed as being a complete, unambiguous, prescriptive and coherent method of estimation; however, there is still underutilized of this estimation approach in epidemiological studies.

The adoption and utilization of the BE inference have been hindered by the difficulties in implementing the Bayes models. One of the main issues statisticians raise on BE inference is the issue of prior subjectivity of in Bayes model which cannot be ignored; however, the BE models can be run with prior references which can mimic the MLE (non-informative priors) to those which are more subjective to bring much more informative estimates (201). Although, BE models are computationally intensive requiring much longer running time of more hours or days compared to the MLE multistate model; however, MLE may fail to converge which can only be achieved through the BE route.

Within the multistate model framework, multistate models can be implemented from the Bayes perspective or the MLE perspective. Most researchers have implemented multistate models in HIV research work from the MLE perspective using the *msm package* in R (147), and none have used the BE perspective using *bayesreg object* in BayesX (75). The model assumptions behind these modelling approaches in these two packages overlap as both can assume the Markov process, time non-homogenous transition rates and right censoring of observations; however, the BE multistate model within the BayesX can further handle time-varying covariates, nonlinear

effects of covariates implemented using splines which MLE only assume to be linear or log-linear by default; account for frailty term-individual heterogeneity and spatial heterogeneity which the MLE model cannot do (52,172). Such flexibility within the BE inference makes these multistate models implemented in BayesX in chapter 6 reflected the reality regarding the HIV disease process at the individual level. Accounting for individual heterogeneity was important in this study as individuals express different immunological responses, suboptimal ART adherence, drug toxicity rates and genetic factors.

Though individual-level data is much for informative and provides more extensive flexibility in modelling, aggregated data usually is accessible on many platforms and intermediate observation times during follow-up studies may not always be supported in most programmes due to financial constraints; hence, data may be partially observed. In the thesis appendix section (Appendix B), an illustration of the Bayesian multistate model on aggregated data using Kolmogorov- Chapman differential equations in WinBUGS has been provided, which is useful in situations where individual-level data is not available. Such flexibility within BE multistate models opens room for future research hypothesis formulation as informed by the partially observed data.

Therefore, this study recommends statisticians to consider implementing Bayesian statistical models which use the probability of the hypothesis and data which most epidemiologists prefer. Models which can make assumptions which mirror the natural processes of events are preferred for decision-making processes in programme planning and implementation of interventions is evidence-based. However, it is crucial to understand the model development process which might be challenging and make use of the sensitivity analysis approach as there could be a problem of the surfeit of posterior distributions due to prior variations to validate the results.

8.5. Strengths of the Study

This thesis has several strengths which include the use of individual data which enabled exploration and adjustment for patient-level covariates associated with outcome, which is not possible if data is aggregated. The period covered by this study was relatively long (13 years), and the data included the ten provinces in Zimbabwe without restriction to specific geographical areas. The data represented all levels of health care in Zimbabwe, namely: quaternary, tertiary, secondary and primary health facilities from both the public and private sector not confining to government-supported health facilities only. To the best of our knowledge, this study could be one of the largest dataset used for Zimbabwe to analyse adult ART outcomes at the individual level over such a long period.

This thesis results are comparable to similar research conducted in SSA and also fits in to support the disproportionate distribution of HIV prevalence in Zimbabwe as reported in the country HIV surveys. This study controlled for confounding at the analysis stage using multivariable regression approach implemented in chapter 3 to 7 of this thesis. Different types of models were used which incorporated categorical covariates (Chapters 3 to 7); continuous covariates with nonlinear effects modelled as P-splines (Chapters 3 and 6) and spatial effects model based on the neighbouring effects using the contiguity matrix (Chapters 3 and 6). Individual heterogeneity was accounted for in chapter 6 model while spatio-temporal heterogeneity was accounted for in chapters 3, and spatial heterogeneity was accounted for in chapter 6 and 7.

The statistical analysis techniques performed in this thesis were very rigorous and helped to explore other statistical modelling fields beyond my comfort zone in statistical analysis. The

statistical computing process was barely on the use of large datasets in different software with estimation centred around BE approaches. The software used was the BayesX (75) and R (174), which are free and flexible in fitting models. The other strength of this study is that it could be the first study to implement BayesX multistate models incorporating a spatial covariate with specific application to HIV infection. Also, this study has managed to fit various types of multistate models, which gives detailed information on the outcome being analysed.

8.6. Study Limitations

The results presented in this thesis should be inferred in light of some limitations. Firstly, the dataset used was part of the ePMS which was launched in 2012 with a huge part of the dataset before 2012 captured retrospectively and in real-time after that. This means there was a possibility of selection bias of patients during data capture from the paper-based system to the electronic system. This resulted in the ePMS giving preference to active ART patients at the time of launch who were coming to health facility site for their reviews and excluded those who might have died in the previous year. This is supported by the low observed mortality rates in this cohort; hence, we had long survivors in the dataset.

There is a possibility of participant selection bias since patients enrolled in the ePMS database could be distinctively different from those not included. The dataset had approximately a third of the total number of people living with HIV in Zimbabwe. This participant selection might have caused overestimation or underestimation of the estimates reported in this study which subsequently impact the generalizability. The participant selection might have biased our estimates in this study; however, our findings were not significantly different judging from the cohorts from other studies which had similar traits.

Moreover, this study covers the time in which ART initiation guidelines changed three times; hence, there could be some bias in the estimates. A significant limitation in this study is the low mortality rate of which most deaths were for those patients who initiated ART between 2013 and 2017. The possible explanation for this could be an issue of a biased dataset in terms of capturing patient's information, as stated earlier. The majority of the deaths which occurred earlier may have been lost during data capturing from patients files to the electronic database since this was a retrospective exercise. So the data has many long term survivors from the early period.

Missing data was a major challenge since the analysis solely relies on programme data which is prone to poor quality in data collection. Variables that influence LTFU, mortality and attrition like VL and CD4 cell count were not fully observed for all the participants; hence, they were not adjusted included in the model. This could be explained by poor documentation (125), limited access to the point of care machines (27,137,138) and the informed differentiated care monitoring approach (139) in some years covered by this study. Multiple imputations (MI) for these variables was not appropriate since more than 60% of the overall observations were missing. In chapters 5, 6 and 7, due to missing information, the sub-sample sizes were only considered in these chapters, which might have influenced the statistical power and unprecise estimates reported while in chapters 3 and 4 these variables were not accounted for in multivariable analysis to maintain sufficient statistical power of the study. This study recommends the use "required field" or "mandatory field" checks during data capture on relevant covariate fields so that missing information is reduced and the data quality is improved. The epidemiologist may also consider hiring well competent data clerks who continuously undertake refresher courses on the importance of data entry accuracy to increase quality and reduce missing data.

Also, the period covered is mainly when the country was conducting targeted differential monitoring, whereby most of the patients who had their CD4 cell counts and VL measurements taken were mostly those done on the discretion of the physician. This might have been a source of missing observations in the laboratory variables in this study, as fewer people had such information based on the design of the data collection process. Such data collection approaches influence the generalizability of the findings to the general population. Therefore, this study recommends strengthening the HIV monitoring system to be provided to everyone on ART regardless of their clinical presentation so that data quality is improved and meaningful, valid inferences can be made. To the policymakers, this study recommends that scaling up of point of care CD4 cell counts machine to increase coverage across the country may also reduce the missing observations observed in this database. Moreover, expanding the VL monitoring in many sites, including rural areas, may also help in reducing missing data.

Missing data might have also occurred due to occasional follow-up visit by patients who at times miss appointments and never returned for follow-up visits after the first baseline visit. This was observed in many individuals who had only the baseline CD4 or VL measurements and lack follow-ups. Such patients' movements within the ART programme may indicate the challenge the ART programme face to retain patients on care, to minimise the LTFU or mortality "leakages". This study recommends the epidemiologist and policymaker to implements strategies which reduce ART attrition and encourage patients to participate in the HIV agenda. At the data analysis stage, missing data is not usually a setback depending on the magnitude of missing information therein. If the missing observations are assumed to be MCAR, multiple imputation techniques, can be an alternative during the data analysis stage. However, if the data are MNAR, then the process that caused the missing should be accounted for in the model for valid results.

However, there is still a challenge in statistical modelling software packages which are not compatible with multiple imputed data or data with missing information. This study recommends the development of novel statistical packages or upgrading existing statistical packages to handle missing information so that such data observations may not be considered redundant.

This study acknowledges the measurement error (25) associated with CD4 cell counts in ART monitoring since a patient's measurement may indicate a lower CD4 when, in fact, the patients had recovered. The illness-death multistate models for HIV disease progression have provided the immune recovery and immune deterioration patterns in this cohort in addition to identifying the subpopulation groups at risk based on CD4 cell counts. The motivation to use CD4 cell counts was based on the fact that most low-to-middle income countries still use CD4 cell counts measurements which have a low cost and increased coverage through efforts are in place to scale up VL monitoring. In such settings, CD4 cell counts findings can give comparable results as observed in this study; hence, useful to run the programme.

This study also acknowledges that differential misclassification of the LTFU outcome could have occurred in this study since some patients might have silently transferred to other health facilities with no electronic capacity; hence, could not be reconciled at the analysis stage. Also, this study could not measure ART adherence due to missing information; therefore, it was not accounted for in the multiple variable models to determine its influence of the ART outcomes directly. Expanding the data collection template in the ePMS should also focus on capturing information that can define ART adherence among ART patients. The transition rates for AIDS-defining state could not be estimated since the information was not available in addition to other comorbidities like hepatitis, non-communicable diseases which influence the transition patterns, especially

among older patients. This study recommends incorporating information with patients' comorbidities in the database as they influence the transition patterns and ART adherence.

Though this study used spatial modelling, there are also aerial data structure issues associated with aggregated spatial data. Generally, spatial analysis of aggregated data is subject to Misaligned Data Problem (MIDP), which transpires when spatial data is analysed based on a spatial unit scale different from what they were originally collected. This limitation fits well in our district-level models; however, sometimes it is important to understand the spatial distribution of an outcome of interest at a higher spatial level to formulate hypotheses for further research(102). Another major drawback in using aggregated data is the issue of ecological fallacy (103) which can be considered as a special case of MAUP. Ecological fallacy happens when aggregated data inferences lead to a different conclusion at individual-level using the same underlying data. This ecological bias can be partitioned into aggregation bias which occurs due to the grouping of individuals and specification bias which occurs due to differential distribution of confounding variables. Modifiable Areal Unit Problem (MAUP) (104) is also a drawback in aggregated data analysis, whereby conclusions may vary between different spatial units using the same underlying data. This spatial unit or aggregation inferred effect occurred, for instance, if the same data is grouped into an increasingly large region like re-aggregating health facility level data into district-level data as we did in this study. Such an approach may provide variation in results as a result of these spatial units alternations; however, in our study, our inferences were comparable between the two spatial units.

In the BE models, the models fitted made use of flat (non-informative) priors. This was done mainly to have estimates which are comparable to the MLE since these prior estimates did not have a significant influence on the posterior estimates. However, with adequate literature

support, informative priors can be used so that much more comprehensive posterior estimates can be used. These limitations might have impacted on the generalizability of our research findings, but comparable conclusive results most relevant to in HIV disease monitoring have been reported.

8.7. Conclusion

8.7.1. Epidemiological conclusion

Significant progress has been made towards achieving the UNAIDS 90-90-90 targets with the ultimate global focus of reducing new HIV incidence to zero by 2030, which is strongly influenced by ART adherence primarily among HIV patients. Attaining and maintaining viral suppression is an ultimate result of the combined efforts of provider practices, suboptimal patients' compliance to clinicians' recommendations and evident immune recovery in the population. Viral suppression measures the overall population health and preventive challenges that face it to inform policy; therefore, HIV and AIDS stakeholders, governments and non-governmental organizations should put forward relevant interventions to curb poor viral suppression due to not taking ART suboptimally or failed treatment; and interventions which support ART adherence maintenance and sustainability.

ART adherence results in improved clinical benefit among PLWHIV through attaining viral suppression; however, significant gaps and challenges still exist within HIV programmes as the global viral suppression rates remain relatively low at 53% (28). Zimbabwe has made remarkable strides toward achieving viral suppression; however, there is still more to be done, especially after ART decentralization. The trailing viral suppression indicator estimate was the epidemiological motivation for this research work to understand the ART adhering patterns after

ART decentralization in Zimbabwe in relations to ART outcomes observed. The most at-risk subpopulation groups of poor viral suppression and ART drop-out; and the heavily burdened regions (hot spots) for ART drop-out and poor viral suppression in Zimbabwe after ART decentralization were identified. The southern and northern regions which had a high risk of poor viral suppression were the same regions which had an increased risk of ART drop-out. Moreover, this meant that HIV prevalence in these regions is likely to be high this is supported by the country survey HIV prevalence estimates above 20% in these same regions (10).

With the substantial contribution towards increasing access to everyone in need through the decentralization of ART services; however, the PHC facilities remains incapacitated in offering laboratory monitoring support which is crucial in attaining viral suppression. Lack of VL monitoring support in PHC means late detection of treatment failure, which results in a high risk of poor ART outcomes. Moreover, the general transmission risk at the individual levels remains unclear, and this may results in increased HIV incidences in these settings. PHC health facilities require sustainable resource supply, skilled personnel and improved infrastructure to strengthen their capacity so that VL testing becomes routine and available for everyone as this is crucial in HIV monitoring.

For individuals to benefit attaining viral suppression in an ART programme, there should be a successful linkage to care of these individuals(131). Failure to a successful linkage to care means increased "leakages" within the HIV continuum of care treatment cascade, which results in HIV disease progression and increased risk of HIV transmission in the general population. Strategies which may retain patients on HIV care include increasing surveillance and strengthening patients' tracing mechanisms to reduce LTFU. Intensive patients monitoring strategy toward patients with immune deteriorated immunological conditions can be an option to improve ART

adherence through the direct observed or assisted therapy to ensure optimum ART adherence; however, less toxic and more efficient ART regimen formulations are encouraged.

With the persisting challenge of ART adherence in HIV prevention and control, interventions which reduce treatment defaulting are a priority. Successful ART adherence interventions are usually multifaceted and address specific ART adherence barriers. These interventions cannot be used in isolation for an impactful result; hence, they should be implemented holistically where possible. Interventions which improve retention of patients on care result in improved ART adherence among HIV patients; however, most interventions which have been implemented are not inclusive of everyone who requires care as most effective interventions in place are most appropriate for adults and miss the adolescents' group while males have been excluded in the HIV agenda for so long due to gender norms. A successful fight against HIV is achieved only when everyone- men and women of all age groups- is engaged.

With the substantial progress which had been made to reduce new HIV incidences globally, a much more significant impact could have been achieved if males were reached out to in their males "spaces" to take part in the HIV agenda. Going forward thriving to increase the high levels of HIV services coverage with the trailing viral suppression estimates of the 90-90-90 fast track targets, the male blind spot in response to HIV becomes a priority. The men's use of health services should be boosted; the harmful gender norms and risk behaviour of men should be changed through countering the male masculinity norms which exacerbate HIV transmission risk. Promoting resilient gender equality in HIV; health systems that understand the gender disparities between male and females health-seeking behaviours; and implementing health services delivery in ways more appealing to males may help mitigate the gender disparities and bring men on board to become the drivers of the HIV agenda. The PrEP strategy among men

who are at high risk of HIV infection may be an alternative to reduce new HIV infections in the quest of achieving the global HIV incidence targets(198).

The adolescents' subpopulation group was associated with poor immune recovery, which could be attributed to ART adherence challenges as this group was also more likely to become LTFU. Interventions which fully engage adolescents to retain to care like implementing early comprehensive adolescents' transition programmes to prepare the children for the paediatric to adults' health care transition are crucial to support this group attain viral suppression. Such programmes help regain adolescents back in care so that successful HIV management across age groups is maintained without tolerating any treatment lapses during the transition. Launching of the social deprivation programmes to break food insecurity pathways, financial support, disrupted families and lack of social support can substantially improve HIV disclosure and eliminated stigma fears in these adolescents; however, community-based interventions for the caregiver support, health facility-based support peer groups have proven to increase ART adherence among adolescents should be sustained(131).

8.7.2. Statistical conclusion

Multistate modelling offers a flexible tool to study disease progression and estimate transition rates using various forms of assumptions, data and estimation methods. Multistate models bring additional information in the disease progression process through the inclusion of the intermediate state which the traditional naïve regression models may ignore using the illness-death models. Furthermore, the absolute risk of time-to-event can be obtained using the competing risk model. Multistate models have the strength to make future predictions which is vital for decision-making in epidemiological studies.

The VL prognostic marker remains the primary laboratory marker for assessing treatment efficacy among ART patients as it is much more sensitive and predicts better ART outcomes than the CD4 cell counts. However, in low-and middle-income countries, there are still low volumes of VL data due to the sparse VL monitoring sites compared to CD4 cell counts data. This results in the continual use of CD4 cell counts in monitoring HIV disease progression. In situations where dual prognostic marker monitoring is done; and CD4 cell counts and VL data are available, joint multistate modelling of these two prognostic markers is preferred compared to separate modelling of VL multistate models as the unobserved effects of the VL marker can be accounted for by the CD4 cell counts marker to improve estimates precision(187).

As much as this study gave useful pointers to some gaps existing within the ART programme which are threats to attain viral suppression and sustain it using multistate models; the small sample sizes considered in this sub-analysis might have affected the generalizability of the findings. Therefore, interventions which increase ART patients retention on care are of concern to minimize missed visits; expansion of VL monitoring from cities to rural sites to increase coverage so that many people can be measured is a priority; training of data clerks and creating "compulsory fields" may reduce missing data during data capture.

In HIV decision-making programmes, model inferences based on BE perspective are the preferred as they provide coherent estimates despite model fitting challenges associated with Bayes models. Though it may be difficult to compute and ensure appropriate posterior distribution, Bayes inference produces prescriptive findings which are comprehensive as existing and new prior information can be incorporated (117). However, prior subjectivity remains an arguable issue among statisticians though not so compelling since the use of flat priors can mimic MLE estimates. Statisticians should consider using BE models in programme

management studies as realistic assumptions can be made, and fixed probability credible intervals which arguably are what programme managers and policymakers need can be estimated (117).

A geostatistical analysis approach is an emerging tool in HIV studies and crucial to guide implementation of area-specific interventions compared to national interventions which are costly(47). This study observed that areas along the country boundaries, particularly in the southern and northern regions of Zimbabwe, had an increased risk of poor viral suppression and ART drop-out. The inclusion of the spatial effects in the multistate model showed that the viral rebound and viral suppression transition rates were not static but varied across the regions. These finding confirmed that there exists a spatial variation of ART outcomes and viral rebound influenced by geographical correlation of the HIV epidemic by provinces or districts due to the social, cultural and population dynamics in Zimbabwe. The main region with poor viral suppression and increased risk of ART drop out were the northern and southern regions. Since these same regions have high HIV prevalence, interventions which accommodate these marginalized communities to adhere to ART are crucial in the HIV agenda to achieve and maintain viral suppression. Innovative interventions tailor-made for these regions are encouraged to reach out to everyone in need coupled with educational support which addresses cultural norms which are a possible threat to poor viral suppression and increased HIV transmission are a priority all in the quest to move forward the global notion of zero HIV incidences by 2030.

8.7.3. Study implications

The trailing national VL suppression estimates of the 90-90-90 fast track targets motivated the needy to undertake this study. The aim was to understand how well HIV patients adhere to ART

through HIV disease progression patterns based on VL and CD4 cell counts, to identify the subpopulation groups at risk and to describe the geospatial distribution of ART outcomes. Determining these epidemiological aspects of HIV required the implementation of novelty statistical techniques (multistate models and geospatial models) using MLE and BE inferences.

The high rates of becoming LTFU observed in this study are a clear indication of ART treatment cascade "leakages" as well as the ART drop-out risks. Such "leakages" in HIV care indicate a persisting challenge in the ART programme of patients' retention in care. Studies have shown that most patients who do not retain on care have an increased risk of poor viral suppression and poor immune recovery as their ART adherence would be compromised. This current study put forward the need to implement interventions which further minimized these "leakages" in the ART programme. The health care facilities should increase surveillance among ART patients and continue with the patient tracing mechanism. Patients' retention in care interventions are multifaceted and vary by subpopulation groups; therefore, subpopulation-specific interventions should be implemented for an effective result in patients' retention in care.

Male patients were found to be highly associated with increased death, poor viral suppression and high risk of becoming LTFU in this study. This study had more females compared to males which indicate that males are not fully engaged in HIV agenda. Involving men in HIV activities has a possibility of increasing HIV prevention and treatment services and subsequently, viral suppression. When male HIV-infected individuals are virally suppressed, the risk of HIV transmission of their sexual partners becomes negligible; fewer women will be HIV infected, and fewer children will be at risk of acquiring HIV from their parents. Therefore, this study suggests that policymakers and HIV programme managers should come-up with interventions which boost the health-seeking behaviour of men; encourage early detection of HIV through self-

testing, discourage men's masculinity norms which increase HIV transmission and reaching out to male in their "male spaces" so that men come on board in the fight of HIV. Lastly, the establishment of male health policy is essential to increase HIV health services uptake by males.

In support of other studies, adolescents were associated with an increased risk of becoming LTFU and poor viral suppression. This makes ART adherence among this group to be a critical component to lower HIV disease progression in the quest to achieve an HIV-free generation. With the high risk of social deprivation as a driving force behind the poor ART outcomes among adolescents, this study suggests interventions which address economic insecurity, food insecurity, fear of stigma and lack of social support and to improve viral suppression among adolescents living in low-and middle-income countries. Moreover, with the increase in the adolescents' population infected by HIV, the paediatric to adult transitions is a major drawback among this group resulting in ART lapses and increased LTFU rates. A comprehensive transitional programme is recommended to prepare the adolescents for adult care to attain a smooth changeover of patients from one care to another.

The WHO recommends VL monitoring to assess ART treatment efficacy and ensure that viral suppression is attained and sustained. Still, there exist huge gaps in global access to VL monitoring in low-and middle-income countries and rural areas. Most PHC facilities in Zimbabwe offering ART services are in rural areas. With the gaps of VL monitoring in these PHC centres, studies have shown that individuals enrolled at these sites have an increased risk of poor immunological outcomes which is supported by this study's findings. This study puts forward the need to capacitate the PHC sites to have self-contained VL monitoring infrastructure accessible by all patients to monitor treatment efficacy which is essential to attain viral suppression. Besides, the policymakers should come up with a model for these PHC sites, which

is more appealing to skilled personnel so that specialized HIV clinicians manage PHC patients in rural sites.

This study managed to identify the spatial variation of ART outcomes in Zimbabwe, which is essential to guide resource allocation. Similar to the ZIMPHIA 2015/16 survey findings, Matabeleland North province was found to be associated with poor viral suppression and LTFU. The occurrence of these outcomes indicates poor ART adherence among individuals in this province. A similar pattern was also observed among areas close to the country's boundaries. These areas typically have sparse health clinics and hard to reach areas due to the poor terrain. This study suggests that programme managers should implement area-specific interventions which can improve ART adherence in these areas compared to implementing national programmes.

Different existing and extended statistical modelling approaches have been used in this study, including the different methods of estimations. The analytical rigour associated with multistate models demonstrates their usefulness in monitoring HIV disease progression patterns when intermediate states are incorporated. This provides additional information which traditional modelling approach cannot provide. However, further use of BE approach results in much more consistent, prescriptive and precise findings due to the flexibility of the Bayes framework. This study suggests the use of BE approach to complement the MLE method since BE approach probability statements are more appealing to researchers as they are based on fixed intervals; however, final results reported should be based on the sensitivity analysis prior variations. As the use of the BE method is encouraged in decision-making processes, this study suggests expanding the BE approach in HIV programmes to guide evidence-based decision making in the fight of HIV.

In the era of big data analysis and the use of programme data to guide programme operations, missing data remains a significant concern. Missing data negatively impacts on the generalizability of the research findings. Though the joint modelling of VL and CD4 cell counts was logical and compelling compared to individual immunological marker models; however, the small sample size might have impacted on the findings since the MLE approach was used. This study suggests that continual training of data clerks is vital to ensure good data quality, use of "compulsory fields" can be considered as a precaution to minimize missing data; expansion of immunological measurements is a priority in HIV monitoring data as these markers form the basis of most HIV monitoring; a collection of additional important covariates in the database like comorbidities is important so that the effects of possible confounders and effect-modifiers can be assessed with minimum amounts of missing information.

In conclusion, a comprehensive HIV response is still a requirement in the fight against HIV to attain the global targets of zero HIV incidences by 2030. With the high coverage of ART in most of the countries including Zimbabwe, HIV transmission still occurs; therefore, HIV testing requires strengthening as many new infections are due to individuals who do not know their status yet, linking HIV patients to care and retaining patients on care is crucial to achieving the clinical benefits of ART; increase in ART access, and optimum ART adherence remains a priority to attain viral suppression; VL monitoring for quick identification of regimen resistance and failure requires strengthening; hence, viral testing sites should be expanded; health education and awareness on the benefits of ART should be enhanced to reduce stigma and discrimination; continual counselling of newly infected individuals not yet on ART long enough to be virally suppressed on their sexual lives should be provided to minimise the risk of HIV transmission; sustaining the current primary combination HIV interventions like condom access and use,

PMTCT, VMMC and PrEP expansion. Not only should the focus of the interventions be on achieving viral suppression but encompass maintaining and sustaining viral suppression and avoid any viral rebound from undetectable levels. As achieving undetectable VL suppression means zero to a minimum untransmittable virus in the general population, a collective effort from the ART patients and service providers is essential in the fight of HIV. Only when everyone is involved –men and women across all age groups- in HIV agenda with their hands on the deck can the global targets be achieved.

8.7.4. Scope for future research

Despite the comparable findings to prior research in monitoring HIV disease progression, going forward, there is still more to be done for future research. This study did not incorporate a variety of factors including 1) ART adherence patterns, 2) time-varying (or time-dependent) covariates like regimen type, CD4 cell counts, WHO stage and VL measurements compared to baseline characteristics considered in this study (124), 3) comorbidities-communicable and non-communicable diseases, 4) HIV interventions implemented in different parts of the country during the period covered by the study-PrEP, mobile clinics, national support and so forth, and 5) changes in the efficacy, dose administration and availability of ART. These aspects should form the basis of future research in monitoring HIV disease progression patterns.

The modelling approaches used in this study only accounted for the direct relationships of covariates with ART outcomes ignoring the existence of any underlying factors which could not be directly measured like socio-economic status, wealth index and availability utilities. These underlying factors can be handled through structural equation modelling (SEM) for continuous outcomes like CD4 change or VL change over time or generalized spatial structural equation

modelling (GSSEM) if the outcome is assumed to be Poisson distributed (count data- e.g. the number of patents who became virally suppressed) or binary outcome. The strength of the GSSEM is its ability to incorporate the spatial covariates to account for any spatial heterogeneity of the outcome under study.

Though the Markov assumption is predominantly used in most studies due to its simplicity; however, some studies have shown that virally suppressed ART patients with no treatment lapses are likely to continue recovering well. This violates the Markov and memory loss properties of these models; hence, future studies may consider non-Markovian, semi-Markovian or hidden Markovian assumptions. In all time-to-event models fitted in this study, right censoring was assumed of which interval censoring reflects the reality in patients' health care in follow-up studies; hence, future studies may focus on assuming interval censoring to improve the precision of the transition estimates since most events occur before observation time.

BE inference modelling approach could be the preferred method by most researchers as it provides the answers most researchers want. However, the model implementation is restricted by the software packages used. The existing software currently cannot handle missing data (incomplete observations) which is important, especially if the missing observation influence the observed outcome and interval-censoring within BE multistate models is another area for future research. There is need to upgrade the existing software (BayesX- *bayesreg object*) or develop packages which expand the BE multistate model features for those in software development or programming.

With the advent increase in the compilation of GIS data, comes the need for analytical tools which can handle a huge amount of data points. The most widely used tools are the OpenBUGS

which models based on Gibbs Sampling and Metropolis-Hastings algorithm and the WinBUGS which estimate based on Gibbs Sampling in addition to R and BayesX software. The most challenges normally faced are the long run time and non-converge of models which were major model implementation drawbacks encountered in this research. Since this study had a huge dataset in some instances, and complex models were fitted, the model running time was long (**Table 1-2**). There is need to have computing programmes which can reduce the model running time and reach convergence. Future studies can also consider investigating the Spatio-temporal patterns of ART adherence on viral suppression. Lastly, advent rise of machine learning techniques calls for the need for future research to employ machine learning techniques in HIV disease monitoring studies for better model predictions.

However, useful findings for policymakers are sorely based on the generalizability of research work. There is a need to expand the ePMS sites so that more health facilities can contribute their data to the national ART database. Since the current ePMS data only have VL testing mostly collected during differential monitoring approach; hence, the data reported for these patients may underestimate the viral suppression levels. Also, the VL testing has been done only for those patients on ART, excluding those who naturally suppress the virus. Future studies may consider the inclusion of patient on ART and those not on ART because they can naturally suppress the virus. Future research may also consider estimating the viral suppression maintenance and sustainability among ART patients which is in line with the global HIV targets.

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10. THESIS APPENDICES

10.1. Appendix A: The Maximum Likelihood Estimation of transition intensities

The frequentist approach has been well documented in the literature(34,50). This method strongly relies on the dataset for parameter estimation. In the frequentist approach, the statistical inference and estimation of the transition rates are based on the maximum likelihood estimation (MLE). To have some in-depth understanding of this modelling approach, detailed theoretical steps behind the estimation of transition rates have been outlined. With reference to the three-staged multistate model shown in **Figure 10-1**, the aim is to estimate the four transition parameters shown in the diagram. For the MLE approach, the first step is to get the product of the distribution function of the parameters. Let the exponential distribution function for the transition rate be:

Let the exponential distribution function for the transition rate be:

$$f\left(\gamma_{jk}\left(t_j\right)\right)=\frac{\left(\gamma_{jk}\left(t_j\right)\right)^{n_{jk}} \exp \left(-\gamma_{jk}\left(t_j\right)\right)}{n_{jk} !} \quad \text { for } j \neq k \quad (1)$$

where γ_{jk} is the transition rate from state j to state k . The number of the observed movements between the states is represented by n_{jk} and t_j is the total observed waiting time in the state j for $j=1, 2$. The likelihood function is:

$$L\left(\gamma_{jk}\left(t_j\right)\right)=\prod_{j \neq k}\left[\frac{\left(\gamma_{jk}\left(t_j\right)\right)^{n_{jk}} \exp \left(-\gamma_{jk}\left(t_j\right)\right)}{n_{jk} !}\right] \quad \text { for } j, k=1, 2, 3 \quad (2)$$

$$=\frac{\left(\gamma_{12}\left(t_1\right)\right)^{n_{12}} \exp \left(-\gamma_{12}\left(t_1\right)\right)}{n_{12} !} \times \frac{\left(\gamma_{13}\left(t_1\right)\right)^{n_{13}} \exp \left(-\gamma_{13}\left(t_1\right)\right)}{n_{13} !} \times \frac{\left(\gamma_{21}\left(t_2\right)\right)^{n_{21}} \exp \left(-\gamma_{21}\left(t_2\right)\right)}{n_{21} !} \times \frac{\left(\gamma_{23}\left(t_2\right)\right)^{n_{23}} \exp \left(-\gamma_{23}\left(t_2\right)\right)}{n_{23} !}$$

Treating the factorial part in the equation as constant and taking logs both sides yields:

$$\begin{aligned} \ln L(\gamma_{jk}(t_j)) &\propto \ln(\gamma_{12}(t_1))^{n_{12}} - \gamma_{12}(t_1) + \ln(\gamma_{13}(t_1))^{n_{13}} - \gamma_{13}(t_1) \\ &\quad + \ln(\gamma_{21}(t_2))^{n_{21}} - \gamma_{21}(t_2) + \ln(\gamma_{23}(t_2))^{n_{23}} - \gamma_{23}(t_2) \end{aligned} \quad (3)$$

which simplifies to

$$\begin{aligned} \ln L(\gamma_{jk}(t_j)) &= n_{12} \ln(\gamma_{12}(t_1)) - \gamma_{12}(t_1) + n_{13} \ln(\gamma_{13}(t_1)) - \gamma_{13}(t_1) \\ &\quad + n_{21} \ln(\gamma_{21}(t_2)) - \gamma_{21}(t_2) + n_{23} \ln(\gamma_{23}(t_2)) - \gamma_{23}(t_2) \end{aligned} \quad (4)$$

Re-arranging these terms gives

$$\begin{aligned} &= n_{12} \ln(\gamma_{12}(t_1)) + n_{13} \ln(\gamma_{13}(t_1)) - [\gamma_{12}(t_1) + \gamma_{13}(t_1)] \\ &\quad + n_{21} \ln(\gamma_{21}(t_2)) + n_{23} \ln(\gamma_{23}(t_2)) - [\gamma_{21}(t_2) + \gamma_{23}(t_2)] \end{aligned} \quad (5)$$

The summation of transition rates from the same state is defined at the *flow rate*, λ_j , which defines the probability of transition from state j . This means:

$$\lambda_j = \sum_{j \neq k} \gamma_{jk} \quad (6)$$

Let $\rho_{i,jk}$ be the conditional probability that the next destination is state k given that the transition from state j to k occurs, the flow rate can be defined in terms of the conditional probability as:

$$\gamma_{jk} = \begin{cases} \lambda_j \rho_{jk} & \text{for } j \neq k \\ -\lambda_j & \text{for } j = k \text{ since } \rho_{jj} = \rho_{kk} = 1 \end{cases} \quad (7)$$

Substituting equation (4) expressions into equation (5), that is, $\lambda_1(t_1) = [\gamma_{12}(t_1) + \gamma_{13}(t_1)]$ and

$\lambda_2(t_2) = [\gamma_{21}(t_2) + \gamma_{23}(t_2)]$ yields:

$$\ln L(\gamma_{jk}(t_j)) = n_{12} \ln(\gamma_{12}(t_1)) + n_{13} \ln(\gamma_{13}(t_1)) - \lambda_1(t_1) + n_{21} \ln(\gamma_{21}(t_2)) + n_{23} \ln(\gamma_{23}(t_2)) - \lambda_2(t_2) \quad (8)$$

The next step is differentiating equation (4) with respect to each transition rate and time

$(\gamma_{jk}(t_j))$ in the equation. Here we demonstrate for the $\gamma_{12}(t_1)$ transition rate, that is,

$$\frac{\partial \ln L(\gamma_{12}(t_1))}{\partial (\gamma_{12}(t_1))} = \frac{\partial}{\partial (\gamma_{12}(t_1))} (n_{12} \ln \gamma_{12}(t_1) - \gamma_{12}(t_1)) = \frac{n_{12}}{\gamma_{12}(t_1)} - 1 \quad (9)$$

Equating the solution of equation (9) to zero and making the transition rate parameter the subject of formula yields a maximum likelihood estimate of the transition rate, that is,

$$\hat{\gamma}_{12} = \frac{n_{12}}{t_1} \quad (10)$$

Similarly, the other maximum likelihood estimates for the other transition rates would be:

$$\hat{\gamma}_{13} = \frac{n_{13}}{t_1}; \quad \hat{\gamma}_{21} = \frac{n_{21}}{t_2} \quad \text{and} \quad \hat{\gamma}_{23} = \frac{n_{23}}{t_2} \quad (11)$$

From this theoretical working, if one knows the number of transitions from state j to k which is n_{jk} ; and the total exposure time in state j which is t_j , then the transition rates can be estimated using equations (10 and 11). Similarly, if the waiting time in a particular state is unknown, that is, t_j , the transition rate γ_{jk} and the number of transitions n_{jk} can give an estimate of the time in a specified state by re-arranging the same equations.

Due to the evolution of computational technology, multistate models from the MLE perspective are commonly implemented in R software(152) using the *msm* package(147). The *msm* package can fit continuous-time Markov models (homogeneous time or non-homogeneous time using the piecewise constant models) and hidden Markov multistate models with misclassification error using individual-level data(52). Within the *msm* package, covariates can be included, survival graphs for each transition can be obtained, all data censoring types can be handled, the total length of stay in each state can be estimated, and model diagnostics can be done(52). In these models, the likelihood ratio test (LRT) is used to choose a better fit model between time-homogeneous and time non-homogeneous (piecewise constant) models(50). The goodness-of-fit (GOF) of the model is assessed by comparing the observed and the predicted number of

individuals in each state at a specified time in a graph(50). The other test normally applied to all multistate Markov model processes, including those models with an absorbing state is the Pearson-type test which tests if the transition rates depend on several predictors(50).

10.2. Appendix B: Use of Kolmogorov-Chapman forward equations in multistate Bayesian models

The Bayesian estimation (BE) approach is a flexible method whose posterior transition estimates are based on the mapping of the prior distribution. The prior distribution constitutes the existing and new belief information for unknown parameters and the likelihood function of the observed data(202). This yields posterior estimates which are much more coherent compared to the MLE approach. Many different models can be fitted within the BE framework; however, the result validation is typically done through the prior sensitivity approach as many different priors can be tried(201). This makes the BE modelling much more rigorous compared to the MLE approach. The nuisance priors within the BE modelling are always marginalised out of the joint posterior distributions, which is a straightforward way to deal with such parameters, and this is hardly done in the MLE approach(201).

