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Modelling space and time patterns of HIV interventions on HIV burden in a high priority district in South Africa

Lucy Chimoyi – Otwombe

0708657E



A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in the fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 31 January 2023

Supervisors: Prof. Eustasius Musenge and Prof. Salome Charalambous

Declaration

This thesis is submitted in the divided block thesis format, approved by the Faculty of Health sciences.

I, **Lucy Chimoyi,** declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

I have read the sections on referencing and plagiarism in the WITS Plagiarism Policy, and I understand that the plagiarism can lead to the suspension or permanent expulsion of students in serious cases. I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise. I have followed the required conventions in referencing the thoughts and ideas of others. I understand the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work, or I have failed to acknowledge the source of the ideas or words in my writing.



Lucy Chimoyi-Otwombe

31 January 2023

Abstract

Background: Ekurhuleni Metropolitan Municipality (EMM) collects monthly data from primary healthcare facilities on the HIV programmes to inform its HIV response. To study patterns of HIV burden and uptake of HIV services at a population level, the application of small area analysis offered a powerful epidemiological approach while investigating on a geographical scale, the risk, and confounding factors of certain health outcomes. This PhD thesis was aimed at highlighting and understanding the heterogeneity of HIV prevalence and selected HIV outcomes at a ward-level between 2012 and 2016. **Materials and Methods:** A mixed-methods approach using the HIV result chain logical framework was applied to several sources of data. Firstly, data from a National HIV Survey, the South African National Census analysed using Bayesian techniques in WINBUGS to provide an epidemiological profile of the risk factors for HIV prevalence, sub-optimal condom use and non-ART use. Secondly, a model of time and space using R-INLA applied to routinely collected HIV program data (clinical and laboratory) assessed the predictors of viral load suppression (VLS) [<1000 copies/mL (WHO) and <400 copies/mL (SA)]. Forecasting of VLS (five years post-2016) was conducted using ARIMA models. Lastly, a thematic analysis using the social cognitive theory framework on in-depth interviews with patients and healthcare staff was conducted to understand factors influencing uptake of selected HIV services in different geographical settings. **Results and findings:** There were several clusters of high HIV infection, sub-optimal condom, non-ART use and VLS in EMM driven by different risk factors discussed in this PhD thesis. The proportion of VLS increased from 2012-2015 and decreased in 2016, and heterogeneity was observed at ward-level. As the female population and ART initiation rates increased at ward-level, VLS increased. However, this observed relationship was strong in some areas and weak in others. Lastly negative sequalae including stigma from healthcare workers and communities prevented optimum uptake of HIV services, particularly in women. Social support, availability of services and differentiated care encourage utilisation of HIV services. **Conclusions:** Findings highlighted the heterogenous nature of health events in EMM and are likely to inform targeted interventions to improve HIV programmes at ward-level towards achieving the 95-95-95 targets.

List of original papers

1. Assessing spatial patterns of HIV prevalence and interventions in semi-urban settings in South Africa: Implications for spatially targeted interventions.

Lucy Chimoyi, Salome Charalambous, Zvifadzo Matsena-Zingoni, Edmore Marinda, Samuel Manda, Eustasius Musenge. Manuscript submitted to the Geospatial Health Journal on 28th February 2022. Published on 05 September 2022

2. Small area analysis of HIV Viral load suppression patterns in a high priority district (2012-2016), South Africa.

Lucy Chimoyi, Eustasius Musenge, Tendesayi Kufa-Chakeza, Salome Charalambous. Manuscript submitted to supervisors. Submitted on 25 January 2023 to Plos Global Public Health Journal for peer review. Awaiting response.

3. Understanding factors influencing utilization of HIV prevention and treatment interventions among patients and providers in a heterogeneous setting: a qualitative study from South Africa.

Lucy Chimoyi, Jeremiah Chikovore, Eustasius Musenge, Tonderai Mabuto, Candice. M. Chetty-Makkan, Reuben Munyai, Tshegang Nchachi, Salome Charalambous, Geoffrey Setswe. Manuscript submitted to the PLOS Global Public Health Journal on 30th May 2021. Published on 03 Feb 2022.

4. Targeting the spatial patterns of HIV viral load suppression in Ekurhuleni, South Africa: A geographically weighted regression analysis.

Lucy Chimoyi, Tendesayi Kufa-Chakeza, Salome Charalambous**,** Eustasius Musenge.

Submitted on 06 September 2022 to BMC Research Notes Journal for peer review. Awaiting response.

The publishers have permitted the reprinting of published articles. For this PhD, I have acquired the quantitative data, managed, and supervised the collection of qualitative data and conducted analysis for each PhD output above.

List of meeting abstracts

1. Assessing spatial patterns of HIV prevalence and uptake of HIV interventions in a high priority district using routine healthcare. SACEMA Research Days 07-09 September 2020

Lucy Chimoyi & Eustasius Musenge.

2. Patient and provider experiences and perceptions influencing uptake of pre-exposure prophylaxis in a high HIV priority district, South Africa. SACEMA Research Days 20-22 September 2021

Lucy Chimoyi, Salome Charalambous & Eustasius Musenge.

3. Targeting the spatial patterns of HIV viral load suppression in Ekurhuleni. 22nd Annual Ekurhuleni Health District Research Conference 24 and 25 November 2022

Lucy Chimoyi, Salome Charalambous & Eustasius Musenge.

4. Exploring the perceptions and experiences in HIV services delivery and uptake in diverse settings across Ekurhuleni Metropolitan Municipality: A qualitative study. 22nd Annual Ekurhuleni Health District Research Conference 24 and 25 November 2022

Lucy Chimoyi, Salome Charalambous & Eustasius Musenge.

Dedication

This thesis is dedicated to all people living with HIV, who we continue to fight for until that silver bullet is found.

A special dedication to my late grandfather Albert Muchibi, and my parents John and Beatrice Chimoyi. Without you, I would not be who I am today.

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I am fortunate to have completed my post-graduate work at the University of the Witwatersrand, Johannesburg since 2007; therefore, there are several people I would like to thank for their part of my success. Prof Hanrahan, from the School of Animal, Plant and Environmental Sciences for supervising my first M.Sc. research project in Environmental Science. Prof Eustasius Musenge, whom I have walked with since 2011 as my M.Sc. Epidemiology and Biostatistics, and PhD supervisor for his encouragement in applying for funding for my PhD studies. I acknowledge the opportunity provided by Prof Musenge to provide guest lectures to students attending the "Spatial techniques in Public Health" courses. I am also grateful to Dr Zodwa Ndlovu for the opportunity to share my experiences on spatial applications with the students registered for the surveillance course in the Implementation Science module. Lastly to Mr Paul Bohloko for making this PhD journey from an administrative point of view, easier to navigate.

I would like to recognize several people instrumental in guiding my choice of a PhD topic. Ms Kerry Schwartz, a Senior GIS Specialist at SiVEST sparked my interest in exploring the field of geographical information systems beyond environmental engineering. Prof Sinead Delany-Moretlwe from Wits RHI for igniting my passion for HIV research. I would like to acknowledge my organization, The Aurum Institute which has been instrumental in honing my scientific capabilities and knowledge by providing the platform to realize certain milestones in my scientific career. Prof Geoffrey Setswe, Prof. Salome Charalambous and Prof. Violet Chihota at the Aurum Institute for pushing the limits of my capabilities in my day-to-day work as well as the completion of this PhD. I also appreciate fellow colleagues, cheerleaders, champions, whom I have had the pleasure of working with and have provided encouragement during seasons of despair.

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Table of contents

Declaration **2**

Abstract **3**

List of original papers **4**

List of meeting abstracts **5**

Dedication **6**

Acknowledgements **7**

Table of contents **8**

List of Appendices **12**

List of Tables **12**

List of Figures **13**

Abbreviations **15**

Key terms and definitions **17**

1 CHAPTER ONE: INTRODUCTION **18**

1.1 National HIV response in South Africa 19
1.2 95-95-95 strategy 19
1.3 The South Africa National Strategic Plan and priority districts 20
1.4 HIV services in South African healthcare facilities and communities 21
1.5 Challenges with the delivery and uptake of HIV services 23
1.6 Addressing heterogeneity in HIV services delivery and uptake 23
1.7 Justification of PhD study 24
1.8 Aim and objectives of the PhD study 25
1.9 Outline of this PhD thesis 26
1.10 Conceptual framework for this PhD study 26

2 CHAPTER TWO: LITERATURE REVIEW **28**

2.1. Introduction 28
2.2. Geographical variation of HIV and HIV services 28
2.3. Barriers to HIV services delivery and uptake 30
2.4. Facilitators of HIV services delivery and uptake 31

2.5. Geographical “high-risk” spaces....32
2.6. Facility level HIV program data use for approximation of community level HIV patterns 33
2.7. Application of space and time modelling techniques in HIV research....34
2.7.1. Spatial cluster analysis....35
2.7.2. Spatial interpolation....35
2.7.3. Spatial regression and modelling....35
2.7.4. Time series analysis and forecasting....36
2.8. Summary of literature review....36
3. CHAPTER THREE: METHODS....38
3.1. Introduction....38
3.2. Data Sources....38
3.2.1. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012....40
3.2.2. District Health Information System (DHIS)....40
3.2.3. National Health Laboratory Services....41
3.2.4. Qualitative in-depth interviews....41
3.2.5. South African National Census data, 2001 and 2011....42
3.3. Study setting....43
3.4. Study outcomes....45
3.5. Study methodology....46
3.6. Study design....47
3.7. Spatial and Bayesian modelling....47
3.7.1. Cross-sectional data....47
3.7.2. Longitudinal data....49
3.8. Spatial interpolation....52
3.9. Statistical modelling....53
3.9.1. Descriptive analysis....53
3.9.2. Regression analysis: Interrupted time series regression....53
3.9.3. Regression analysis: non-spatial Bayesian regression....54
3.9.4. Ordinary least squares and geographical weighted regression....54
3.9.5. Forecasting....55
3.9.6. Sensitivity analysis....55
3.10. Summary of Chapter....56
4. CHAPTER FOUR: KNOWING YOUR EPIDEMIC....58
4.1. Introduction....58

4.2. Methods 60
4.2.1. Description of study outcomes 60
4.2.2. Spatial and non-spatial risk factor analysis 61
4.2.3. Geospatial mapping of risk factor analysis estimates 61
4.3. Findings 61
4.3.1. Characteristics of survey population 61
4.3.2. HIV prevalence and factors associated with HIV infection 63
4.3.3. Male condom use coverage and factors associated with sub-optimal condom use 65
4.3.4. ART initiation and factors associated with non-ART use 67
4.4. Summary of findings 69
4.5. Strength and limitations 71
4.6. Summary of chapter 71
5. CHAPTER FIVE: EXPLORING THE HETEROGENEITY OF VIRAL LOAD SUPPRESSION ACROSS SPACE AND TIME 73
5.1. Introduction 73
5.2. Methods 74
5.2.1. Data sources 74
5.2.2. Viral load measures 74
5.2.3. Viral load suppression 75
5.2.4. Ward-level measures 75
5.2.5. Space and time analysis of high viral load suppression 76
5.3. Results 76
5.3.1. Summary of HIV indicators in Ekurhuleni 76
5.3.2. Five-year viral load suppression rates in Ekurhuleni 77
5.3.3. Viral load suppression rates in 2016 79
5.3.4. Spatial autocorrelation of viral load suppression 79
5.3.5. Spatio-temporal distribution of viral load suppression 81
5.3.6. Spatio-temporal predictors for viral load suppression 81
5.3.7. Temporal changes in predictors associated with viral load suppression 84
5.4. Summary of findings 86
5.5. Strengths and limitations 87
5.6. Summary of chapter 88
6. CHAPTER SIX: UNDERSTANDING THE UNDERLYING INFLUENCES FOR HETEROGENOUS DELIVERY AND UPTAKE OF HIV SERVICES 89
6.1. Introduction 89