In this section, we provide the theoretical aspects of BE regarding the Kolmogorov-Chapman forward equations. In general, the transition rates and transition probabilities are mapped using the Kolmogorov-Chapman forward equation, which has the following solution:

$$P(t) = \exp(Q(t)) = \sum_{n=0}^{\infty} \frac{t^n}{n!} Q^n = \sum_{n=0}^{\infty} \frac{(Q(t))^n}{n!} \quad (12)$$

where $P(t)$ is the transition probability matrix, $Q(t)$ is the transition rate matrix and similarly, the number of observed transitions is defined by n while t defines the time. Let γ_{jk} be the transition rate elements within the 3x3 matrix, let the *flow rate* from a defined state j be λ_j , for instance, $(\lambda_1 = \gamma_{12} + \gamma_{13})$. Therefore, the transition rate matrix is defined as:

$$Q(t) = \begin{pmatrix} -(\gamma_{12} + \gamma_{13}) & \gamma_{12} & \gamma_{13} \\ \gamma_{21} & -(\gamma_{21} + \gamma_{23}) & \gamma_{23} \\ 0 & 0 & 0 \end{pmatrix} = \begin{pmatrix} -\lambda_1 & \gamma_{12} & \gamma_{13} \\ \gamma_{21} & -\lambda_2 & \gamma_{23} \\ 0 & 0 & 0 \end{pmatrix}.$$

whose row totals sum to 0. Since state 3 is the absorbing state, the last row entries are equal to zero. With the $Q(t)$ matrix, the Kolmogorov-Chapman forward equations solutions defined in equation (12) can be used to map the $P(t)$ matrix which has the transition probability $\pi_{jk}(t)$ elements, that is,

$$P(t) = \begin{pmatrix} \pi_{11}(t) & \pi_{12}(t) & \pi_{13}(t) \\ \pi_{21}(t) & \pi_{22}(t) & \pi_{23}(t) \\ 0 & 0 & 1 \end{pmatrix}$$

where the row totals add to 1. To fully define each transition probability $\pi_{jk}(t)$ component of the matrix, we modified slightly the solutions given elsewhere (73) to get comparable estimates to those obtained in R using *msm* library, assuming one has individually observed data. We considered this as a sensitivity approach to validate proper transcription of the code in

WinBUGS. Let $h = \sqrt{(\lambda_1 - \lambda_2)^2 + 4\gamma_{12}\gamma_{21}}$ for $\lambda_1 = \gamma_{12} + \gamma_{13}$ and $\lambda_2 = \gamma_{21} + \gamma_{23}$ and

$e1 = \exp\left(-\frac{1}{2}(\lambda_1 + \lambda_2 - h) \times (2 \times t)\right)$ and $e2 = \exp\left(-\frac{1}{2}(\lambda_1 + \lambda_2 + h) \times (2 \times t)\right)$. Then the

Kolmogorov-Chapman solution for each transition probability $\pi_{jk}(t)$ element simplifies to:

$$\begin{aligned}
\pi_{11}(t) &= \frac{e1 \times (-\lambda_1 + \lambda_2 + h) + e2(\lambda_1 - \lambda_2 + h)}{2h} \\
\pi_{12}(t) &= \frac{(-\lambda_1 + \lambda_2 + h) \times (\lambda_1 - \lambda_2 + h) \times (e1 - e2)}{4h\gamma_{21}} \\
\pi_{13}(t) &= 1 - \pi_{11}(t) - \pi_{12}(t) \\
\pi_{21}(t) &= \frac{\gamma_{21}(e1 - e2)}{h} \\
\pi_{22}(t) &= \frac{e1 \times (\lambda_1 - \lambda_2 + h) + e2 \times (-\lambda_1 + \lambda_2 + h)}{2h} \\
\pi_{23}(t) &= 1 - \pi_{21}(t) - \pi_{22}(t)
\end{aligned} \tag{13}$$

Let n_{jk} be the number of transitions from state j to k for $j \neq k$. If the data is partially observed over two points and intermediate transitions are unknown, then n_{jk} is equal to the number of individuals since each individual contributes a single transition. In some instances, the data summaries may be available (aggregated data); that is, no individual information is available, then this modelling approach becomes relevant to use. The likelihood function of the number of transitions (n_{jk}) can assume a multinomial distribution with probability parameters:

$$(n_{j,1}, n_{j,2}, \dots, n_{j,m}) \sim \text{Multinomial}(\pi_{j,1}, \pi_{j,2}, \dots, \pi_{j,m}; n_j) \tag{14}$$

Since this is fully BE approach, the next step is to assign the prior information for the unknown transition rates parameters. These priors can either be informative or non-informative. Non-informative priors have little impact on the posterior distribution making the data (likelihood distribution) to contribute more to the posterior estimates. Normally, non-informative priors are attained by using dispersed variance parameters or very small shape parameter values for the exponential distribution. Informative priors express exact and definite information about the unknown parameters being estimated. For such, information may be drawn from existing literature.

In this study, we assigned non-informative the priors for the unknown transition rate parameters $(\gamma_{12}, \gamma_{13}, \gamma_{21} \text{ and } \gamma_{23})$. Since the transition rates for an exponential family distribution, we considered an exponential distribution with a small parameter value $\beta = 0.001$. The exponential probability density function is expressed as:

$$P(\gamma_{jk}) \propto \beta \exp(-\beta \gamma_{jk}) \quad (15)$$

We further performed a sensitivity analysis of the exponential priors to assess if the choice of the prior distribution does not influence the transition rates estimated. A Weibull distribution prior with a scale of 0.001 and shape of 0.1; and a Gamma distribution prior with shape and scale of 0.1 were used to define the unknown transition rates priors. Since the shape and scale parameter values for Weibull and Gamma distributions were specified, we did not have any hyper-priors to specify further. The Deviance Information Criterion (DIC) was reported for each model.

The posterior distribution fitted is given by equation (16) below, which reflects a joint distribution of the multinomial likelihood and the exponential prior distributions.

$$P(\pi_{jk}, \gamma_{jk} / n_j) \propto \left[\frac{\Gamma(\sum_j n_j + 1)}{\prod_j \Gamma(n_j + 1)} \prod_{j=1}^m \pi_{jk}^{n_j} \right] \times [\beta \exp(-\beta \gamma_{jk})] \quad (16)$$

Therefore, in this regard, the BE can be viewed as being a complete, unambiguous, prescriptive and coherent method of estimation as it combined both the likelihood information and the prior information to get the posterior estimates.

10.3. Appendix C: Use of Kolmogorov-Chapman forward equations in multistate Bayesian models

This is an illustration on the use of Kolmogorov -Chapman forward equations and the contents of this section are part of the multistate model review paper submitted in the Statistical Methods in Medical research Journal now at the interactive review stage.

In this application, we implemented the method for estimation transition rates using partially observed aggregated data using Kolmogorov-Chapman forward equations explained in section 2.2 using data from the Zimbabwe National ART programme and fitted in WinBUGS (203). We extracted individual viral load data collected within a year from ART patients whose information was linked to the ePMS (49).

Following the WHO guidelines, individuals who are initiated on ART are monitored over time using CD4 cell counts and viral load to assess the regimen efficacy over time (114). In this example, the main focus was on using viral load measurements taken at baseline of ART initiation and repeatedly after 6 months. We extracted patient's information spanning over a one year cycle of follow-up. We assumed that if individuals are initiated on potent and effective ART regimen and are adhering on treatment, after a year, a significant improvement in the immune response can be observed(204). It is based on this dataset that motivated our choice of model for illustration, which falls under disease progression models.

In this study, we have data for individuals who had viral load measurements at baseline (at ART initiation) and one year after ART initiation. The in-between viral load clinical information was unknown since the data was partially observed with only two-time points. Since the data came from a routine ART programme setting, it is important to acknowledge that the period in which the data was captured was when differential monitoring was done(22,27); hence, few ART

patients had their viral load measurement taken, and participant selection bias cannot be overlooked. Therefore, our final sample size had 5,596 participants with two observations taken at ART initiation (baseline) and after one year on ART.

For our illustration, a three-staged reversible multistate model, with states defined based on viral load measurements, was considered, and a schematic presentation of the diagram is shown in

Figure 10-1.

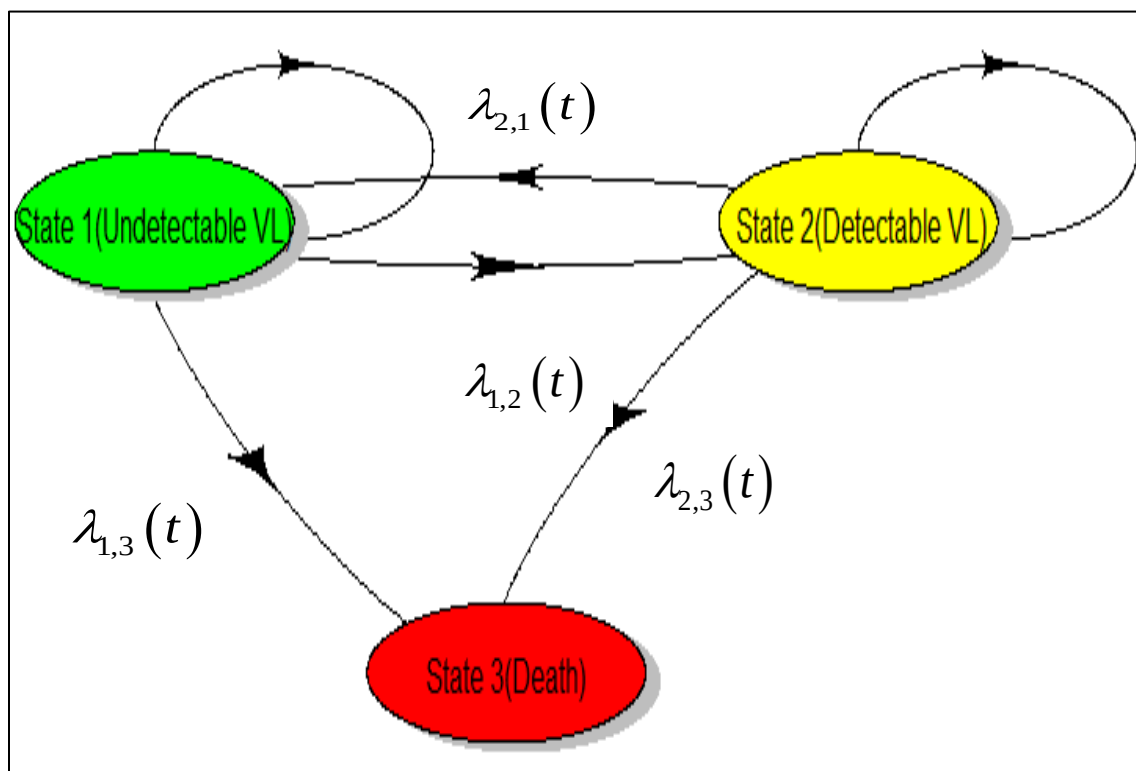


Figure 10-1: The schematic presentation of three states partially observed the multistate model and the corresponding individual-specific transition intensities (State 1=Viral load<50copies/uL (undetectable); State 2= Viral load ≥50copies/uL(detectable))

In this model, we assumed that individuals from state 1 (VL<50copies/uL) with an undetectable viral load may die (state 3) via state 2 (VL≥50copies/uL) which indicates a viral load rebound or

detectable viral load, or directly from state 1 ($VL < 50 \text{ copies/uL}$). Again individuals may move back to state 1 ($VL < 50 \text{ copies/uL}$) once they are in state 2 ($VL \geq 50 \text{ copies/uL}$) after ART which shows a reversible transition. We also assumed a time-homogeneous Markov model and the data were aggregated having been observed over two-time points in a single year follow-up. Since the data was partially observed, this means, the initial state at ART initiation and the final states after one year were known, but the route to the last observed state was unknown. In other terms, the intermediate transitions (viral load patterns) which occurred between the initial state and the last observed states are unknown. In other words, individuals with undetectable viral load (state 1) at time 0 who later died after a year may have died directly from the state 1 (undetectable viral load) or may have died via state 2 (viral load rebound).

The used partially observed aggregated vial load data is displayed in **Table 10-1**. The total number of participants was 5,596 with 2,490 (44.5%) with an undetectable viral load (state 1) while 3,106 (55.5%) had a viral load rebound above 50copies/uL (state 2). At the end of one year, 165 (2.95%) participants had died of which 87 (53%) were initially in state 2 (viral load rebound) at baseline. Majority of the participants remained in their initial state; hence, assumed not to have made any transition out of their initially observed state.

Guided by the set of equations described in **Appendix B** (equation 13) above, we implemented our model in WinBUGS software based on Gibbs sampling estimation. We estimated the transition rates using the partially observed aggregated data captured over a cycle of one year, as explained earlier. We set 15,000 Markov chain Monte Carlo (MCMC) simulations, a burn-in period of 1,000 simulations and thinning of 10.

The code used is provided in **Appendix E**, and this code may be viewed as a transcription of $P(t)$ matrix each element fully defined (Equation 13), the likelihood function (equation 14) and prior function (equation 15). A further sensitivity analysis to validate the transcription of the WinBUGS code was done using R *msm* package, and the used R code is provided in **Appendix E**. The MLE and BE posterior estimates for transition rates are shown in **Table 10-2**.

Since this data is partially observed, there is uncertainty as to the exact route, an individual who reached State 3 followed. However, there are four possibilities to describe this:

- 1) Participant arrived directly from State 1 having not visited State 2 during the follow-up period (State 1 to State 3)
- 2) Participant arrived directly from State 2 having not visited State 1 during the follow-up period (State 2 to State 3)
- 3) Participant arrived from State 2 via State 1 (State 1 to State 2 to State 3)
- 4) Participant arrived from State 1 via State 2 (State 2 to State 1 to State 3)

When we compared the model estimates from the MLE approach and the BE approach, both methods gave comparable transition estimates. However, the posterior transition from state 1 (VL<50copies/uL) to state 2 (VL≥50copies/uL) was 0.0633 (95% credible interval (CI): 0.053-0.074). Movement from state 1 (VL<50copies/uL) to state 2 (VL≥50copies/uL) was 1.29 times (95%CI: 1.03-1.63) more likely than the transition from state 2 (VL≥50copies/uL) to state 1(VL<50copies/uL). Similarly, participants initially in state 1(VL<50copies/uL) were 13% (1.1.31 95%CI: 0.81-1.59) more likely to die compared to those in state 2 (VL≥50copies/uL); however, this was not statistically significant.

Table 10-1: Partially observed data for viral load suppression among adult ART patients from the Zimbabwe national ART programme after a year time cycle for a three-state model

	Number of participants at baseline	Initial state, j	Final state after a year of follow-up, k		
			State 1	State 2	State 3
	2490	State 1	2269	143	78
	3106	State 2	137	2882	87
	0	State 3	0	0	0
Totals	5596		2406	3025	165

Table 10-2: Posterior estimates and correlations for the transition rates for the three-state model using partially observed data from the adult ART patients in the Zimbabwe national ART data after a year of follow-up.

Transition rate parameter estimates								
Parameter	MLE		BE		BE Correlations			
	No prior information (AIC=3700.88)	Weibull priors (DIC=33.859)	Gamma priors (DIC=33.724)	Exponential priors (DIC=33.325)				
	TR coefficient (95% CI)*	TR coefficient (95% CI)	TR coefficient (95% CI)	TR coefficient (95% CI)	γ_{12}	γ_{13}	γ_{21}	γ_{23}
	γ_{12}	0.06242 (0.053-0.074)	0.0625 (0.053-0.073)	0.0627 (0.053-0.075)	0.0633 (0.053 to 0.074)	1.0	0.068	0.124
γ_{13}	0.0315 (0.025-0.039)	0.0317 (0.024-0.041))	0.0319 (0.026-0.039	0.0323 (0.026 to 0.040)		1.0	0.121	0.046
γ_{21}	0.0481 (0.041-0.051)	0.0478 (0.004-0.056)	0.048 (0.040-0.057)	0.0485 (0.041 to 0.056)			1.0	0.015
γ_{23}	0.0279 (0.022-0.035)	0.0284 (0.0232-0.028)	0.028 (0.023-0.035)	0.0285 (0.023 to 0.035)				1.0

MLE=maximum likelihood estimation, BE=Bayesian estimation, TR=transition rate, CI=credible interval, CI*=confidence interval, AIC=Alkaike's Information criterion, DIC=Deviance Information Criterion

Those participants initially in state 1 ($VL < 50 \text{ copies/uL}$) were 1.98 times (95%CI: 1.48-2.65) more likely to have a viral rebound compared to have died after 1 year while those participants initially in state 2 ($VL \geq 50 \text{ copies/uL}$) were 1.73 times (95%CI: 1.29-2.29) to have attained viral suppression to undetectable levels compared to have died. However, the correlations between the transition rates are positive, which means the data on reaching State 3 is compatible with an increase in each of the transition. This is also evident in the bivariate scatter plots for these four transitions in **Figure 10-2**.

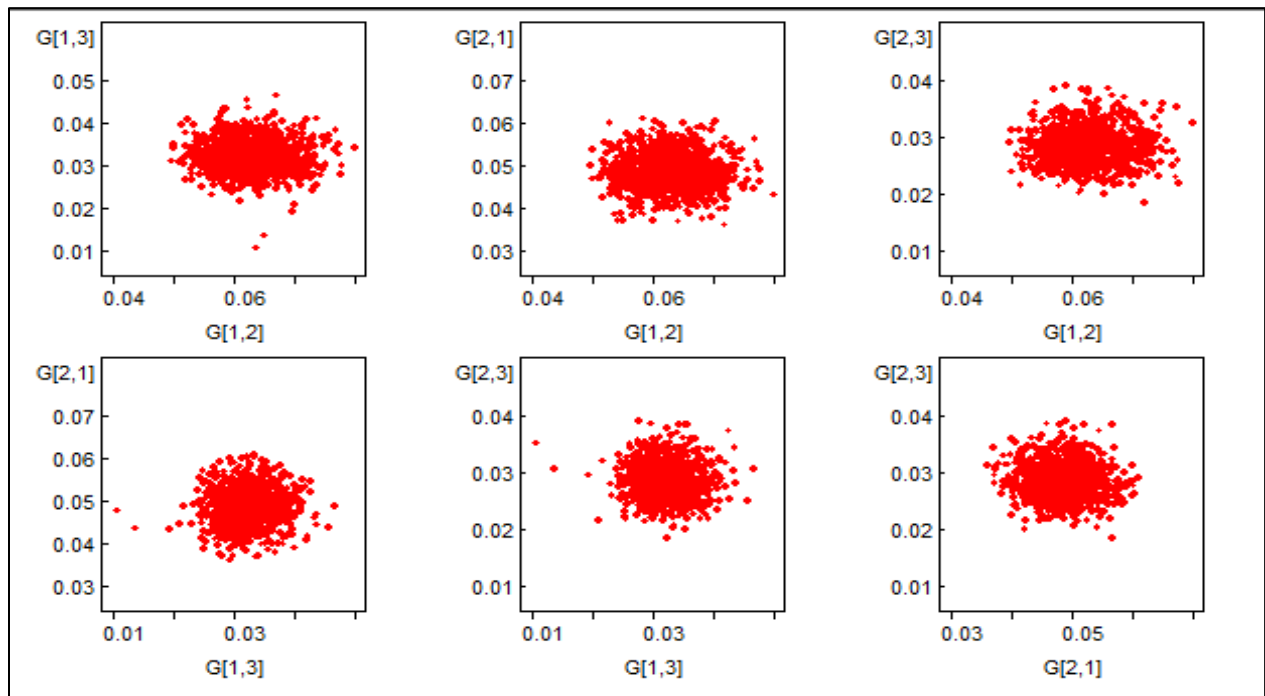


Figure 10-2: Bivariate scatter plots rates for the four transition rates parameters from the partially observed data

The transition probabilities are shown in **Table 10-3** for the three-cycle times, 3 months, 6 months and 1years cycles for both the BE approach and the MLE approach. Similarly, the transition probabilities were similar for both the MLE and the BE approaches.

Table 10-3: Posterior estimates for the transition probabilities during three months, 6months and a one year cycle for the three-state model using partially observed data from the adult ART patients in the Zimbabwe national ART data after a year of follow-up.

Parameter	3 months		6 months		1 year	
	BE	MLE	BE	MLE	BE	MLE
	Transition rate estimate (95% CI)	Transition rate estimate (95% CI)	Transition rate estimate (95% CI)	Transition rate estimate (95% CI)	Transition rate estimate (95% CI)	Transition rate estimate (95% CI)
$\pi_{11}(t)$	0.9765 (0.973 to 0.980)	0.976877 (0.974 to 0.980)	0.9530 (0.945 to 0.960)	0.95447 (0.948 to 0.960)	0.9103 (0.898 to 0.922)	0.91170 (0.899 to 0.922)
$\pi_{12}(t)$	0.0155 (0.013 to 0.018)	0.015278 (0.013 to 0.018)	0.0302 (0.026 to 0.036)	0.02992 (0.025 to 0.035)	0.0580 (0.048 to 0.068)	0.05737 (0.049 to 0.067)
$\pi_{13}(t)$	0.0081 (0.006 to 0.010)	0.007845 (0.006 to 0.010)	0.0160 (0.012 to 0.020)	0.01562 (0.012 to 0.020)	0.0318 (0.026 to 0.039)	0.03093 (0.025 to 0.039)
$\pi_{21}(t)$	0.0119 (0.010 to 0.014)	0.011770 (0.010 to 0.014)	0.0231 (0.019 to 0.027)	0.02305 (0.019 to 0.027)	0.0442 (0.037 to 0.052)	0.04419 (0.037 to 0.052)
$\pi_{22}(t)$	0.9810 (0.979 to 0.983)	0.981280 (0.979 to 0.984)	0.9626 (0.958 to 0.967)	0.96309 (0.958 to 0.967)	0.9273 (0.918 to 0.936)	0.92823 (0.918 to 0.936)
$\pi_{23}(t)$	0.0071 (0.006 to 0.009)	0.006951 (0.006 to 0.009)	0.0142 (0.011 to 0.017)	0.01386 (0.011 to 0.017)	0.0285 (0.023 to 0.035)	0.02758 (0.023 to 0.034)

BE-Bayesian estimation; MLE-maximum likelihood estimation, CI-credible/confidence interval

From these estimates, the probability of leaving the initial state increases as the cycle time increases, that is, for a transition from state 1 ($VL < 50 \text{copies/uL}$) to state 2 ($VL \geq 50 \text{copies/uL}$), the probability at 3 months cycle was smaller than the probability at 6 months cycles, and both were smaller than the probability at 1-year cycle: ($\pi_{12}(t = 3 \text{months}) = 0.0155 < \pi_{12}(t = 6 \text{months}) = 0.0302 < \pi_{12}(t = 1 \text{year}) = 0.058$). This pattern was similar across other transitions and was as anticipated for such types of models.

10.3.1. Discussion

In this manuscript, we have highlighted the usefulness of multistate models as they account for the time change, and individuals multiple outcomes can be estimated simultaneously in epidemiological studies compared to the traditional survival models. We have also discussed two methods of statistical inference with emphasis on the BE approach, which has not been fully utilised and reviewed in the literature. Various types of multistate models disposable to use in different science fields to answer different kinds of research questions from longitudinal time to event data have been outlined. Multistate model assumptions and data featured have also been highlighted. Finally, an application of the Kolmogorov-Chapman forward equation in estimating transition rates has been demonstrated using partially observed aggregated viral load data for the first time in HIV disease progression modelling. The application model estimates were comparable to existing epidemiological work on viral transitions patterns(76,204).

This manuscript put forward the advantage of using multistate modelling as this approach may bring out new and important biological insights in understanding the intermediate processed of a disease which ordinary regression models like Cox proportional hazard model may be ignoring. Multistate models' transition processes are easy to understand as they can be drawn into

schematic diagrams of mutually exclusive states which help to understand the model better. Prediction of an individual's disease progression trajectories through time is another advantage of multistate models, and this is helpful for programme managers to make informed decisions which traditional survival models cannot do.

This manuscript further put forward the strengths of BE multistate models over MLE multistate models. It is undebatable that individual-level data is much for informative and provides more extensive flexibility in modelling. However, aggregated data usually is accessible on many public platforms and intermediate observation times during follow-up studies may not always be supported in most programs due to financial constraints. In such instances, partially observed aggregated data becomes readily available and disposable to everyone without requiring much stringent permission to use it. Moreover, clinical trials studies may also report partially observed time to clinical outcomes (endpoints) data without reporting any intermediate states (205). This motivated the example application provided in this manuscript, as it emphasised the use of BE multistate model in handling partially observed aggregated data using the Kolmogorov-Chapman forward equations on a new dataset on viral load measurement in HIV studies. Our application also put forward how partially observed data in principle can be used in an epidemiologically realist model(205). Handling of such aggregated data is precluded within MLE multistate models implemented in R using *msm* package which only favours individual-level data. The ability of BE multistate models to handle aggregated data affirms how important aggregated data could be in instances where there is no individual-level data, and quick baseline information is required for a more informative hypothetical formulation for future researches.

The MLE approach generally relies on the available data defined through the maximum likelihood function; hence, it is generally affected by the small sample sizes of data(201). The

small sample sizes may result in the inferential process to be internally logically inconsistent. In contrast, the BE approach integrates the likelihood function and the prior function, which contains existing information to give comprehensive posterior estimates of the transition rates, and this is an advantage of the BE approach. The addition of prior information in the BE approach allows the operating characteristics of the Bayesian methods in small sample sizes and overall, to be dependable. Bayesian methods tend to perform well with limited data, while frequentist MLE inference appeals to large sample theory and thus may break down with small sample sizes. This advantage is more evident if informative priors are used which have a strong impact on the posterior estimates compared to when non-informative priors are used since using non-informative priors mimic the MLE results.

Results interpretations of the MLE approach are customarily based on the repeated sampling property, which may be ambiguous; the probability of the hypothesis is non-applicable, unlike the BE approach which makes use of the probabilities for both the hypothesis and data, which is what is required precisely to make decisions (117). The direct probability statements in BE inference about the parameters is much more useful compared to the frequentist statistics. In other terms, BE inference provides fixed probability intervals for unknown quantities compared to the random intervals for fixed quantiles from the MLE inference. This makes the BE approach much more compelling than the MLE approach as it provides the kind of answers most researchers require. In most studies, the BE approach has proven to outperform the MLE approach (201).

As much as BE approach is theoretically simpler, more robust, more flexible and easier to implement with minimum support as compared to the MLE approach (205); the adoption and utilisation of the BE approach have been hindered by the difficulties faced by researchers in

implementing the Bayes models. The main hindrance of Bayesian models is the prior specification choices, which is normally subjective. This is quite a debatable issue in Bayesian modelling since the observed posterior estimates are heavily dependent on the prior specification, especially for informative prior choices. However, to override this argument, assigning diffuse (vague/non-informative) priors is encouraged, and results are comparable with the frequentist estimates(46,73). In other words, the BE models can be run with prior references which can mimic the MLE (non-informative priors) as compared to the use of informative priors (201). This point can be validated by our posterior transition rates estimates which were similar to those estimated through the MLE using R *msm* package since we used purely non-informative priors in our modelling approach. This similarity puts forwards that even if aggregated data is used, the findings are comparable to the MLE and decisions can be informed accordingly. Also, prior sensitivity analysis is encouraged as an excellent modelling courtesy to validate that the choice of the prior used did not influence the results obtained.

Although, BE models are computationally intensive requiring much longer running time of more hours or days to converge compared to the MLE multistate model(76). Still, MLE models may fail to converge if the models are complex of which model convergence can be only achieved through the BE route. This leaves the issue of longer running times invalid since the BE approach will be the only route to consider in such instances. Moreover, multistate models, particularly those fitted in BayesX using the *bayesreg* object have a limitation of model comparison techniques since the Deviance Information Criterion (DIC) cannot be estimated in such models(117). This favours the MLE, which uses Akaike's Information Criterion (AIC) and LRT for model comparison to validate the obtained estimates.

Moreover, as much as the BE multistate model on aggregated data using Kolmogorov- Chapman differential equations in WinBUGS is useful in situations where individual-level data is not available, proper implementation of the model might be a constraint to other researchers as the modelling approach require technical expertise to achieve convergence in terms of correct model specification (transcription of the Kolmogorov-Chapman forward equations). However, this hindrance can be solved by strengthening resource sharing between researchers through including codes in publications and other platforms. Another limitation of the BE multistate model in WinBUGS could be explicitly solving for the Kolmogorov's forward equations solution to be able to transcribe the solutions into the model code. This exercise becomes hectic and tedious if the model has many model states, reversible transitions; hence, the model becomes complex. However, the WinBUGS Differential Interface (WinDiff) software can be used instead to mitigate such challenges(73).

As much as the use of Kolmogorov-Chapman forward equations on partially observed aggregated data could be helpful in epidemiological researches, it is important to note that this modelling approach has some limitations too. There are conditions under which an analysis of aggregated data (i.e., summary data over individuals) would be biased. Firstly, the method restricts attention to a situation whereby only two observations are made on an individual (at baseline and the end of study). One may think this approach violated the natural process of events in medical research as participants go through various intermediate processes between the stipulated times (one year cycle in this case) which are not incorporated in the model leading to biased estimates. However, by assuming that the observed states follow a multinomial distribution with respect to the initial state and the transition probability are depend on the total observation time lined through the Kolmogorov-Chapman forward equations leverages this

problem. Also, with only a few observations, BE shows to be more sensitive to the prior distribution for parameters, and a lot of pressure for the posterior estimates is based on the correct prior choices.

Moreover, the other condition under which an analysis of aggregated data would be biased is that there is uncertainty as to the exact route, an individual who reached state 3 (death) followed. This uncertainty compromises the validity of the reported posterior estimates, which is what researchers in epidemiological studies are interested in. In our application, the fitted model assumed constant transition rates over time (time-homogeneous), an assumption well known to be unrealistic in many kinds of epidemiological researches. This assumption may result in biased estimates; hence, time-inhomogeneous transition rates should be considered for unbiased estimates. Lastly, this method needs to be improved so that its covariates effects on the aggregated transition rates can be accounted for.

In conclusion, multistate modelling offers a flexible tool in studying disease progression and estimating transition rates using various forms of assumptions, estimation methods and data features. Multistate models bring out significant disease progression understandings which the traditional naïve regression models may ignore. Hence, multistate models should be used as a supplement to the traditional naïve regression models to gain additional information. As much as the frequentist (MLE) approach continues to dominate research, particularly in life sciences, it is restrictive in providing comprehensive estimates based on assumptions which reflect reality in disease progression models. Therefore, this research study recommends the use of BE models which can implement assumptions reflect natural processes of events and use the probability of the hypothesis and data which most epidemiologists prefer. The use of the Kolmogorov-Chapman forward equations on aggregated data also helps to open the way to a more formal and

systematic use of available literature like national reports or clinical trials to inform Markov models in decision making. However, it is crucial to understand the model development process which might be challenging and make use of the sensitivity analysis approach as there could be a problem of the surfeit of posterior distributions due to prior variations to validate the results in BE approach.

10.4. Appendix D: The Statistical software and some challenges

In addition to the use of *msm* package in R which can handle maximum likelihood estimation (MLE) multistate models, the other library within R software is the *tdc.msm* library developed by Meira-Machado *et al.* (2009) which can fit five different multistate models including time-homogeneous and non-homogeneous Markov multistate models; and Cox Markov and Cox semi-Markov multistate models (50). The *tdc.msm* library is a comprehensive package for modelling multistate longitudinal data since different models can be fitted within one library, and model comparison can be done easily (50). For nonparametric estimation, the *msSurv* library within R can be used to estimate state occupation probabilities, initial and ending time in a state, and the marginal integrated transition rate for the non-Markov multistate process (206). The other R package is the *mstate* developed by Wreede *et al.* (2011) for both the competing risk models and multistate models (207). Additional R libraries are the *etm* library Allignol *et al.* (2011) for empirical transition probabilities and the *changeLOS* (change length of hospital stay) library introduced by Wangler *et al.* 2006) for the Aalen-Johansen Estimator is implemented within R software. The limitation of the *changeLOS* library is that it does not support the inclusion of covariates in the multistate model and left truncated data (208). However, the *mvna* library can handle both left truncated and right censored multistate data (208).

The STATA software (licensed for use) (118) can fit the MLE multistate models using the *multistate model ado files* developed by Cowther and Lambert (2016) which restructures and declares the multistate data as survival and any survival model within STATA can be used (209). This package can estimate each transition rate by its unique model structure, assuming either a Markov or semi-Markov process (209). Uniquely to the STATA models is the ability to estimate each transition rate assuming different hazard functions which best fit the transition as compared to the R *msm* models which assumes the same hazard function on all the model transition processes. Another option in STATA is using *illdprep* and *stpm2illd* commands which can perform a similar analysis as described elsewhere (210).

The Bayesian estimation (BE) multistate models can be implemented in BayesX software using the *bayesreg* object. This package can handle several data features which the MLE cannot handle like non-linear effects of continuous covariates, time-varying effects, adjust for individual and spatial random effects accounting for unobserved heterogeneity. The WINBUGS software which estimates using Gibbs Sampling also can handle BE multistate model through the use of Kolmogorov-Chapman forward equations. This modelling approach promotes the use of partially observed aggregated data which the MLE approach cannot do.

Most of these statistical packages which can handle multistate models, both from the MLE and BE are free while few may require licensing. Here we highlight a couple of strengths and limitations associated with each software type which handles multistate models, some of which might not have been discussed in detail in this manuscript. Firstly, most of the existing software assumes the Markov property and time-homogeneous by default which makes it difficult if these assumptions are violated. Secondly, the Markov assumption can be difficult to test, and in most cases, studies are silent on pre-model assumption testing of the Markov property; however,

markovchain library implemented in R is one of the packages which can test for Markov property (60). Thirdly, not all software types are freely available for use like BayesX, WinBUGS and R, some of the software types require a license to be granted access, for instance, STATA and SAS. Fourthly, data argumentation (structure) is different in each of the software, which may be a major drawback if one wishes to make a comparison across the software. In addition to this, at times convergence is an issue in multistate models depending on the size of the data, the model complexity of the proposed model (number of states, reversible transition and number of covariates included) and the preferred method of estimation (BE or MLE) as the models may take much longer (hours or days) to converge or may fail to converge at all. Lastly and most importantly, the result outputs vary moving from one software package to another; hence, methodological background theory for each package is crucial to enable results comparison. For instance, in the R *msm* library, one gets the exact transition rate values which can be interpreted directly while in BayesX outputs, the estimates are based on the flexible predictor on a log scale (46).

10.5. Appendix E: The WinBUGS three state reversible multistate model code based on the Kolmogorov-Chapman differential equation

```
model {

#####Multinomial likelihood for observed data
  for (i in 1:2)
  {
    r[i,1:3] ~ dmulti(P[i,1:3],n[i])
  }

#####Find transition probabilities (for given time) in terms of rates

h<- sqrt(pow(lambda[1]-lambda[2], 2) + 4*G[1,2]*G[2,1])
e1<-exp(-.5*(lambda[1] + lambda[2] - h)*(2*t.obs))
e2<-exp(-.5*(lambda[1] + lambda[2] + h)*(2*t.obs))

P[1,1]<-((-lambda[1]+lambda[2]+h)*e1+ (lambda[1]-lambda[2]+h)*e2)/(2*h)
```

```

P[1,2]<-((-lambda[1]+lambda[2]+h)*(lambda[1]-lambda[2]+h)*(e1-e2))/(4*h*G[2,1]) P[1,3]<- 1-
P[1,1] - P[1,2]
P[2,1]<- G[2,1]*(e1-e2)/h
P[2,2]<- ((lambda[1]-lambda[2]+h)*e1+ (-lambda[1] + lambda[2] + h)*e2)/(2*h)
P[2,3]<-1 - P[2,1] - P[2,2]

```

#Give exponential priors for unknown transition rate parameters

```

for (i in 1:2)
{
for (j in (i+1):3)
{
G[i,j] ~ dexp(.001)
}
}
for (i in 2:2)
{
for (j in 1:(i-1))
{
G[i,j] ~ dexp(.001)
}
}
lambda[1]<- G[1,2] + G[1,3]
lambda[2]<- G[2,1] + G[2,3]

```

#####Find P(t.new) for given new time of interest=1 years

```

e1.new<-exp(-.5*(lambda[1] + lambda[2] - h)*(2*t.new))
e2.new<-exp(-.5*(lambda[1] + lambda[2] + h)*(2*t.new))
Pt[1,1]<-((-lambda[1]+lambda[2]+h)*e1.new+ (lambda[1] -lambda[2]+h)*e2.new)/(2*h)
Pt[1,2]<-((-lambda[1]+lambda[2]+h)*(lambda[1]-lambda[2]+h)*(e1.new-e2.new))/(4*h*G[2,1])
Pt[1,3]<- 1-Pt[1,1] - Pt[1,2]
Pt[2,1]<- G[2,1]*(e1.new-e2.new)/h
Pt[2,2]<- ((lambda[1]-lambda[2]+h)*e1.new+ (-lambda[1] + lambda[2] + h)*e2.new)/(2*h)
Pt[2,3]<- 1-Pt[2,1] - Pt[2,2]

```

P(t.final)=half a year (put 0.25 in the data)

```

e1.final<-exp(-.5*(lambda[1] + lambda[2] - h)*(2*t.final))
e2.final<-exp(-.5*(lambda[1] + lambda[2] + h)*(2*t.final))
Ptn[1,1]<-((-lambda[1]+lambda[2]+h)*e1.final+ (lambda[1] -lambda[2]+h)*e2.final)/(2*h)
Ptn[1,2]<-((-lambda[1]+lambda[2]+h)*(lambda[1]-lambda[2]+h)*(e1.final-
e2.final))/(4*h*G[2,1])
Ptn[1,3]<-1 - Ptn[1,1] - Ptn[1,2]
Ptn[2,1]<- G[2,1]*(e1.final-e2.final)/h
Ptn[2,2]<- ((lambda[1]-lambda[2]+h)*e1.final+ (-lambda[1] + lambda[2] + h)*e2.final)/(2*h)

```



```
Ptn[2,3]<-1 - Ptn[2,1] - Ptn[2,2]
}
```

###DATA

```
list(r=structure(.Data=c(2269,143,78,137,2882,87),.Dim=c(2,3)),n=c(2490,3106),t.obs=0.5,
t.new=0.25, t.final=0.125)
```

###INITIAL VALUES

```
list(G=structure(.Data=c(NA,.1,.1,.1,NA,.1),.Dim=c(2,3)))
```

R code for comparable results if one has individual-level data

```
#StepVL1-is the name of the dataset as saving name
#ID-is the unique identifier
#States-is the variable which defines individual states
#Time1-if the cumulative time
```

```
library(haven)
StepVL1 <- read_stata("C:/Users/ WinBUGS/VL_KOL_1.dta")
statetable.msm(States, ID, data=StepVL1)
twoway3.q <- rbind(c(0.25, 0.5, 0.25), c(0.25, 0.5, 0.25), c(0, 0, 0))
crudeinits.msm(States ~ Time1, ID, data=StepVL1, qmatrix=twoway3.q)
StepVL1.msm <- msm( States ~ Time1, subject=ID, data = StepVL1,
                    qmatrix = twoway3.q, deathexact = 3,
                    control = list (fnscale = 5000, maxit= 500 ))
```

###To get the transition rates

```
StepVL1.msm
```

###To get the transition probabilities

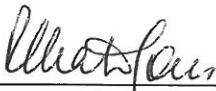
```
P_1year<-pmatrix.msm(StepVL1.msm,t=1)
P_6months<-pmatrix.msm(StepVL1.msm,t=0.5)
P_3months<-pmatrix.msm(StepVL1.msm,t=0.25)
```

10.6. Appendix F: The Wits Ethic Letter Published papers in their journal formats



R14/49 Ms Zvifadzo Matsena-Zingoni et al

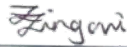
HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M170673

NAME: Ms Zvifadzo Matsena-Zingoni et al
(Principal Investigator)
DEPARTMENT: Division of Epidemiology and Biostatistics - School of Public Health
PROJECT TITLE: Monitoring HIV Disease Progression among Antiretroviral Therapy Patients in Zimbabwe from 2004 to 2016:
A Multistate Modelling Approach
DATE CONSIDERED: 30/06/2017
DECISION: Approved unconditionally
CONDITIONS:
SUPERVISOR: Dr Eustasius Musenge
APPROVED BY: 
Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL: 03/07/2017

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report.** The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).