6.2. Methods 90
6.3. Results and discussion 92
6.3.1. Characteristics of study participants 92
6.3.2. Themes and sub-themes from thematic analysis 93
6.4. Benefits from HIV care engagement 98
6.5. Possible negative consequences from engagement in HIV prevention or treatment care 98
6.6. Good knowledge of existing HIV prevention or treatment services 99
6.7. Ability to correctly use the available HIV prevention or treatment services 100
6.8. Interpersonal or environmental dynamics supporting use of HIV prevention or treatment services 101
6.9. Summary of findings 103
6.10. Strengths and limitations 104
6.11. Summary of chapter 105
7. CHAPTER SEVEN: EVALUATING IMPACT OF IMPROVING COVERAGE OF ART ON VIRAL LOAD SUPPRESSION 106
7.1. Introduction 106
7.2. Methods 107
7.2.1. Data sources 108
7.2.2. Measures of viral load suppression 108
7.2.3. Statistical analysis 108
7.2.4. Model validation 109
7.2.5. Forecasting viral load suppression post 2016 109
7.3. Results and discussion 109
7.3.1. Sample characteristics 109
7.3.2. Global and local predictors of high viral load suppression 109
7.3.3. Forecasting viral load suppression 111
7.4. Summary of findings 113
7.5. Strengths and limitations 115
7.6. Summary of chapter 115
8. CHAPTER EIGHT: DISCUSSION AND POLICY IMPLICATIONS 116
8.1. Introduction 116
8.2. Key findings 116
8.2.1. Heterogenous factors for sub-optimal uptake of available HIV services 116

8.2.2. Intersectional stigma: Identifying and addressing stigma to improving the delivery and uptake of HIV services 118

8.2.3. Variations in viral load suppression pre-and post- UTT 119

8.2.4. Sustaining ART coverage to achieve viral load suppression 120

8.2.5. Finding missing women and men at a community level for sustained engagement in care 121

8.3. Strengths and limitations 122

8.4. Methodological aspects to improve understanding of HIV dynamics at a local scale 123

8.5. Remaining gaps from the study for future research direction 124

8.6. Policy implications from PhD findings 126

8.7. Conclusions 126

9. REFERENCES 129

10. APPENDICES 148

List of Appendices

Appendix A: Ethics approval – Wits HREC 148
Appendix B: Ethics approval- NHLS CDW 149
Appendix C: Ethics approval- Ekurhuleni District 151
Appendix D: Permission to use data from GDoH 153
Appendix E: Turnitin plagiarism report 154
Appendix F: Copies of PhD outputs – Manuscript 1 173
Appendix G: Copies of PhD outputs – Manuscript 2 184
Appendix H: Copies of PhD outputs – Manuscript 3 203
Appendix I: Copies of PhD outputs – Manuscript 4 222

List of Tables

Table 3-1: Overview of PhD objectives and data sources 39
Table 3-2: Study outcomes, the source, and their initial measurement 45
Table 4-1: Survey weighted population profile of 2012 HSRC survey participants by subdistrict in Ekurhuleni, South Africa 62
Table 4-2: Posterior summaries of Odds Ratio for HIV infection in Ekurhuleni 64
Table 4-3: Posterior summaries of Odds Ratio for sub-optimal condom use in Ekurhuleni .. 66
Table 4-4: Posterior summaries of Odds Ratio for non-ART initiation in Ekurhuleni 68
Table 5-1: Characteristics of samples collected from primary health care facilities in Ekurhuleni (2012-2016) 76
Table 5-2: Estimated ART coverage for female PLHIV (2012-2016) in antenatal care in Ekurhuleni Metropolitan Municipality 77

Table 5-3: Spatio-temporal predictors of high viral load suppression 82
Table 5-4: Spatio-temporal changes of parameters associated with high viral load suppression 84
Table 6-1: Socio-demographic characteristics of qualitative IDI participants 92
Table 6-2: Themes and sub-themes from IDIs and their relevant social cognitive theory (SCT) constructs and domains 93
Table 6-3: Overview of similarities and differences in themes across heterogenous settings and selected quotes 95
Table 7-4*:* Overall estimates from GWR including model diagnostic checks 109
Table 7-5: Model fit for viral load suppression rates in Ekurhuleni using <1000 copies/mL and <400 copies/mL thresholds 111

List of Figures

Figure 1-1: The HIV response in SSA 18
Figure 1-2: 90-90-90 targets 20
Figure 1-3: The HIV result chain logical framework (Adapted from Rosenberg et al., 1970 [56]) 27
Figure 3-1: Areas for recruitment of qualitative participants 41
Figure 3-2: Recruitment and enrolment of qualitative study participants [73]. 42
Figure 3-3: The study area and inset maps showing study area in relation to South Africa and Gauteng province 44
Figure 3-4: Explanatory sequential mixed-methods study design 47
Figure 3-4: A summarized Box-Jenkins methodology for forecasting viral load suppression 55
Figure 4-1: A smoothed HIV prevalence map of Ekurhuleni Metropolitan Municipality using 2012 HSRC national survey 64
Figure 4-2: A smoothed map showing the expected posterior OR of HIV infection in Ekurhuleni Metropolitan Municipality using 2012 HSRC national survey 65
Figure 4-3: A smoothed distribution of male condom coverage in Ekurhuleni Metropolitan Municipality using routinely collected programmatic data 66
Figure 4-4: A smoothed map showing the expected posterior OR for sub-optimal condom use in Ekurhuleni Metropolitan Municipality using 2012 HSRC national survey 67
Figure 4-5: A smoothed map showing the distribution of ART initiation rates in Ekurhuleni Metropolitan Municipality using routinely collected programmatic data 68
Figure 4-6: A smoothed map of showing expected posterior OR for non-ART use in Ekurhuleni Metropolitan Municipality using 2012 HSRC national survey 69
Figure 5-1: Overall proportion of viral load suppression (<1 000 copies/mL) Ekurhuleni Metropolitan Municipality (2012-2016). 95% confidence interval bands are shown. 78
Figure 5-2: Overall proportion of viral load suppression (<400 copies/mL) by sub-district in Ekurhuleni Metropolitan Municipality (2012-2016). 95% confidence interval bands are shown. 78
Figure 5-3: Proportions of viral load suppression rates in EMM before and after roll-out of universal test and treat (2016) 79
Figure 5-4: Location of clusters of high and low proportions of viral load suppression in Ekurhuleni Metropolitan Municipality 80

Figure 5-5: The spatio-temporal trend of viral load suppression (<1 000 copies/mL) from 2012 to 2016. 81
Figure 5-6: Heterogeneity of predicted viral load suppression (<1 000 cp/mL) rates in Ekurhuleni Metropolitan Municipality (2012-2016) 83
Figure 5-7: Spatial-temporal changes in the proportion of female population and viral load suppression (<1 000 cp/mL) rates in Ekurhuleni Metropolitan Municipality (2012-2016) 85
Figure 5-8: Spatial-temporal changes in the proportion initiating ART and viral load suppression (<1 000 cp/mL) rates in Ekurhuleni Metropolitan Municipality (2012-2016) 85
Figure 6-1: Adaptation of the social cognitive theory in uptake and delivery of HIV services in EMM 91
Figure 7-1: The overall relationship between proportion of females (A) and ART initiation (B) per ward and viral load suppression 110
Figure 7-2: Observed (2012-2016) and forecasted (2017-2021) viral load suppression rates by ARIMA modelling technique 112
Figure 7-3: Observed (2012-2016) and forecasted (2017-2021) viral load suppression rates by ARIMA modelling technique 113

Abbreviations

AGYW	Adolescent girls and young women
AIDS	Acquired Immunodeficiency syndrome
ARIMA	Auto regressive integrated moving average
ART	Anti-retroviral treatment
CAR	Conditional autoregressive
CDC	Centers for Disease Control and Prevention
CDW	Central data warehouse
DHIS	Department of Health Information system
DIC	Deviance information criteria
EA	Enumerated areas
EMM	Ekurhuleni Metropolitan Municipality
EMR	Electronic medical records
FSW	Female sex worker
GIS	Geographical information systems
GWR	Geographically weighted regression
HIV	Human Immuno-deficiency virus
HPTN	HIV prevention trials network
HSRC	Human Sciences Research Council
HTS	HIV testing services
IDI	In-depth interview
IDU	Injection drug user
INLA	Integrated Nested Laplace Approximation
ITS	Interrupted time series
LASSO	Least absolute shrinkage and selection operator
LGBT	Lesbian, gay, bisexual, and transsexual
LISA	Local indicator spatial autocorrelation
MCMC	Markov Chain Monte Carlo
MSM	Men having sex with other men
NDoH	National Department of Health
NHLS	National Health Laboratory Services
NSP	National strategic plan
OLS	Ordinary least squares
PEP	Post-exposure prophylaxis
PEPFAR	President's Emergency Plan for AIDS Relief

PHC	Primary healthcare clinic
PLHIV	People living with HIV
PMTCT	Prevention of child and mother HIV transmission
POR	Posterior odds ratio
PrEP	Pre-exposure prophylaxis
RW1	Random walk of order 1
SSA	Sub-Saharan Africa
UNAIDS	Joint United Nations Programme on HIV/AIDS
UTT	Universal test and treat
VMMC	Voluntary male medical circumcision
VLS	Viral load suppression

Key terms and definitions

Clusters: Geospatial areas with significantly higher or lower numbers than expected of the outcome under investigation, especially when randomly distributed.

Decant: A strategy aimed at facilitating the decongestion and efficient transfer of stable chronic HIV patients eligible for decentralised drug delivery from the primary healthcare facilities to collect chronic medicines at designated pick-up points.

High ART initiation rate: In this study, wards with at least 75% of PLHIV reporting initiation were considered having a high ART initiation rate.

High HIV prevalence: In this study wards with at least 75% of people reporting a positive HIV status were considered having a high HIV prevalence.

High male condom use coverage: In this study wards with at least 75% of people reporting consistent condom use were considered having a high male condom use coverage.

High viral load suppression rate: According to the 90-90-90 strategy, proportion of wards with high viral load suppression was considered to be those with above 74%.

Meta-inference: An overall conclusion of findings through an integration of inferences from quantitative and qualitative of mixed-method study.

Viral load: A measure of the amount of HIV in the body. Having a high VL means HIV can be passed on more easily. In other words, the higher the VL, the greater the chance of transmission.

Viral load suppression: When ART is taken long enough to reduce the ability of the virus to make copies of itself in someone's body (VL<1000 copies/ml according to the WHO or <400 copies/ml according to South African National guidelines).

1 CHAPTER ONE: INTRODUCTION

> *"Progress against HIV has been uneven. The gains made through people-centred approaches within the highest performing HIV programmes have been tempered by insufficient action in other countries." (Global AIDS Report 2021)*

To advance and widen the scope of HIV research, innovative techniques for analysing, visualizing, and synthesizing routinely collected HIV program data are increasingly being applied. To date, there has been a gradual uptake of new techniques, but more emphasis is observed at a national and provincial level rather than district or ward level.

This PhD thesis presents the possibilities of applying non-traditional analytical techniques on routinely collected data with emphasis on accounting for the random, spatial, and temporal effects. The lack of detailed socio-demographic data at a sub-national level overlooks the inherent spatial heterogeneity of health outcomes in small areas. This prevents the exploration of relationships between exposures of health outcomes over time and place. This gap, however, can be filled by applying these non-traditional analytical techniques. For starters, an understanding of the universal HIV response illustrated in Figure 1-1 below is needed.