Principal Investigator Signature

Date 15/07/2017

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

BMJ Open Competing risk of mortality on loss to follow-up outcome among patients with HIV on ART: a retrospective cohort study from the Zimbabwe national ART programme

Zvifadzo Matsena Zingoni ^{1,2}, Tobias Chirwa ¹, Jim Todd ³, Eustasius Musenge ¹

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ABSTRACT

Objective To determine the loss to follow-up (LTFU) rates at different healthcare levels after antiretroviral therapy (ART) services decentralisation among ART patients who initiated ART between 2004 and 2017 using the competing risk model in addition to the Kaplan-Meier and Cox regressions analysis.

Design A retrospective cohort study.

Setting The study was done in Zimbabwe using a nationwide routinely collected HIV patient-level data from various health levels of care facilities compiled through the electronic patient management system (ePMS).

Participants We analysed 390 771 participants aged 15 years and above from 538 health facilities.

Outcomes The primary endpoint was LTFU defined as a failure of a patient to report for drug refill for at least 90 days from last appointment date or if the patient missed the next scheduled visit date and never showed up again. Mortality was considered a secondary outcome if a patient was reported to have died.

Results The total exposure time contributed was 1 544 468 person-years. LTFU rate was 5.75 (95% CI 5.71 to 5.78) per 100 person-years. Adjustment for the competing event independently increased LTFU rate ratio in provincial and referral (adjusted sub-HRs (AsHR) 1.22; 95% CI 1.18 to 1.26) and district and mission (AsHR 1.47; 95% CI 1.45 to 1.50) hospitals (reference: primary healthcare); in urban sites (AsHR 1.61; 95% CI 1.59 to 1.63) (reference: rural); and among adolescence and young adults (15–24 years) group (AsHR 1.19; 95% CI 1.16 to 1.21) (reference: 35–44 years). We also detected overwhelming association between LTFU and tuberculosis-infected patients (AsHR 1.53; 95% CI 1.45 to 1.62) (reference: no tuberculosis).

Conclusions We have observed considerable findings that ‘leakages’ (LTFU) within the ART treatment cascade persist even after the decentralisation of health services. Risk factors for LTFU reflect those found in sub-Saharan African studies. Interventions that retain patients in care by minimising any ‘leakages’ along the treatment cascade are essential in attaining the 90–90–90 UNAIDS fast-track targets.

Strengths and limitations of this study

- The analysis is based on a huge national routinely collected individual-level dataset that has a long follow-up period making our findings generalisable to the patients with HIV on antiretroviral therapy in Zimbabwe.
- This study fitted a competing risk model based on the cumulative incidence function to explore the association between selected covariates and the absolute risk, which is an essential modelling approach for medical decision making so that appropriate subpopulation interventions can be implemented.
- Variable selection of the numerous independent factors was performed using the regularisation (shrinkage) lasso regression technique alongside the stepwise selection methods.
- Important factors known to influence LTFU like CD4 cell counts and viral load were not accounted for in the model due to the high percentage of missingness, and the independent factors adjusted for were not time dependent.
- This study has a possibility of participant selection bias since only participants enrolled in health facilities linked to the electronic patients’ management database were used in the analysis.

INTRODUCTION

Globally, remarkable progress has been made on the treatment of HIV-infected people using antiretroviral therapy (ART), particularly in sub-Saharan Africa (SSA).¹ In Zimbabwe, the ART programme is a comprehensive care and support package aiming to slow disease progression,² improve survival and quality of life³ and minimise HIV transmission by reducing the viral load. Therefore, it is imperative to monitor individuals on ART to ensure treatment efficacy, support adherence and identify treatment failure and resistance.

At the national level, aggregated health facility data are usually used for monitoring the ART programme. However, there is an inherent difficulty in using aggregated data to make statistical inferences about individual-level outcomes. This promoted the increasing use of patient-level data worldwide to assess the impact of the ART programme.^{4–8} With efforts to achieve zero HIV incidences by 2030, the 90–90–90 UNAIDS targets were launched, whereby 90% of the people living with HIV (PLWHIV) should know their status, 90% of those diagnosed should be initiated on ART and 90% of those on ART should achieve viral suppression.⁹ In Zimbabwe, strides have been made towards achieving these targets; however, limitations exist. For instance, in Zimbabwe, only 73% of PLWHIV who are on ART have achieved viral suppression.¹⁰ To improve the proportion of those who achieve viral suppression, it is crucial to come up with broad efforts that minimise long-term ART attrition due to loss to follow-up (LTFU), mortality, drop-outs and withdrawals.

In Zimbabwe, the health service delivery can be categorised into four levels of care, namely the primary, secondary, tertiary and quaternary.¹¹ The primary care consists of clinics and facilities offering basic preventive and curative services. Majority of these primary healthcare (PHC) facilities are in the rural areas, and health problems beyond the scope of these facilities are referred to the secondary healthcare centres, which are mainly the district and mission hospitals. In the secondary care category, private and company health facilities may fit in if they can handle emergency services as the district hospitals. The tertiary care consists of the provincial hospitals that received referral patients from the district hospitals.¹² The quaternary care is the last referral care level that received patients from provincial hospitals. These facilities are mainly in the two largest cities in Zimbabwe.¹² The quaternary healthcare offers much more advanced healthcare; hence, there is modern equipment, medical specialists and pharmaceutical, which could be missing in the lower levels of care.¹¹

The ART services were initially centralised at the higher levels of care—quaternary and tertiary healthcare facilities—normally situated in urban areas. This means rural residents and poorer people were less likely to access HIV testing, care and treatment due to transport cost. In 2010/2011, one of the strategies to mitigate the transport barrier was the decentralisation of ART services to lower levels of care.¹³ These devolved care models were implemented in Zimbabwe to improve patients' access to HIV care, ART adherence and retention in care of PLWHIV. The impact of HIV care and ART decentralisation has been well documented in the SSA region.¹⁴ Understanding ART retention patterns after the implementation of decentralised care is vital to guide the ART programme and policy as well as reflecting on the gaps that may contribute to the poor viral suppression. LTFU is one of the main threats to patient retention and may persist even after the decentralisation of ART services.

This may be due to social (stigmatisation, social deprivation and health literacy issues) and individual factors (perception and misconceptions over ART benefits) that still hinder retention in care.¹⁵

This study aims to determine LTFU rates at different healthcare levels after ART services decentralisation among ART patients who initiated ART between 2004 and 2017. The study period covers the pre-ART and post-ART decentralisation period to get an overall picture of the LTFU patterns over time. The LTFU rates were compared between the different healthcare facility types (PHC, district/mission and provincial/referral hospitals) in Zimbabwe using routinely collected patients-level data from the Zimbabwe national ART database. We further adjusted for the individual-level demographic and clinical characteristics as predisposing or independent factors for LTFU using a statistical model that adjusted for the competing risk (CR) of mortality on the LTFU outcome.

METHODS

Study population

This study was conducted in Zimbabwe, a landlocked country in SSA with roughly 1.4 million PLWHIV. The HIV prevalence dropped from 25% in 2004 to 13.7% in 2017 among adults.^{10 16} Individual patients aged 15 years and above, who initiated ART between 1 January 2004 and 31 December 2017, were eligible for this analysis. A full description of how the final sample size was achieved is illustrated in figure 1.

Study design and data sources

This study was a secondary data analysis from a retrospective cohort study of routinely collected patient data from the Zimbabwe national ART programme. The data came from the national ART programme, which started in 2004. The ART sites expanded from 5 health facilities in 2004 to 1566 by 2017.^{10 17} Treatment guidelines followed WHO recommendations; hence, the ART eligibility criteria and treatment regimens changed over time. The initial regimen for an ART-naïve patient is the first-line ART, a combination of two nucleoside reverse transcriptase inhibitors (NRTIs), the first drug that can be zidovudine, tenofovir (TDF) (the most common) or stavudine (D4T) and the second drug is mainly lamivudine (3TC), and one non-NRTI that can either be nevirapine (NVP) or efavirenz (EFV). Majority of the participants were receiving three-drug combination therapy of TDF+3TC+EFV therapy as the first-line treatment. Once the patient experienced treatment failure or intolerance, switch to second-line ART (a three-drug combination of protease inhibitor and two NRTIs) can be made.¹⁸

Monitoring and evaluation system

The monitoring and evaluation system of the ART programme in Zimbabwe has been described elsewhere.¹⁹ Briefly, since the inception of ART, all patient monitoring

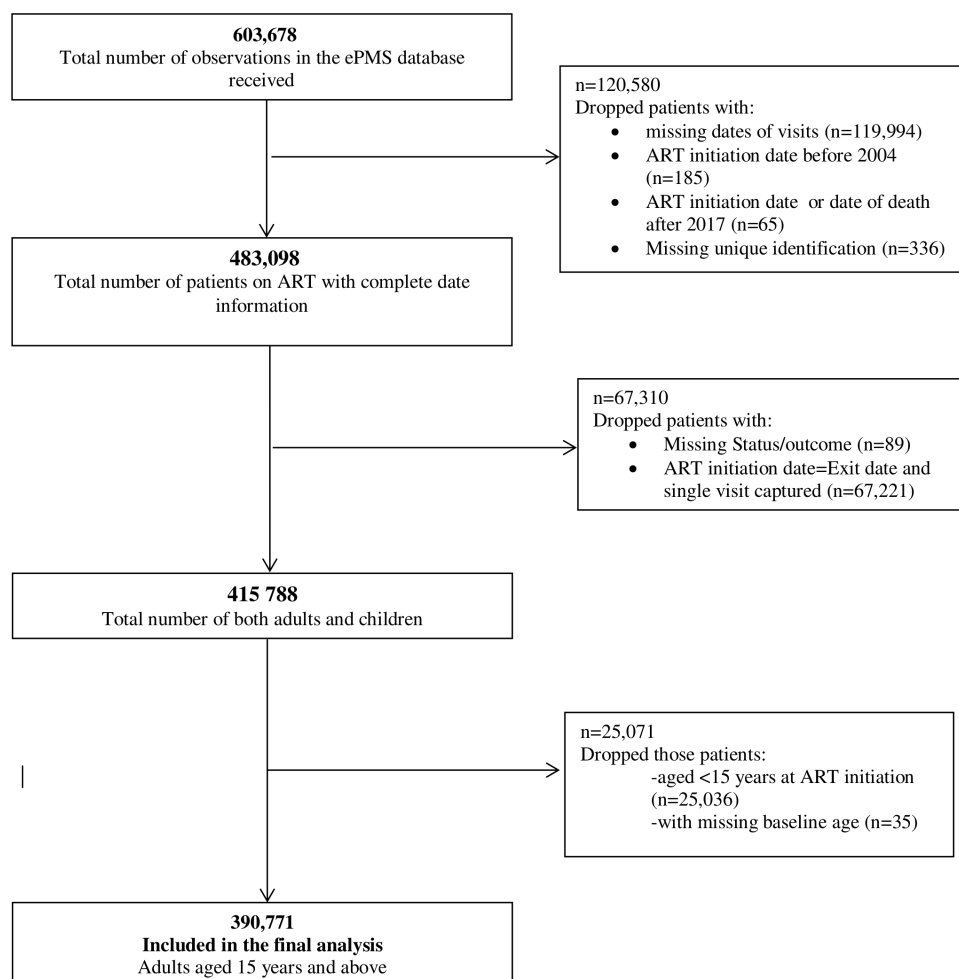


Figure 1 Flow chart of the inclusion criteria for analyses of adult ART patients enrolled in Zimbabwe ART Programme followed up between 2004 and 2017. ART, antiretroviral therapy; ePMS, electronic patient management system.

records had been collected manually using a paper-based system and kept at the health facility where the patient is registered. Since 2012, the paper-based system was no longer functioning properly due to high volumes of ART patients.¹⁰ This upsurge in patients' volumes began to affect the accurate ART monitoring and reporting process as the paper-based system could not cope. Moreover, the paper-based system translated into huge workloads and became strenuous to the already overburdened health workers. As a result, the electronic patient management system (ePMS) was launched in 2012. The ePMS increased efficiency and effective management of ART patients through improving follow-ups to subsequently increase ART adherence.¹⁹ The ePMS provided a platform to compile quality patient-level data to accurately make forecast and evaluate the ART intervention, enabling a more effective programme.¹⁰

The ePMS was rolled out in systematic phased approach with priority given to those HIV sites with high volumes of patients with HIV at the same time maintaining a good representation of the four healthcare levels in the country.¹⁹ From the ePMS Strategic Plan document, the first phase target was 83 sites in 2013 comprising of central, provincial and district hospitals that covered

approximately 61% of ART patients nationwide. Additional 267 city polyclinics, rural/large mission hospitals sites were included to make a total of 350 sites by the end of 2014.¹⁹ The last phase included 184 static ART follow-up sites to bring the total to 534 sites by the end of 2017. By the end of 2018, there were 622 sites with a functional ePMS with the inclusion of private hospitals, which meant that approximately 95% of all patients receiving ART were linked to the ePMS database.¹⁰

The final database of the ePMS has patients' information from all levels of care (quaternary, tertiary, secondary and primary healthcare levels). It, therefore, reflects the overall ART management services in the country, although the database includes all HIV-related data. At enrolment, the patient's demographic data are captured. At each subsequent clinic visit, information on ART regimen type, clinical information, laboratory investigations and physical examination is captured. Outcomes are assessed and captured as death, LTFU, transfer-out to another health facility or alive and active on treatment. Already existing patient's information prior to 2012 from the paper-based system was retrospectively transcribed into the electronic database at each clinic, and all subsequent clinic visits were recorded prospectively with a real-time entry of patient records.

The introduction of the ePMS for monitoring patients with HIV in 2012 has provided a platform for huge data repository in the country that may be used to answer some of the public health questions on the HIV aspects using statistical models. Moreover, the ePMS platform provides readily available data archiving for robust statistical analysis approaches to guide evidence-based decision making and programme interventions planning at patients level while eliminating the aggregated data. Therefore, this rich, huge patient-level database was of preference and suitable to answer our study objective.

Study endpoints

The primary endpoint was LTFU defined as a failure of a patient to report for drug replenishment within 90 days from last appointment date or if the patient missed the next scheduled visit date and never showed up again. Patients, who returned after having been LTFU, were classified as alive and active on treatment. We also consider the mortality outcome as a competing event of LTFU if a patient was reported to have died.

Data analysis methods

Descriptive summaries were reported as frequencies and proportions stratified by health facility type. The pattern of LTFU was explored by calendar year. Incidence rates were calculated from the ART initiation date to outcome occurrence date on a quarterly time

scale. Kaplan-Meier non-parametric curves (equations 1–4 in online supplemental appendix) were used to describe the probability of LTFU over time stratified by selected covariates. The log-rank test was used to assess the equality of these patient retention probabilities. Estimated hazard rates (HRs) (equations 5–9 in online supplemental appendix) were reported as per 100 person-years.

Important variable selection was done using the lasso regression regularisation technique. Variable selection sensitivity analysis was done using the subset selection techniques (best subset selection, stepwise forward variable selection and stepwise backward variable selection methods). All these methods yield the same independent factors considered in the seven different multiple adjusted time-to-event models fitted (figure 2). The baseline predictors used for adjustment were all categorical, namely: health facility type, degree of urbanisation of the health facility (rural/urban), age groups (15–24, 25–34, 35–44 and 45 and above), tuberculosis status (positive/negative), body functional status—which is the patient's ability to perform normal daily activities expected for the well-being of an individual—(working body, ambulatory body and bed-ridden body), WHO clinical stages (stage 1, II, III and IV), ART enrolment calendar period (2004–2007; 2008–2011; 2012–2014; and 2015–2017) and regimen type (D4T, AZT or TDF based combination

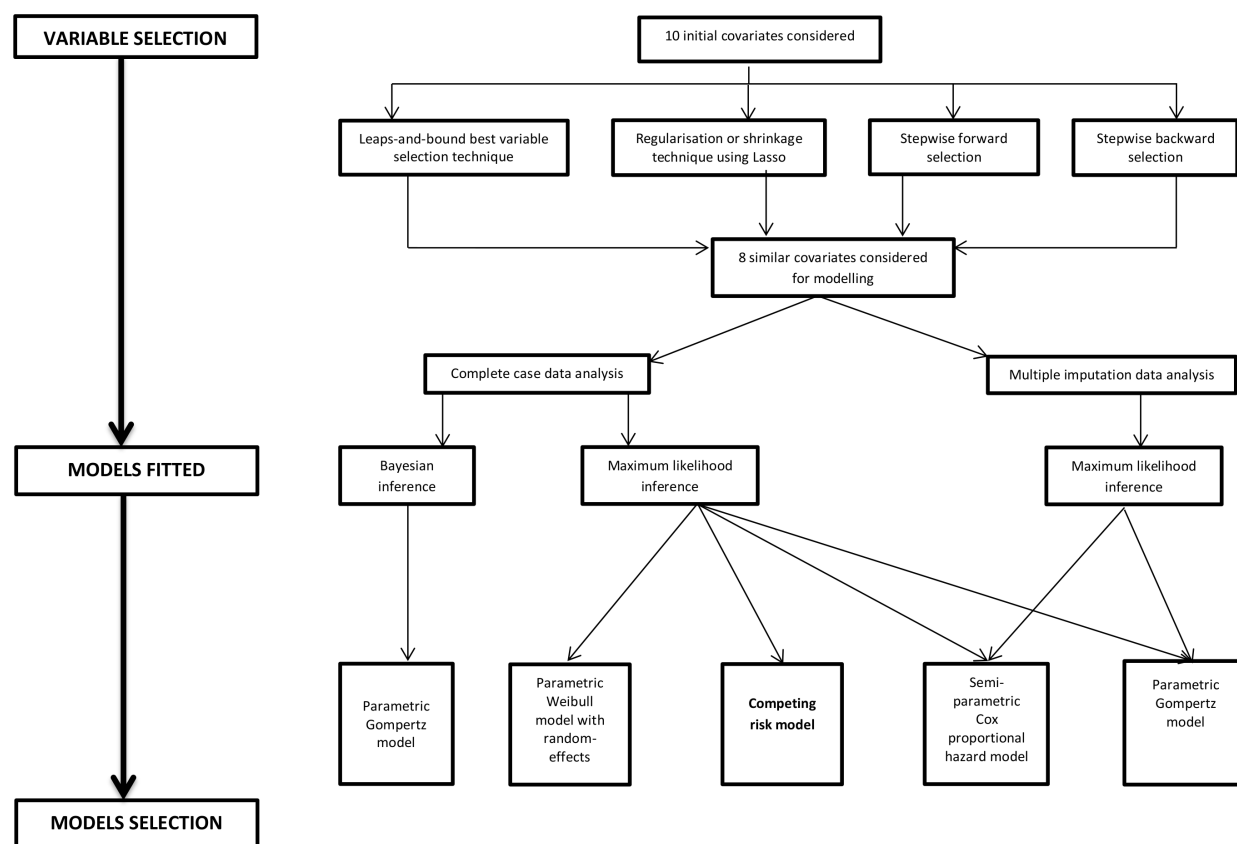


Figure 2 Schematic illustration of the variable of importance selection steps and subsequent models fitted for sensitivity analysis of the results.

therapy). The stratification of the health facility type into primary healthcare, district/mission hospitals and provincial/referral hospitals was based on the level of care classification of the corresponding health facility an individual was enrolled in, and the grouping of the health facilities was based on the patients' care similarities. For those individuals who had moved from one health facility to the other during the study period covered, the last recorded health facility site was considered for this analysis. Therefore, the health level of care classification was mutually exclusive as one individual was assigned to the last captured health facility.

The standard Cox regression model defined in equations 10–12 in the online supplemental appendix is normally used for a time-to-event analysis; however, this method may give biased estimates in the presence of competing events. We fitted the CR model of mortality on LTFU through the cumulative incidence function defined in equations 13–18 in online supplemental appendix.²⁰ CR analysis assumes that patients are exposed to at least two risks (mortality and LTFU). One of the events is of interest (LTFU), while the other is a competing event (mortality) that inhibits the outcome of interest from occurring. The competing events may not be independent, and the baseline hazard may differ between them. The covariates used were time independent; however, we adjusted for time to take into account the period the country experienced an economic turmoil around 2008, which resulted in a mass withdrawal of health personnel in the public sectors and an increased scarcity of vital medical supplies in health system including HIV medication.^{21 22} The adjusted sub-HRs (AsHR) for covariates on LTFU were reported with 95% CIs. We censored on 31 December 2017 for those who had not experienced the event of interest and at the last observed date for those who had transferred to other health facilities.

We performed a sensitivity analysis of our key findings through multiple imputations of the missing explanatory covariates using Rubin's method, which assumes that the data are missing at random.²³ We compared imputed data and the complete case data estimates based on the maximum likelihood estimation (MLE) perspective for both the Cox proportional hazard and Gombertz parametric models. Within the Gombertz parametric models, estimates from the Bayesian estimation (BE) and MLE were compared.²⁴ We assumed non-informative normal priors for all unknown parameters to be estimated with a mean of zero and variance of 100 or precision of 0.001 for the parametric Bayesian model. We fitted a parametric Weibull model with random effects to account for any individual heterogeneity.²⁵ Model comparison between BE and MLE was done using the Akaike's information criterion (AIC), Bayesian information criterion (BIC) and deviance information criterion. In contrast, model comparison between complete case analysis and imputed data analysis was done using the precision of the CI for the estimates. All data management and analysis were performed using Stata V.15.1.²⁶

Patient and public involvement

This study acknowledges the importance of patients and public involvement in research studies; however, this research was done without patient involvement in all research stages since it was secondary data analysis.

Ethical approval

Since this study was secondary data analysis, we did not have direct contact with the participants. We received only anonymised data for analyses.

RESULTS

Descriptive analysis

At the end of study, 268 896 (68.81%) patients were alive, 18 328 (4.7%) had died, 88 744 (22.71%) were LTFU and 14 803 (3.79%) had transferred out from the initial health facility another health facility. Over 1 544 468 person-years of ART, mortality and LTFU rates were 1.19 (95% CI 1.17 to 1.20) and 5.75 (95% CI 5.71 to 5.78) per 100 person-years, respectively. The quarterly trend analysis graph of LTFU over time showed a general increase in LTFU over time with significant peaks in 2012, 2014 and 2016 (figure 3).

The descriptive characteristics of 390 771 patients from 538 health facilities are presented in table 1. The study participants were enrolled at PHC (45.1%), districts/mission (49.2%) or provincial/referral (5.7%) hospitals. Most patients were enrolled in rural health facilities (66.52%). At ART initiation, the majority of the patients were female 255 844 (65.47%), the mean (SD) age was 37.5 (10.2) years and only 6.44% (n=25, 143) patients had either an ambulatory (n=24,332; 6.23%) or a bed-ridden (n=811; 0.21%) body functional status.

Most patients were married (59.5%) with secondary education (31.8%), while 54.2% were classified in WHO stage III or IV and 34.18% were in the 35–44 years age group. The majority of the participants were on first-line ART treatment (97.7%), and only a few had confirmed tuberculosis infection (1.2%). There were missing data on some covariates, including baseline CD4 cell counts recorded for only 35.3% of the study participants.

The time-to-event rates for LTFU stratified by baseline characteristics are shown in table 2. LTFU rate per 100 person-years was 5.92 for patients enrolled at district and mission hospitals, 6.60 among patients from rural health facilities and 17.09 among patients diagnosed with tuberculosis.

The cumulative incidence probability (CIP) curve for death was lower than the CIP for LTFU as the outcome (figure 4A). The LTFU CIP curve increased in the first 3 years on ART and became steady after that. We observed overwhelmingly significant variation between LTFU and selected covariates, log-rank p value <0.001. Higher risk of LTFU was observed among patients aged 15–24 years (figure 4B), females (figure 4C), patients enrolled at urban health facilities (figure 4D), tuberculosis-infected

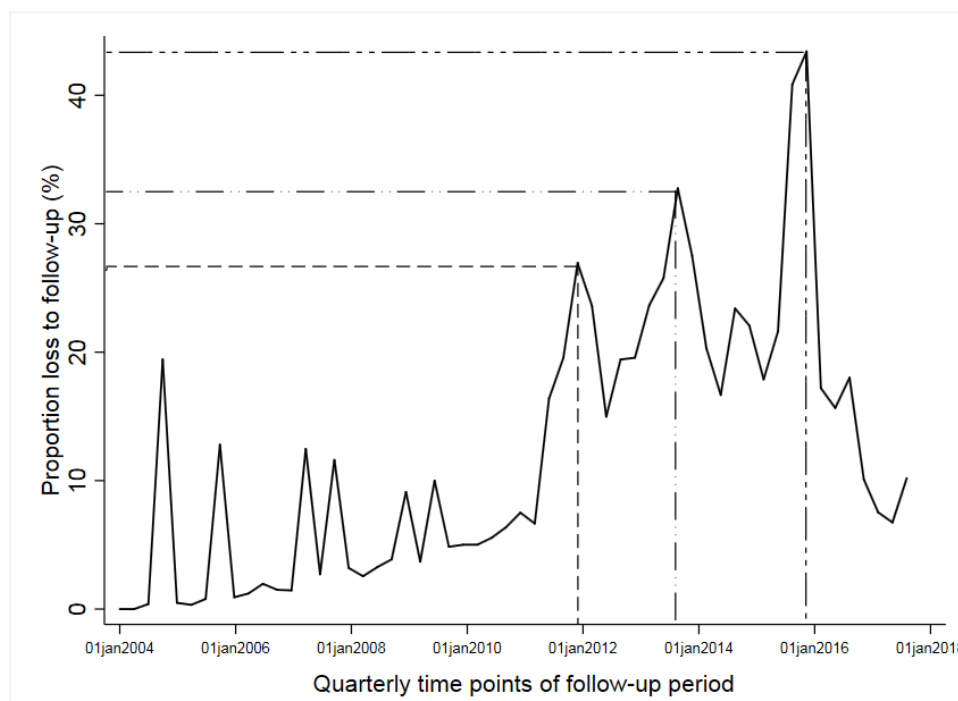


Figure 3 Trend analysis of loss to follow-up outcome among patients receiving ART in Zimbabwe national ART programme on a quarterly time scale, 2004–2017.

patients (figure 4E) and WHO stage I/II patients (figure 4F).

LTFU outcome

To determine the possible independent risk factors associated with LTFU, seven models were fitted, and the results are shown in table 3. An additional pictorial view of the estimates is provided in the online supplemental appendix figure A1 to compare the different model estimates. The data had approximately 10% of missing information in the explanatory covariates. There was no difference in the model estimates between imputed data and complete case data (model 1 vs model 2 and model 4 vs model 5). Comparing the MLE (model 3) and the BE (model 4) models, the estimates were almost similar for most regression parameters, and inclusion of the individual random effects did not improve the model estimates (model 4 vs model 6). Lastly, adjusting for the competing effects of mortality on LTFU showed some significant improvement to the model based on the reduced AIC and BIC values compared with the Cox proportional hazard model. Hence, the CR model was considered a better fit compared with other models, and the interpretation of the results will be based on this model.

The multivariable CR model revealed that patient factors predicting LTFU included: being enrolled at a provincial/referral (AsHR 1.22; 95% CI 1.18 to 1.26) or district/mission (AsHR 1.47; 95% CI 1.45 to 1.50) hospitals (reference: PHC), urban sites (AsHR 1.61; 95% CI 1.59 to 1.63) (reference: rural) and 15–24 years group (AsHR 1.19; 95% CI 1.16 to 1.21) (reference: 35–44 years). We also detected an overwhelming association between LTFU and tuberculosis-infected patients (AsHR

1.53; 95% CI 1.45 to 1.62) (reference: no tuberculosis) and a protective effect of LTFU for patients classified in WHO stage III or IV (AsHR 0.74; 95% CI 0.73 to 0.75) (reference: WHO I/II). Patients who were taking stavudine combination therapy as a first-line ART treatment had an increased risk of becoming LTFU relative to patients taking TDF+3TC+EFV first-line combination therapy, that is, D4T(30)+3TC+NVP (AsHR 5.47; 95% CI 5.52 to 5.75) and D4T(30)+3TC+EFV (AsHR 7.98; 95% CI 6.41 to 9.94). We also observed that patients who initiated ART between 2015 and 2017 had a pronounced risk of becoming LTFU compared with patients who enrolled between 2012 and 2014 (AsHR 6.02; 95% CI 5.91 to 6.12).

DISCUSSION

This study aims to determine the LTFU rates at different healthcare levels after ART services decentralisation among ART patients who initiated ART between 2004 and 2017 and determine other potential independent factors using the CR model approach. Our study followed similar studies adjusting for the competing effect of mortality on LTFU, recognising that those who die are no longer at risk of LTFU.^{27 28} We found the LTFU rate of 5.7 per 100 person-years, which was lower than that reported in Ethiopia of 8.2 per 100 person-years.²⁹ The lower LTFU rates in our study put forward the positive impact of the decentralised models implemented in Zimbabwe to increase patients' retention in HIV care. However, there is still a considerable magnitude of LTFU outcome in ART programmes contributing to the 'leakages' or attrition of patients within the continuum of care cascade in

Table 1 Patients' sociodemographic and clinical characteristics at ART initiation in Zimbabwe national ART programme, 2004–2017

Characteristics	Categories	Primary healthcare (PHC) n=176 253 (45.1%) (n (%))	District/mission hospitals n=192 238 (49.2%) (n (%))	Provincial/referral hospitals n=22 280 (5.7%) (n (%))	Total n=390 771 (100%) (n (%))
Patient demographics					
Age (years) at ART initiation	15–24	20 314 (11.53)	21 057 (10.95)	2601 (11.67)	43 972 (11.25)
	25–34	54 416 (30.87)	58 874 (30.63)	6979 (31.32)	120 269 (30.78)
	35–44	59 284 (33.64)	66 418 (34.55)	7875 (35.35)	133 577 (34.18)
	45+	42 239 (23.96)	45 889 (23.87)	4825 (21.66)	92 953 (23.79)
Degree of urbanisation	Rural	113 738 (66.92)	137 380 (73.57)	432 (2.01)	251 550 (66.52)
	Urban	56 223 (33.08)	49 348 (26.43)	21 055 (97.99)	126 626 (33.48)
Sex	Female	117 567 (66.70)	124 141 (64.58)	14 136 (63.45)	255 844 (65.47)
	Male	58 686 (33.30)	68 097 (35.42)	8144 (36.55)	134 927 (34.53)
Education status at ART initiation	None	3854 (2.19)	4136 (2.15)	227 (1.02)	8217 (2.10)
	Primary	33 735 (19.14)	34 062 (17.72)	2248 (10.09)	70 045 (17.92)
	Secondary	59 181 (33.58)	58 349 (30.35)	6593 (29.59)	124 123 (31.76)
	Tertiary	2921 (1.66)	4423 (2.30%)	1177 (5.28)	8521 (2.18)
	Missing	76 562 (43.44)	91 268 (47.48)	12 035 (54.02)	179 865 (46.03)
Marital status at ART initiation	Single	24 438 (13.87)	24 489 (12.74)	3530 (15.84)	52 457 (13.42)
	Married	105 504 (59.86)	113 953 (59.28)	12 935 (58.06)	232 392 (59.47)
	Widowed	25 798 (14.64)	30 994 (16.12)	3523 (15.81)	3523 (15.81)
	Divorced	13 429 (7.62)	14 732 (7.66)	1677 (7.53)	29 838 (7.64)
	Missing	7084 (4.02)	8070 (4.20)	615 (2.76)	15 769 (4.04)
Calendar time of starting ART	2004–2007	6635 (3.76)	8942 (4.65)	2962 (13.29)	18 539 (4.74)
	2008–2011	38 990 (22.12)	61 321 (31.85)	7899 (35.45)	108 120 (27.67)
	2012–2014	67 759 (38.44)	90 582 (47.12)	9472 (42.51)	167 813 (42.94)
	2015–2017	62 869 (35.67)	31 483 (16.38)	1947 (8.74)	96 299 (24.64)
Clinical factors					
WHO staging at ART initiation	I/II	82 203 (46.64)	69 629 (36.22)	7690 (34.52)	159 519 (40.82)
	III/IV	79 279 (44.98)	118 113 (61.44)	14 425 (64.74)	211 817 (54.20)
	Missing	14 771 (8.38)	4499 (2.34)	165 (0.74)	19 435 (4.97)
Baseline CD4 (cell/μL) at ART initiation	Above 500	4783 (2.71)	4950 (2.57)	601 (2.70)	10 334 (2.64)
	351–500	8227 (4.67)	8790 (4.57)	940 (4.22)	17 957 (4.60)
	200–350	17 908 (10.16)	24 895 (12.95)	2866 (12.86)	45 669 (11.69)
	Below 200	23 796 (13.50)	35 020 (18.22)	4982 (22.36)	63 798 (16.33)
	Missing	121 539 (68.96)	118 583 (61.69)	12 891 (57.86)	253 013 (64.75)
Treatment regimen at the time of data extraction	First line	170 662 (98.29)	184 321 (97.37)	20 724 (94.32)	375 704 (97.65)
	D4T(30)+3TC+NVP	625 (0.35)	2942 (1.53)	629 (2.82)	4196 (1.07)
	D4T(30)+3TC+EFV	42 (0.02)	155 (0.08)	20 (0.09)	217 (0.06)
	AZT+3TC+NVP	1349 (0.77)	1933 (1.01)	349 (1.57)	3631 (0.93)
	AZT+3TC+EFV	212 (0.12)	425 (0.22)	56 (0.25)	693 (0.18)
	TDF+3TC+NVP	6541 (3.71)	16 334 (8.50)	2923 (13.12)	25 798 (6.60)
	TDF+3TC+EFV	161 288 (91.51)	162 006 (84.27)	16 628 (4.63)	339 922 (86.99)
	Other first lines	3236 (1.84)	3474 (1.81)	428 (1.92)	7138 (1.83)
	Second line	2960 (1.68)	4969 (2.58)	1247 (5.60)	9176 (2.35)
Tuberculosis status at ART initiation	Negative	156 072 (88.55)	170 869 (88.88)	20 218 (90.75)	347 159 (88.84)
	Positive	2092 (1.19)	2423 (1.26)	301 (1.35)	4816 (1.23)
	Not assessed	15 743 (8.93)	16 387 (8.52)	1347 (6.05)	33 477 (8.57)
	Missing	2346 (1.33)	2559 (1.33)	414 (1.86)	5319 (1.36)

Continued

Table 1 Continued

Characteristics	Categories	Primary healthcare (PHC) n=176 253 (45.1%) (n (%))	District/mission hospitals n=192 238 (49.2%) (n (%))	Provincial/referral hospitals n=22 280 (5.7%) (n (%))	Total n=390 771 (100%) (n (%))
Body functional status at ART initiation	Working	162 710 (92.32)	180 417 (93.85)	20 024 (89.87)	363 151 (92.93)
	Ambulatory	11 789 (6.69)	10 454 (5.44)	2089 (9.38)	24 332 (6.23)
	Bed ridden	331 (0.19)	452 (0.24)	28 (0.13)	811 (0.21)
	Missing	1423 (0.81)	915 (0.48)	139 (0.62)	2477 (0.63)

Missing category refers to information that is unavailable in the dataset for that particular variable.

ART, antiretroviral therapy; AZT, zidovudine; D4T, stavudine; EFV, efavirenz; NVP, nevirapine; 3TC, lamivudine; TDF, tenofovir.

Zimbabwe. This requires continual upscaling of interventions that minimise the LTFU rates and retain patients in care since patients who are LTFU are associated with increased treatment interruptions that can trigger ART treatment defaulting, treatment non-adherence, treatment failure or treatment resistance.^{30 31}

Similar to other studies, LTFU independently increased at higher levels of care (provincial and referral (AsHR 1.22; 95% CI 1.18 to 1.26) and district and mission (AsHR 1.47; 95% CI 1.45 to 1.50) hospitals) relative to PHC in this study.⁵ This finding supports the fact that decentralisation is associated with better patients' retention in care as there are high risks of LTFU rate in higher levels of care compared with the PHC facilities. This finding supports the assumption that if patients seek care from health facilities closer to their homes with cheaper transport cost and less congested hospital environments, there is improved patient retention as compared with seeking care to faraway health facilities.³² Moreover, the high rates of LTFU in secondary and tertiary/quaternary levels of care could be explained by 'silent transfers' whereby patients self-transfer themselves to these decentralised PHC facilities based on individual preferences of where to seek care, and the system fails to track it. These 'silent transfers' could be a good indication of the upsurge of the decentralisation of services.³² However, such 'silent transfers' may result in inflated LTFU rates in higher levels of care as most these patients would be classified as LTFU when in fact they might have self-transferred and the patient tracking system is not efficient enough to pick such scenarios due to significantly high patients' volumes persisting at these health facilities.⁵ Similarly, the quarterly trend analysis of LTFU rates showed an increase over time, peaking in the period when decentralised models were implemented. The same issue of 'silent transfers' of patients to nearer health facilities can also explain this trend pattern finding.

On the contrary, not everyone would prefer to seek care from these decentralised health facilities. Some may intentionally avoid these nearby health facilities to conceal their HIV status from the community. These individuals remain enrolled in faraway health facilities and most probably the higher levels of care. These individuals may contribute to the observed high rates of LTFU in this cohort as they may still face transport cost challenges to

replenish their ART supplies.³³ Moreover, tertiary and quaternary levels of care may receive much sicker patients with a high risk of death, hoping to get better treatment through the healthcare referral system.³⁴ This means some of these much ill patients are more likely to become LTFU eventually as severe immune deterioration hinders one to keep up to date with their treatment replenishments. Earlier studies have also reported that much sicker patients with severe immune deterioration are more likely to become LTFU compared with those with no significant immunodeficiency.³⁵ Other studies have also shown that a significant portion of these severely ill patients who eventually become LTFU from higher levels of care health facilities, if tracked, could be found dead.³⁶ Our findings put forward that though the decentralisation uptake might have been taken up by the majority of the ART patients and improved patient's retention in the ART programme in overall; those groups of individuals who still seek healthcare from the higher levels of care are still more at risk of becoming LTFU; hence, interventions that may retain patients in the higher levels of care facilities are a priority.