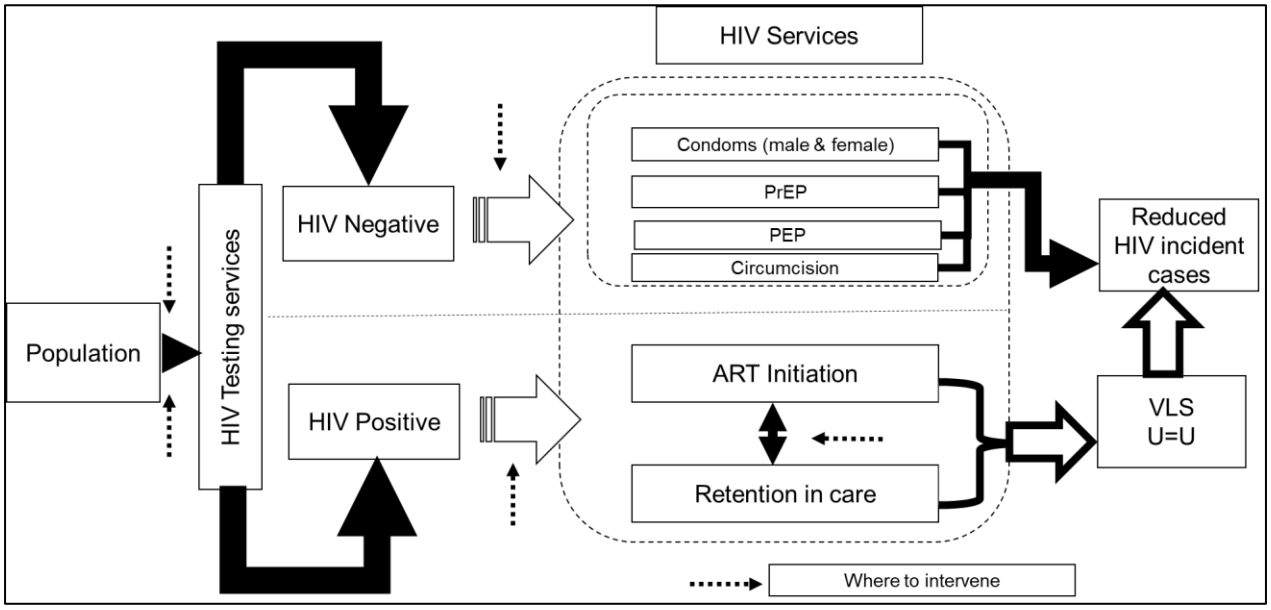


Figure 1-1: The HIV response in SSA

1.1 National HIV response in South Africa

There have been considerable gains in the South African National HIV response. Almost 20% of adults are living with HIV and differentials in terms of age, geography, gender and key populations exist [1]. HIV in South Africa disproportionately affects adolescent girls and young women (AGYW), and key populations [1-3]. New HIV infections in South Africa have declined by 38% with marked progress reported in the prevention of mother-to-child HIV transmission (PMTCT) [2, 3]. Despite this progressive step, more than 26% of these new infections are reported in AGYW [2]. Part of the HIV national response is the HIV treatment programme, which is the largest worldwide despite a delayed start due to lack of political will to support and fund ART programmes [4]. More than 3.5 million PLHIV have initiated on antiretroviral therapy (ART) which has resulted in an increased life expectancy to 61.2 years (men) and 69.7 years (women) by 2015 [2]. Worldwide, AIDS-related illnesses and deaths have declined with the rapid scale-up of ART. This is more apparent in the sub-Saharan African (SSA) region, which is disproportionately afflicted by HIV burden. Randomized controlled trials have showed great impact in reducing HIV transmission with consistent ART [5, 6]. From there on, the concept of treatment as prevention introduced new public health approaches dubbed 'universal test-and-treat' (UTT) where, all patients diagnosed HIV-positive are eligible to initiate ART irrespective of the CD4 count or any other staging criteria previously used to determine when to start ART.

The national response has further benefitted from significant increases in both local and global funding for expanding routine HIV programmes. The multilateral Global Fund to Fight AIDS, Tuberculosis and Malaria (Global Fund) and United States President's Emergency Plan for AIDS Relief (PEPFAR) have funded the expansion of HIV programmes in many low and middle income countries (LMIC) towards HIV elimination since 2003 [7]. South Africa has been a beneficiary of both.

1.2 95-95-95 strategy

In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) developed a global plan to accelerate momentum towards ending the HIV/AIDS epidemic by 2030 [57]. This plan, the 90-90-90 cascade (Figure 1-2) was a framework which views HIV medical care services along a cascade or a care continuum, to achieve virologic suppression among people aware that

they are living with HIV. Each '90' represents a specific programme target. The goal of the 'first 90' is to ensure that 90% of all PLHIV are aware of their HIV status. The goal of the 'second 90' is to ensure that 90% of all PLHIV diagnosed with HIV infection receive ART. Lastly, the goal of the 'third 90' is to ensure that 90% of all PLHIV receiving ART, achieve virologic suppression. If the 90-90-90 targets are met, at least 80% of all PLHIV will be on ART, and 73% of all PLHIV on ART will have virologic suppression. Modelling studies have predicted that achieving this scenario is likely to prevent 28 million new HIV infections globally, between 2015 and 2030. Furthermore, savings of approximately US$ 24 billion in HIV medical care and treatment service costs [57] will be realised. By 2019, South Africa's scorecard for the 90-90-90 strategy was as follows: 92% with knowledge of their HIV status; 75% initiated on ART and 92% on treatment and virally suppressed [3]. Overall, the total percentage of PLHIV and those virally suppressed, according to the 2020 Global AIDS Report was 64% [3]. This highlighted the unachieved targets that were lower than the required 74% were reported. The 2030 targets of 95-95-95 requires a minimum of 86% of PLHIV to achieve viral road suppression [1, 3]. Focusing on efforts at a national, provincial, district and ward levels to bridge this gap is necessary.

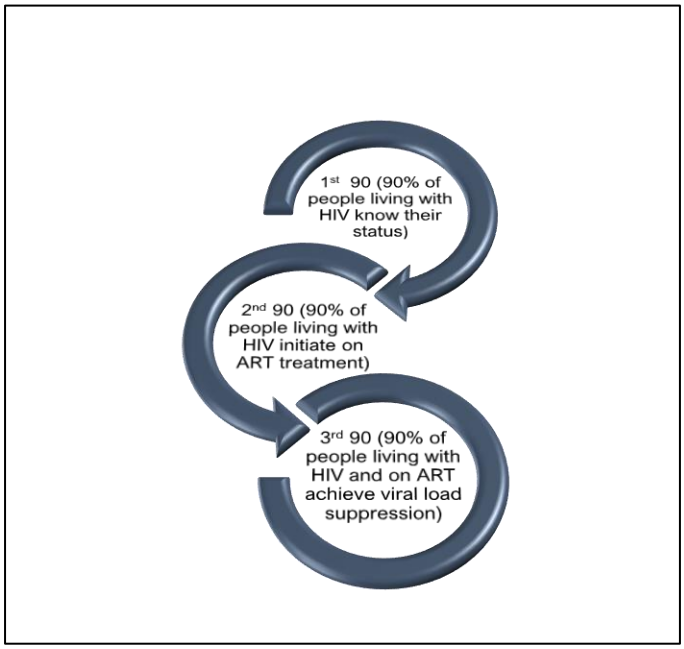


Figure 1-2: 90-90-90 targets

1.3 The South Africa National Strategic Plan and priority districts

The South Africa National Strategic Plan (NSP) 2017-2022 was borne out of the need to achieve the 90-90-90 targets by 2030 and is mandated to focus on the national HIV response and highlight where the impact is needed. This approach intensifies efforts in what are known as high priority districts, where concerted efforts will be needed to identify populations that are at greatest risk of HIV and appropriate interventions implemented in accordance with the national HIV response. Twenty-seven districts have been earmarked based on their high HIV