Patients enrolled at urban health facilities had increased risk to become LTFU compared with those at rural sites. This finding contradicts a study done in Ethiopia whereby rural residents had an increased risk of LTFU due to availability of transport costs, long distances to ART health facilities, social stigma as well as low levels of HIV knowledge in these communities.¹⁵ However, our study finding can be explained by the decentralisation of health facilities to walkable distances in favour of rural residents.^{4 37} Mobility of residents in urban areas is disproportionate relative to rural residents; hence, most of these LTFU in urban areas could be part of the silent transfers to other nearer ART health facilities in their relocated areas.

Another interesting finding was high LTFU among the 15–24 years group. The adolescent's group is known to be associated with additional intricacy in their HIV management due to different types of chronic comorbidities, and this whole complexity may impact on their ART outcomes including LTFU.^{38 39} The high risk of becoming LTFU among adolescents can be attributed to structural deprivation due to medical and psychological reasons that contribute to poor adherence in this subpopulation group as a result of becoming LTFU.⁴⁰ The most common

Table 2 Rates per 100 person-years of LTFU and log-rank tests for ART patients' baseline characteristics in Zimbabwe national ART programme, 2004–2017

Characteristics	Category	LTFU cases	Person-years	Rate per 100 person-years	95% CI of rate	Log-rank p value
Health facility level	Primary healthcare	34 958	6200	5.6502	5.5913 to 5.7097	<0.001*
	District/mission hospitals	48 188	8100	5.9169	5.8643 to 5.9700	
	Provincial/referral hospitals	5598	1100	5.0273	4.8973 to 5.1608	
Age (years) at ART initiation	15–24	32 790	4500	7.3252	7.2463 to 7.4049	<0.001*
	25–34	12 617	1500	8.4301	8.2843 to 8.5785	
	35–44	27 504	5500	4.9671	4.9087 to 5.0261	
	45+	15 833	3900	4.0242	3.9620 to 4.0874	
Degree of urbanisation	Rural	52 629	10 000	5.2756	5.2307 to 5.3209	<0.001*
	Urban	36 115	5500	6.6039	6.5362 to 6.6724	
Sex	Females	59 695	10 000	5.8703	5.8234 to 5.9175	<0.001*
	Male	29 049	5300	5.5063	5.4433 to 5.5700	
Education status at ART initiation	None	1470	354	4.1582	3.9509 to 4.3762	<0.001*
	Primary	14 786	2800	5.3558	5.2702 to 5.4429	
	Secondary	32 629	4700	6.9961	6.9206 to 7.0725	
	Tertiary	1803	409	4.4097	4.2108 to 4.6180	
	Missing	38 056	7300	5.2435	5.1911 to 5.2965	
Marital status at ART initiation	Single	13 078	1900	6.9036	6.7863 to 7.0230	<0.001*
	Married	7548	1100	6.6112	6.4637 to 6.7620	
	Widowed	9375	2900	3.1872	3.1233 to 3.2524	
	Divorced	55 985	8800	6.3313	6.2790 to 6.3839	
	Missing	2758	625	4.416	4.2543 to 4.5840	
Calendar time of starting ART	2004–2007	790	1900	0.4255	0.3968 to 0.4562	<0.001*
	2008–2011	4572	6900	0.6593	0.6405 to 0.6787	
	2012–2014	43 565	5300	8.1802	8.1038 to 8.2574	
	2015–2017	39 817	1300	29.9903	29.6972 to 30.2863	
WHO staging at ART initiation	I/II	47 410	5100	9.208	9.1255 to 9.2912	<0.001*
	III/IV	38 919	9500	4.0957	4.0552 to 4.1366	
	Missing	2415	794	3.0432	2.9242 to 3.1671	
Baseline CD4 (cell/uL) at ART initiation	Above 500	4341	257	16.919	16.4231 to 17.4299	<0.001*
	351–500	7614	455	16.7362	16.3645 to 17.1164	
	200–350	11 556	1700	6.7428	6.6210 to 6.8669	
	Below 200	15 271	2700	5.7338	5.6436 to 5.8254	
	Missing	49 962	10 000	4.8245	4.7823 to 4.8669	
Treatment regimen at the time of data extraction	First line	88 050	15 000	5.9066	5.8677 to 5.9457	<0.001*
	D4T(30)+3TC+NVP	2685	168	15.9847	15.3914 to 16.6009	
	D4T(30)+3TC+EFV	141	10	14.7353	12.4932 to 17.3797	
	AZT+3TC+NVP	448	184	2.4374	2.2218 to 2.6738	
	AZT+3TC+EFV	158	30	5.3159	4.5484 to 6.2129	
	TDF+3TC+NVP	9652	1100	9.1737	8.9925 to 9.3586	
	TDF+3TC+EFV	71 378	13 000	5.371	5.3318 to 5.4106	
	Other first lines	3588	175	20.559	19.8972 to 21.2429	
	Second line	694	538	1.29	1.1985 to 1.3908	

Continued

Table 2 Continued

Characteristics	Category	LTFU cases	Person-years	Rate per 100 person-years	95% CI of rate	Log-rank p value
Tuberculosis status at ART initiation	Negative	81 119	14 000	5.9418	5.9010 to 5.9828	<0.001*
	Positive	2235	131	17.0906	16.3966 to 17.8141	
	Not assessed	4188	1400	2.9328	2.8453 to 3.0230	
	Missing	1202	234	5.1455	4.8627 to 5.4447	
Body functional status at ART initiation	Working	81 122	14 000	5.6445	5.6057 to 5.6834	<0.001*
	Ambulatory	7059	930	7.5897	7.4147 to 7.7688	
	Bed ridden	215	26	8.4201	7.3666 to 9.6243	
	Missing	348	117	2.9723	2.6758 to 3.3015	

*Significant at 5%. Missing category refers to information that is unavailable in the dataset for that particular variable.

ART, antiretroviral therapy; AZT, zidovudine; D4T, stavudine; EFV, efavirenz; LTFU, loss to follow-up; NVP, nevirapine; 3TC, lamivudine; TDF, tenofovir.

medical barrier that has been found to affect ART adherence include treatment side effects, multiple doses and health system dissatisfaction. Research has found that ART has improved perinatal HIV infection into a controllable disease through optimal ART adherence. This opens up an additional challenge among adolescents who were prenatally or perinatally infected in the transition stage to adult care to experience ART adherence lapses and develop worse clinical outcomes as they become LTFU.⁴⁰ The transition from the paediatric care to adult care would mean changing care providers, absence of youth-friendly facilities, tight and hectic schedules, new responsibilities and deprivation of caregiver support for some of these adolescents. Some of the social deprivation issues

among adolescents include inadequate financial support to cover transport costs to health facilities for treatment refill since this group heavily depends on their caregivers.⁴¹ Some of the social deprivations faced by adolescents include lack of family support as some adolescents come from disrupted family structures with deprived caregiver-child relationships, fear-perceived HIV-related stigma and discrimination to disclose their status.^{15 41 42}

Therefore, this study recommends that policymakers should strengthen the social protection support to address the complex vulnerability, disadvantages and risks faced by HIV-positive adolescents in order to foster resilience among the HIV-positive adolescents population. The social protection support can interrupt some of the

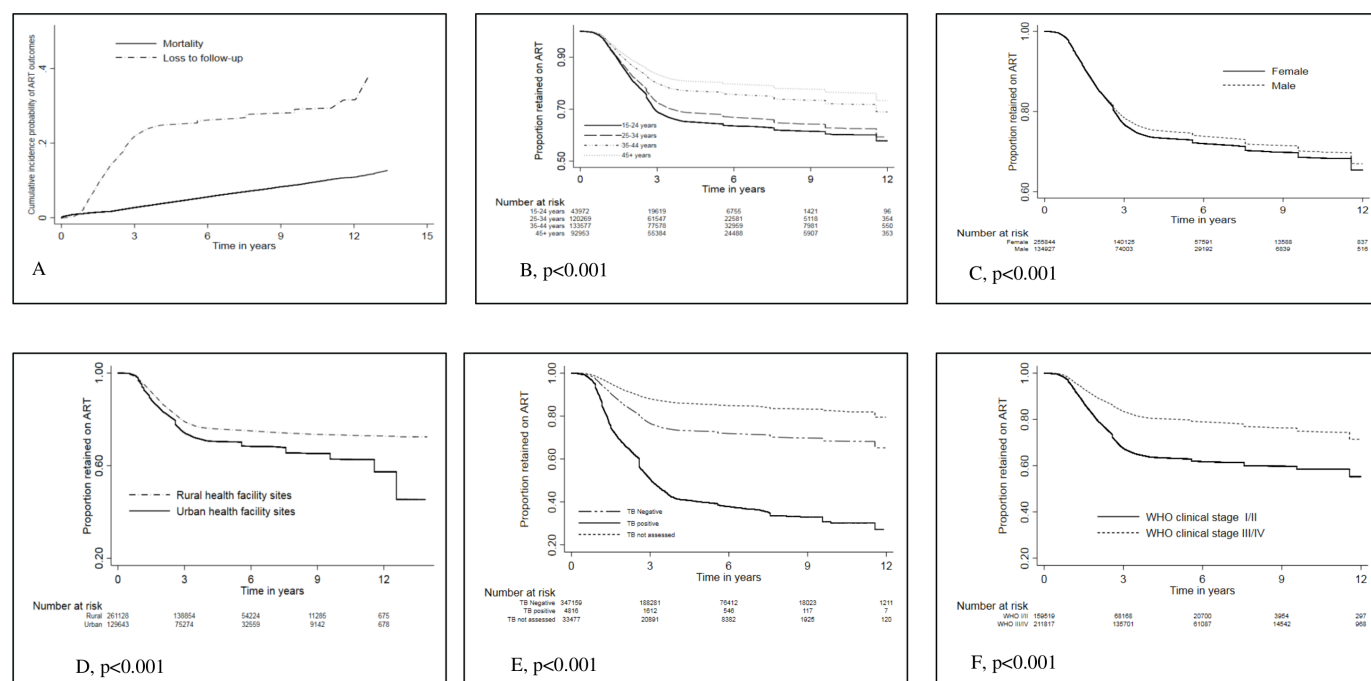


Figure 4 The cumulative incidence probability of mortality and loss to follow-up (A), and Kaplan-Meier curves for loss to follow-up stratified by baseline age categories (B), gender (C), level of urbanisation of the health facilities (D), baseline tuberculosis infection status (E) and baseline WHO clinical stages for ART patients from the Zimbabwe national ART programme electronic patient monitoring data, 2004–2017. ART, antiretroviral therapy.

Table 3 Multiple regression models results of LTFU among ART patients in Zimbabwe national ART programme, 2004–2017, for different models

Characteristics	Category	Cox proportional hazard		Parametric Gompertz model			Weibull model with random effects		Competing risk model of mortality on LTFU
		CC+MLE (model 1)	MI+MLE (model 2)	CC+BE (model 3)	CC+MLE (model 4)	MI+MLE (model 5)	CC+MLE (model 6)	CC+MLE (model 7)	
Health facility level	Primary healthcare	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Secondary hospitals*	1.48 (1.46–1.50)	1.51 (1.49–1.53)	1.53 (1.51–1.54)	1.53 (1.51–1.55)	1.57 (1.54–1.59)	1.48 (1.45–1.51)	1.47 (1.45–1.50)	
	Tertiary hospitals†	1.17 (1.14–1.21)	1.23 (1.20–1.27)	1.23 (1.21–1.25)	1.23 (1.20–1.27)	1.30 (1.26–1.34)	1.10 (1.06–1.14)	1.22 (1.18–1.26)	
Age (years) at ART initiation	15–24	1.16 (1.13–1.19)	1.17 (1.14–1.19)	1.12 (1.11–1.14)	1.13 (1.10–1.15)	1.14 (1.12–1.17)	1.23 (1.20–1.27)	1.19 (1.16–1.21)	
	25–34	1.18 (1.17–1.20)	1.19 (1.17–1.21)	1.18 (1.16–1.19)	1.18 (1.16–1.20)	1.19 (1.17–1.20)	1.24 (1.21–1.27)	1.19 (1.17–1.21)	
	35–44	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
	45+	0.88 (0.87–0.89)	0.87 (0.86–0.89)	0.88 (0.87–0.89)	0.88 (0.86–0.90)	0.87 (0.85–0.88)	0.86 (0.84–0.88)	0.87 (0.85–0.89)	
Degree of urbanisation	Rural	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
	Urban	1.70 (1.68–1.72)	1.67 (1.65–1.72)	1.67 (1.65–1.69)	1.67 (1.65–1.70)	1.64 (1.61–1.66)	2.06 (2.01–2.10)	1.61 (1.59–1.63)	
Calendar time of starting ART	2004–2007	0.04 (0.04–0.05)	0.04 (0.04–0.05)	0.02 (0.02–0.02)	0.02 (0.01–0.02)	0.02 (0.01–0.02)	0.01 (0.01–0.01)	0.09 (0.09–0.10)	
	2008–2011	0.07 (0.7–0.08)	0.07 (0.07–0.08)	0.04 (0.04–0.04)	0.04 (0.0–0.04)	0.05 (0.04–0.05)	0.02 (0.02–0.02)	0.11 (0.10–0.11)	
	2012–2014	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
	2015–2017	8.48 (8.34–8.63)	8.40 (8.26–8.54)	5.95 (5.90–6.00)	5.97 (5.88–6.06)	5.90 (5.81–5.99)	16.09 (15.56–16.63)	6.02 (5.91–6.12)	
WHO staging at ART initiation	I/II	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
	III/IV	0.73 (0.72–0.74)	0.74 (0.73–0.75)	0.73 (0.73–0.74)	0.73 (0.72–0.75)	0.74 (0.73–0.75)	0.67 (0.65–0.68)	0.74 (0.73–0.75)	
Treatment regimen at the time of data extraction	D4T(30)+3TC+NVP	5.96 (5.72–6.21)	6.00 (5.77–6.25)	6.065.92–6.22)	6.09 (5.84–6.34)	6.06 (5.82–6.30)	15.05 (13.98–16.21)	5.47 (5.52–5.75)	
	D4T(30)+3TC+EFV	8.55 (7.21–10.12)	8.34 (7.09–9.90)	8.71 (8.21–9.20)	8.47 (7.16–10.03)	8.29 (7.01–9.79)	19.88 (15.23–25.87)	7.98 (6.41–9.94)	
	AZT+3TC+NVP	0.73 (0.67–0.80)	0.72 (0.66–0.79)	0.74 (0.71–0.78)	0.74 (0.67–0.81)	0.72 (0.65–0.79)	0.74 (0.66–0.83)	0.75 (0.68–0.83)	
	AZT+3TC+EFV	1.19 (1.02–1.40)	1.19 (1.01–1.39)	1.19 (1.16–1.23)	1.21 (1.03–1.42)	1.21 (1.03–1.40)	1.27 (1.03–1.56)	1.09 (0.91–1.30)	
	TDF+3TC+NVP	2.41 (2.36–2.47)	2.46 (2.40–2.51)	2.46 (2.42–2.50)	2.45 (2.40–2.51)	2.50 (2.44–2.55)	3.58 (3.45–3.70)	2.29 (2.23–2.34)	
	TDF+3TC+EFV	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
Tuberculosis status at ART initiation	Other first lines	1.97 (1.90–2.04)	1.97 (1.91–2.04)	1.88 (1.83–1.93)	1.89 (1.82–1.95)	1.89 (1.83–1.96)	2.44 (2.32–2.57)	1.61 (1.54–1.68)	
	Second line	0.46 (0.42–0.49)	0.45 (0.42–0.49)	0.45 (0.43–0.47)	0.44 (0.41–0.48)	0.44 (0.41–0.47)	0.39 (0.36–0.42)	0.48 (0.44–0.52)	
	Negative	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	
	Positive	2.14 (2.05–2.24)	2.13 (2.04–2.23)	2.03 (1.99–2.09)	2.02 (1.94–2.11)	2.01 (1.93–2.10)	2.66 (2.50–2.83)	1.53 (1.45–1.62)	
	Not assessed	0.58 (0.56–0.59)	0.59 (0.57–0.61)	0.60 (0.59–0.60)	0.60 (0.58–0.62)	0.61 (0.59–0.63)	0.51 (0.49–0.53)	0.60 (0.58–0.62)	

Continued

Table 3 Continued

Characteristics	Category	Cox proportional hazard			Parametric Gompertz model			Weibull model with random effects		Competing risk model of mortality on LTFU	
		CC+MLE (model 1)	MI+MLE (model 2)	CC+BE (model 3)	CC+MLE (model 4)	MI+MLE (model 5)	CC+MLE (model 6)	CC+MLE (model 6)	CC+MLE (model 7)	CC+MLE (model 7)	CC+MLE (model 7)
Body functional status at ART initiation	Working	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
	Ambulatory	1.22 (1.19–1.24)	1.23 (1.20–1.26)	1.23 (1.21–1.26)	1.23 (1.20–1.27)	1.25 (1.22–1.28)	1.28 (1.23–1.32)	1.08 (1.05–1.11)	1.08 (1.05–1.11)	1.08 (1.05–1.11)	1.08 (1.05–1.11)
	Bed ridden	1.34 (1.17–1.53)	1.33 (1.16–1.52)	1.32 (1.29–1.35)	1.34 (1.16–1.53)	1.32 (1.15–1.51)	1.42 (1.18–1.72)	0.64 (0.54–0.75)	0.64 (0.54–0.75)	0.64 (0.54–0.75)	0.64 (0.54–0.75)
	AIC	196 416.4 196 439.1			379 948.9		445 559.7			195 708.7	195 708.7
	BIC				380 197.6		445 819.3			195 731.4	195 731.4
	DIC			379 925.9							

Bold face=low values of the information criterion.

*District and mission hospitals.

†Provincial and referral hospitals.

AIC, Akaike's information criterion; ART, antiretroviral therapy; AZT, zidovudine; BE, Bayesian estimation; BIC, Bayesian information criterion; CC, complete case; DIC, deviance information criterion; D4T, stavudine; EFV, efavirenz; MI, multiple imputation; MLE, maximum likelihood estimation; NVP, nevirapine; 3TC, lamivudine; TDF, tenofovir.

social deprivations faced by adolescents through poverty reduction and economic development, improved access to healthcare, access to health services, reduced stigma and discrimination and improved caregiver psychosocial and physical well-being. Another recommendation is the use of health facility-based peer-supporters programmes for adolescents to improve ART adherence and, ultimately, viral suppression.^{43 44} The peer support activities involve peer-to-peer counselling, peer support groups and treatment buddy programmes among adolescents with the aim of ART adherence and ultimately achieving viral suppression, reducing the HIV-related illnesses among adolescents. As adolescents may exit the HIV care through becoming LTFU or withdrawals due to transition adjustments challenges from paediatric care to adult care, an early multidisciplinary and developmentally suitable transition preparedness mechanism is an alternative. The mechanism should be a comprehensive package addressing inherent adolescents' health issues like cognitive health, ART adherence, stigma, disclosure and socio-economic issues.^{38 44} Besides, a simple regimen, directly observed therapy and technological interventions like cellphone reminders have been found to increase ART adherence in adolescents.

We observed an overwhelming association of tuberculosis infection and becoming LTFU that concurs with an earlier study that reported that the risk of becoming LTFU was two times more likely in HIV patients with tuberculosis infection compared with those who did not have tuberculosis.²⁹ This finding can be explained by overlapping toxicity of HIV and tuberculosis drugs, leading to adverse reactions that have a direct consequence of becoming LTFU.²⁹ Therefore, a push towards integrated care of HIV and tuberculosis service delivery would elevate HIV uptake and tuberculosis screening and reduce travel inconveniences on patients.^{34 45} Also, tuberculosis treatment before ART initiation reduces the risk to LTFU⁴²; hence, it is profound to increase efforts in tuberculosis screening and treatment of patients with HIV. However, issues around tuberculosis drug resistance cannot be ignored. Nowadays, HIV studies also consider information on non-communicable diseases like cancer, diabetes and hypertension; however, this information was missing from this current study database.

We also detected that patients classified in WHO stage III or IV were less likely to become LTFU relative to those classified in WHO stage I or II. However, our finding contradicts with earlier studies that have reported that experiencing a severe AIDS-defining ailment was associated with reduced risk of becoming LTFU.^{27 46} Our study finding may put forward the fact that there could have been an upsurge of health-seeking behaviour among patients with advanced WHO clinical stages in this database cohort or this finding could be attributed to expansions of community awareness through health promotion in these health facilities communities.

Strengths and weaknesses of this study

This study highlights several strengths. A regularisation variable selection technique was used to identify important covariates. The lasso model shrinks the variable coefficient to zero and produces a simpler model that can be interpreted easily. For the survival analysis, the standard Cox regression model overestimated the risk in the presence of CRs, and we used the Fine and Gray CR model instead.⁴⁷ Ignoring CRs alters the probabilities of occurrence of the outcome giving biased estimates. Standard survival methods normally used in many studies censor the CR; however, this is improper because those who have died can no longer become LTFU. Such analysis will either overestimate or underestimate the risk ratios. We also used individual data that enabled exploration and adjustment for patient-level covariates associated with the outcome to get robust information on the ART outcome patterns as compared with aggregated data.^{33 48} The study follow-up period was relatively long (13 years), and the data came from all the 10 provinces in Zimbabwe without restriction to specific geographical areas. The data represented quaternary, tertiary, secondary and primary health facilities from private and public sectors. This makes our results generalisable to the whole of Zimbabwe since the data reflect a true representation of all PLWHIV in the country. To the best of our knowledge, this study has used one of the largest datasets to analyse adult ART outcomes at the patient level.

Our study results should be inferred in light of some limitations. Missing data was of concern, particularly to those variables that influence LTFU like viral load and CD4 cell count in addition to non-communicable diseases comorbidities. The presence of missing data could be explained by poor documentation of information³⁴ or limited access to the point of care machines for viral load and CD4 cell counts measurements.^{4 49 50} The missing patterns for some covariates like viral load and CD4 cell count measurements were likely to be informative and missing not at random since differentiated care monitoring approach was used in some years covered by this study.⁵¹ Therefore, to maintain sufficient power, covariates with a high percentage of missing observations were excluded at the multivariable analysis stage. In future, we recommend that the data clerks should be trained on the importance of capturing full information and to the programme managers to consider expanding the HIV routine data collection tool to capture non-communication diseases conditions of the HIV patients. The sociodemographic and clinical characteristics in the database were only taken at baseline or last observed at the time of data extraction; hence, we could not incorporate the time dependency of some covariates. We also acknowledge that there could be differential misclassification of the LTFU outcome in this study in the sense that some of those recorded as LTFU may be 'silent transfers' who have enrolled in a different health facility as a result of ART decentralisation and have been given a different unique identifier number; hence, this might have biased

our LTFU estimates in this study. There is also a possibility of participant selection bias since we only considered patients whose information was captured through the ePMS; as a result, the reported findings could be systematically different from those patients not included. However, it is of paramount importance to note that the dataset used was huge, and representation of the health facilities in Zimbabwe was reflected; hence, our findings could be generalised to all ART services health facilities in Zimbabwe.

While our findings for the common predictors of LTFU may be comparable with earlier studies conducted in sub-Saharan African region, we had also hypothesised that those ART patients who enrolled around 2008 would have a higher risk of becoming LTFU. This was done taking note of the hyperinflation that occurred in Zimbabwe during the part of the study period under review. The economic turmoil was allied to the increased mass departure of qualified health professionals and scarcities of vital medical supplies in health facilities.^{21 22} Despite this situation, we detected a protective effect of becoming LTFU between 2008 and 2011 in this study. This could be explained by the support the country received through Global Fund,⁴ and ART sites increased from 282 sites in 2008 to 1006 in 2012.³⁷ For further studies, we recommend the use of time-varying covariates like regimen type, CD4 cell counts, WHO stages and viral load measurements and the use of spatial analysis of ART outcome to identify high burdened regions that the policymakers may use to allocate resources, especially in resource-constrained settings.

Conclusion

The results from this current study using the data spanning over 13 years agree with the evident decline of the HIV incidence and prevalence in Zimbabwe, and the findings are comparable with similar HIV studies' findings, even from Demographic Health Survey.⁵² Our results indicate that patient retention in care is still a drawback in HIV prevention and control. Policymakers and programme managers should come up with strategies to retain patients on ART. These strategies may include increased patient surveillance and strengthened patient tracing mechanisms to reduce LTFU at health facilities, strengthened community-based caregiver and peer support,¹⁴ and nutritional aid support especially for adolescents and young adults (15–34 years). In addition, interventions that minimise 'leakages' in the HIV treatment cascade including the use of ART adherence clubs to reduce ART resistance⁵³ and advice on sexual abstinence should remain the cornerstone of HIV prevention and control. As much as most of the observed LTFU outcome at higher levels of care (district, provincial and central hospitals) could be 'silent transfers', most patients who become LTFU are likely to have poor ART adherence if not dead. Poor ART adherence leads to poor viral suppression that affects achieving the third 90% UNAIDS targets, which state that 90% of those patients on ART

should be virally suppressed. Clinicians should provide continual educational support on the importance of ART adherence to increase life expectancy among the HIV population and other benefits of ART. More important than not meeting the UNAIDS targets is the impact that poor viral suppression has on patients' health.

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HIV Disease Progression Among Antiretroviral Therapy Patients in Zimbabwe: A Multistate Markov Model

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Background: Antiretroviral therapy (ART) impact has prolonged survival of people living with HIV. We evaluated HIV disease progression among ART patients using routinely collected patient-level data between 2004 and 2017 in Zimbabwe.

Methods: We partitioned HIV disease progression into four transient CD4 cell counts states: state 1 ($CD4 \geq 500$ cells/ μ l), state 2 (350 cells/ μ l $\leq CD4 < 500$ cells/ μ l), state 3 (200 cells/ μ l $\leq CD4 < 350$ cells/ μ l), state 4 ($CD4 < 200$ cells/ μ l), and the absorbing state death (state 5). We proposed a semiparametric time-homogenous multistate Markov model to estimate bidirectional transition rates. Covariate effects (age, gender, ART initiation period, and health facility level) on the transition rates were assessed.

Results: We analyzed 204,289 clinic visits by 63,422 patients. There were 24,325 (38.4%) patients in state 4 ($CD4 < 200$) at ART initiation, and 7,995 (12.6%) deaths occurred by December 2017. The overall mortality rate was 3.9 per 100 person-years. The highest mortality rate of 5.7 per 100 person-years (4,541 deaths) was from state 4 ($CD4 < 200$) compared to other states. Mortality rates decreased with increase in time since ART initiation. Health facility type was the strongest predictor for immune recovery. Provincial or central hospital patients showed a diminishing dose-response effect on immune recovery by state from a hazard ratio (HR) of 8.30 [95% confidence interval (95% CI), 6.64–10.36] (state 4 to 3) to HR of 3.12 (95% CI, 2.54–4.36) (state 2 to 1) compared to primary healthcare facilities. Immune system for male patients was more likely to deteriorate, and they had a 32% increased mortality risk (HR, 1.32; 95% CI, 1.23–1.42) compared to female patients. Elderly patients (45+ years) were more likely to immune deteriorate compared to 25–34 years age group: HR, 1.35; 95% CI, 1.18–1.54; HR, 1.56; 95% CI, 1.34–1.81 and HR, 1.53; 95% CI, 1.32–1.79 for states 1 to 2, state 2 to 3, and states 3 to 4, respectively.

Conclusion: Immune recovery was pronounced among provincial or central hospitals. Male patients with lower CD4 cell counts were at a higher risk of immune deterioration and

mortality, while elderly patients were more likely to immune deteriorate. Early therapeutic interventions when the immune system is relatively stable across gender and age may contain mortality and increase survival outcomes. Interventions which strengthen ART services in primary healthcare facilities are essential.

Keywords: antiretroviral therapy, disease progression, human immunodeficiency virus, mortality, multistate Markov models, Zimbabwe

INTRODUCTION

Over the last 15 years, remarkable strides have been made to tackle the human immunodeficiency virus (HIV) pandemic globally. The Sub-Saharan Africa (SSA) region is disproportionately affected by the pandemic, accounting for more than 50% of people living with HIV (PLHIV) (1, 2). Antiretroviral therapy (ART) treatment remains the backbone of HIV treatment and prevention. Globally, it was estimated that 59% of PLHIV were receiving ART in 2017 (2).

Zimbabwe is one of the countries in SSA affected by HIV infection. The country had an estimated 1.3 million PLHIV and an adult prevalence of 13.3% in 2017 (3). The country's ART coverage was estimated at 84% for adult patients in the same year (3). There has been a reduction in the number of new HIV infections and HIV-related deaths between 2010 and 2016 (4), and this can be attributed to ART as the main driver. ART drugs help boost the immune system of the PLHIV (5), which leads to viral load suppression, and an increase in CD4 cell counts. Both CD4 cell counts and viral load are key prognostic markers in measuring HIV disease progression (6). The World Health Organization (WHO) recommends the use of viral load in monitoring HIV disease progression among ART patients. Viral load suppression has been incorporated as one of the ultimate indicators in the UNAIDS 90-90-90 fast track targets (7). However, over the years, CD4 cell counts have been extensively used as a marker for HIV disease progression.

Disease progression and immune recovery can be evaluated using either time homogenous or time inhomogenous semiparametric multistate Markov models using CD4 cell counts (8). Application of these models in the assessment of HIV progression has been used in the past decades (9), and many studies have recently employed them (9–14). The use of CD4 cell counts as a prognostic marker for HIV disease progression has been well-documented (11, 12, 15–17). However, across studies, there is variation in terms of the number of discrete multistate model states, the cutoff points defining each state, the type of transitions which can either be reversible or irreversible, and the number of transitions to be estimated.

In this new era of “test and treat all” regardless of CD4 cell counts, HIV patients are initiated on ART as soon as they are tested positive. However, this does not rule out the possibility of having patients who present late for HIV diagnosis with an advanced immune deterioration. This put forward the importance of understanding the HIV disease progression across all possible disease states since patients are initiated on ART with different immune stages. Once the HIV-infected patients are initiated on ART, they are still exposed to difference factors which

may still affect their ART adherences. Therefore, it is important to understand the different trajectories that patients follow in HIV disease progression to inform policy makers on possible interventions to be carried out and encourage the patients on the need to adhere on ART for their own improved health outcomes, all in the quest to achieve zero HIV incidences by 2030 (18).

Zimbabwe adopted the WHO recommendation on the decentralization of ART services from higher levels of care to primary healthcare (PHC) facilities to increase ART coverage, access and uptake to those in need, and increase ART patient retention. This approach resulted in lessening the work burden in the higher levels of care (19) through task shifting of HIV management and ART service cascading down to PHC facilities (20–23). As a result, the ART sites in Zimbabwe increased from 282 in 2008 to 1,556 in 2017 (3). However, in primary health care, patient turnaround time is increased, there is lack of resources and skilled personnel, which may compromise the quality of service delivery; consequently, ART outcomes are compromised. Therefore, there is a gap to understand HIV progression patterns among ART patients after ART decentralization since the health facility type that a patient is enrolled in may influence their progression or recovery patterns.

This study aims to describe HIV disease progression and immune recovery implementing the multistate model approach based on CD4 cell counts intermediate states among adult patients on ART in Zimbabwe using patient-level data adjusting for the health facility type. The multistate model provides an in-depth understanding on the general immune deterioration (decrease in CD4 cell count) patterns, immune recovery (increase in CD4 cell count) patterns, and death outcome. Unique to this study is the inclusion of the health facility type in the analysis to account for ART services decentralization effect on transition rates.

MATERIALS AND METHODS

The study was carried out in Zimbabwe, a country with eight provinces and two metropolitans. The country is landlocked bordered by South Africa, Botswana, Mozambique, and Zambia. We conducted a retrospective analysis of cohort data from a sample of PLHIV receiving ART under the Zimbabwe national ART program. We used individual records from 538 health facilities linked to the electronic patient management system (ePMS) (3). From patients attending these health facilities, all routine clinic visits with CD4 count data were used from 1st January 2004 to 31st December 2017 in this analysis.

We included patients aged 15 years and above at ART initiation (baseline) with complete ART initiation dates, gender, and subsequent follow-up information from the dataset. We excluded patients with no information on CD4 cell counts and patients with baseline CD4 measurements only. We also excluded patients who were classified as lost to follow-up or who transferred to other health facilities to reduce the complexity of the multistate model. The patients who were alive at the end of the study were right censored at their last clinic visit before 31st December 2017.

We extracted demographic characteristics such as age (15–24, 25–34, 35–44, and 45+ years), gender, and education level (none, primary, secondary, tertiary). We also extracted data on health facility type (primary health care, district, provincial, or central hospitals) and time of ART initiation (2004–2007, 2008–2012, and 2013–2017). Clinical characteristics included for analysis were regimen type (first line, second line), WHO clinical staging (WHO I/II, WHO III/IV), tuberculosis status (negative, positive, not assessed) from the routine monitoring records of each visit to the clinic by the patients. HIV disease progression was defined using the WHO-based CD4 cell counts bands of HIV-related immunodeficiency: the no significant immunodeficiency ($CD4 \geq 500$ cells/ μ l) as state 1, the mild immunodeficiency ($350 \text{ cells}/\mu\text{l} \leq CD4 < 500 \text{ cells}/\mu\text{l}$) as state 2, the advanced immunodeficiency ($200 \text{ cells}/\mu\text{l} \leq CD4 < 350 \text{ cells}/\mu\text{l}$) as state 3, the severe immunodeficiency ($CD4 < 200 \text{ cells}/\mu\text{l}$) as state 4, and the absorbing state death as state 5.

Statistical Analysis

The patient's retrieved data were cleaned and managed in Stata 15.1 (24). All the preliminary analyses were conducted in Stata software. After data argumentation, the five-staged semiparametric time homogenous multistate Markov model was fitted in R software (25) using the *msm* package. We fitted a model with reversible

transitions (26); therefore, states 1–4 were transient states, while state 5 was non-transient as depicted in Figure 1.

The fitted model was adjusted for demographic factors (sex, health facility type, and ART initiation period). The semiparametric time homogenous multistate Markov estimated transition intensities (transition rates or hazard rates), transition probabilities (survival function) between the defined CD4 cell count states, mean sojourn time, and the total length of stay in states before making any transitions. Time-varying mortality rates were estimated using time inhomogenous model, which assumes that the transitions change with time, and this reflect the reality in infectious disease progression models; hence, this is normally the preferred model. These models usually assume the Markovian process that the transition intensity depends only on the current time and state occupied, i.e., it is independent of the previous transitions. In other terms, these models were assumed to have “memory loss.” We used the *markovchain* library in R to test if the Markov assumption is satisfied. The null hypothesis of this test is that the Markov property holds. We randomly selected patients' sequences to be tested and we obtained $p > 0.05$; therefore, we failed to reject the null hypothesis that the sequences are Markovian.

The Multistate Markov Model

A multistate process is a stochastic process $[X(t), t \in T]$ with finite state space $S = \{1, 2, 3, 4, 5\}$ where $T = [0, \tau]$ $\tau < \infty$ is the period of observation (27). These models can either be discrete-time Markov chains (transitions occur at fixed points in time) or continuous-time Markov chains (transitions occur at any point in time) (28). For a continuous time Markovian process, the transition intensity (instantaneous incidence rate), $\lambda_{jk}(t)$, of a patient from state $X(t) = j$ at time t to state k at time

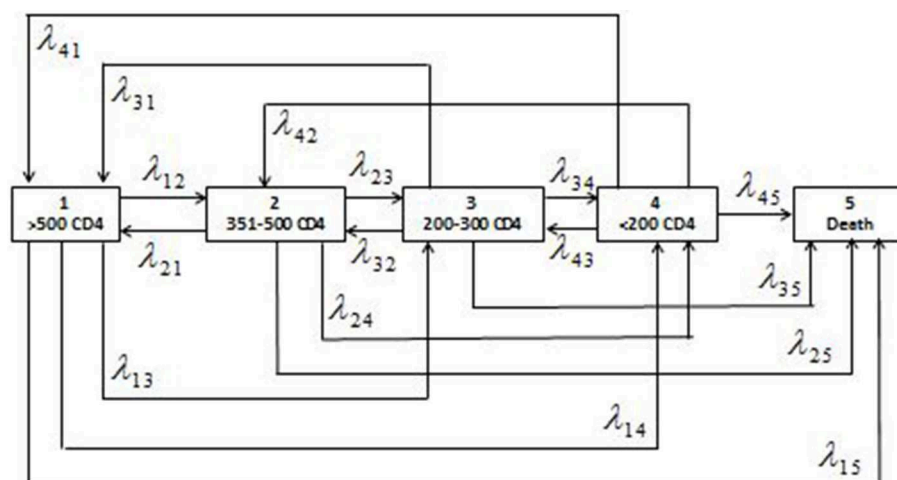


FIGURE 1 | Schematic presentation of the five-staged reversible multistate Markov model with the states of HIV defined as the ranges of CD4 cell counts (cells/ μ l) and the corresponding individual transition intensities (λ_{jk} where $j = 1, 2, 3, 4$ and $k = 1, 2, 3, 4, 5$).

$t + \delta t$ is defined as:

$$\begin{aligned}\lambda_{jk}(t) &= \frac{d}{dt} p_{jk}|_{t=0} = \lim_{\delta t \rightarrow 0} \frac{p_{jk}(t, t + \delta t)}{\delta t} \\ &= \lim_{\delta t \rightarrow 0} \frac{p_{jk}\{X(t + \delta t) = k | X(t) = j\}}{\delta t}\end{aligned}\quad (1)$$

where p_{jk} is the probability from state j to k , δt is the change in time. For example, in our case, the transition intensities in Equation (1) form the (j, k) entry of the transition rate matrix, denoted by $Q(t)$:

$$Q(t) = \begin{pmatrix} -\lambda_{1\cdot} & \lambda_{12} & \lambda_{13} & \lambda_{14} & \lambda_{15} \\ \lambda_{21} & -\lambda_{2\cdot} & \lambda_{23} & \lambda_{24} & \lambda_{25} \\ \lambda_{31} & \lambda_{32} & -\lambda_{3\cdot} & \lambda_{34} & \lambda_{35} \\ \lambda_{41} & \lambda_{42} & \lambda_{43} & -\lambda_{4\cdot} & \lambda_{45} \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}$$

whose rows sum to 0, that is $\sum_{k \in S} \lambda_{jk} = 0$ for all j , and the diagonal entries (interpreted as changes in transition probability) are defined by conversion as $\lambda_{jj}(t) = \lambda_j = -\sum_{j \neq k} \lambda_{jk}(t)$ for all $j \in S$.

These transition intensities under the Markov process can be calculated as the product of the flow rate μ_j and the conditional probability of a transition to state k , given that a transition is made $j \neq k$ (ρ_{jk}). From the $Q(t)$ values, we can calculate the probability that the next state after state j is state k , for each j and k calculated as $(p_{jk} = -\lambda_{jk}/\lambda_j)$. Once the transition intensity matrix is obtained, the transition probability matrix can be obtained using the Chapman–Kolmogorov forward differential equations. The detailed explanation is provided in **Appendix**. The probability matrix can be computed from the estimated transition intensities using $P(t) = \exp[Q(t)]$ where $[P(t)]$ is the transition probability matrix defined as:

$$P(t) = \exp[Q(t)] = \begin{pmatrix} \pi_{11} & \pi_{12} & \pi_{14} & \pi_{14} & \pi_{15} \\ \pi_{21} & \pi_{22} & \pi_{23} & \pi_{24} & \pi_{25} \\ \pi_{31} & \pi_{32} & \pi_{33} & \pi_{34} & \pi_{35} \\ \pi_{41} & \pi_{42} & \pi_{43} & \pi_{44} & \pi_{45} \\ 0 & 0 & 0 & 0 & 1 \end{pmatrix}$$

The probability (π_{jk}) that a patient in state j at time t will be in state k at time $t + \delta t$ is given by:

$$\pi_{jk}(s, t) = P\{X(t + \delta t) = k | X(s) = j\} \quad (2)$$

where, $t \in T$, and $s \leq t$. These transition probabilities satisfy the following conditions:

- (i) $\pi_{jk}(t + s) = \sum_{r \in S} \pi_{jr}(t) \pi_{rk}(s)$ for all $t \geq 0, s \geq 0$ and $j, k \in S$;
- (ii) $\sum_{k \in S} \pi_{jk}(t) = 1$ for all $j \in S$ and $t \geq 0$ and
- (iii) $\pi_{jk}(t) \geq 0$ for all $j, k \in S$ and $t \geq 0$.

The maximum likelihood procedures (8, 29) can be used to estimate these transition intensities as a product of probabilities of transition between observed states, overall individuals $i =$

1, 2, ..., M and observation times r which are observed n times, as shown below:

$$L(Q) = \prod_{i=1}^M \prod_{r=1}^{n_i-1} L_{i,j} = \prod_{i,r} \pi_{s(t_{ir})s(t_{i,r+1})} (t_{i,r+1} - t_{ir}) \quad (3)$$

Each component $L_{i,r}$ is the entry of the transition probability matrix and the $s(t_{ir})^{th}$ row and the $s(t_{i,r+1})^{th}$ column, evaluated at a pair of consecutive observed state at time t_r and t_{r+1} . This likelihood function, $L(Q)$, is maximum in terms of $\log(\lambda_{jk})$ to compute the estimates of λ_{jk} , using the standard optimization algorithms which make use of the derivatives of the likelihood. This likelihood assumes that the sampling times are ignorable (non-informative).

The Total Length of Stay and Mean Sojourn Time

The mean sojourn time is defined as the mean expected holding time or the average time a patient spends in each state in a single stay before making any transition to other states. The average length of stay in a single state before making any transitions to either lower or higher CD4 cell count states is estimated by a negative inverse of the j^{th} diagonal entry of $Q(t)$, that is $(-1/\lambda_{jj})$. The total length of stay, L_k , in each of the four states excluding death is defined as the anticipated exposure time spent by an individual in each state during the study period before death. This time is estimated as time spent in state k between two successive time points (t_1, t_2) given by:

$$L_k = \int_{t_1}^{t_2} P_{jk}(t) dt \quad (4)$$

where j is the initial state which usually is equal to one and is useful in the presence of reversible transitions.

Semiparametric Regression Model

To adjust for the effects of the covariates on the transition rates, we proposed a semiparametric Cox proportional hazard regression model. The transition rates depend on the covariates vector matrix $\mathbf{Z}$, that is,

$$\lambda_{jk}[t|\mathbf{Z}(t)] = \lambda_{jk0} \exp[\beta_{jk}^T \mathbf{Z}(t)] \quad (5)$$

where $\beta_{jk} = (\beta_{jk1}, \beta_{jk2}, \dots, \beta_{jkn})^T$ is a vector of the regression coefficients associated with vector $\mathbf{Z}(t)$ for the transition from state j to state k . The baseline hazard function is denoted by λ_{jk0} . In this study, we assumed time-independent covariates. Parameter estimation was based on the maximization of the hazard function (the transitional intensities). We fitted eight models in total [starting with a no covariates (unadjusted) model, followed by four univariate models and three with at least two covariates]. The additional covariates after the univariate models were added sequentially and only covariates without missing information were considered in the adjusted model.

Model Diagnostics

Selection of model of best fit with covariates was performed using a likelihood ratio test define as $-2\ln(L_s(\hat{\theta})/L_g(\hat{\theta}))$, where $L_s(\hat{\theta})$ is the likelihood of the reduced (no covariate) model $L_g(\hat{\theta})$ and is the likelihood of the full (with covariates) model, which follows a chi-square distribution with n degrees of freedom. Significance was set at 5% level of significance. The aim was to get a parsimonious model that explains best the model.

Ethical Considerations

We used data with no personal identification; however, we used the individual unique identifier for the analysis. We sort permission to use the dataset from the Ministry of Health and Child Care, Zimbabwe, and this study was granted ethical approval by the University of Witwatersrand's Human Research Ethics Committee (Medical) (Clearance Certificate No. M170673).

RESULTS

Descriptive Characteristics of Patients and Total Transitions Observed

From the 538 clinics, a total of 390,771 patients were seen between 1st January 2004 and 31st December 2017. Of these total patients, we excluded 197,618 (50.6%) patients with no CD4 cell counts and 129,731 (33.2%) patients with one CD4 cell count measurement. The remaining 63,422 patients of whom 65.4% were female contributed 205,711 years of total analysis time at risk and under observation from 491 health facilities form part of the analysis. The descriptive characteristics are shown in **Table 1**. Most patients were enrolled in district or mission hospitals (45.7%) and from facilities in the rural areas (74.7%). There was an overwhelming significant difference in the baseline characteristics by CD4 count states in this cohort, $p < 0.05$. The median follow-up time was 2.63 [interquartile range (IQR), 1.14–4.94] years, median duration between visits was 0.63 (IQR, 0.25–1.88) years, and the median number of visit was 3 (IQR, 2–4) visits. Most patients were classified in WHO clinical stage III/IV (58.6%, $n = 36,626$).

Observed Transitions Between States

As displayed in **Table 2**, the 63,422 patients contributed 140,867 transitions between the follow-up period of which 12.6% ($n = 7,995$) were mortalities. The highest contribution of the observed transitions of 114,561 (81.3%) came from those patients who remained in the same state over time without making any transition to other states. At baseline, majority of the patients were in state 4 ($CD4 < 200$) (38.4%, $n = 24,325$) and state 3 ($200 \leq CD4 < 350$) (29.1%, $n = 18,437$). Similarly, this was the picture at the end of the study; however, relative to baseline numbers, there was a non-significant decline in the total number of patients in state 3 ($200 \leq CD4 < 350$) ($p = 0.2621$), while a significant decline was observed in state 4 ($p = 0.0478$). Majority of the deaths at the end of the study came from state 4 ($CD4 < 200$)

and state 3 [$200 \leq CD4 < 350$], which accounted for 27.6% ($n = 2,208$) and 56.8% ($n = 4,541$), respectively.

Immune recovery is observed when a patient makes a transition from lower CD4 cell counts states to higher CD4 cell counts states (particularly $350 \leq CD4 < 500$ state to $CD4 \geq 500$ state, $200 \leq CD4 < 350$ state to $350 \leq CD4 < 500$ state and $CD4 < 200$ state 4 to $200 \leq CD4 < 350$ state), while immune deterioration is experienced if a patient makes a transition from higher CD4 cell count states to lower CD4 cell count states (particularly $CD4 \geq 500$ state to $350 \leq CD4 < 500$ state, $350 \leq CD4 < 500$ state to $200 \leq CD4 < 350$ state, and $200 \leq CD4 < 350$ state to $CD4 < 200$ state). There were more transitions ($n = 8,031$) from lower CD4 cell counts states to higher CD4 cell counts states (state 2 to 1 = 2,493, state 3 to 2 = 2,606, and state 4 to 3 = 2,932) as compared to higher CD4 cell counts states to lower CD4 cell counts states transitions of the corresponding reversible transitions ($n = 5,425$). This result is an indication of immune recovery in this cohort.

Time Homogenous Transition Rates and Probabilities

The transition rates and probabilities were estimated using the time-homogenous multistate Markov model incorporating the semiparametric Cox survival function, and results are displayed in **Table 3**. Generally, there were higher transition rates from lower CD4 cell count states to lower CD4 cell counts states compared to the reversible corresponding transitions. Results show that moving from state 2 ($350 \leq CD4 < 500$) to state 1 ($CD4 \geq 500$) was 1.49 (0.16085/0.10783) times more likely than moving from state 1 ($CD4 \geq 500$) to 2 ($350 \leq CD4 < 500$); hence, a high probability of immune recovery. Patients in state 2 ($350 \leq CD4 < 500$) were 1.38 (0.11264/0.08188) times more likely to move to state 3 ($200 \leq CD4 < 350$) compared to moving from state 3 ($200 \leq CD4 < 350$) to state 2 ($350 \leq CD4 < 500$). This finding was a clear indication of immune deterioration between the two states. Transition rate from state 4 ($CD4 < 200$) to state 3 ($200 \leq CD4 < 350$) was 1.02 (0.05261/0.05147) times more likely compared to the transition from state 3 ($200 \leq CD4 < 350$) to state 4 ($CD4 < 200$) indicating immune recovery from state 4 ($CD4 < 200$), but this was not statistically significant.

We estimated the probabilities for which state is next after the currently occupied state. The results show that an individual in state 1 ($CD4 \geq 500$) had a probability of 41.2% to move to state 2 ($350 \leq CD4 < 500$); an individual in state 2 ($350 \leq CD4 < 500$) had a 45.7% probability to move to state 1 ($CD4 \geq 500$); an individual in state 3 ($200 \leq CD4 < 350$) had 35.3% probability to move to state 1 ($CD4 \geq 500$); and an individual in state 4 ($CD4 < 200$) had 28.1% probability of death. The cumulative probability of moving from higher CD4 cell counts states to lower CD4 cell counts states increased over time. The probability of moving from state 1 ($CD4 \geq 500$) to state 2 ($350 \leq CD4 < 500$) changed from 8.3% at 1 year to 16.2% at 6 years; state 2 ($350 \leq CD4 < 500$) to state 3 ($200 \leq CD4 < 350$) transition changed from 9.2% at 1 year to 20.2% at 6 years and state 3 ($200 \leq CD4 < 350$) to state 4 ($CD4 < 200$) transition changed from 4.7% at 1 year to 15.3% at 6 years. Similarly, the probabilities of moving

TABLE 1 | Sociodemographic and clinical baseline characteristics at antiretroviral therapy (ART) initiation of all study participants from the Zimbabwe national ART program, 2004–2017.

Variables	Total (%)	Baseline CD4 states for patients				Chi-square p-value
		<200	200 ≤ CD4 < 350	350 ≤ CD4 < 500	≥500	
Health facility type						
Primary health care	31,150 (49.1)	4,989 (44.4)	4,801 (51.0)	9,223 (50.0)	12,137 (49.9)	<0.0001
District/mission hospital	28,971 (45.7)	5,465 (48.6)	4,141 (44.0)	8,401 (45.6)	10,964 (45.1)	
Provincial/central hospital	3 301 (5.2)	790 (7.0)	474 (5.0)	813 (4.4)	1,224 (50.3)	
Health facility site						
Rural	47,348 (74.7)	8,401 (74.7)	7,256 (77.1)	14,109 (76.5)	17,582 (72.3)	<0.0001
Urban	16,074 (25.3)	2,843 (25.3)	2,160 (22.9)	4,328 (23.5)	6,743 (27.7)	
Age categories (years)						
15–24	3,960 (6.2)	933 (8.3)	671 (7.1)	1,162 (6.3)	1,194 (4.9)	<0.0001
25–34	17,352 (27.4)	3,347 (29.8)	2,757 (29.3)	5,158 (28.0)	6,090 (25.0)	
35–44	4,060 (36.1)	3,447 (36.6)	6,843 (37.1)	9,842 (40.5)	24,192 (38.1)	
45 and above	17,918 (28.3)	2,904 (25.8)	2,541 (27.0)	5,274 (28.6)	7,199 (29.6)	
Sex						
Female	41,505 (65.4)	9,068 (80.7)	6,508 (69.1)	12,027 (65.2)	13,902 (57.2)	<0.0001
Male	21,917 (34.6)	2,176 (19.3)	2,908 (30.9)	6,410 (34.8)	10,423 (42.8)	
Educational level*						
None	1,499 (4.4)	266 (4.7)	250 (4.9)	445 (4.5)	538 (4.1)	<0.027
Primary	11,804 (34.9)	1,996 (35.2)	1,782 (34.9)	3,501 (35.3)	4,525 (34.4)	
Secondary	18,956 (56.0)	3,124 (55.0)	2,843 (55.6)	5,552 (56.0)	7,437 (56.5)	
Tertiary	1,598 (4.7)	290 (5.1)	263 (4.6)	419 (4.2)	653 (5.0)	
Marital status**						
Single	7,604 (12.4)	1,276 (11.8)	1,144 (12.5)	2,095 (11.7)	3,089 (13.1)	<0.0001
Married	37,993 (62.0)	6,580 (60.7)	5,680 (62.3)	11,460 (64.2)	14,273 (60.7)	
Widowed	11,243 (18.3)	2,250 (20.7)	1,643 (18.0)	3,083 (17.3)	4,267 (18.2)	
Divorced	4,494 (7.3)	741 (6.8)	655 (7.1)	1,216 (6.8)	1,882 (8.0)	
Functional status***						
Working	59,519 (94.5)	10,685 (95.5)	8,963 (94.7)	17,373 (94.9)	22,598 (93.6)	<0.0001
Ambulatory	3,270 (5.2)	494 (4.4)	477 (5.1)	877 (4.8)	1,422 (5.9)	
Bedridden	193 (0.3)	11 (0.1)	21 (0.2)	43 (0.2)	118 (0.5)	
First line regimen	61,654 (97.2)	11,056 (98.3)	9,264 (98.4)	18,082 (98.1)	23,252 (95.6)	
D4T (30) + 3TC + NVP	389 (0.6)	11 (0.0)	18 (0.2)	91 (0.5)	269 (1.1)	<0.0001
D4T (30) + #TC + EFV	11 (0.0)	1 (0.0)	1 (0.0)	3 (0.0)	6 (0.0)	
AZT + 3TC + NVP	486 (0.8)	91 (0.8)	59 (0.6)	150 (0.8)	186 (0.8)	
AZT + 3TC + EFT	82 (0.1)	13 (0.1)	10 (0.1)	17 (0.1)	42 (0.2)	
TDF + 3TC + NVP	2,919 (4.6)	303 (2.7)	255 (2.7)	907 (4.9)	1,454 (6.0)	
TDF + 3TC + EFV	57,085 (90.0)	10,358 (92.1)	8,841 (93.9)	16,807 (91.2)	21,079 (86.7)	
Other first lines	682 (1.1)	279 (2.5)	80 (0.9)	107 (0.6)	216 (0.9)	
Second line regimen	1,768 (2.8)	188 (1.7)	152 (1.6)	355 (1.9)	1,073 (4.4)	
AZT + 3TC + ATV/r	560 (0.9)	374 (1.5)	107 (0.6)	41 (0.4)	38 (0.3)	<0.0001
AZT + 3TC + LPV/r	84 (0.1)	48 (0.2)	15 (0.1)	7 (0.1)	14 (0.1)	
TDF + 3TC + ATV/r	563 (0.9)	275 (1.1)	131 (0.7)	70 (0.7)	87 (0.8)	
TDF + 3TC + LPV/r	89 (0.1)	49 (0.2)	21 (0.1)	7 (0.1)	12 (0.1)	
ABC + DDI + ATV/r	73 (1)	50 (0.2)	13 (0.1)	7 (0.1)	3 (0.0)	
ABC + DDI + LPV/r	389 (0.6)	273 (1.1)	69 (0.4)	19 (0.2)	37 (0.3)	
Other second lines	683 (1.1)	220 (0.9)	106 (0.6)	81 (0.9)	276 (2.5)	

(Continued)

TABLE 1 | Continued

Variables	Total (%)	Baseline CD4 states for patients				Chi-square <i>p</i> -value
		<200	200 ≤ CD4 < 350	350 ≤ CD4 < 500	≥500	
Tuberculosis status****						
Negative	54,474 (87.0)	9,869 (88.6)	8,172 (87.7)	15,830 (86.9)	20,603 (86.0)	<0.0001
Positive	618 (1.0)	48 (0.4)	56 (0.6)	140 (0.8)	374 (1.6)	
Not assessed	7,524 (12.0)	1,220 (11.0)	1,090 (11.7)	2,240 (12.3)	2,974 (12.4)	
WHO clinical staging*****						
I/II	25,891 (41.4)	4,680 (42.0)	4,277 (46.0)	8,322 (45.9)	8,612 (36.0)	<0.0001
III/IV	36,626 (58.6)	6,460 (58.0)	5,012 (54.0)	9,826 (54.1)	15,328 (63.0)	

*The denominator of the proportions for this variable is 33,857.

**The denominator of the proportions for this variable is 61,334.

***The denominator of the proportions for this variable is 62,982.

****The denominator of the proportions for this variable is 62,616.

*****The denominator of the proportions for this variable is 62,517.

TABLE 2 | Number of the total observed patients' transitions between the five states, the total number of patients at antiretroviral therapy (ART) initiation ("beginning state") and the total number of patients at 31st December 2017 (and the "end state") among ART patients in Zimbabwe national ART from 2004 to 2017.

From	To	State 1 (> 500 cell/ml)	State 2 (351–500 cells/ml)	State 3 (200–350 cells/ml)	State 4 (<200 cells/ml)	State 5 (Death)	Total transitions
A summary of the total observed patients' transition between the five states							
State 1 (>500 cell/ml)		24,709	1,971	1,639	1,396	606	30,321
State 2 (351–500 cells/ml)		2,493	17,169	1,691	1,134	640	23,127
State 3 (200–350 cells/ml)		3,459	2,606	28,645	1,763	2,208	38,681
State 4 (<200 cells/ml)		2,879	2,343	2,932	36,043	4,541	48,738
Total		33,540	24,089	34,907	40,336	7,995	140,867
Total number of patients by CD4 state at ART initiation and the end of follow-up (denominator = 63,422)							
Beginning state n (%)		11,244 (17.7)	9,416 (14.9)	18,437 (29.1)	24,325 (38.4)	–	63,422
End state n (%)		14,463 (22.8)	10,378 (16.4)	14,663 (23.1)	15,923 (25.1)	7,995 (12.61)	55,427 (alive) 7,995 (dead)

from lower CD4 cell counts states to higher CD4 cell counts states increased over time. The probability of moving from state 2 ($350 \leq \text{CD4} < 500$) to state 1 ($\text{CD4} \geq 500$) changed from 13.6% at 1 year to 26.2% at 6 years; state 3 ($200 \leq \text{CD4} < 350$) to state 2 ($350 \leq \text{CD4} < 500$) transition changed from 6.8% at 1 year to 14.7% at 6 years and state 4 ($\text{CD4} < 200$) to state 3 ($200 \leq \text{CD4} < 350$) transition changed from 4.5% at 1 year to 14.5% at 6 years.

Time Inhomogenous Mortality Rates

The transition rates for mortality were also estimated, and results are shown in **Table 4**. The overall mortality rate in this cohort was 3.9 (95% CI, 3.8–4.0) per 100 person-year. Stratifying by the CD4 states, the mortality rates per 100 person-years increased with a decrease in CD4 cell counts: state 1 ($\text{CD4} \geq 500$) (rate

= 1.8; 95% CI, 1.1–2.1), state 2 ($350 \leq \text{CD4} < 500$) (rate = 2.7; 95% CI, 2.4–3.1), state 3 ($200 \leq \text{CD4} < 350$) (rate = 3.3; 95% CI, 3.1–3.8), and state 4 ($\text{CD4} < 200$) (rate = 5.9; 95% CI, 5.7–6.1). Hence, the mortality burden was highest in state 4 ($\text{CD4} < 200$) compared to other states, and these mortality rates were significantly different (log rank test $p < 0.001$). The Kaplan–Meier curve further confirmed the survival probabilities of this cohort stratified by state, that mortality risk increases with a decrease in CD4 cell count (**Figure 2**). However, the fundamental difference was between the mortality in state 3 ($200 \leq \text{CD4} < 350$) and state 4 ($\text{CD4} < 200$) vs. the mortality in state 1 ($\text{CD4} \geq 500$), and state 2 ($350 \leq \text{CD4} < 500$).

In general, the time-varying mortality rates decrease with an increase in time since ART. The cohort experienced high

TABLE 3 | Estimates of transition rates (intensities) per person-years and probability matrices and 95% confidence intervals (CI) for the time-homogenous multistate Markov model among antiretroviral therapy (ART) patients in Zimbabwe national ART from 2004 to 2017.

Transitions	Crude transition intensity (95% CI)	Covariates adjusted transition intensity (95% CI)	Transition probabilities (95% CI)	The probability that each state is next
1 → 1	−0.26548 (−0.273 to −0.258)	−0.26950 (−0.278 to −0.261)	0.779 (0.772 to 0.784)	0
1 → 2	0.10928 (0.104 to 0.115)	0.10783 (0.102 to 0.114)	0.083 (0.08 to 0.086)	0.41162 (0.397 to 0.427)
1 → 3	0.07823 (0.074 to 0.083)	0.08184 (0.0772 to 0.087)	0.067 (0.063 to 0.070)	0.29468 (0.280 to 0.309)
1 → 4	0.05980 (0.056 to 0.063)	0.06313 (0.059 to 0.067)	0.052 (0.050 to 0.055)	0.22526 (0.214 to 0.238)
1 → 5	0.01817 (0.016 to 0.021)	0.01669 (0.014 to 0.019)	0.020 (0.018 to 0.022)	0.06844 (0.061 to 0.077)
2 → 1	0.18073 (0.173 to 0.189)	0.16085 (0.153 to 0.169)	0.136 (0.132 to 0.142)	0.45731 (0.443 to 0.472)
2 → 2	−0.39520 (−0.406 to −0.384)	−0.37098 (−0.382 to −0.360)	0.686 (0.679 to 0.692)	0
2 → 3	0.11767 (0.112 to 0.124)	0.11264 (0.106 to 0.119)	0.092 (0.088 to 0.096)	0.29775 (0.285 to 0.312)
2 → 4	0.06960 (0.065 to 0.074)	0.07160 (0.067 to 0.077)	0.058 (0.055 to 0.061)	0.17613 (0.165 to 0.186)
2 → 5	0.02719 (0.024 to 0.031)	0.02589 (0.023 to 0.029)	0.027 (0.025 to 0.030)	0.06881 (0.061 to 0.077)
3 → 1	0.09501 (0.091 to 0.099)	0.08428 (0.080 to 0.088)	0.080 (0.077 to 0.083)	0.35266 (0.340 to 0.365)
3 → 2	0.08723 (0.083 to 0.091)	0.08188 (0.078 to 0.086)	0.068 (0.065 to 0.071)	0.32376 (0.312 to 0.336)
3 → 3	−0.26942 (−0.276 to −0.263)	−0.24886 (−0.256 to −0.243)	0.772 (0.768 to 0.776)	0
3 → 4	0.05397 (0.051 to 0.057)	0.05147 (0.049 to 0.055)	0.047 (0.045 to 0.045)	0.20032 (0.190 to 0.210)
3 → 5	0.03321 (0.031 to 0.035)	0.03122 (0.029 to 0.034)	0.032 (0.031 to 0.034)	0.12325 (0.116 to 0.131)
4 → 1	0.04814 (0.046 to 0.051)	0.04363 (0.041 to 0.046)	0.044 (0.042 to 0.045)	0.22794 (0.218 to 0.238)
4 → 2	0.04584 (0.044 to 0.048)	0.04360 (0.041 to 0.046)	0.038 (0.036 to 0.040)	0.21708 (0.207 to 0.228)
4 → 3	0.05793 (0.055 to 0.061)	0.05261 (0.050 to 0.055)	0.049 (0.048 to 0.051)	0.27430 (0.263 to 0.285)
4 → 4	−0.21118 (−0.215 to −0.207)	−0.19535 (−0.200 to −0.191)	0.814 (0.810 to 0.817)	0
4 → 5	0.05928 (0.057 to 0.061)	0.05551 (0.053 to 0.058)	0.055 (0.053 to 0.057)	0.28069 (0.272 to 0.290)

mortality rates in the first year of ART initiation averaging at 3.5 (95% CI, 3.4–3.7) per 100 person-years. There was a sharp drop (seven-fold) in mortality rate from first to the second year [hazard ratio (HR) = 6.95(0.3512/0.0505); 95% CI, 6.78–7.14]. Gradually, the mortality rates further decrease over time by the end of the follow-up period. Mortality patterns across states followed this similar trend to the overall pattern. In the first 3 years, mortality rates had an inverse relationship with the CD4 cell counts, and there was an overwhelming difference in these rates between the states.

This study forecasted the total length spent in each of the CD4 states by HIV patients on ART before death and estimated the mean sojourn (holding) time for each state as shown in **Table 5**. The results show that, when an individual enters state 4 (CD4 < 200), the time he or she spends in this state for a single stay before moving to another state was estimated to be 4.74 (4.64–4.83) years on average. This result could be linked to the time taken by a patient in this state to respond to ART and subsequently boost immunity since this is the worst state in our HIV progression model. Since the holding times for all states are relatively long, therefore, HIV disease progression in this cohort was relatively slow.

It was also of interest to forecast the total length of stay for states 1–4 before death, which is and quite informative in the presence of reversible transitions. The results show that an individual will stay 11.3 years in state 1 (CD4 ≥ 500), 5.5 years in state 2 (350 ≤ CD4 < 500), 7.2 years in state 3 (200 ≤ CD4 < 350) and 6.9 years in state 4 (CD4 < 200) before death. In general,

these results reflected that an HIV patient on ART is expected to spend more time in the highest CD4 cell counts state compared to other states.

Covariates Effects on Immune Recovery and Deterioration Transition Rates

We further included time-independent covariates (health facility level, ART initiation period, and sex) and age in the multistate Cox proportional hazard model, and the results are displayed in **Table 6**. This model was a better fit using a likelihood ratio test compared to the model without covariates ($p < 0.001$). Adjusting for other covariates, the higher levels of health facility are more likely to have patients moved from lower to higher CD4 cell count states. Provincial or central hospital individuals were predominantly more likely to move from state 4 (CD4 < 200) to state 3 (200 ≤ CD4 < 350) (HR = 8.30; 95% CI, 6.64–10.36) followed by the state 3 (200 ≤ CD4 < 350) to state 2 (350 ≤ CD4 < 500) transition (HR = 8.04; 95% CI, 6.41–10.10) compared to PHC patients. This means that patients at the provincial or central hospital had a high probability of immune deterioration once they are on ART compared to PHC patients. For district or mission hospital patients, state 3 (200 ≤ CD4 < 350) to state 2 (350 ≤ CD4 < 500) was the predominant transition (HR = 4.41; 95% CI, 3.96–4.87), followed by the state 4 (CD4 < 200) to state 3 (200 ≤ CD4 < 350) transition (HR = 3.97; 95% CI, 3.61–4.37), compared to PHC patients. Similarly, this was a positive indication of immune recovery for patients in district or mission hospital compared to PHC patients.

TABLE 4 | Estimated time-varying mortality rates per person-years and 95% confidence intervals for the time-inhomogenous multistate Markov model among ART patients in Zimbabwe national ART from 2004 to 2017.

Time period	Time-varying transition rates (95% confidence interval)					Log rank p-value
	Overall mortality rate	State 1 to 5	State 2 to 5	State 3 to 5	State 4 to 5	
0 < time ≤ 1	0.3512 (0.3368–0.3661)	0.1006 (0.0863–0.1172)	0.1490 (0.1292–0.1719)	0.2790 (0.2534–0.3071)	0.7609 (0.7225–0.8013)	<0.0001
1 < time ≤ 2	0.0505 (0.0472–0.0540)	0.0186 (0.0147–0.0234)	0.0291 (0.0239–0.0355)	0.0383 (0.0330–0.0444)	0.1010 (0.0925–0.1102)	<0.0001
2 < time ≤ 3	0.0591 (0.0563–0.0621)	0.0245 (0.0206–0.0290)	0.0287 (0.0244–0.0338)	0.0687 (0.0632–0.0747)	0.0885 (0.0825–0.0950)	<0.0001
3 < time ≤ 4	0.0416 (0.0392–0.0441)	0.0200 (0.0162–0.0247)	0.0186 (0.0148–0.0233)	0.0441 (0.0400–0.0486)	0.0581 (0.0535–0.0631)	<0.0001
4 < time ≤ 5	0.0312 (0.0291–0.0334)	0.0135 (0.010–0.0179)	0.0162 (0.0121–0.0217)	0.0312 (0.0277–0.0351)	0.0412 (0.0375–0.0453)	<0.0001
5 < time ≤ 6	0.0221 (0.0204–0.0240)	0.0076 (0.0053–0.0109)	0.0133 (0.0099–0.0180)	0.0214 (0.0185–0.0247)	0.0310 (0.0278–0.0346)	<0.0001
6 < time ≤ 7	0.0160 (0.0145–0.0178)	0.0079 (0.0057–0.0111)	0.0092 (0.0061–0.0137)	0.0160 (0.0133–0.0193)	0.0215 (0.0188–0.0247)	<0.0001
7 < time ≤ 8	0.0112 (0.0097–0.0128)	0.0041 (0.0025–0.0066)	0.0052 (0.0029–0.0095)	0.0117 (0.0088–0.0155)	0.0159 (0.0134–0.0189)	<0.0001
8 < time ≤ 9	0.0108 (0.0092–0.0128)	0.0050 (0.0030–0.0083)	0.0044 (0.0021–0.0093)	0.0132 (0.0094–0.0186)	0.0142 (0.0116–0.0175)	<0.0001
9 < time ≤ 10	0.0070 (0.0055–0.0089)	0.0014 (0.0005–0.0044)	0.0019 (0.0048–0.0076)	0.0082 (0.0049–0.0136)	0.0103 (0.0077–0.0138)	0.0001
10 < time ≤ 11	0.0066 (0.0050–0.0088)	0.0021 (0.0008–0.0056)	0.0021 (0.0005–0.0084)	0.0072 (0.0036–0.0145)	0.0104 (0.0074–0.0147)	0.0005
11 < time ≤ 12	0.0034 (0.0020–0.0058)	0.0015 (0.0004–0.0061)	0.0046 (0.0012–0.0184)	0.0066 (0.0025–0.0176)	0.0033 (0.0014–0.0080)	0.2154
12 < time ≤ 13	0.0030 (0.0011–0.0081)	0.0058 (0.0014–0.0230)	0	0.0031 (0.0004–0.0220)	0.0021 (0.0003–0.0151)	0.7305

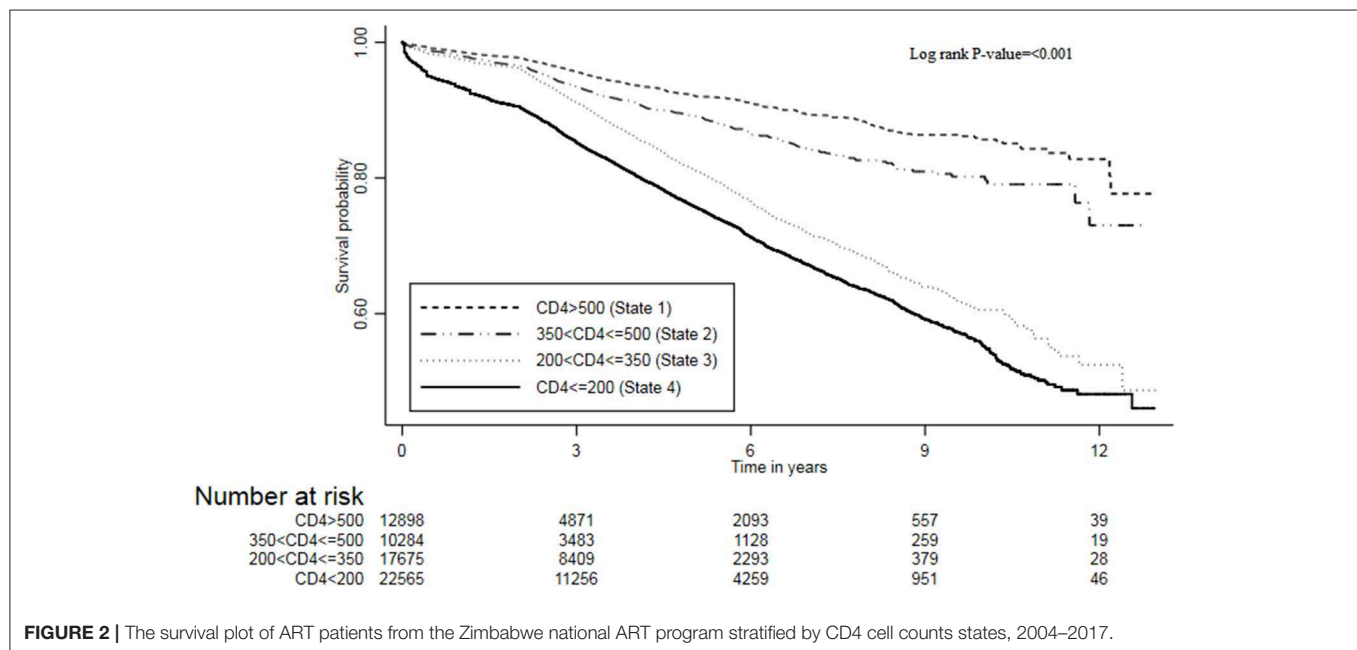
**FIGURE 2 |** The survival plot of ART patients from the Zimbabwe national ART program stratified by CD4 cell counts states, 2004–2017.

TABLE 5 | Estimates of mean sojourn time and the total length of stay for the time-homogenous multistate Markov model among antiretroviral therapy (ART) patients in Zimbabwe national ART from 2004 to 2017.

States	Mean sojourn time		The total length of stay (years)
	Estimate (95% CI) (years)	Standard error	
State 1 (>500 cell/ μ l)	3.77 (3.66–3.88)	0.054	11.33
State 2 (351–500 cells/ μ l)	2.53 (2.46–2.60)	0.036	5.51
State 3 (200–350 cells/ μ l)	3.71 (3.63–3.80)	0.042	7.17
State 4 (<200 cells/ μ l)	4.74 (4.64–4.82)	0.047	6.86

Adjusting for other covariates, age was generally associated with immune deterioration transitions ($CD4 \geq 500$ state to $350 \leq CD4 < 500$ state, $350 \leq CD4 < 500$ state to $200 \leq CD4 < 350$ state, and $200 \leq CD4 < 350$ state to $CD4 < 200$ state). Compared to the 25–34 years age group, there was no significant difference in immune deterioration transitions. However, the results showed that the older the patient, the more likely he or she is to become immune deteriorated. This result was observed in elderly patients (45+ years) with a pronounced risk of immune deterioration across age groups. With reference to 25–34 years age group, both the 35–44 years and the 45+ years age groups were predominantly more likely to move from state 2 ($350 \leq CD4 < 500$) to state 3 ($200 \leq CD4 < 350$) transition (HR = 1.31; 95% CI, 1.14–1.51) and (HR = 1.56; 95% CI, 1.34–1.81), respectively. Holding other covariates constant, sex was significantly associated with immune deterioration transitions. Male patients had an increased risk of immune deterioration compared to female patients: state 1 ($CD4 \geq 500$) to state 2 ($350 \leq CD4 < 500$) (HR = 1.15; 95% CI, 1.01–1.28), state 2 ($350 \leq CD4 < 500$) to state 3 ($200 \leq CD4 < 350$) (HR = 1.23; 95% CI, 1.10–1.38) and state 3 ($200 \leq CD4 < 350$) to state 4 ($CD4 < 200$) (HR = 1.67; 95% CI, 1.49–1.86). Moving from state 3 ($200 \leq CD4 < 350$) to state 4 ($CD4 < 200$) was predominant in male compared to female patients.

Covariates Effects on Mortality Rates

In overall, mortality was high among patients in state 4 ($CD4 < 200$) in this cohort. The mortality risk was pronounced among patients in provincial or central hospitals than those in district hospitals if in state 1 ($CD4 \geq 500$) (HR = 1.89; 95% CI, 1.32–2.67), state 2 ($350 \leq CD4 < 500$) (HR = 3.36; 95% CI, 2.05–5.52), state 3 ($200 \leq CD4 < 350$) (HR = 1.25; 95% CI, 0.73–2.16), and state 4 ($CD4 < 200$) (HR = 2.23; 95% CI, 1.80–2.74). State 2 ($350 \leq CD4 < 500$) mortality risk was predominant in the provincial or central hospitals. This means that PHC facilities had a low risk of mortality in this cohort compared to both a higher level of care facilities. Interestingly, the mortality risk was much more pronounced among the 15–25 years age groups than other age groups. The mortality risk for state 1 ($CD4 \geq 500$) was 3.71 (95% CI, 2.90–4.76), state 2 ($350 \leq CD4 < 500$) (HR = 1.66; 95% CI,

1.09–2.53), state 3 ($200 \leq CD4 < 350$) (HR = 1.71; 95% CI, 1.32–2.21, and state 4 ($CD4 < 200$) (HR = 1.71; 95% CI, 1.47–1.98). Patients who were aged 45 years and above were more likely to immune deteriorate compared to 25–34 years age group: HR, 1.35; 95% CI, 1.18–1.54; HR, 1.56; 95% CI, 1.34–1.81, and HR, 1.53; 95% CI, 1.32–1.79 for state 1 to 2, state 2 to 3, and state 3 to 4, respectively. Male patients were more likely to die compared to female patients: state 1–5 (HR = 1.56; 95% CI, 1.26–1.92), state 3–5 (HR = 1.32; 95% CI, 1.15–1.51), and state 4 to 5 (HR = 1.32; 95% CI, 1.23–1.42). Considering the ART initiation period, mortality risks were pronounced among patients who initiated ART in 2013–2017: state 2 ($350 \leq CD4 < 500$) (HR = 4.89; 95% CI, 2.22–10.79), state 3 ($200 \leq CD4 < 350$) (HR = 4.14; 95% CI, 2.47–6.96), and state 4 ($CD4 < 200$) (HR = 9.15; 95% CI, 7.12–11.79).