prevalence (>15%) and incident cases and large populations. Among the NSP recommendations are HIV testing services (HTS) as well test and treat regarded as effective strategies in HIV prevention efforts [2]. Test and treat strategies have demonstrated health benefits by improving individual health outcomes in high income countries [8]. To highly impact HIV prevention, broad coverage and high uptake of interventions must be implemented in populations/areas with the highest odds of HIV transmission [9, 10]. The efforts include using the existing data to strengthen effective HIV prevention and treatment services that address socio- structural factors that increase HIV risk. The NSP recommends innovative approaches in evaluating current interventions as existing analyses do not account for disparities in the health indicators, health system performance and implementation of interventions locally [2].

1.4 HIV services in South African healthcare facilities and communities

Early on, HIV interventions such as condom use focused on preventing sexual transmission through behavioural change. More recently, a combination of interventions has been recommended to account for the underlying socio-cultural and other contextual factors by making use of complementary behavioural and biomedical prevention strategies. HIV testing services (HTS), considered a behavioural intervention, include pre- and post-counselling and testing, and is widely accepted in many countries. The main component that HTS provides is an entry into care including access to antiretroviral therapy. Counselling provides HIV status awareness and personalised risk reduction counselling to prevent acquisition or further transmission of HIV [8, 11]. PLHIV are then rapidly engaged in support, care, and treatment. Furthermore, counselling assists in addressing challenges associated with HIV/AIDS prevention such as denial, stigma, and discrimination while mobilizing support for HIV/AIDS control effort in communities [12].

Condom use is cost-effective and prevents sexually transmitted infections, and unwanted pregnancies [13]. Globally, an estimated 45 million HIV infections have been averted between 1990 and 2015 [14]. Modelling studies have shown up to 47% new HIV infections averted with increased condom use [15, 16]. In South Africa, condoms are freely distributed in public places including health facilities, hospitals, educational facilities among others. Despite this, provision of condoms and condom use has been inconsistent within many populations [17, 18], mostly women.

Randomised controlled trials on male medical circumcision have shown a reduction in HIV risk in men by 60% and modelling studies have shown an extended benefit to women through a lowered risk of exposure [19, 20]. A six-year observational study showed a protective effect of up to 58% against HIV seroconversion [21]. As a result, several programmes introducing and promoting safe circumcisions have been scaled-up in South Africa. Voluntary medical male circumcision (VMMC) has reportedly reduced female-to-male transmission of HIV by 60% and is highly recommended for high HIV burdened countries with low levels of male circumcision [22, 23]. VMMC facilitates access of men and adolescent boys via behavioural and clinical health programs which were deemed inaccessible [24]. In about 50% of the identified priority VMMC countries, low HIV testing rates among men have been reported (<25 %) [20]. In routine settings, VMMC clients are linked to HTS testing pre-circumcision and because of this, awareness of HIV status is increased for many young boys/men in these programmes [25]. From these programmes, males living with HIV are identified and linked to HIV care where ART-induced viral suppression by those adhering to therapy is achieved and the downstream effects include reducing HIV incidence in women [24].

Nationwide UTT was implemented in South Africa from September 2016 as another strategy for reducing HIV transmission and controlling the HIV epidemic [26]. Granich *et al,* in his modelling study, showed a reduction in HIV incidence to zero seven years after UTT implementation [8]. To achieve this, ART is provided to all PLHIV upon HIV diagnosis, regardless of CD4 cell count or WHO clinical staging [27, 28]. The intended outcome is that the undetectable viral load levels most PLHIV will have will prevent most onward HIV transmissions [29]. In developed countries, it has been shown that UTT almost eliminated HIV transmissions in men who have sex with other men (MSM) [30]. Granich *et al*, showed that a 99.4% reduction in HIV infectiousness while on treatment was possible [8]. Other studies corroborating this finding showed that an effectiveness of 96% from the HIV prevention trials network (HPTN) 052 trial [31] and 86% from a Cochrane review that included nine observational studies and one randomised controlled trial [32].

More recently, after approval in 2017, pre-exposure prophylaxis (PrEP) has been introduced in at least one public healthcare facility in each district in South Africa [2]. The pill, a combination of two ART medicines (tenofovir disoproxil fumarate and emtricitabine) is prescribed to people not living with HIV to prevent seroconversion [33]. The South African PrEP model is established from both a rights and the needs of the population [34]. It was initially

intended for sex workers, men who have sex (MSM) with other men and AGYW, groups with the highest HIV prevalence and incident rates in South Africa and face high levels of stigma and discrimination [34, 35]. User-friendly clinics have been designed in collaboration with these groups; however, the decision for PrEP uptake remains a voluntary and personal choice [36, 37].

1.5 Challenges with the delivery and uptake of HIV services

There is a strong demand for HIV prevention and treatment services in South Africa from people at considerable risk of HIV infection and living with HIV, but in some areas, this demand is unmet due to social and structural challenges. The HIV continuum analyses show gaps in the uptake and coverage of HTS and treatment adherence [38, 39]. Challenges associated with stigma, non-disclosure of HIV status, ART side effects, and reduced HIV risk perception interrupt optimal uptake of HIV services [38, 40]. For women, actual or anticipated violent reactions from male partners reduces their engagement in HIV care [41, 42]. Men's health outcomes are poorer as they are less likely to test for HIV, link to and retain in HIV care compared to women [43]. Due to their poor health-seeking behaviour AIDS morbidity and mortality is higher [44-46]. Structural factors including the lack of confidential spaces, medication stock-outs, lengthy queues, and negative patient-provider relationship are barriers to optimal uptake of HIV services [38, 40]. Furthermore, lack of awareness on the available services at a community-level and constrained human resources at facility level prevents patient uptake of these services [40]. By January 2021, NDoH reported that only 1 227 (36%) of the 3 408 public health facilities offered PrEP. Without well-structured delivery programmes, patients may obtain this service it through unofficial and unmonitored avenues.