DISCUSSION

This study's objective was to describe HIV disease progression (immune deterioration) and immune recovery among adult patients on ART in Zimbabwe using patient-level data after ART decentralization. This study made use of semiparametric time homogenous and time inhomogenous multistate Markov models based on four CD4 cell counts intermediate transient states and mortality as the absorbing state. This study was a quantitative secondary data analysis of the routinely collected patient-level data through ePMS among HIV-infected patients on ART in Zimbabwe between 2004 and 2017. The study findings were comparable to other earlier studies and indicated a poor immune recovery in PHC facilities compared to higher levels of care facilities. This study observed significant findings to evaluate HIV disease progression and immune recovery based on CD4 cell counts among ART patients between 2004 and 2017 in Zimbabwe after the decentralization of ART services. The estimated mortality rate of 3.9 per 100 person-years is low and patients in state 4 ($CD4 < 200$) had the highest risk of death (5.9 per 100 person-years on average) compared to other states. This finding was evident throughout in the time-varying analysis of rates. The high rates in state 4 ($CD4 < 200$) were consistent over time; however, there was a sharp drop by seven-fold from 1 to 2 years since ART initiation. There finding of high rates in lower CD4 cell count states is comparable to finding from previous work in India and South Africa (13, 14). Immune deterioration pronounced in patients aged 45 years and above, provincial or central hospital levels of care and male patients. However, immune recovery was also observed in this cohort since there were higher transitions and transition rates from lower CD4 cell counts states to higher CD4 cell counts states. Moreover, patients in the high levels of care (district and provincial or central hospitals) had an increased probability of immune recovery compared to PHC facilities; however, mortality was high in the high levels of care. Male patients had an increased risk of mortality compared to female patients in this cohort.

Generally, there was a gradual improvement in CD4 cell count after ART initiation. This result was evident by the higher immune recovery rates compared to immune deterioration rates.

TABLE 6 | Multiple variable estimates of the hazard ratios and 95% confidence intervals from the time-homogenous multistate Cox proportional hazard model among antiretroviral therapy (ART) patients in Zimbabwe national ART from 2004 to 2017.

Transitions	Health facility type*		Age categories in years**			Sex ***	ART initiation period****	
	District/mission	Provincial/central	15–24	35–44	45+	Male	2008–2012	2013–2017
1 → 2	2.36 (2.12–2.62)	2.10 (1.69–2.62)	0.78 (0.61–0.99)	1.25 (1.10–1.41)	1.35 (1.18–1.54)	1.15 (1.01–1.28)	0.78 (0.67–0.93)	0.90 (0.76–1.07)
1 → 3	1.28 (1.14–1.43)	0.58 (0.39–0.85)	0.80 (0.62–1.04)	1.11 (0.96–1.27)	1.32 (1.14–1.53)	1.04 (0.91–1.19)	1.65 (1.31–2.10)	1.62 (1.27–2.07)
1 → 4	1.01 (0.90–1.14)	0.33 (0.22–0.50)	0.90 (0.68–1.21)	1.05 (0.91–1.22)	1.32 (1.13–1.54)	0.91 (0.78–1.05)	0.35 (0.30–0.42)	0.25 (0.21–0.31)
1 → 5	1.48 (1.19–1.84)	1.89 (1.32–2.67)	3.71 (2.90–4.76)	0.68 (0.51–0.91)	0.94 (0.70–1.24)	1.56 (1.26–1.92)	3.26 (2.07–5.14)	3.02 (1.87–4.89)
2 → 1	2.84 (2.57–3.13)	3.12 (2.54–4.36)	0.98 (0.80–1.19)	1.05 (0.94–1.18)	1.06 (0.93–1.20)	0.57 (0.51–0.64)	0.56 (0.47–0.67)	0.54 (0.45–0.64)
2 → 3	3.18 (2.83–3.58)	3.33 (2.54–4.36)	0.74 (0.54–1.00)	1.31 (1.14–1.51)	1.56 (1.34–1.81)	1.23 (1.10–1.38)	0.88 (0.71–1.08)	0.39 (0.30–0.52)
2 → 4	1.27 (1.11–1.46)	1.20 (0.83–1.73)	0.76 (0.52–1.10)	1.25 (1.05–1.48)	1.33 (1.11–1.60)	1.10 (0.96–1.27)	0.64 (0.49–0.83)	0.54 (0.43–0.67)
2 → 5	1.51 (1.17–1.95)	3.36 (2.05–5.52)	1.66 (1.09–2.53)	0.87 (0.63–1.20)	1.37 (1.01–1.86)	0.89 (0.69–1.15)	2.67 (1.20–5.95)	4.89 (2.22–10.79)
3 → 1	2.54 (2.32–2.79)	4.28 (3.45–5.30)	1.12 (0.94–1.36)	0.91 (0.81–1.01)	0.92 (0.81–1.03)	0.46 (0.41–0.52)	1.11 (0.87–1.43)	1.11 (0.86–1.44)
3 → 2	4.41 (3.96–4.87)	8.04 (6.41–10.10)	0.79 (0.61–1.03)	1.24 (1.10–1.40)	1.35 (1.18–1.54)	0.96 (0.87–1.06)	0.70 (0.57–0.87)	0.66 (0.53–0.82)
3 → 4	2.62 (2.34–2.93)	2.28 (1.59–3.28)	0.98 (0.73–1.32)	1.29 (1.12–1.50)	1.53 (1.32–1.79)	1.67 (1.49–1.86)	0.43 (0.35–0.54)	0.51 (0.40–0.63)
3 → 5	1.16 (0.99–1.13)	1.25 (0.73–2.16)	1.71 (1.32–2.21)	0.93 (0.77–1.08)	1.18 (0.99–1.42)	1.32 (1.15–1.51)	1.69 (0.99–2.85)	4.14 (2.47–6.96)
4 → 1	2.29 (2.05–2.55)	0.63 (0.34–1.17)	1.39 (1.09–1.77)	1.01 (0.89–1.16)	1.20 (1.04–1.38)	0.36 (0.31–0.41)	0.28 (0.24–0.34)	0.18 (0.15–0.22)
4 → 2	2.70 (2.41–3.03)	4.88 (3.55–6.71)	0.82 (0.60–1.11)	1.07 (0.94–1.24)	1.20 (1.04–1.40)	0.72 (0.64–0.81)	1.01 (0.77–1.33)	0.89 (0.67–1.18)
4 → 3	3.97 (3.61–4.37)	8.30 (6.64–10.36)	0.84 (0.64–1.09)	1.11 (0.99–1.25)	1.25 (1.10–1.42)	1.28 (1.17–1.41)	0.95 (0.76–1.19)	1.42 (1.13–1.78)
4 → 5	1.60 (1.49–1.73)	2.23 (1.80–2.74)	1.71 (1.47–1.98)	0.95 (0.86–1.04)	1.08 (0.98–1.20)	1.32 (1.23–1.42)	2.18 (1.69–2.82)	9.15 (7.12–11.79)

The covariates included in the adjusted model were those with complete observation information and considered possible risk factors for the individual transitions.

*Reference: Primary health care facilities.

**Reference: 25–34 years age group.

***Reference: female patients.

****Reference: 2004–2007 time period.

Bold face values are significant at 5%.

This is an indication of effective ART treatment to HIV infected individuals and that if ART is initiated at early phases of HIV infection (with baseline CD4 cell count at least 350), immune recovery and reduced progression can be achieved since the immune system is intact. This matches the findings reported in South Africa in a similar population (17). This study also found out that a patient in state 1 ($CD4 \geq 500$) is estimated to spend 11.3 years in higher CD4 cell count state before death, which is similar to other findings (11). This means that if individuals have a good immunity which can be attributed to the ART regimen efficacy, they tend to live longer than those with weak immunity. This study further found that the probability of mortality increases with a decrease in CD4 cell count, which concurs with findings from similar settings (17, 30). This is explained by the fact that being in an AIDS-defining stage leads to the highest probability of mortality. The highest mean sojourn time was in state 4 ($CD4 < 200$) compared to other states. This finding can be explained by the fact that patients with deteriorated immunity (low CD4 cell count) take a longer time to respond to treatment and boost their immunity before moving to lower states (31). Research has shown that CD4 cell count may remain unchanged despite the suppressed viral load due to weak CD4 cell recovery in other patients (32). This is the limitation of using CD4 cell count; hence, use of viral load in monitoring the efficacy of ART treatment is recommended (33).

We found that the higher the level of care, the better the probability of immune recovery. Patients enrolled in either provincial or central hospitals and district facilities had an

increased probability of immune recovery relative to those in PHC. The risk of immune recovery increased with an increase in care regardless of the immune status of the patient. This result can be supported by high resources through government channels or donor-funded and skilled personnel at the high levels of care (21). As much as patients prefer PHC facility for ART services because of reduced transport cost, easy to access (20), they are most likely understaffed. In addition, PHC are at times overburdened resulting in a high patient care turnaround time (34–37). Surprisingly, we observed relatively high mortality rates among patients enrolled in higher levels of care since one would anticipate the opposite to occur. However, this finding could be explained by either the referral system of patients within the patient care cascade or “silent-transfer” of patients from one health facility to another seeking better care (38–40). This means that the tertiary health facilities were more likely to receive patients who are more seriously ill and with a greater likelihood of death (38, 41, 42).

As we accounted for interindividual variability effects to get more insight on HIV disease progression in this cohort, we found that HIV patients who were aged 15–24 years at ART initiation tend to have a higher mortality than patients aged 25–34 years, and the progression to death was much more pronounced if a patient was coming from state 1 ($CD4 \geq 500$) or state 2 ($350 \leq CD4 < 500$). This finding supports other earlier studies which showed that adolescents are heavily burdened by chronic complications; hence, require high level of patients management (43). In addition, this group

is prone to stigma, vulnerable, and prone to various chronic comorbidities as well as being in the transitional stage of becoming independent without much parental care. Intensifying community-based support for caregivers can help reduce poor health outcomes in adolescence (44). However, more research is required to further confirm this observed association in our study. Patients aged 45 years and above showed a higher risk of immune deterioration compared to younger patients (25–34 years), which was similar to other studies which reported that younger people have a higher probability of immune recovery than the elderly (11, 12). In addition, this could be explained by the immune response in older patients is weak compared to young people, that is, the capacity to generate CD4 cell counts and suppress viral load is reduced in elderly patients (45). Moreover, this could be explained by the fact that this age group is highly associated with non-communicable diseases like hypertension and diabetes. Managing an HIV patient with multiple comorbidities is known to be complex and also intake of different drugs results in overlapping drug toxicity and lowering of the ART drug effect (35). As a result, most patients with comorbidities (communicable or non-communicable diseases) may either default ART treatment or ART drug becomes less effective due to the presence of other medications an individual is on; therefore, these patients subsequently get worse. These results confirm the need for test and treat regardless of disease stage and age which have much positive influence in patients aged 45 years and above (46, 47).

In our study, we found that male patients had higher rates of immune deterioration. This was quite pronounced on the transition from state 3 ($200 \leq \text{CD4} < 350$) to state 4 ($\text{CD4} < 200$). In addition to this, we also observed poor survival outcomes among male patients. This finding is consistent with other results from Shoko and Chikobvu (17) who found out that men were six times more likely to move to higher CD4 cell count state. Another study which supports this result reported that male patients gain fewer CD4 cell counts as compared to female patients, and they have an increased immunological non-response than female patients (48). However, this finding contradicts other earlier studies which documented that gender difference does not exhibit any significant differences in HIV disease progression (11, 12). The participants in this study were predominantly female, and this could mirror the fact that female patients have better involvement in HIV issues and their health-seeking behavior compared to male patients. Female patients have multiple entry points in HIV care like efficient linkage of ART treatment in antenatal clinics and prevention-of-mother-to-child programs which results in better immune recovery than male patients (48). Male involvement in HIV care strategies needs to be enhanced to complement female role in HIV prevention (49–53). Therefore, there is a need to scale up HIV testing rate among men and intensify repeated testing and increasing acceptance of HIV care linkages. With the critical societal role played by men, they improve decision making within a household and society at large if they are fully involved in HIV programs (54). There is need to intensify existing strategies like male circumcision, self-testing, HIV programs at workplaces, and recreational places and also come up with flexible clinic hours and conditions which

accommodate men like shortening clinic turnaround time and increase privacy (48).

Our results should be viewed in light of some limitations. The dataset used had incomplete information especially in the clinical parameters which resulted in dropping off a considerable portion of the data. In addition, this study could not adjust for ART adherence, which is an important issue in HIV disease progression since it directly associated with the probability of moving to a lower CD4 cell count state if a patient fails to adhere to treatment. This study also considered patients from ART centers linked to the ePMS; this might have caused overestimation or underestimation of the transition intensities reported in this study. The analysis was solely based on the time homogenous assumption which is much more useful in the presence of heavy right censoring. Earlier studies have shown that, if a patient on ART is virally suppressed, if there is no treatment uptake violation, that patient is likely to continue recovering well. However, this violates the Markov and memory loss properties of these models, and this limitation affects the time-homogenous Markov process models. Other assumptions like non-Markovian, semi-Markovian, or hidden Markovian can be explored incorporating interval censoring and assuming time-varying effects. This model could not account for frailty terms to explain unobserved individual heterogeneity and spatial effects to show regions with an increased likelihood for a particular transition.

Moreover, this study covers the period in which ART initiation guidelines were changed three times; hence, there could be some bias in the estimates. In addition, the period covered is mainly when the country was conducting targeted differential monitoring, whereby most of the patients who had their CD4 measurement taken were mostly those carried out on the discretion of the physician. Authors acknowledge the measurement error (55) associated with CD4 cell counts in ART monitoring since a patient's measurement may indicate a lower CD4 when in fact the patients had recovered, hence the switch to use viral load in ART monitoring.

There could be possible participant inclusion bias in this study since we excluded those who were lost to follow-up (LTFU) ending up with a subsample. The exclusion of this group was to have a less complicated model with fewer states since this group would be a stand-alone compartment. However, this may have impacted in the generalizability of our research findings in that the model used is not a complete picture of the transition patterns in an ART program as some of the exit points have been excluded. Majority of the patients who became LTFU were mainly those who were very sick (with a $\text{CD4} < 200$) and if tracked there could be a possibility that some of them would have died (56). The implications of such a LTFU pattern normally lead to data missing not at random in longitudinal time to event studies. Had we included the LTFU group and right censored them in their last observed states, this would have caused an upward bias of the Kaplan–Meier curve, which at times may affect the generalizability of the findings (57). In future studies, it would be essential to include the LTFU and withdrawals states in the model to have detailed transition patterns of these outcomes in an ART program. Our data could not allow us to estimate transitions to AIDS since the information was not

available and exhaustively adjust for comorbidities which might be linked to the observed transition patterns in this cohort other than tuberculosis. However, tuberculosis was not included as a covariate because of the highly computational intensive of this reasonably huge dataset if many covariates are added. Hence, we restricted our analysis to demographic covariate so that we attain convergence. A notable limitation in this study is the low mortality rate of which most deaths were for those patients who initiated ART in the 2013–2017-year period. The plausible explanation for this could be an issue of a biased dataset in terms of capturing patient's information. It is most likely that the majority of the deaths that occurred earlier may have been lost during data capturing from patients files to the electronic database since this was a retrospective exercise. Thus, we are most likely to have the long-term survivors from the early period.

CONCLUSION

Multistate models are crucial in providing the general disease trajectories through intermediates states to alert program response before an adverse event occurs. Our findings have significant implication in the continuum of HIV care. It is prudent to target early ART treatment initiation to prevent subsequent immune deterioration. Once this is achieved, survival outcomes and quality of life can be improved with the subsequent reduction in opportunistic infections. Strengthening of PHC facilities in ART is imperative in decentralization environment. More aggressive male involvement strategies should be enhanced to strengthen male involvement in HIV care, and adolescents/young adult management has to be upscaled to prevent ART defaulting and avert poor health outcomes.

DATA AVAILABILITY STATEMENT

The dataset used for this study can be found through an application process from the Ministry of Health and Child Care in Zimbabwe which is the custodian of the ePMS data through the AIDS/TB Unit who manages and oversees the ePMS data collection process.

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AUTHOR CONTRIBUTIONS

ZM cleaned and analyzed the data and drafted the manuscript. JT and TC reviewed the manuscript and advised on analysis. EM guided and oversaw the analysis and reviewed the manuscript. All authors reviewed the final manuscript before submission.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fpubh.2019.00326/full#supplementary-material>

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Spatial Heterogeneity of Viral Suppression and Viral Rebound Patterns among ART Patients in Zimbabwe from 2004 to 2017: A Bayesian Mixed Effects Multistate Model

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Abstract: Augmenting the global efforts towards HIV control and prevention, spatial modelling helps identify areas with poor viral suppression to inform programme planning. This study aims to describe the spatial viral suppression and viral rebound trajectories among ART patients. This is the first application of the fully Bayesian geospatial semiparametric multistate Markov models to account for unobserved geographical heterogeneity. Time-varying log-baseline effects of the transition intensities and non-linear effects of continuous covariates were estimated as smoothed functions of time using penalised splines. Non-parametric effects of fixed covariates and frailty effects to account for individual variability were also considered. Viral load was the preferred marker for better prediction of HIV/AIDS disease progression; therefore, a three staged model was proposed based on two viral load transient states defined by undetectable viral cut-off limits and death as the third absorbing state. Model application was based on the routinely collected individual-level data of ART patients from the Zimbabwe national ART programme. Amongst 18,150 participants, both the log-baseline transition rates of attaining undetectable viral suppression and attaining a viral rebound increased with increase in ART duration. Viral rebound transition was significantly prevalent among patients living on the long-distance truck route region (Matabeleland North province) which borders with Botswana and Zambia. Interventions which address health literacy and misconceptions over ART benefits and the gravity of attaining and sustaining viral suppression are a priority in the fight of HIV to increase patients' life expectancy and lower HIV transmission.

Keywords: Bayesian estimation, multistate Markov models, spatial heterogeneity, viral suppression, viral rebound.

1. INTRODUCTION

Multistate models are useful in the management of chronic diseases since intermediate transitions give quick insights into the complex pathways patients experience before the final event, death, occurs [1]. Regarding Human immune-deficiency virus (HIV) infections, multistate models can be used to evaluate the performance of antiretroviral therapy (ART) programmes and identify patients who are at a high risk of immune deterioration so that appropriate interventions can be implemented.

Numerous studies assessing HIV disease progression using multistate models have used the frequentist estimation approach implemented in R using the *msm* package [2]; however, these frequentist multistate models have some limitations. Firstly, they are unable to account for unexplained individual heterogeneity in transition rates which may be represented by the random-effects model. Accounting

for individual variation is crucial in infectious disease modelling since individuals respond differently to treatment [2]. Secondly, frequentist multistate models are restrictive on the types of covariates they can handle, as the functional form of the effects of the predictive factors is assumed to be linear (or log-linear). As a result, the effects of the covariates may be poorly estimated and penalized-splines (P-splines) may better estimate non-linear functions for these covariates. Such errors in covariate misspecification may lead to inaccurate statistical conclusions, increased bias in estimates and decreased statistical power for statistical significance tests [2]. Besides, most of the previous studies focusing on HIV disease progression have used CD4 cell count measurements to define the finite number of states which is known to have measurement error; hence, may not be sensitive enough to assess HIV disease progression [3]. In line with the global recommendation to use viral load in HIV monitoring, a recent study confirmed the superiority of viral load measurements in predicting ART outcomes compared to CD4 cell counts [4].

The work by Kneib and Hennerfeind (2008) [5] on the use of Bayesian inference in multistate models forms the basis of this study analysis [5]. In this model.

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the transition (hazard) rates are estimated in a multiplicative Cox-type way whereby the nonparametric effects of the log-baseline hazard are simultaneously estimated with other predictor components and assumed to be time-varying. The flexible linear predictor of the model can handle non-linear effects of continuous covariates modelled using P-splines [6]. Additional components may include covariates with time-varying effects; non-linear effects of a continuous covariate modelled non-parametrically with a smoothing function; parametric fixed effects and frailty terms [5]. However, to our knowledge, no studies have included the spatial random effects in the flexible predictor using multistate models; hence, this current study aims to incorporate the spatial covariate in a multistate model framework which is crucial to account for unobserved heterogeneity. Despite the recent emerging of spatial modelling in HIV monitoring indicators [7], there has not been extensive use of spatial data on time-varying viral suppression and time-varying viral rebound indicators to monitor HIV disease progression among ART patients.

The World Health Organization (WHO) HIV monitoring guidelines recommend the use of viral load which also became one of the indicators in the UNAIDS 90-90-90 fast track targets whereby 90% of all people living with HIV (PLWHIV) know their status, 90% of those who know their status receive ART and 90% of those on ART achieve viral suppression [8]. In Zimbabwe, only 73% of ART patients were estimated to be virally suppressed in 2018, which is a concern for HIV prevention and control in the country [9]. With the global quest to achieve zero new HIV infections by 2030, the focus is on attaining an undetectable viral load among HIV-infected population since undetectable HIV results in un-transmittable virus (U=U) [10]. The use of viral load monitoring in HIV disease progression is important to enhance understanding of HIV infection to the various stakeholders and provides a motivation on the need of encouraging ART adherence. Therefore, it is imperative to understand the viral suppression and viral rebound (HIV disease progression) patterns among ART patients. With the scarce resources in low-middle income countries like Zimbabwe, it was also of interest to be able to link these transition trajectories to the geographical regions to pinpoint high burdened areas so as to guide resource allocation and to inform policy on targeted interventions; hence, the inclusion of the spatial frailty term.

This manuscript aimed to describe the spatial heterogeneity of viral suppression to undetectable

levels and viral rebound to detectable levels trajectories among ART patients using the Bayesian semi-parametric geosadditive multistate model. The model was fitted on patient-level data from the Zimbabwe national ART programme for patients who initiated ART between 2004 and 2017. In addition to the non-linear continuous covariates, the model accounted for time-varying transition rates and individual heterogeneity which reflects the reality. The spatial component assumed that the viral load transitions were likely to be induced characteristics of geographical units, which may depend on neighboring regions but may as well be heterogenic. We hypothesized that there is spatial heterogeneity of viral suppression and rebound in this cohort and these transition rates change with time. Findings from this study may provide additional information on HIV disease progression and give a proxy on how well the ART patients are adhering to ART so as to achieve un-transmittable virus levels. The knowledge gained from this analysis may also be used to encourage HIV patients to understand the importance of ART adherence.

Data management and preliminary analyses were handled in Stata Statistical Software Version 15.1 [11]. Inference procedures were implemented in free BayesX software package Version 3.0.2 [12] using Markov Chain Monte Carlo (MCMC) simulation technique. Results visualization was performed in RStudio [13]. The rest of the paper is structured as follows: **Section 2** describes the fully Bayesian multistate model formulation (likelihood, prior, posterior), MCMC inference, model validation and diagnostics; **Section 3**, we apply the proposed model to the Zimbabwe national ART program data collected over 13 years; and **Section 4**, we discuss the advantages of these models and highlight the Public Health and statistical implications of our findings. The Supplementary material provides additional detail to Section 2 in addition to the BayesX code used.

2. BAYESIAN GEOADDITIVE MULTISTATE MODEL

2.1. Description of the Multistate Model

In this study, we considered a time-continuous Markov process $\{X(t), t \geq 0\}$ with two reversible transient states and one absorbing (death) state defining the finite states ($S=1,2,3$) as depicted in Figure 1. The viral load cutoff points were based on guidelines for undetectable viral load [10], that is, “undetectable viral suppression (<50copies/mL)” state as state 1, “detectable viral rebound (≥ 50 copies/mL)”



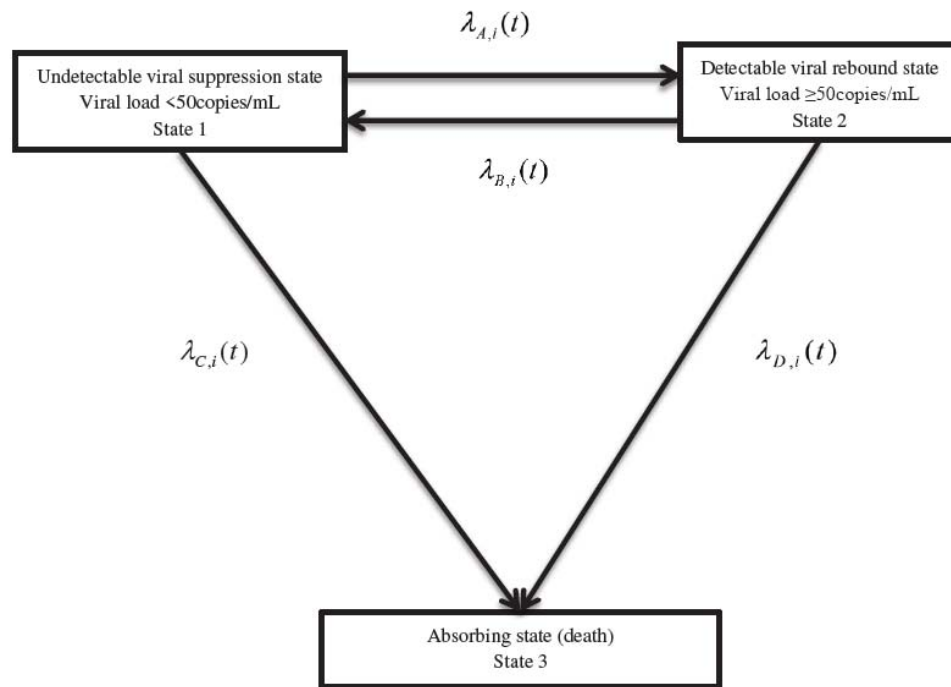


Figure 1: The schematic presentation of HIV disease progression stages multistate model and the corresponding individual-specific transition intensities.

state as state 2 and the absorbing state, death, as state 3.

The multistate model is described by a group of individual-specific hazard rates $\lambda_{jk,i}(t)$ where jk , ($j=1,2,\dots,J$ and $k=1,2,\dots,K$), indexes the type of transition from state j to k and $i=1,2,3,\dots,n$ indexes the individuals. These hazard rates are specified in analogy to hazard rates for continuous-time survival analysis (Appendix 1-4) in a multiplicative semi-parametric regression model way:

$$\lambda_{jk,i}(t) = \exp(\eta_{jk,i}(t)) \quad (1)$$

where $\eta_{jk,i}(t)$ is an flexible additive predictor expressed as

$$\eta_{jk,i}(t) = g_{jk,0}(t) + \sum_{r=1}^L g_{jk,r}(t) u_{r,i}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + v_i(t)' \gamma_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \quad (2)$$

This flexible predictor's components are defined as:

- i. A time-varying, nonparametric baseline effect $g_{jk,0}(t)$ mutual for all observations. Generally, in the conventional Cox approach, the baseline hazard $\lambda_{jk,0}(t)$ remained unspecified; however, in this model, the baseline hazard is

reparameterised through $g_{jk,0}(t) = \log(\lambda_{jk,0}(t))$ function (Appendix A3). Instead of modelling the hazard rates through a piecewise exponential model assuming that all time depended values are piecewise constant [14], this study estimated the non-linear shape of the log-baseline effect by a P-spline prior of arbitrary degree with a second-order penalty [15].

- ii. Covariates $u_{r,i}(t)$ with time-varying effects $g_{jk,r}(t)$. However, in this study, covariates with time-varying effects were not included in the model since no time-varying covariates were included in the received dataset.
- iii. Non-linear effects $f_{jk,r}(t)x_{r,i}(t)$ of a continuous covariate $x_{r,i}(t)$. In this study, we considered individual age in years as a continuous covariate modelled non-parametrically with a smoothing function $f_{jk,r}(t)$ as it is directly proportional to time. Similarly, these non-linear effects were modelled by the P-spline prior.
- iv. Parametric fixed effects γ_{jk} of covariates $v_i(t)$. The vector of the regression coefficients $\gamma_{jk,c}$ contains the usual linear effects of the vector of fixed effects $v_i(t)$ which were WHO clinical stages (I/II or III/IV) and gender (male or female) in this study.



- v. The spatial structural effects $f_{jk,spat}(t)(s_i)$ which form the unique part of our multistate model, where $s = 1, 2, \dots, S$ is a spatial index, with $s_i = s$ if individual i is from region or site s to account for spatial heterogeneity assuming a Gaussian Markov random field (GMRF) prior. The spatial effects in this study were split into two components, that is, $f_{jk,spat}(t)(s_i) = f_{jk,str}(t)(s_i) + f_{jk,unstr}(t)(s_i)$ where $f_{jk,str}(t)(s_i)$ defines the structured (correlated) part and $f_{jk,unstr}(t)(s_i)$ defines the unstructured (uncorrelated) part.
- vi. Random effects (frailty) term $b_{jk,i}$ was included to account for individual-specific unobserved heterogeneity.

Additional information on model components is provided in Appendix 5.

To estimate viral suppression, viral rebound and mortality transition rates; and determine the associated spatial heterogeneity of these transitions, the model in Figure 1 assumed that: a patient initiated on potent and effective ART treatment may become virally suppressed to undetectable virus levels, may have detectable viral rebound due to poor adherence or treatment failure, ART defaulting or treatment failure; or may die from any of the states. Baseline characteristics effects (WHO clinical stage at ART initiation and gender) were adjusted for in addition to the spatial and individual frailty terms. Therefore, the four transitions estimated were:

$$\begin{aligned}\lambda_{A,i}(t) &= \exp\left(\eta_{A,i}(t) = g_{A,0}(t) + f_{A,age_i}(t) + \gamma_{A,1}(WHOstage) + \gamma_{A,2}(sex) + \gamma_{A,3}(province) + b_{A,i}\right) \\ \lambda_{B,i}(t) &= \exp\left(\eta_{B,i}(t) = g_{B,0}(t) + f_{B,age_i}(t) + \gamma_{B,1}(WHOstage) + \gamma_{B,2}(sex) + \gamma_{B,3}(province) + b_{B,i}\right) \\ \lambda_{C,i}(t) &= \exp\left(\eta_{C,i}(t) = g_{C,0}(t) + f_{C,age_i}(t) + \gamma_{C,1}(WHOstage) + \gamma_{C,2}(sex) + \gamma_{C,3}(province) + b_{C,i}\right) \\ \lambda_{D,i}(t) &= \exp\left(\eta_{D,i}(t) = g_{D,0}(t) + f_{D,age_i}(t) + \gamma_{D,1}(WHOstage) + \gamma_{D,2}(sex) + \gamma_{D,3}(province) + b_{D,i}\right)\end{aligned}\quad (3)$$

where A defines the viral rebound transition, B defines the undetectable viral suppression transition, C and D defines the mortality transition from undetectable virally suppressed and viral rebound states, respectively.

2.2. The Likelihood Function

The likelihood contribution in a multistate model for each individual $i = 1, 2, 3, \dots, n$ is derived from a counting process $N_{jk,i}(t)$, counting j to k transitions for

individual i . If we consider $S_{iz}, z = 1, 2, \dots, m_i$ as the individual transition times corresponding to a transition process under the non-informative censoring, the intensity process of the counting process is defined as $\alpha_{jk,i} = I_{jk,i}(t)\lambda_{jk,i}(t)$ where $I_{jk,i}(t)$ is the predictable at risk indicator process and the hazard rate $\lambda_{jk,i}(t)$ defined as in Equation (1). Therefore, the individual log-likelihood function is given by:

$$\log L_i(\gamma, \beta, \tau^2) = \sum_{jk=1}^{JK} \left[\int_0^{S_{i,m_i}} \log(\lambda_{jk,i}(t)) dN_{jk,i}(t) - \int_0^{S_{i,m_i}} \lambda_{jk,i}(t) I_{jk,i}(t) dt \right] \quad (4)$$

where $\gamma = (\gamma'_{jk,1}, \gamma'_{jk,2}, \dots, \gamma'_{jk,d})'$ for $c = 1, 2, \dots, d$ is a vector of

all fixed effects parameters, $\beta = (\beta_{jk,1}, \beta_{jk,2}, \dots, \beta_{jk,p})'$ is a vector of (regression) coefficients,

$\tau^2 = (\tau^2_{jk,1}, \tau^2_{jk,2}, \dots, \tau^2_{jk,y})'$ for $q = 1, 2, \dots, y$ is a vector of all variance components under consideration and S_{i,m_i} denotes the time until an individual i has been observed. In survival models, the first term can be viewed as the log-hazard for uncensored data while the second term reflects the cumulative intensities.

Alternatively, the likelihood can be defined in terms of each individual contributions defined in terms of transition censoring indicators $\delta_{jk,i}(t)$ which is equal to one if a jk transition occurs before time (t) and zero otherwise and the observed transition times $S_{iz}, z = 0, 1, \dots, m_i$ defined by the time an individual experience the transition. The alternative log-likelihood formula is given by:

$$\log L_i(\beta, \gamma, \tau^2) = \sum_{z=1}^m \sum_{j,k=1}^{JK} \left[\delta_{jk,i}(S_{iz}) \log(\lambda_{jk,i}(S_{iz})) - I_{jk,i}(S_{iz}) \int_{S_{i,z=1}}^{S_{iz}} \lambda_{jk,i}(t) dt \right] \quad (5)$$

where $\lambda_{jk,i}(t)$ is defined by Equation (1) and this whole expression reflects the commonly known hazard rate models fitted for continuous survival times. If the degree of the P-spline prior for the log-baseline hazard function is greater than one, then the likelihood integral can no longer be solved in a closed form. Detailed steps of the log-likelihood are provided in Appendix 6.

2.3. The Prior Specifications

We performed a fully Bayesian inference since all unknown parameters were assigned prior information.



We assigned non-informative diffuse prior, $P(\gamma) \propto \text{const}$ to the *fixed-effects parameters*; alternatively, a weak (large variance) normal prior can be used. The *individual random effects* $b_{jk,i}$ were assumed to be independent and identically distributed (iid) Gaussian distributed with a transition specific precision, $b_{jk,i} \sim N(0, \tau_{jk,b}^2)$. Priors for the *random effects (regression) coefficients parameter vector* $\beta_{jk,r}$ for $r=0,1,\dots,p$ were assumed to be Gaussian distributed computed as a product of conditional densities defined by the random walk smoothness priors. The general form of the prior for $\beta_{jk,r}$ is given by:

$$P(\beta_{jk,r} / \tau_{jk,r}^2) \propto \exp\left(-\frac{\beta_{jk,r}' W_{jk,r} \beta_{jk,r}}{2\tau_{jk,r}^2}\right) \quad (6)$$

where $W_{jk,r} \geq 0$ is a precision or penalty matrix of rank $(W_{jk,r}) = h_{jk,r}$. The variance $\tau_{jk,r}^2$ acts as an inverse smoothness hyper-parameter controlling for the trade-off between smoothness and flexibility. That is a small value of $\tau_{jk,r}^2$ corresponds to an increase of the penalty or shrinkage (error) or vice-versa.

Unknown *nonparametric effects* $f_{jk,r}(t)$ of continuous smooth covariate x_r were estimated using Bayesian P-splines [6] as a linear combination of a larger number of B-splines basic functions B_d , i.e.,

$$f_{jk,r}(x_r) = \sum_{d=1}^{D_r} \beta_{jk,rd} B_d(x_r). \text{ The basic functions } B_d \text{ are the}$$

B-splines of a known degree l on a set of equally spaced knots $x_r(\text{max}) = \varsigma_0 < \varsigma_1 < \varsigma_2 < \dots < \varsigma_{s-1} < \varsigma_s = x_r(\text{max})$ within the main domain of x_r , $D_r = l + s$. The Bayesian analogue is the second order random walk smoothness priors of the form:

$$\beta_{jk,rd} = 2\beta_{jk,r,d-1} - \beta_{jk,r,d-2} + \varepsilon_{jk,rd}, d=3,4,\dots,D \quad (7)$$

with iid Gaussian errors $(\varepsilon_{jk,rd} \sim N(0, \tau_{jk,\varepsilon}^2))$ where $\tau_{jk,\varepsilon}^2 = 1/\sigma^2$. The linear trend coefficients' initial values of the random walk were assigned diffuse priors, $P(\beta_{jk,r1}) \propto \text{const}$ and $P(\beta_{jk,r2}) \propto \text{const}$.

The *spatial effects* were modelled separately to distinguish between the different effects on the outcome, that is, $f_{jk,spat}(t)(s_i) = f_{jk,str}(t)(s_i) + f_{jk,unstr}(t)(s_i)$. For the spatial correlated (structured) effects

$(f_{jk,str}(t)(s))$ we assumed a GMRF [16] prior. In this case, we defined areas as neighbors if they share a common boundary and assume that the effect of an area $s \in \{1,2,3,\dots,S\}$ is conditionally Gaussian. The spatial smoothness prior for the spatial function evaluation $f_{jk,str}(s) = \beta_s^{str}$ is given by:

$$f_{jk,str}(s) = \beta_s^{str} = \frac{1}{N_s} \sum_{s' \in \partial_s} \beta_{s'} + u_s, u_s \sim N\left(0, \frac{\tau_{jk,str}^2}{N_s}\right) \quad (8)$$

where $s' \in \partial_s$ denotes that province s' is a neighbor of province s . The conditional mean of β_s is an unweighted average of function evaluations of neighboring provinces. The number of parameter D equals the number of distinct areas S and the $n \times S$ design matrix Z_{str} is a 0-1 incidence matrix. Its values on the i^{th} row and s^{th} column is a one if an observation is located in the province s and zero otherwise. The $S \times S$ penalty matrix W_{str} has the form of the adjacency matrix with $\text{rank}(W_{str}) = S - 1$. The dimension of the penalty matrix in GMRF equals to the number of different spatial regions (provinces in our case) S ; hence, the computational burden is less compared to the stationary GRF priors approach. The *unstructured spatial effects* $f_{unstr}(s)$ were assumed to be iid Gaussian priors, $f_{unstr}(s) \sim N(0, \tau_{unstr}^2)$. In real situations, usually it is not known how much spatial variation is explained by both the structured and the unstructured effects; therefore, the interpretation of the spatial effects is based on the sum of these two effects.