1.6 Addressing heterogeneity in HIV services delivery and uptake

High HIV burden settings in Africa have variations in both HIV prevalence [43-45] and uptake of available services [39]. Uneven distribution of resources implies that the dynamics associated with uptake or delivery of HIV services varies spatially. Having a context-specific perception of these factors is needed to allow for targeted interventions to improve uptake, delivery, and coverage of existing HIV services [46].

It is often too early to report what effect prompt ART and PrEP is having on the HIV epidemic as scale-up has been more recent for PrEP and may not explain the declines in prevalence observed in developing countries [37]. Techniques such as spatial modelling can address this gap by describing the existing patterns of HIV risk and outcomes, understanding the mechanisms that lead to the health outcomes after roll-out of interventions and estimate what is likely to happen in the short, medium to long-term future [37, 39]. In addition, techniques including time-series and forecasting may show patterns of future demand for VL monitoring in resource-constrained settings as scale up of effective interventions continues. Space and time techniques provide an avenue where stakeholders including funding organizations, government and implementing partners can ensure that adequate and equitable human and financial resources are in place to meet current and future demand [47].

1.7 Justification of PhD study

Health outcomes across space are clustered [48-51]. Previous research shows a higher uptake of health services is associated with close proximity of health facilities in a community [52] and contraceptive use [53]. A study in rural South Africa showed a reluctance in receiving HIV test results with an increasing distance from health facilities [52]. Another study in Mozambique revealed that more sexual and reproductive health services were accessed due to the closeness of the clinics to residents [51]. Efforts in scaling-up of global HIV/AIDS activities require context-specific efficient and evidence-based health planning and estimation tools [49].

In South Africa, key health-related indicators and relevant interventions have been repeatedly monitored through national surveys. HIV prevalence is estimated from the National HIV survey conducted by HSRC every five years. Often about 22% of the survey respondents decline testing for HIV [54]. Despite the substantial non-participation, the HIV prevalence estimates are robust enough to draw inferences from the survey data [54]. Although this data contributes to an evidence base, the information extracted is scant and limited to national aggregates, overlooking smaller scale heterogeneities and disparities. This is likely to introduce underestimation of various health outcomes due to the reduced number of data points in the analysis when the resolution of the scale is increased [55]. To address this gap, the use of techniques such as geospatial modelling is encouraged to link health intervention and system performance data at a local scale. Techniques such as Bayesian geostatistical modelling, in addition to estimating local disease burden and measuring the impacts of interventions from

national survey data over a period of time, may be used to assess future impacts. The HIV epidemic can be controlled by increasing the delivery of all-inclusive HIV-prevention and treatment programs accompanied with sufficient duration of elevated levels of coverage and quality. Coverage of effective interventions such as ART and condom use, need to be examined using a framework that considers the availability and accessibility of appropriate quality services resulting in increased use by the target population. To highly impact HIV prevention, broad coverage and high uptake of these interventions must be implemented in populations/areas exposed to or transmit HIV. Heterogeneity between areas of high and low HIV prevalence has been overlooked and to ensure equity in distribution of resources for HIV control in a generalised epidemic, it is important to focus HIV control in areas of greatest need. Gaining insights on the different drivers in heterogenous settings including the perceptions of patients and healthcare providers, may go a long way in identifying where the major gaps lie and start the process of closing them.

1.8 Aim and objectives of the PhD study

This PhD thesis aims to assess the HIV care outcomes through utilisation of selected HIV services from 2012-2016 while understanding how the roll-out of these services at a clinic-level have impacted the HIV control efforts in Ekurhuleni Metropolitan Municipality (EMM). It is anticipated that findings from this research will not only add to the existing body of evidence but will strengthening the implementation of existing HIV programmes in other high priority districts.

The objectives are:

- To establish pre-existing patterns of HIV prevalence, coverage, and uptake of selected HIV services in the study area *(Paper 1).*
- To examine the predictors of viral load suppression in Ekurhuleni while adjusting for non-spatial and spatial effects *(Paper 2).*
- To investigate facilitators of and barriers to optimal uptake of HIV interventions at an individual and clinic level. *(Paper 3).*
- To estimate the impact of selected services on HIV burden in Ekurhuleni. *(Paper 4).*

1.9 Outline of this PhD thesis

- **Chapter 1** outlines the scope of the thesis which sets the background, the research gap, the justification, the conceptual framework this PhD is based upon and the main objectives.
- **Chapter 2** reviews the existing literature on HIV response, individual, social, and structural risk factors for HIV infection and the uptake of HIV services. It presents an overview of the application of facility-based data in South Africa, spatial application in health data and the suitable methods used to address spatial variation. This chapter builds on an important foundation for understanding the importance of small area analysis for focused impact.
- **Chapter 3** describes the methods used in this thesis. I describe the study setting and the different secondary data sources for the quantitative component of this study and the primary data sources for the qualitative part. I provide detailed analytical techniques employed to answer the PhD objectives.
- **Chapters 4, 5, 6 and 7,** present the findings from each four objectives. This chapter begins with an introduction of the topic, the methods used, the results, a summary of the findings and lastly, a summary of the chapter.
- **Chapter 8** provides an integrated discussion of the study findings and their implications on delivery and uptake of HIV services. In addition, innovative methodological techniques used to analyse small area data are discussed in this chapter. I finally conclude the chapter outlining the key policy implications and the proposed areas for future research.