The variance parameter vector $\tau_{jk,q}^2 = (\tau_{jk,1}^2, \tau_{jk,2}^2, \dots, \tau_{jk,y}^2)'$ for $q=1,2,\dots,y$ contains variance parameters for the error term $\tau_{jk,\varepsilon}^2$, frailty term $\tau_{jk,b}^2$, structured spatial terms $\tau_{jk,str}^2$, the unstructured spatial terms $\tau_{jk,unstr}^2$ and the generic random effects (regression) coefficients $\tau_{jk,r}^2$. Routinely, each of these variance hyperparameters is assigned a non-informative inverse Gamma priors with known parameter values $a=b=0.001$, that is, $(\tau_{jk,q}^2 \sim IG(a_q, b_q))$

$$P(\tau_{jk,q}^2) \propto \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(-\frac{b_q}{\tau_{jk,q}^2}\right), \text{ for } a_q, b_q > 0 \quad (9)$$

Additional information is given in the Appendix 7.



2.4. Posterior Distribution

The fully Bayesian inference is based on the entire posterior distribution, and more detail is shown in Appendix 8:

$$P(\beta, \gamma, \tau^2 / \text{data}) \propto L(\text{data} / \beta, \gamma, \tau^2) P(\beta, \gamma, \tau^2) \quad (10)$$

The likelihood as defined in Section 2.2 and the joint prior made up of the individual prior distributions of the specified parameters yield the posterior distribution. Due to conditional independence assumptions, the joint prior factorizes into:

$$P(\beta, \gamma, \tau^2) = \left\{ \prod_{r=0}^m P(\beta_{jk,r} / \tau_{jk,q}^2) P(\tau_{jk,q}^2) \right\} P(\gamma) \propto \left\{ \prod_{q,j,r=0}^m \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp \left(\left(\frac{b_q}{\tau_{jk,q}^2} \right) - \frac{\beta'_{jk,r} W_{jk,r} \beta_{jk,r}}{2\tau_{jk,q}^2} \right) \right\} \quad (11)$$

The component $P(\gamma)$ can be omitted since it represents fixed effects prior. The posterior distribution $P(\beta, \gamma, \tau^2 / \text{data})$ is then an approximation of the product of Equation (5) and (11).

2.5. Markov Chain Monte Carlo Inference

Since this posterior distribution is not in a closed form, we used the MCMC simulation method based on updating full conditionals of single parameters or blocks of parameters (for the same transition rate), given the rest of parameters and data. To update the parameter vector $\beta_{jk,r}$ which corresponds to the time-independent functions, spatial effects, fixed effects and random effects; we used the Metropolis-Hastings (MH) algorithm based on iteratively weighted least squares (IWLS) proposals for generalized linear mixed effects models (GLMM) [17] and adapted to generalized structure additive models (GSAM) [18]. Suppose we want to update $\beta_{jk,r}$ with current value $\beta_{jk,r}^c$ of the chain, the new value $\beta_{jk,r}^p$ is proposed by drawing a random vector from the high-dimensional multivariate Gaussian proposal distribution $q(\beta_{jk,r}^c, \beta_{jk,r}^p)$ which is attained from the quadratic approximation to the posterior by a second-order Taylor expansion with respect to $\beta_{jk,r}^c$ explicitly illustrated in Appendix 9. Other parameters corresponding to the time-varying log-baseline effects were estimated using a computationally faster MH-algorithm based on conditional prior proposals. Unlike the ILWS algorithm which requires derivatives, MH-algorithm requires the evaluation of the log-likelihood since the derivatives are computationally intensive for these parameters due to

the additional integrals involved. As the full conditionals of the variance parameters are inverse Gamma distributions, updating the hyper-parameters was done using Gibbs sampling.

2.6. Model Diagnostics and Sensitivity Analysis

The convergence of the Markov chains to their stationary distributions was assessed by inspecting the sampling paths and autocorrelation functions of the sampled parameters. Trace plots and visual autocorrelation plots were used to evaluate the performance of the model. In running the MCMC algorithm, 10,000 iterations were made with a burn-in of 2,000 and a thinning parameter of 20. We also performed a sensitivity analysis to ensure that the choice of the priors did not have an influence on the obtained results. In the initial run, default Gamma priors with hyper-parameters ($\alpha = \beta = 0.001$) were used then two more trials using values of $\alpha = \beta = 0.0001$ and $\alpha = 1$ with $\beta = 0.001$. The results reported are those of the model with default prior values.

3. APPLICATION OF THE MODEL

3.1. The Zimbabwe National ART Programme Data

The national ART programme was introduced in Zimbabwe in 2004 to provide treatment for PLWHIV and support the fight against HIV [19]. Patients' data are routinely collected at ART initiation, and subsequent follow-up visits, through the electronic patient management system (ePMS) [20]. The ePMS was introduced to improve and increase efficiency in patient monitoring compare to the paper-based system and allows analysis at the national level of suitably anonymized patient data.

At baseline, demographic and clinical information is captured including gender, age, and WHO clinical stage, while viral load and CD4 measurements are captured at baseline as well as in subsequent visits. WHO recommends the use of laboratory monitoring to manage HIV patients on ART, using viral load measurements at baseline (6 months after ART initiation) and then every six months to guide patient management. Practically, this patient-level information is taken intermittently over time; hence, missing data is common due to patients' travels, patients' social circumstances, patients' treatment non-adherence or errors during data capturing. Missing data in program data may also be due to program guidelines and policies, the data used in this study covers the period when differential monitoring was done [21]. These aspects lead to missing and irregular compilation of



longitudinal data points which are likely to be missing not at random (MNAR). In this study, we considered primarily those individuals who had at least two subsequent viral load measurements.

3.2. Study Design and Ethics

This study was a secondary data analysis of a retrospective cohort of anonymous HIV positive patients initiated on ART between 2004 and 2017, and whom their routine data was captured through the ePMS system linked with the Zimbabwean Ministry of Health and Child Care (ZMOHCC). Permission to use the data was obtained from ZMOHCC, and ethical clearance was granted by the University of Witwatersrand's Human Research Ethics Committee (Medical) (Clearance Certificate No. M170673).

4. RESULTS

4.1. Descriptive Analysis of the Baseline Characteristics

Of the 18,150 participants with two or more viral load measurements following ART initiation: 64.3%

(n=11,671) participants had detectable viral load (>50copies/mL) while 35.7% (n=6,479) had undetectable viral load (<50copies/mL). There was a significant difference between these baseline proportions of patients with undetectable viral load and those with detectable viral load, p-value<0.001. The mean (standard deviation) age and weight was 39.1(10.2) years and 62.4(13.5) Kgs at ART initiation, respectively. Majority of the patients were females (67.1%), enrolled at the primary health care (PHC) facilities (68.2%) within rural areas (52.4%). Majority of the patients were on first-line regimen (95.0%) and 53.3% in WHO clinical stage III/IV. Most of the patients did not move out of their initially occupied state, particularly the viral rebound state (68.74%). A total of 496 patients (2.73%) had died at the end of the study (Table 1).

4.1. Fully Bayesian Time-Varying Transition Intensities Pattern Results

We fitted an unadjusted (no covariate) and covariate adjusted models to obtain the time-varying log-baseline hazard plots. The unadjusted model gave

Table 1: Participants' Baseline Characteristics (Sociodemographic and Clinical) and the Observed Transitions during the Follow-Up Period in the Zimbabwe National ART Programme, 2004-2017

Variable	Category	Frequency	Percentage
Health facility type	Primary Health Care	12 385	68.24
	District /Mission hospital	4 527	24.94
	Provincial/Referral hospital	1 238	6.82
Degree or urbanization of health facilities	Rural	9 700	53.44
	Urban	8 450	46.56
Sex	Female	12 169	67.05
	Male	5 981	32.95
Regimen type	First line	17 234	94.95
	D4T(30)+ 3TC+NVP	9	0.05
	AZT+3TC+NVP	353	1.94
	AZT+3TC+EFT	38	0.21
	TDF+3TC+NVP	280	1.54
	AZT+3TC+EFV	16 554	91.21
	Second line	916	5.05
WHO clinical states	I/II	7 700	42.42
	III/IV	9 679	53.33
	Missing	771	4.25
Baseline viral load states	Suppressed state (State 1)	6 401	35.27
	Unsuppressed state (State 2)	11 749	64.73
Transitions between states	1 → 1	21 645	24.39
	1 → 2	2 803	3.16
	1 → 3	200	0.23
	2 → 1	2 804	3.16
	2 → 2	61 015	68.74
	2 → 3	296	0.33



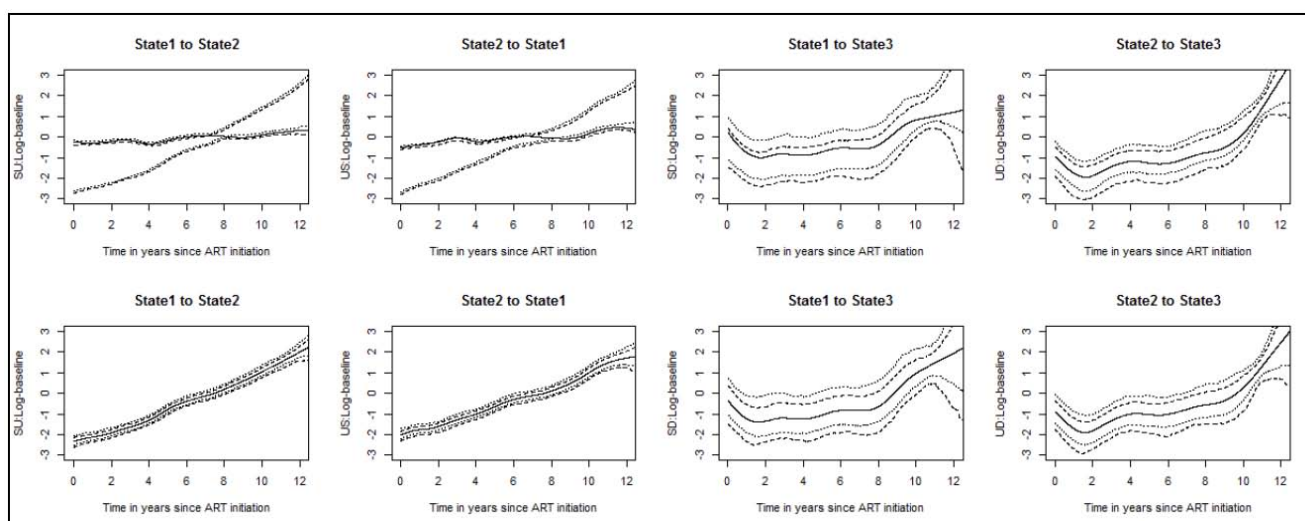


Figure 2: Estimated time-varying log-baseline transitions (middle line) and their 95% and 80% credible intervals from the fully Bayesian inference estimation of univariate analysis/no covariates (top panel) and multiple covariate model with non-linear, fixed and spatial covariates (bottom panel).

wide credible intervals (CI) for both the viral rebound (undetectable (state 1) to detectable (state 2)) and viral suppression (detectable (state 2) to undetectable (state 1)) transitions as shown in Figure 2 (top panel). Adjusting for the other covariates narrowed the time-varying log-baseline CI. Therefore, we reported results based on the adjusted model Figure 2 (bottom panel). We observed an increase in the log-baseline hazard rates with time since ART initiation for both the viral suppression (state 2 to state 1) and viral rebound (state 1 to state 2) transitions. The two time-varying log-baseline mortality transition rates steadily increased with time.

Comparing the viral suppression (state 2 to state 1) and viral rebound (state 1 to state 2) transitions on one plane, we observed that the log-baseline effects of attaining viral suppression (state 2 to state 1) were higher from ART initiation till the 7.2 year mark before going down thereafter (Figure 3a). The log-baseline hazard rates of mortality from either state showed a fluctuating pattern over time (Figure 3b). Among virally suppressed (state 1) patients, the risk of attaining viral suppression was higher in the early years of ART initiation compared to the risk of attaining viral rebound; however, after the 10 year mark, there was no difference between the two transitions (Figure 3c). Contrary, among the patients who attained viral rebound (state 2), the risk of regaining immune recovery was higher than that of death in overall (Figure 3d).

Table 2 presents the results of the effects of the fixed covariates on each of the transitions. Although the

effects of WHO clinical stage were not significant for the viral suppression (state 2 to state 1) transition and on the risk of death from any state; patients in WHO clinical stage III/IV had a higher risk of a viral rebound compared to those in WHO I/II (posterior hazard ratio (PHR) =1.26; 95%CI: 1.03-1.48). Compared to females, male patients were 64% times less likely to attain a viral rebound (PHR=0.36; 95%CI: 0.29-0.45); 1.57 times (95%CI: 1.28-1.90) more likely to become virally suppressed and 1.68 times (95%CI: 1.32-2.05) more likely to die if they have a viral rebound. However, there was no significant difference in gender on the risk of death if an individual was virally suppressed.

The effects of age on the risk of the four transitions are presented in Figure 4. The age effects on the risk of mortality and viral rebound for an individual with suppressed viral load was high if a patient was either an adolescents/young adult (below 30years) or older (above 60years) as shown by the bath-tub “U” shaped splines; however, the effects for older patients were not significant due to fewer numbers of participants in this category. Contrarily, the age effects on the risk of viral suppression followed a doom “∩” shape. This means individuals aged 30-60 years with viral load rebound had a higher risk of experiencing the reverse transition and subsequently attaining viral suppression. Also, the age effects on the risk of mortality for an individual with viral rebound increased with an increase in age until 30 years before remaining constant thereafter.

The smooth geographical effects are shown in Figure 5 with their corresponding 95%CI for each transition based on Zimbabwe provinces as the spatial



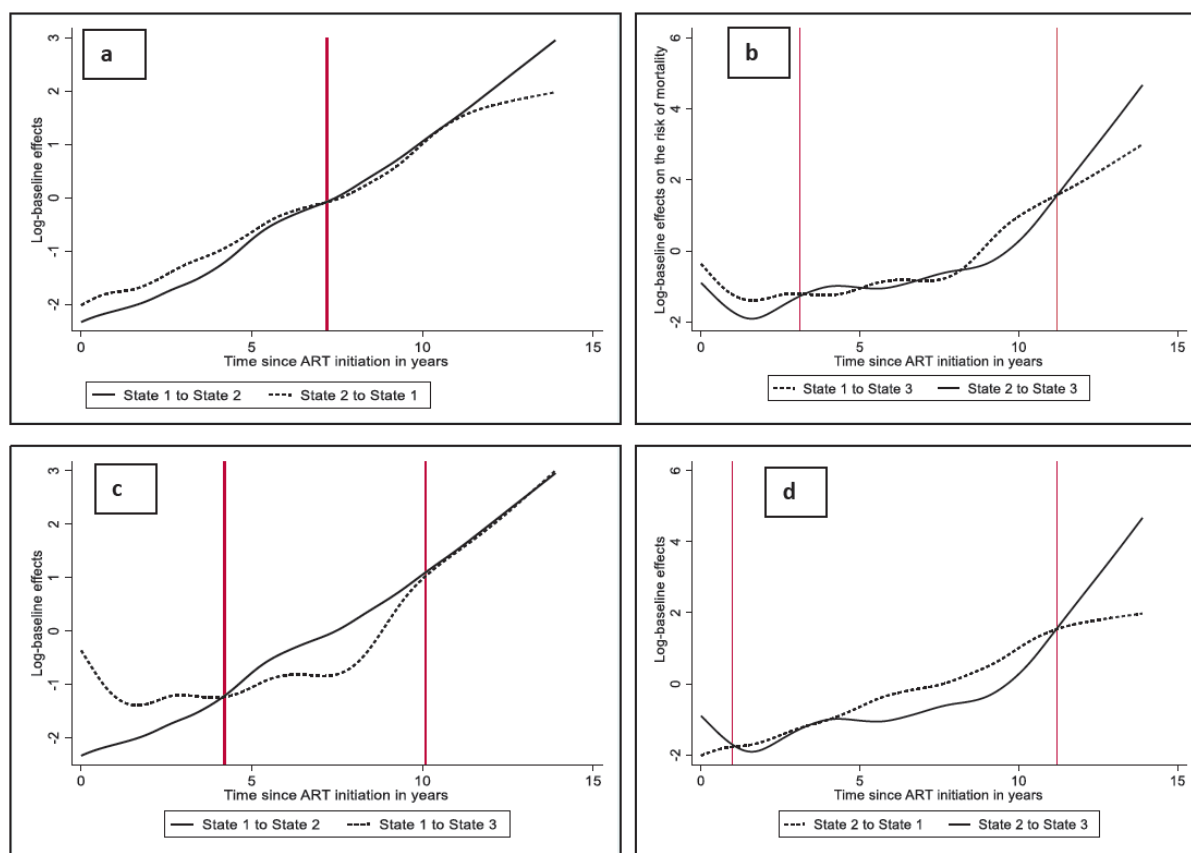


Figure 3: Comparison of the estimated time-varying log-baseline transitions from the fully adjusted Bayesian multistate model.

Table 2: Fixed Effect Covariates Results for the Estimated Transition Intensities Coefficients and Ratios in the Zimbabwe National ART Programme Based on Viral Load Measurements, 2004 to 2017

Covariates Transitions		WHO III/IV (Reference: WHO I/II) Mean(95% Credible Intervals)	Sex (Reference: Female) Mean(95% Credible Intervals)
Viral rebound (state 1 to 2)	Coefficients	0.23 (0.03 to 0.39)*	-1.02 (-1.24 to -0.79)*
	Exponents	1.26 (1.03 to 1.48)*	0.36 (0.29 to 0.45)*
Viral suppression (state 2 to 1)	Coefficients	-0.12 (-0.29 to 0.04)	0.45 (0.25 to 0.64)*
	Exponents	0.89 (0.75-1.04)	1.57 (1.28-1.90)*
Viral suppression mortality (state 1 to 3)	Coefficients	0.19 (-0.11 to 0.51)	-0.17 (-0.49 to 0.11)
	Exponents	1.21 (0.90-1.67)	0.84 (0.61-1.12)
Viral rebound mortality (state 2 to 3)	Coefficients	-0.43 (-0.53 to 0.17)	0.52 (0.28 to 0.76)*
	Exponents	0.65 (0.59-1.19)	1.68 (1.32-2.05)*

*Significant at 5%.

unit. The yellow colour represents regions with non-significant spatial effects for all the transitions. For the risk of viral rebound and the risk of mortalities from either state, the red colour indicates an increased spatial effect while green colour indicates a decreased spatial effect. The region which borders with Botswana and Zambia (Matabeleland North province) had a significant highest likelihood of viral rebound (state 1 to

state 2) transition compared to other regions. For the risk of viral suppression, the red colour indicates decreased spatial effects while green colour indicates increased spatial effects. The southern region which borders with Botswana, the middle region in the central parts of the country and northern regions bordering Zambia and Mozambique had a low likelihood of the viral suppression (state 2 to state 1) transition. This



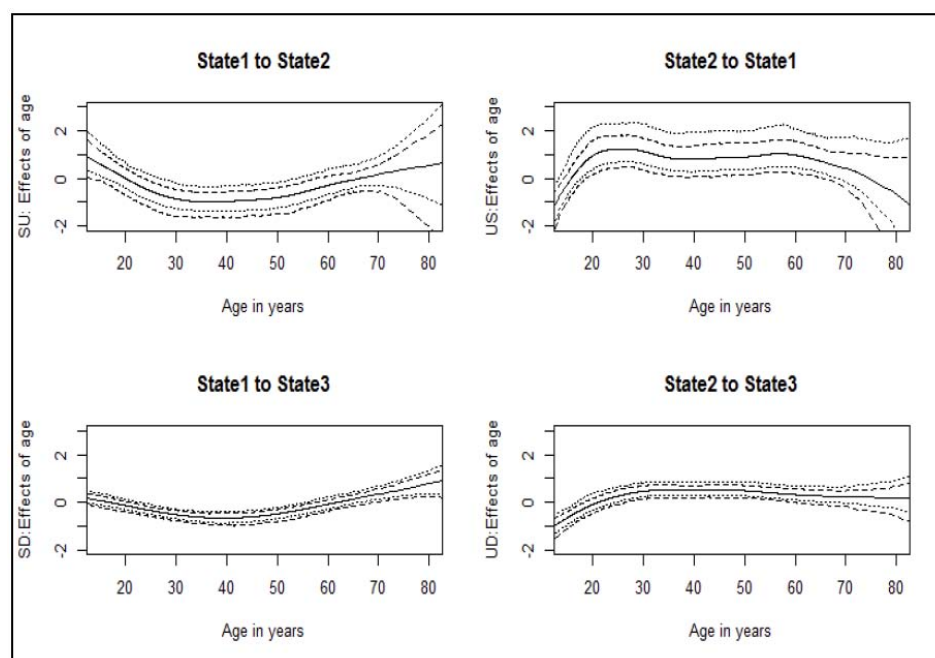


Figure 4: Estimated nonparametric effects of the continuous covariate (age) (middle line) and their 95% and 80% credible intervals from the fully Bayesian inference for the four transitions.

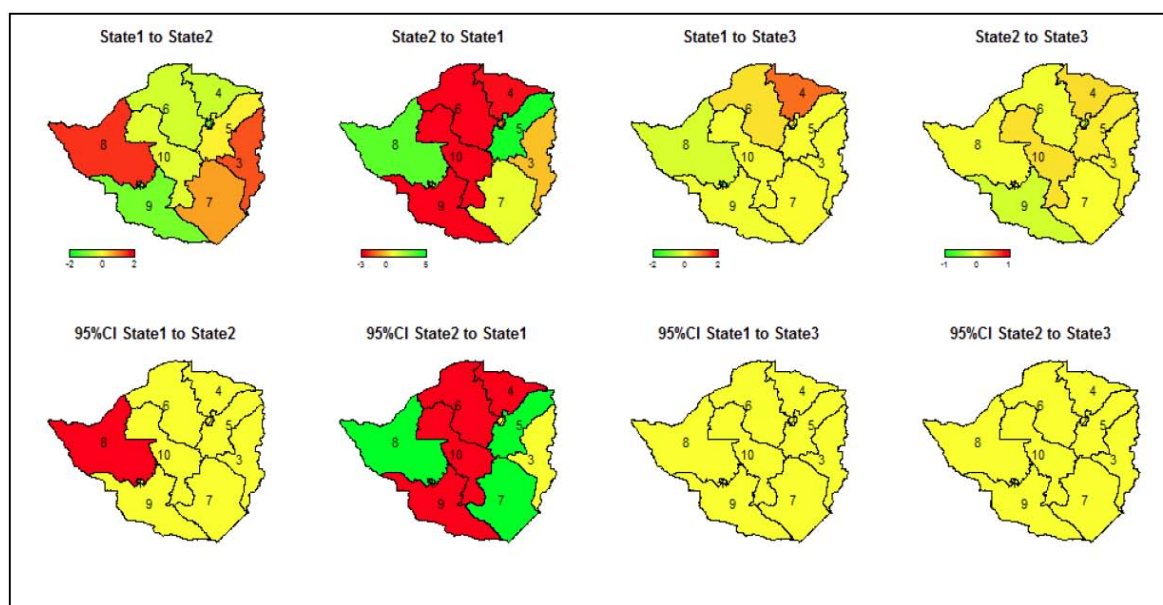


Figure 5: Smooth spatial effects posterior means of provinces in Zimbabwe (top panel) and their corresponding 95% credible intervals (bottom panel) from the fully Bayesian inference [1-Bulawayo, 2-Harare, 3-Manicaland, 4-Mashonaland Central, 5-Mashonaland East, 6-Mashonaland West, 7-Masvingo, 8-Matabeleland North, 9-Matabeleland South, 10-Midland].

means that patients in these regions were less likely to attain undetectable viral suppression compared to other regions.

5. DISCUSSION

The aim of this study was to determine the spatial heterogeneity of viral suppression and viral rebound trajectories from a subset of the Zimbabwe national

ART programme data using a Bayesian geospatial multistate model. To our knowledge, this is the first application of spatial effects within the multistate models' framework since none of the models in the original design has included the spatial random effects. Use of Bayesian multistate models in HIV studies is also scarce in the literature compared to the maximum likelihood multistate models; however, these Bayesian models are equally robust despite being



computationally intensive. Bayesian models give more comprehensive information through the use of priors which results in much more precise estimates as compared to the frequentist models [7]. Moreover, the spatial modelling has not been fully utilized in HIV monitoring to guide policy, particularly in resource constrained areas. We observed variations on viral suppression and viral bound transition patterns by geographical region, age, gender and WHO status in this cohort.

5.1. Epidemiological Discussion

The study findings showed that the log-baseline hazard rates for the viral load suppression to undetectable levels (state 2 to state 1) transition were as expected. The longer the patient was on ART, the more likely that patient was to attain viral suppression to undetectable levels. This is a good indication of how ART helps one to regress to a better state with time by improving viral suppression. This finding affirms the primary objective of ART which is to sustain viral suppression, decrease HIV transmission and improve survival outcomes of the individuals through immune function reconstitution [22]. Moreover, attaining a viral suppression is crucial for PLWHIV so that their life expectancy can be comparable to HIV-uninfected population [22]. The study results also assert that patients who are initiated on ART with advanced illness tend to adhere to their medication anticipating to recover and prolong their lives together with their families [23]. Surprisingly, male patients were more likely to attain viral suppression compared to female patients; however, male patients with high viral load measurements were more likely to die than recover. The higher risk of mortality among males can be explained by their association with poor immunological response to treatment resulting in death [24]. Male patients also have poor health-seeking behaviour compared to females which may result in late HIV diagnosis and delayed ART initiation [25]. To achieve and sustain viral suppression, interventions which minimize mortality, target high-risk behaviour changes and increase the gravity of ART adherence are crucial for males. For instance, rapid roll-out and promotion of self-testing campaigns [26] may be considered for people who do not usually seek voluntary HIV testing in health facilities to promote community-based testing among male subpopulation [27, 28]. The 30-60 years aged patients showed a higher effect of attaining viral suppression in this study, while adolescents and young adult subpopulations showed lower effects. This finding aligns with previous studies indicating that adolescents

and young adult subpopulations experience suboptimal clinical outcomes and face different challenges which may result in treatment non-adherence [22]. The adolescence group is also known to be vulnerable as they are in the dynamic life transition of becoming independent [29]. Young adults group may not fully understand the gravity of ART adherence; hence, health care and social service providers should compassionately offer continual counselling support to improve young adults' retention.

The log-baseline hazard rates for the viral rebound transition also increased with increase in time. In the presents of potent and effective ART treatment, it would be logical to expect a decrease in the viral rebound (state 1 to state 2) transition rates over time; however, this was not the case in this study. The results assert that sustaining viral suppression is still a challenge in HIV treatment. This finding can be explained by the fact that once individuals attain viral suppression, they may think that they are fully healthy again and no longer see the importance of continual treatment intake. This results in treatment interruptions which can trigger treatment defaulting, non-adherence, failure or resistance [30, 31]. Other studies have shown that majority of patients who attain a viral rebound with low CD4 cell counts are more likely to experience poor ART outcomes like HIV disease progression, loss to follow-up and mortality resulting in poor patient retention in HIV care [3, 22].

Interestingly, this study observed that adolescence and young adults aged below 30 years were found to have a higher risk of viral rebound. This finding supports previous studies that have shown that adolescents and young adults are less likely to achieve and sustain viral suppression [32]; hence, their risk of mortality is higher than older patients [3]. This finding can be explained by the fact that the below 30 years age group faces different life encounters which may lead to treatment non-adherence putting them at risk of unsustained viral load suppression and consequently viral rebound [22]. We also observed that older patients aged 60 years and above had a high risk of attaining viral rebound in this cohort. This can be explained by the fact that this group is associated with non-communicable comorbidities like hypertension diabetes and cancers in addition to communicable illnesses like tuberculosis associated with HIV infection [33]. These comorbidities result in multiple drug toxicity which may trigger non-adherence and subsequently viral rebound. Therefore, pharmacological services should aim to continue providing potent and effective ART regimens



with minimum side-effects and less prone to resistance to achieve treatment adherence and viral suppression. Not only can viral rebound results in death outcomes but also in an upsurge in vulnerability to opportunistic infections since the immune system becomes weaker; and this is supported by the observed high risk of viral rebound among patients with advanced WHO clinical stages in this study.

The smooth spatial effects show that patients from the Matabeleland North province had a higher risk of viral rebound. This finding could be supported by the fact that this region has a lot of movement of residents to Botswana and Zambia seeking jobs or informal trading which may attribute to poor retention and subsequently poor treatment adherence. Moreover, due to tourism activities which attract diverse people and the existence of the long truck route connecting into neighbouring countries, this region has a high risk of multiple sex partners [34] and is prone to sex for money activities [35] which may contribute to acquiring new HIV strains. This becomes a threat to viral suppression and promotes viral rebound through ART resistance or failure resulting in the need of a different HIV regimen. Besides, the viral rebound spatial patterns depicted in this region could be due to non-adherence to treatment yielding from poor provider-patient relationships; therefore, professional training of service providers on the proper code of conduct towards HIV patients is critical. Another reason could be the short treatment dispensary period of 3 months, especially for informal traders to neighbouring countries; hence, revising these guidelines to 6 months can be an option. Also, rural residents in this region may face transport challenges due to the poor road networks and terrain. Interventions like ART adherence clubs functional mobile clinics, community-based dispensing points or other optional ART distribution strategies for these communities may be of benefit [36,37]. The smooth spatial effects for viral suppression show that patients from the intra-regions stretching from the Botswana border to Zambia/Mozambique border were less likely to attain viral suppression. This finding could be explained by late presentation leading to delayed ART initiation [38,39]; hence, immune recovery becomes slow in most instances. Interventions which were found to be effective include strengthening and intensifying index testing, lay testing and community mobilization for testing-HIV musical galas campaigns in addition to self-testing campaigns [27, 28].

5.2. Statistical Discussion

Our modelling approach incorporated the spatial random effects in the flexible predictor of the multistate model. This controlled for unobserved heterogeneity in addition to individual random effects which frequentist models cannot handle [40]. Such modelling approaches in epidemiological studies are of importance to get unbiased estimates as they reflect reality. This convolution modelling approach of the spatial component was preferred since it fully accounts for the spatial correlation and address essential public health aspects that are beyond the scope of a simple pictorial analysis [41]. Moreover, time-varying transition intensities were considered to account for the dynamic natural events.

Our findings should be interpreted cautiously; participants used in this study were conveniently sampled from the Zimbabwe national ART program ePMS database on the basis of having two consecutive viral load measurements leading to participant selection bias. This small sample might not be a true representation of all ART patients in Zimbabwe over this period in time and may negatively impact on the generalizability and inference of the observed results. This means the data should be viewed as a non-random representation from all those who are on ART in Zimbabwe. Relatively few death outcomes were observed in this study which could be due to under-reporting of the deaths in the ePMS database; hence, it is likely that the mortality transitions were underestimated in this study. Moreover, the model used assumed right censoring of observations since it cannot support interval censoring. However, going forward the statistical analysis approach used provides useful information to epidemiologist, patients and policymakers on the spatial variations of viral load transitions for HIV/AIDS disease progression and death.

This study acknowledges how ART policies have been changing over the years. ART regimen prescription has changed from multiple-tablets daily regimen to single-tablet once daily regimens. The impact of the single-tablet once daily regimens prescription has resulted in improved adherence, improved patient satisfaction and improved virological response [42,43]; however, this study could not adjust for these time-varying covariates since they were not available in the analysed data. Also, there have been changes in ART monitoring policy moving from WHO clinical monitoring to CD4 cell counts monitoring and



now the use of viral load monitoring. The overall policy impact of using viral load monitoring has resulted in a faster switch of ART regimen when treatment failure is indicated from first-line to second-line therapy [44]. This subsequently leads to patients attaining viral suppression and reduced HIV transmission; however, most developing countries still have centralized laboratories which can be logistically challenging to meet WHO recommendations to measure viral load at baseline and after every 6 months [44, 45]. Over the years, most resource-limited settings including Zimbabwe have been doing differential monitoring targeting those patients with clinical signs which require viral load assessment as recommended by the clinician. This means, after achieving viral suppression, most of these patients did not have another viral load measurement taken until they had clinical signs which justify a viral load measurement to be taken. This differential monitoring approach may give biased inferences through participants' selection bias since we are likely to have considered predominantly those patients with conditional viral load measurements based on the physician discretion. However, since 2016, there have been significant strides towards viral loads measurements monitoring are per WHO recommendations for HIV monitoring in Zimbabwe [46].

We also did not consider ART adherence in this study which is an important predictor of viral suppression and viral rebound since it was not measured in the data; therefore, future research should consider these influential variables. Additionally, the difference between the spatial regions in viral suppression or viral rebound patterns may be due to the small sample sizes of participants in these regions which might not completely represent the regional picture had the estimates been weighted or sample size increased. However, our results for the spatial viral rebound transitions align with the national surveys in that, the region we found to have the highest likelihood of viral rebound was ranked the second-highest HIV prevalence region in ZIMPHIA 2015/16 national survey [46]. This affirms that regions with high viral rebound are susceptible to high risk of viral transmission leading to high HIV infections in the general population. Moreover, the differences in health facilities which offer ART services in Zimbabwe could have influenced the observed results in that, regions with fewer dispersed health facilities are associated with poor HIV disease progression outcomes since access to treatment is not as easy as those regions with multiple health facilities. Besides, health facilities in urban or cities usually

perform better in terms of ART patients support and service provision compared to rural health facilities. However, despite these limitations, important information regarding viral suppression and viral rebound transitions and the associated spatial heterogeneity patterns were determined; and the subpopulation groups of people with a high risk of suboptimal viral rebound and mortality were also identified using the Bayesian geoadditive multistate model.

6. CONCLUSION

This study demonstrated the first inclusion of spatial random effects in Bayesian multistate models' framework implemented in the C++ BayesX free software and we observed that the viral suppression transitions were not static. The inclusion of spatial effects in multistate models is of profound relevance in resource-limited settings in the evolving modelling techniques. Structured maps are useful for policymakers to visually identify high-risk regions and interventions on those areas unveiling eminent outcome risk [47]. Further studies need to consider the effects of CD4 cell counts on the viral load suppression and rebound transitions to get improved outcomes from a Bayesian perspective [4]; adjust for the effects of time-varying covariates like regimen change on the viral suppression and viral rebound transition; consider regional donor funds or HIV interventions to get much more informative findings. Also, the viral suppression and viral rebound spatial correlation can be extended to district levels spatial units or different subpopulation groups to precisely guide targeted intervention to specific subpopulation groups.

Suboptimal adherence and poor retention in care increase the risk of viral rebound, particularly among adolescents and young adult subpopulation. Holistic intervention approaches which may be considered include self-monitoring, peer support, patient follow-ups, treatment refill mobile phone reminders, and patient and caregiver educational support. Health literacy and belief are significant barriers to ART adherence; hence, interventions which include education sessions on ART addressing the negative effects of beliefs in divine healing, the inclination for traditional medicine and misconceptions over ART benefits and safety are crucial to achieve and sustain viral suppression. Moreover, models which expedite treatment uptake for the newly diagnosed patients coupled with tailored approached for adolescents, young adults and male subpopulations should be



developed to promote early diagnostics and ART uptake, reduce barriers to care and subsequently to achieve optimal health of these subpopulations. Most promising interventions which improve ART adherence and patient retention in care through minimizing "leakages" in the HIV continuum of care cascade are essential for all patients in care and should be the focus of HIV treatment and prevention in the pursuit of the UNAIDS 90-90-90 fast track targets.

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AUTHOR'S CONTRIBUTION

ZMZ conceived the idea and performed all the analyses. EM guided and oversaw the analysis. ZMZ, EM, JT and TFC contributed to the interpretation of the results. ZMZ drafted the manuscript. All authors reviewed the manuscript critically for and approved the final version submitted for publication.

SUPPLEMENT MATERIAL

The supplemental materials can be downloaded from the journal website along with the article.

CONFLICT OF INTEREST

The authors declare that they have no competing interests for this work.

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SUPPLEMENTARY MATERIAL

INTRODUCTION

Modelling data with the following characteristics: a dependent variable is the waiting time until the occurrence of an event; observations are censored where the event of interest has not occurred during the observed time and the data has predictors whose effect on the waiting time is of interest. To be able to tackle this, we make use of survival models and their basic functions are the survival and hazard functions which are illustrated below.

APPENDIX 1: THE SURVIVAL FUNCTION

Assuming T to be a continuous random variable with a known probability density function $f(t)$; the cumulative distribution function is defined as the probability that the event has occurred by duration time t :

$$F(t) = P(T < t) = 1 - \int_0^t f(s) ds \quad (\text{A.1})$$

Often, much interest is on getting the probability that the event of interest has not occurred by duration time t . This leads to the following expression which is a complement of the cumulative distribution function, the *survival function* in convectional survival models:

$$S(t) = P(T \geq t) = 1 - F(t) = \int_t^\infty f(x) dx \quad (\text{A.2})$$

APPENDIX 2: THE HAZARD FUNCTION

An alternative characterization of T is the *hazard function* $\lambda(t)$ defined as instantaneous rate of occurrence of the event. In continuous time, $\lambda(t)$ is expressed as:

$$\lambda(t) = \lim_{\delta t \rightarrow 0} \frac{P(t \leq T < (t + \delta t) / T \geq (t))}{\delta t} = \lim_{\delta t \rightarrow 0} \frac{P(t, t + \delta t)}{\delta t} \quad (\text{A.3})$$

The numerator of the Equation (A.3) is the conditional probability that the event will occur in the interval $(t, t + \delta t)$ given that it has not occurred before while the denominator is the width of the interval. This conditional probability may be written as a ratio of a joint probability that T is in the interval $(t, t + \delta t)$ and $T \geq (t)$, to the probability of the condition $T \geq (t)$. In other words, the hazard rate is a quotient of the probability density function $f(t)$ and the survival function $S(t)$. Further expanding Equation (A.3) yields:

$$\lambda(t) = \lim_{\delta t \rightarrow 0} \frac{P(T \geq (t) / t \leq T < (t + \delta t)) P(t \leq T < (t + \delta t))}{P(T \geq (t)) \delta t} \quad (\text{A.4})$$

But $f(t) = \lim_{\delta t \rightarrow 0} \frac{P(t \leq T < (t + \delta t))}{\delta t}$, $P(T \geq (t) / t \leq T < (t + \delta t)) = 1$ and from Equation (A.2) $P(T \geq t) = S(t)$. Substituting these into Equation (A.4) yields:

$$\lambda(t) = \frac{f(t)}{S(t)} \quad (\text{A.5})$$

From Equation (A.5) above, $-f(t)$ is the derivative of $S(t)$, explicitly expressed as $f(t) = \frac{d}{dt} F(t) = \frac{d}{dt} P(T < t) = \frac{d}{dt} (1 - S(t)) = -\frac{d}{dt} S(t)$. Therefore, Equation (A.5) becomes

$$\lambda(t) = \frac{f(t)}{S(t)} = \frac{-\frac{d}{dt}S(t)}{S(t)} = \frac{-S'(t)}{S(t)}. \quad (\text{A.6})$$

Integrating both sides of this latest expression: $\int_0^t \lambda(t) dt = \int_0^t -\frac{d}{dt}S(t) \times \frac{1}{S(t)} dt$ and simplifying the right hand side (RHS) using integration by parts, $u = -\frac{d}{dt}S(t)$ and $v = \frac{1}{S(t)}$ yields:

$$\int_0^t \lambda(t) dt = -\frac{d}{dt}S(t) \left(\frac{1}{S(t)} \right) - \int_0^t \frac{1}{S(v)} dv = -[\log S(t) - \log S(0)] \quad (\text{A.7})$$

If we differentiate both sides, $\frac{d}{dt} \int_0^t \lambda(t) dt = \frac{d}{dt} -\log S(t)$, we get the hazard rate expressed in terms of the derivative of log survival function:

$$\lambda(t) = \frac{d}{dt} -\log S(t) \quad (\text{A.8})$$

To obtain the expression of the survival function, we integrate both sides of Equation (A.8):

$$\int_0^t \lambda(t) dt = \int_0^t \frac{d}{dt} -\log S(t) dt = -\log S(t)$$

Re-arranging this expression above gives the survival function as an exponential distribution with a parameter $\lambda(t)$ as:

$$S(t) = \exp \left[-\int_0^t \lambda(t) dt \right] \quad (\text{A.9})$$

The integral expression is called the *cumulative hazard* (or cumulative risk) $\Lambda(t)$, which is a sum of all risks from duration 0 to t , denoted by:

$$\Lambda(t) = \int_0^t \lambda(t) dt \quad (\text{A.10})$$

In summary these results show that, the survival function and the hazard function give equivalent characterization of the distribution of the random variable T . If provided with $S(t)$, we differentiate to obtain $f(t)$ and estimate $\lambda(t)$ using Equation (A.5). Alternatively, starting with $\lambda(t)$, we can integrate and obtain $\Lambda(t)$ and exponentiate to get $S(t)$ using Equation (A.9).

In time to event modeling, the probability density function $f(t)$ plays a central role. Similarly, we can obtain the density as follows, using Equation (A.5), we integrate both sides

$$\int_0^t \lambda(t) dt = \int_0^t \left(\frac{f(t)}{S(t)} \right) dt = \int_0^t \left(\frac{f(t)}{1 - F(t)} \right) dt = \int_0^t \left(\frac{f(s)}{1 - \int_0^s f(s) ds} \right) ds. \quad \text{If we integrate the RHS by parts}$$

$$u = f(s), v = \frac{1}{1 - \int_0^s f(s) ds} \text{ this gives:}$$

$$\begin{aligned}
\int_0^t \left(\frac{f(s)}{1 - \int_0^s f(v) dv} \right) ds &= \frac{f(s)}{1 - \int_0^s f(v) dv} - \int_0^t \left(\frac{1}{1 - \int_0^v f(v) dv} \right) dv \\
&= \frac{-\frac{d}{dt} S(t)}{\left[1 - F(t) = S(t) \right]} - \log \left[1 - \int_0^t f(v) dv \right]_0^t \\
&= -\log \left[1 - \int_0^t f(t) dt \right]
\end{aligned} \tag{A.11}$$

With this expression, $\int_0^t \lambda(t) dt = -\log \left[1 - \int_0^t f(t) dt \right]$ can be rearranged as:

$$S(t) = \exp \left(- \int_0^t \lambda(t) dt \right) = 1 - \int_0^t f(t) dt, \tag{A.12}$$

and if we differentiate both side of Equation (A.12), we get:

$$\begin{aligned}
\frac{d}{dt} \exp \left(- \int_0^t \lambda(t) dt \right) &= \frac{d}{dt} \left(1 - \int_0^t f(t) dt \right) \\
\frac{d}{dt} \exp \left(- \int_0^t \lambda(t) dt \right) &= \frac{d}{dt} (1 - F(t)) \\
-\lambda(t) \exp \left(- \int_0^t \lambda(t) dt \right) &= -f(t)
\end{aligned} \tag{A.13}$$

This solution leads to the probability density function, which is fundamental in time to event analysis:

$$f(t) = \lambda(t) \exp \left(- \int_0^t \lambda(t) dt \right) \tag{A.14}$$

From Equation (A.14), we can see that the probability density function is a product of transition (hazard) rate and the survival function.

APPENDIX 3: LIKELIHOOD FUNCTION

The likelihood function of the survival model is just a product of the probability density function, Equation (A.14).

$$L = \prod_{i=1}^n \lambda_i(t_i)^{\delta_i} \exp \left(- \int_0^t \lambda_i(t) dt \right) = \prod_{i=1}^n \lambda_i(t_i)^{\delta_i} S(t_i) \tag{A.15}$$

where $i = 1, 2, \dots, n$ individuals and δ is the censoring indicator for the process. Taking the logs, and recalling the link between $S(t)$ and $\Lambda(t)$, we obtain the log-likelihood function of the censored survival data. Simplifying the product sign:

$$\begin{aligned}
L &= \prod_{i=1}^n \lambda_i(t_i)^{\delta_i} \exp \left(- \int_0^t \lambda_i(t) dt \right) \\
L &= \lambda(t_i)^{\sum_{i=1}^n \delta_i} \exp \left(\sum_{i=1}^n - \int_0^t \lambda_i(t) dt \right)
\end{aligned} \tag{A.16}$$

Taking logs both sides:

$$\begin{aligned}
\log L &= \log \lambda(t_i)^{\sum_{i=1}^n \delta_i} \left(\sum_{i=1}^n - \int_0^t \lambda_i(t) dt \right) \\
\log L &= \sum_{i=1}^n \delta_i \log \lambda(t_i) - \left(\sum_{i=1}^n \Lambda(t_i) \right)
\end{aligned} \tag{A.17}$$

Hence, the final expression for the log-likelihood would be:

$$\log L = \sum_{i=1}^n (\delta_i \log \lambda(t_i) - \Lambda(t_i)) \quad (\text{A.18})$$

From this expression, we can get the maximum likelihood estimator as follows: Let $D = \sum_{i=1}^n \delta_i$ be the total observed outcomes during the period under observation, $T = \sum_{i=1}^n t_i$ be the total observation/exposure time and $\lambda(t_i) = \lambda$ for all t and the cumulative risk is the integral of a constant; hence, is equal to $\lambda(t)$. If we differentiate with respect to λ we get:

$$\log L = D \log \lambda(t) - \lambda T, \text{ i.e., } \frac{d \log L}{d \lambda} = D \lambda - T = 0$$

Therefore, the maximum likelihood estimator will be:

$$\hat{\lambda} = \frac{D}{T} \quad (\text{A.19})$$

APPENDIX 4: THE COX PROPORTIONAL HAZARD

A conventional method for analyzing the effects of covariates on right-censored survival data defined by observed lifetimes t_i with censoring indicators for individuals $i = 1, 2, 3, \dots, n$, and additional covariate observations v_i is the semi-parametric Cox proportional hazard model (1972). The model focuses directly on the hazard function, where the hazard at time t for an individual with a vector of covariates v is assumed to be:

$$\lambda_i(t) = \lambda_i(t/v) = \lambda_0(t) \exp(v_i' \gamma) \quad (\text{A.20})$$

where $\lambda_0(t)$ is the baseline hazard function. Taking logs, the proportional hazard model becomes a simple additive model for the log of the hazard and separates clearly the effects of time from the covariates, i.e.,

$$\log \lambda_i(t) = \log \lambda_i(t/v) = \log \lambda_0(t) + v_i' \gamma \quad (\text{A.21})$$

The cumulative hazards are obtained by integrating Equation (A.21):

$$\int_0^t \lambda_i(t/v) dt = \exp(v_i' \gamma) \int_0^t \lambda_0(t) dt, \text{ i.e., } \Lambda_i(t/v) = \Lambda_0(t) \exp(v_i' \gamma) \quad (\text{A.22})$$

The survival function is obtained by multiplying Equation (A.22) by a negative sign and exponentiating both sides. This gives:

$$\exp \int_0^t -\lambda_i(t/v) dt = \exp \left(\int_0^t -\lambda_0(t) \exp(v_i' \gamma) dt \right), \text{ i.e., } S_i(t/v) = S_0(t) \exp(v_i' \gamma) \quad (\text{A.23})$$

APPENDIX 5: THE DESCRIPTION OF THE MULTISTATE MODEL

When an individual is observed longitudinally, he/she is likely to experience multiple outcomes in the course of the follow-up period. In such scenario, Cox proportional hazards are not appropriate since there will be multiple outcomes; hence, multiple possible transitions. In this regard, multistate model are preferred to simultaneously estimate the transition rates/intensities of these individuals.

A multistate process is a stochastic process $(X(t), t \in T)$ with finite state space $S = \{1, 2, \dots, R\}$ where $T = [0, \tau]$ is a

non-negative, continuous random variable denoting the survival time of an individual, and $X(t)$ is the state occupied by an individual at time $t > 0, X(t) \in S$ [1]. The common functions governing the multistate models are the transition intensities (hazard rates) and transition probabilities (survival function). The individual-specific transition intensity for transition j to k , ie, $\lambda_{jk,i}(t)$, with covariates $\mathbf{v}_i(t)$ and parametric effects γ_{jk} is estimated in a multiplicative proportional hazard model way define in Equation (A.20) as:

$$\lambda_{jk,i}(t) = \lambda_{jk,i}(t/\mathbf{v}) = \lambda_{jk,0}(t) \exp(\mathbf{v}_i'(t) \gamma_{jk}) \quad (\text{A.24})$$

This semiparametric model hazard rate can be estimated in two ways, either through a piecewise exponential model assuming that all time dependent values are piecewise constant [14] or through estimating the log-baseline effect by a P-spline prior of arbitrary degree with a second order penalty [15]. The latter is a more general way to model the non-linear shape of the baseline effect. The log-baseline is defined as $\lambda_{jk,0}(t) = \exp[\log\{\lambda_{jk,0}(t)\}]$, this updates Equation (A.24) to

$$\lambda_{jk,i}(t) = \exp(\eta_{jk,i}(t)) \quad (\text{A.25})$$

where

$$\eta_{jk,i}(t) = \exp(\log \lambda_{jk,0}(t) + \mathbf{v}_i'(t) \gamma_{jk}) = \exp(g_{jk,0}(t) + \mathbf{v}_i'(t) \gamma_{jk}) \quad (\text{A.26})$$

and the log-baseline hazard rate is reparameterised to $g_{jk,0}(t) = \log(\lambda_{jk,0}(t))$ which is the nonparametric baseline effects uniform for all individuals. The linear predictor $\eta_{jk,i}(t)$ is flexible and different types of covariates can be added including continuous covariates with nonparametric effects, spatial terms and random effects in addition to the fixed parametric effects. Including such covariates use in this study, we have:

$$\eta_{jk,i}(t) = g_{jk,0}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + \mathbf{v}_i'(t) \gamma_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \quad (\text{A.27})$$

where $f_{jk,r}(t) x_{r,i}(t)$ are non-linear effects of a continuous covariate $x_{r,i}(t)$ (age; parametric fixed effects γ_{jk} of covariates $\mathbf{v}_i(t)$ we had WHO clinical stages (I/II or III/IV) and gender (male or female; the function $f_{jk,spat}(t)(s_i)$ is a structured spatial effect, where $s, s=1, 2, \dots, S$, is a spatial index with $s_i = s$ if individual i is from province s to account for spatial heterogeneity. The spatial can be split into structured (correlated) and unstructured (uncorrelated), that is, $f_{jk,spat}(t)(s_i) = f_{jk,str}(t)(s_i) + f_{jk,unstr}(t)(s_i)$. Parameter $b_{jk,i}$ is a subject or group specific frailty or random effect.

APPENDIX 6: LIKELIHOOD SPECIFICATION IN MULTISTATE MODELS

Similarly, the likelihood in the multistate model is the product of the probability density function within the survival data which is generally exponentially distributed, as defined in Equation (A.14); however, we specify the transition as:

$$f_{jk,i}(t) = \lambda_{jk,i}(t) \exp\left(-\int_0^t \lambda_{jk,i}(t) dt\right) \quad (\text{A.28})$$

In this case, the integral evaluates or sum all transitions the corresponding individual is at risk for the period under observation. We assume that a full transition path occurs for each individual of the following parts: A set of ordered time points $0 = S_{i0} < S_{i1} < \dots < S_{iz} < \dots < S_{im_i}$ indicating the transition times for an individual i , the state $Y_i(S_{iz}), z = 0, \dots, m_i$, the individual moves to at the end of the time interval and where each individual contributions is defined in terms of transition indicators $\delta_{jk,i}(t)$ which is equal to one if a jk transition before time (t) and zero. We

can deduce the duration time in the z^{th} state as $T_{iz} = S_{iz} - S_{i,z-1}$, $z = 1, \dots, m_i$.

Rewriting the observation model (Equation A.27) in a generic matrix notation, we define some matrices. Let $\eta_{jk} = (\eta_{jk,1}, \eta_{jk,2}, \dots, \eta_{jk,n})'$ be a predictor vector, where $\eta_{jk,i} = \eta_{jk,i}(t_i)$ is the predictor value (Equation A.27) at the observed time t_i , $i = 1, 2, \dots, n$. Correspondingly, let $f_{jk,r} = (f_{jk,r}(x_{1r}), f_{jk,r}(x_{2r}), \dots, f_{jk,r}(x_{nr}))'$ denotes the vector of functions $f_{jk,r}(x_r)$, $r = 1, 2, \dots, R$; $f_{jk,spat} = (f_{jk,spat}(s_1), f_{jk,spat}(s_2), \dots, f_{jk,spat}(s_n))'$ denotes the vector of spatial effects and $b_{jk,i} = (b_{jk,i,1}, b_{jk,i,2}, \dots, b_{jk,i,n})'$ denote a vector of uncorrelated spatial and individual-specific random effects. The predictor components $f_{jk,r}$, $f_{jk,spat}$ and $b_{jk,i}$ can be expressed as the matrix product of a defined design matrix Z and a (high dimensional) vector of random effects $\beta = (\beta_{jk,1}, \beta_{jk,2}, \dots, \beta_{jk,p})'$ of (regression) coefficients parameters for $r = 1, 2, \dots, p$; for instance, $(f_{jk,r} = Z_{jk,r} \beta_{jk,r})$. After reindexing the observable transitions in the multistate model, we can represent the predictor vector η_{jk} in a generic notation as:

$$\eta_{jk} = V\gamma + Z_{jk,1}\beta_{jk,1} + Z_{jk,2}\beta_{jk,2} + \dots + Z_{jk,p}\beta_{jk,p} \quad (A.29)$$

With reference to this current study, the generic notation becomes $\eta_{jk} = V\gamma + Z_{jk,1}\beta_{jk,1} + Z_{jk,2}\beta_{jk,2} + Z_{jk,3}\beta_{jk,3}$ for 1=non-linear continuous effects, 2=spatial effects and 3= random effects accounting for heterogeneity. The individual likelihood for continuous survival data assumes non-informative censoring, given the parameters $\gamma_{jk,c} = (\gamma'_{jk,1}, \gamma'_{jk,2})'$, $\tau^2_{jk,q} = (\tau^2_{jk,r}, \tau^2_{jk,gi}, \tau^2_{jk,spat})'$ and $\beta_{jk,r} = (\beta'_{jk,1}, \beta'_{jk,2}, \beta'_{jk,3})'$, the probability density function with specified transition expressed as:

$$L(\gamma, \beta, \tau^2) = \prod_{i=1}^{JK} \lambda_i(t_i)^{\delta_{jk,i}(t_i)} \exp\left(-\int_0^{t_i} \lambda_i(t) dt\right) \quad (A.30)$$

Considering the individual transition times S_{zi} , $z = 1, 2, \dots, m_i$ corresponding to a transition process yields:

$$L(\gamma, \beta, \tau^2) = \prod_{z=1}^{m_i} \prod_{i=1}^{JK} \lambda_i(S_{zi})^{\delta_{jk,i}(S_{zi})} \exp\left(-\int_{S_{i,z-1}}^{S_{zi}} \lambda_i(t) dt\right) \quad (A.31)$$

If we take logs both sides and simplify the product, we get:

$$\log L(\gamma, \beta, \tau^2) = (\log \lambda_i(S_{zi})) \sum_{i=1}^{m_i} \sum_{j=1}^{JK} \delta_{jk,i}(S_{zi}) - \sum_{z=1}^{m_i} \sum_{i=1}^{JK} \left(\int_{S_{i,z-1}}^{S_{zi}} \lambda_i(t) dt \right) \quad (A.32)$$

From the classical counting process theory, the intensity processes $\alpha_{jk,i}(t)$ are a product of the hazard rate for a specified transition $(\lambda_{jk,i}(t))$ constructed in terms covariates as shown in Equation (A.27); and a predictable at risk indicator process $(I_{jk,i}(t))$ which is equal to one if an individual is at risk of a jk transition before time (t) and zero otherwise, that is,

$$\alpha_{jk,i}(t) = \lambda_{jk,i}(t) \times I_{jk,i}(t) \quad (A.33)$$

Considering the log-likelihood formula for the same data by including the risk indicator process $(I_{jk,i}(t))$ yields:

$$\log L(\gamma, \beta, \tau^2) = \left(\log \lambda_i(S_{zi}) \times I_{jk,i}(S_{zi}) \right) \sum_{i=1}^{m_i} \sum_{j=1}^{JK} \delta_{jk,i}(S_{zi}) - \sum_{z=1}^{m_i} \sum_{i=1}^{JK} \left(\int_{S_{i,z-1}}^{S_{zi}} (I_{jk,i}(S_{zi})) \lambda_i(t) dt \right) \quad (\text{A.34})$$

which simplifies to

$$\begin{aligned} \log L(\gamma, \beta, \tau^2) &= \left(\sum_{i=1}^{m_i} \sum_{j=1}^{JK} \delta_{jk,i}(S_{zi}) \log \lambda_i(S_{zi}) \times I_{jk,i}(S_{zi}) \right) - \sum_{z=1}^{m_i} \sum_{i=1}^{JK} \left(\int_{S_{i,z-1}}^{S_{zi}} (I_{jk,i}(S_{zi})) \lambda_i(t) dt \right) \\ &= \sum_{i=1}^{m_i} \sum_{j=1}^{JK} \left[\left(\delta_{jk,i}(S_{zi}) \log \lambda_i(S_{zi}) \times I_{jk,i}(S_{zi}) \right) - \left(I_{jk,i}(S_{zi}) \int_{S_{i,z-1}}^{S_{zi}} \lambda_i(t) dt \right) \right] \end{aligned} \quad (\text{A.35})$$

where $\lambda_i(S_{zi})$ is defined by Equation (A.27) to give the final expression as:

$$\begin{aligned} \log L(\gamma, \beta, \tau^2) &= \sum_{i=1}^{m_i} \sum_{j=1}^{JK} \left[\delta_{jk,i}(S_{zi}) \times I_{jk,i}(S_{zi}) \times \right. \\ &\quad \left. \log \left(g_{jk,0}(S_{zi}) + \sum_{r=1}^R f_{jk,r}(S_{zi}) x_{r,i}(S_{zi}) + v_i(S_{zi})' \gamma_{jk} + f_{jk,spat}(S_{zi})(s_i) + b_{jk,i} \right) \right. \\ &\quad \left. - \left(I_{jk,i}(S_{zi}) \times \int_{S_{i,z-1}}^{S_{zi}} \left(g_{jk,0}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + v_i(t)' \gamma_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \right) dt \right) \right] \end{aligned} \quad (\text{A.36})$$

Let $\delta_{jk,i} = (\delta_{jk,1}, \delta_{jk,2}, \dots, \delta_{jk,n})'$ be a vector of censoring indicators and $\Lambda_{jk,i} = (\Lambda_{jk,1}(t)_1, \Lambda_{jk,2}(t)_2, \dots, \Lambda_{jk,n}(t)_n)'$ the vector of cumulative hazard rates $\Lambda_{jk,i}(t_i) = \int_0^{t_i} \lambda_{jk,i}(t) dt$. Then the log-likelihood can be expressed in terms of cumulative hazard function as:

$$\log L(\gamma, \beta, \tau^2) = \delta'_{jk,n} \eta_{jk,n} - \mathbf{1}' \Lambda_{jk,n} \quad (\text{A.37})$$

If the degree of the P-spline prior for the log-baseline hazard function is greater than one, then the likelihood integral can no longer be solved in a closed form.

APPENDIX 7: THE PRIOR SPECIFICATIONS

- (1) Priors for functions and spatial components (*random effects (regression) coefficients parameter vector $\beta_{jk,r}$*) are defined by a suitable design matrix $\mathbf{Z}_{jk,r}$ for $r = 0, 1, \dots, p$ and a joint prior of the parameter vector $\beta_{jk,r}$ in Equation (A.29) is Gaussian expressed as:

$$P(\beta_{jk,r} / \tau_{jk,r}^2) \propto \exp \left(-\frac{\beta_{jk,r}' \mathbf{W}_{jk,r} \beta_{jk,r}}{2\tau_{jk,r}^2} \right) \quad (\text{A.38})$$

where $\mathbf{W}_{jk,r} \geq 0$ is a precision or penalty matrix of rank $(\mathbf{W}_{jk,r}) = h_{jk,r}$ with a band structure that is very useful for computationally efficient Markov chain Monte Carlo (MCMC) updating schemes.

- (2) Unknown *nonparametric effects* $f_{jk,r}(t)$ of continuous smooth covariate x_r are estimated using Bayesian penalized splines (P-spline) [6] as a linear combination of a larger number of B-splines basic functions B_d , that is,

$$f_{jk,r}(x_r) = \sum_{d=1}^{D_r} \beta_{jk,rd} B_d(x_r) \quad (\text{A.39})$$

The Bayesian analog are the second order random walk smoothness priors of the form:

$$\beta_{jk,rd} = 2\beta_{jk,r,d-1} - \beta_{jk,r,d-2} + \varepsilon_{jk,rd}, d = 3, 4, \dots, D \quad (\text{A.40})$$

The error terms of the smoothing term $(\varepsilon_{jk,rd})$ identically and independently distributed assuming a normal distribution prior with mean zero and variance in form of precision $(1/\sigma^2 = \tau_{jk,\varepsilon}^2)$, that is $(\varepsilon_{jk,rd} \sim N(0, \tau_{jk,\varepsilon}^2))$. The linear trend coefficients' initial values of the random walk were assigned diffuse/ vague priors, that is, $P(\beta_{jk,r1}) \propto \text{const}$ and $P(\beta_{jk,r2}) \propto \text{const}$.

- (3) For *fixed effects parameters* $\gamma_{jk,c}$, we assigned non-informative diffuse prior, $P(\gamma) \propto \text{const}$. Alternatively, a weak (large variance) normal prior would be another choice.
- (4) For the *spatial effects*, we assumed the Gaussian Markov Random Field (GMRF) [16] priors expressed as:

$$f_{jk,str}(s) = \beta_s^{str} = \frac{1}{N_s} \sum_{s' \in \partial_s} \beta_{s'} + u_s, u_s \sim N\left(0, \frac{\tau_{jk,str}^2}{N_s}\right) \quad (\text{A.41})$$

where $s' \in \partial_s$ denotes that province s' is a neighbor of province s . The unstructured spatial effects $f_{unstr}(s)$ were assumed to be independent and identically distributed Gaussian priors, that is, $f_{unstr}(s) \sim N(0, \tau_{unstr}^2)$.

- (5) The individual *random effects and uncorrelated (unstructured) area-specific spatial effects* $b_{jk,i}$ were assumed identically and independently distributed Gaussian priors with transition specific variances to the frailty terms:

$$b_{jk,i} \sim N(0, \tau_{jk,b}^2) \quad (\text{A.42})$$

- (6) The *variance parameter vector* $\tau_{jk,q}^2 = (\tau_{jk,1}^2, \tau_{jk,2}^2, \dots, \tau_{jk,y}^2)'$ for $q = 1, 2, \dots, y$ contains variance parameter for the error term $\tau_{jk,\varepsilon}^2$, frailty term $\tau_{jk,b}^2$, spatial terms $\tau_{jk,str}^2$ and $\tau_{jk,unstr}^2$ and the generic regression coefficients $\tau_{jk,r}^2$. These variance parameters are normally assigned weakly informative inverse Gamma hyper-priors, that is, the vector $(\tau_{jk,q}^2 \sim IG(a_q, b_q))$ in fully Bayesian inference with the following probability density function:

$$P(\tau_{jk,q}^2) \propto \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(-\frac{b_q}{\tau_{jk,q}^2}\right), \text{ for } a_q, b_q > 0 \quad (\text{A.43})$$

Updating $\tau_{jk,q}^2$ is done using Gibbs Sampler by sampling from an inverse Gamma distribution. The Bayesian model specification is complete by assuming that all priors for parameters are conditionally independent and all priors are mutually independent. All the priors for the parameters are assumed independent. Estimation is based on MCMC simulation technique.

APPENDIX 8: POSTERIOR DISTRIBUTION

Let full Bayesian inference is based on the entire posterior distribution:

$$P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2 / \text{data}) \propto L(\text{data} / \boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) \quad (\text{A.44})$$

The likelihood is:

$$L(\text{data} / \boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) = \prod_{z=1}^{m_i} \prod_{i=1}^{JK} \left\{ \left[\left(g_{jk,0}(S_{zi}) + \sum_{r=1}^R f_{jk,r}(S_{zi}) x_{r,i}(S_{zi}) + \mathbf{v}_i(S_{zi})' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(S_{zi})(s_i) + b_{jk,i} \right) (S_{zi}) \right]^{\delta_{jk,i}(S_{zi})} \right. \\ \left. \times \exp \left(- \int_{S_{i,z-1}}^{S_{i,z}} \left(g_{jk,0}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + \mathbf{v}_i(t)' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \right) (t) dt \right) \right\} \quad (\text{A.45})$$

The joint prior is made up of the individual prior distributions for the parameters. With particular reference to this current study, $\boldsymbol{\beta}_{jk,r} = (\boldsymbol{\beta}'_{jk, \text{fixed\_effects}}, \boldsymbol{\beta}'_{jk, \text{non\_linear\_effects}}, \boldsymbol{\beta}'_{jk, \text{frailty\_term}})'$ is a vector of all coefficients parameters from the generic formulation equation, and $\boldsymbol{\gamma}_{jk,c} = (\gamma_{jk,WHO}, \gamma_{jk,sex})'$ is the vector of fixed effects and $\boldsymbol{\tau}_{jk,q}^2 = (\tau_{jk,e}^2, \tau_{jk,r}^2, \tau_{jk,spat}^2, \tau_{jk,b}^2)'$ the vector of all variance parameters, that is,

- the variance parameter of the error terms in the second random walk for non-parametric effects of continuous covariates $(\tau_{jk,e}^2)$
- the variance parameter of the individual ad spatial uncorrelated random effects $(\tau_{jk,b}^2)$
- the variance parameter of the correlated (structured) random effects $(\tau_{jk,spat}^2)$
- variance parameter for the regression coefficients parameters $(\tau_{jk,r}^2)$

This means the variance vector $\boldsymbol{\tau}_{jk,q}^2 = (\tau_{jk,e}^2, \tau_{jk,r}^2, \tau_{jk,spat}^2, \tau_{jk,b}^2)'$ also follow an inverse Gamma distribution as follows: $P(\boldsymbol{\tau}_{jk,q}^2) \propto \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(-\frac{b_q}{\tau_{jk,q}^2}\right)$, for $a_q, b_q > 0$. Due to conditional independence assumptions, the joint prior factorizes into taking into consideration that $\tau_{jk,r}^2$ is same as $\tau_{jk,q}^2$, therefore:

$$P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) = \left\{ \prod_{q,r=0}^m P(\boldsymbol{\beta}_{jk,r} / \tau_{jk,q}^2) P(\boldsymbol{\tau}_{jk,q}^2) \right\} P(\boldsymbol{\gamma}) \\ = \left\{ \prod_{q,r=0}^m \exp\left(-\frac{\boldsymbol{\beta}'_{jk,r} W_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,q}^2}\right) \times \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(-\frac{b_q}{\tau_{jk,q}^2}\right) \right\} P(\boldsymbol{\gamma}) \quad (\text{A.46}) \\ = \left\{ \prod_{q,r=0}^m \frac{1}{(\tau_{jk,q}^2)^{a_q+1}} \exp\left(\left(-\frac{b_q}{\tau_{jk,q}^2}\right) - \frac{\boldsymbol{\beta}'_{jk,r} W_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\tau_{jk,q}^2}\right) \right\} P(\boldsymbol{\gamma})$$

The last component $P(\boldsymbol{\gamma})$ can be omitted since it represents fixed effects prior, the expression can be further simplified to:

$$\begin{aligned}
 P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2) &\propto \prod_{q,r=0}^m \frac{1}{(\boldsymbol{\tau}_{jk,q}^2)^{a_q+1}} \exp\left(\left(\frac{b_q}{\boldsymbol{\tau}_{jk,q}^2} - \frac{\boldsymbol{\beta}'_{jk,r} W_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\boldsymbol{\tau}_{jk,q}^2}\right)\right) \\
 &= \frac{1}{(\boldsymbol{\tau}_{jk,q}^2)^{m(a_q+1)}} \exp\left(\sum_{r=0}^m \left(\frac{b_q}{\boldsymbol{\tau}_{jk,q}^2} - \frac{\boldsymbol{\beta}'_{jk,r} W_{jk,r} \boldsymbol{\beta}_{jk,r}}{2\boldsymbol{\tau}_{jk,q}^2}\right)\right) \\
 &= \left(\frac{1}{\boldsymbol{\tau}_{jk,q}^{2m(a_q+1)}}\right) \exp\left(b_q m - \frac{1}{2} \sum_{r=0}^m \boldsymbol{\beta}'_{jk,r} W_{jk,r} \boldsymbol{\beta}_{jk,r}\right)
 \end{aligned} \tag{A.47}$$

The posterior distribution $P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2 / \text{data})$ will be an approximation of the product of Equation (A.45) and (A.47) as shown below:

$$\begin{aligned}
 P(\boldsymbol{\beta}, \boldsymbol{\gamma}, \boldsymbol{\tau}^2 / \text{data}) &\propto \prod_{z=1}^m \prod_{i=1}^{JK} \left\{ \left[\left(g_{jk,0}(S_{zi}) + \sum_{r=1}^R f_{jk,r}(S_{zi}) x_{r,i}(S_{zi}) + v_i(S_{zi})' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(S_{zi})(s_i) + b_{jk,i} \right) (S_{zi}) \right]^{\delta_{jk,i}(S_{zi})} \right. \\
 &\quad \times \exp\left(- \int_{S_{i,z-1}}^{S_{i,z}} \left(g_{jk,0}(t) + \sum_{r=1}^R f_{jk,r}(t) x_{r,i}(t) + v_i(t)' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(t)(s_i) + b_{jk,i} \right) (t) dt \right) \Big\} \\
 &\quad \times \left(\frac{1}{\boldsymbol{\tau}_{jk,q}^{2m(a_q+1)}} \right) \exp\left(b_q m - \frac{1}{2} \sum_{r=0}^m \boldsymbol{\beta}'_{jk,r} W_{jk,r} \boldsymbol{\beta}_{jk,r} \right)
 \end{aligned} \tag{A.48}$$

Since this posterior distribution is not in a closed form, we therefore update the full conditionals of single parameters or blocks of parameters, given the rest of data. For updating the parameter vector $\boldsymbol{\beta}_{jk,r}$, which correspond to the time dependent functions, spatial effects, fixed effects and random effects, we use the MH algorithm based on iteratively weighted least squares (IWLS) proposals.

APPENDIX 9: ITERATIVELY WEIGHTED LEAST SQUARES (IWLS): THE TAYLOR EXPANSION

For updating the parameter vector $\boldsymbol{\beta}_{jk,r}$, we use the Metropolis- Hastings (MH) algorithm based on iteratively weighted least squares (IWLS) proposals. For instance, we want to update $\boldsymbol{\beta}_{jk,r}$ with current value, $\boldsymbol{\beta}_{jk,r}^c$, of the chain. The new value $\boldsymbol{\beta}_{jk,r}^p$ is proposed by drawing a random vector from the high-dimensional multivariate Gaussian proposal distribution $q(\boldsymbol{\beta}_{jk,r}^c, \boldsymbol{\beta}_{jk,r}^p)$ which is attained from the quadratic approximation to the posterior by a second order Taylor expansion with respect to $\boldsymbol{\beta}_{jk,r}^c$.

To explicitly illustrate of the Taylor expansion, the primary goal is to approximate the posterior by Gaussian distribution obtained by accomplishing one IWLS step in each of the iterations of the sampler. Then random samples have to be drawn from a high dimensional multivariate Gaussian distribution with the precision matrix and mean:

$$\tilde{\boldsymbol{P}}_{jk,r} = \boldsymbol{Z}'_{jk,r} \boldsymbol{K}(\boldsymbol{\beta}_{jk,r}^c) \boldsymbol{Z}_{jk,r} + \boldsymbol{W}_{jk,r} \boldsymbol{\tau}_{jk,r}^{-2}, \tilde{\boldsymbol{m}}_{jk,r} = \tilde{\boldsymbol{P}}_{jk,r}^{-1} \boldsymbol{Z}'_{jk,r} \boldsymbol{K}(\boldsymbol{\beta}_{jk,r}^c) (\tilde{\boldsymbol{y}} - \tilde{\boldsymbol{\eta}}) \tag{A.49}$$

where $\tilde{\boldsymbol{\eta}}_{jk,i} = \boldsymbol{\eta}_{jk,i}(t_i) - f_{jk,r}(x_{ir})$ and $\boldsymbol{K}(\boldsymbol{\beta}_{jk,r}^c) = \text{diag}(k_{jk,1}, k_{jk,2}, \dots, k_{jk,n})$ with the weight matrix for IWLS with weights

$$k_{jk,i} = \exp\left(\sum_{r=1}^R f_{jk,r}(S_{iz}) x_{r,i}(S_{iz}) + v_i(S_{iz})' \boldsymbol{\gamma}_{jk} + f_{jk,spat}(S_{iz})(s_i) + b_{jk,gi}\right) I_{jk,i} \tag{A.50}$$

obtained from the current state $\beta_{jk,r}^c$. The working observations are: $\tilde{y}_{jk,i} = \eta_{jk,i}(t_{jk,i}) + \frac{\delta_{jk,i}}{k_{jk,i}} - 1$.

The proposed vector $\beta_{jk,r}^p$ is accepted as the new state of the chain with probability:

$$\alpha(\beta_{jk,r}^c, \beta_{jk,r}^p) = \min \left(1, \frac{p(\beta_{jk,r}^p / \cdot) q(\beta_{jk,r}^c, \beta_{jk,r}^p)}{p(\beta_{jk,r}^c / \cdot) q(\beta_{jk,r}^c, \beta_{jk,r}^p)} \right) \quad (\text{A.51})$$

where $p(\beta_{jk,r} / \cdot)$ is the full conditional for $\beta_{jk,r}$ (that is, the conditional distribution of $\beta_{jk,r}$ given all other parameters and the data).

APPENDIX 10: BAYESX CODE USED TO FIT THE BAYESIAN GEOADDITIVE MULTISTATE MODEL

Note: - The computations are time-consuming. The models took 6 days to converge

The dataset contains the following variables

ID: patient unique identifier

tsu= transition from undetectable viral load state to viral rebound state

tus= transition from viral rebound state to undetectable viral load state

tsd=transition from undetectable viral load state to death

tud=transition from viral rebound state to death

sex= gender coded 1 "Males" and 0 "Females" (ref=females)

whoadv=baseline WHO clinical stages 1 "III/IV" and 0 "I/II" (ref WHO stage I/II)

age= the individual baseline age at ART initiation (continuous variable)

end= the last observed time at exit from a state

start= is the initial time at entry into a state

states= the currently occupied state

Province= spatial unit of analysis present on both the data file and the spatial map file

states=state the process jumps to at the end of the current interval

Create regression objects and reading the data

bayesreg sp

map m

dataset d

m.infile using C:\Users\sph-user\Desktop\Zvifadzo\Zimbabwesort.bnd

d.infile using C:\Users\sph-user\Desktop\Zvifadzo\VLdata2.raw

```
sp.outfile=C:\Users\sph-user\Desktop\Zvifadzo\VLresults9\results
```

```
logopen, replace using C:\Users\sph-user\Desktop\Zvifadzo\VLresult\result.log
```

Change the delimiter to allow for linebreaks in commands

```
delimiter=;
```

The model code

```
sp.mregress tus = end(baseline, nrknots=40) + ID(random) + sex + whoadv +  
age(psplinerw2) + Province(random) + Province(spatial,map=m):
```

```
tsd = end(baseline, nrknots=40) + ID(random) + sex + whoadv +  
age(psplinerw2) + Province(random) + Province(spatial,map=m):
```

```
tsu = end(baseline, nrknots=40) + ID(random) + sex + whoadv +  
age(psplinerw2) + Province(random) + Province(spatial,map=m):
```

```
tud = end(baseline, nrknots=40) + ID(random) + sex + whoadv +  
age(psplinerw2) + Province(random) + Province(spatial,map=m),
```

```
family=multistate state=states begin=start noposteriormode iterations=12000  
burnin=2000 step=20 predict using d ;
```

```
logclose;
```

```
sp.autocor;
```

```
sp.getsample;
```

```
% restore usual delimiter
```

```
delimiter = return;
```