1.10 Conceptual framework for this PhD study

The HIV result chain logical framework for the health system response to HIV (Figure 1-3) was adopted for this PhD study to measure indicators of the linkages, and outcomes of the health sector response to HIV at a local level. This framework sequentially arranges indicators following a context analysis of inputs, outputs, outcomes, and impact which allows for the review of the HIV result chain. This identifies and tackles existing bottlenecks thus, improve the overall quality of the programmatic response. Subsequently, the result chain provides a structure for analysis and facilitates alignment in support of local data systems.

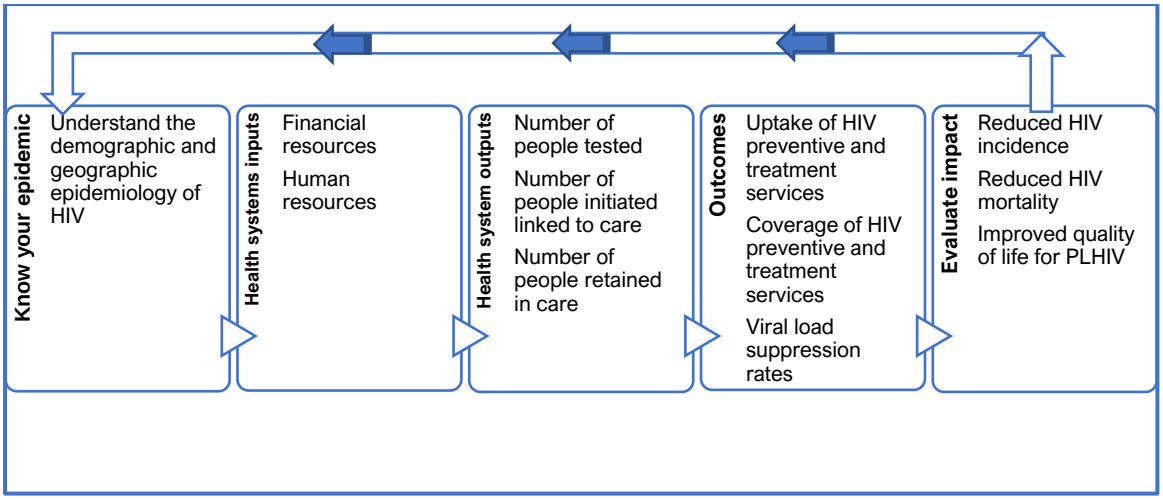


Figure 1-3: The HIV result chain logical framework *(Adapted from Rosenberg et al., 1970 [56])*

The elements of this framework are explained as follows:

- **Knowing your epidemic:** This entails understanding the HIV epidemic in terms of the demographic and geographic profile of the study area. In particular, the populations that are mostly affected and their size and location. Understanding this disaggregation defines the focus of the response in terms of direction, priority, and scale.
- **Inputs:** These are the resources invested in the health sector as a response to the HIV epidemic. They include financial and human resources, health services infrastructure and health policies.
- **Outputs:** These are from the activities of the different HIV programmes rolled-out in the study area. They include, for example, the number of HIV testing services (HTS) conducted, the number of condoms distributed and linkage to and retention in ART.
- **Outcomes:** These are the immediate effects of outputs from the rolling out HIV programmes. Behaviour changes is a prevention outcome whereas viral load suppression is a treatment outcome. Both, which need carefully monitoring.
- **Impacts**: Known impact measures that reflect the progress of HIV programmes include reduced HIV incidence, mortality rate and mother to child transmission. Overall, progress is reflected by an equitably improved quality of life for PLHIV.

2 CHAPTER TWO: LITERATURE REVIEW

"First law of geography - Everything is related to everything else, but near things are more related than distant things." (Tobler 1970)

2.1. Introduction

This literature review focuses on published findings from studies conducted in sub-Saharan Africa (SSA) applying spatial and temporal techniques on health data, including routinely collected data and surveys. The following databases were accessed in order to review publications of relevant studies: Medline/PubMed, Google Scholar, and EBSCOhost. There was no restriction to the years of the publications reviewed but only articles in English language were considered. Reference list of the retrieved articles was also checked for additional articles. The keywords which were used to identify relevant literature included: HIV prevention, HIV services, HIV treatment, Spatial and temporal analysis, and heterogeneity. The review is presented under the following subheadings:

2.2 Geographical variation of HIV and HIV services

2.3 Barriers to HIV services delivery and uptake

2.4 Facilitators for HIV services delivery and uptake

2.5 Geographical high-risk spaces

2.6 Facility level HIV program data in South Africa

2.7 Application of space and time techniques in HIV research

2.8 Summary of literature review

2.2. Geographical variation of HIV and HIV services

Visually displaying geographic variations of health outcomes such as HIV has unearthed settings where prioritizing targeted interventions is needed [57-60]. Most studies in SSA investigating the geographical variation of HIV prevalence, treatment and prevention have focused on the provincial/regional differences [57, 58, 61-67]. Population-based surveillance data has been largely used to show geographical variability of HIV in SSA [67]. HIV prevalence surveys in South Africa have been used to understand the drivers of the national epidemic and

resource allocation planning [54]. A study conducted using routinely collected data in South Africa and Tanzania showed the feasibility of measuring spatial variability when population-based data is not readily available [65]. The spatial analysis of HIV prevalence in four countries in SSA using the demographic health and survey data showed geographical variation at a national and subnational level [58]. The study further showed localized areas where the HIV burden was concentrated mostly in lower administrative levels such as urban areas which are characterized by rapid urbanization and high population [58]. A recent study in Malawi identified higher HIV prevalence in urban areas driven by high-risk sexual behaviour defined as having three or more lifetime partners [60], a finding different from Cuadros et al 2018 where higher prevalence was driven by urbanization [58]. Over a seven-year period (2000-2017), HIV prevalence in SSA was mapped and differences in its direction and rate of change within and between several countries were highlighted [68]. Understanding these different patterns in HIV prevalence is likely to maximize the effect and efficacy of the individual national AIDS responses. Increasingly, stakeholders at a local and global level are leaning towards spatially targeted resource allocation as a way of balancing the decreasing financial resources allocated to the HIV response [69].

Using geospatial analysis, targeted HIV testing in high burden or combining different HIV prevention services areas was seen to maximize cost-effectiveness for different populations and locations. Geographical variation in HIV testing was observed when using the 2017 national household survey in South Africa. [59]. At a district-level, the chances of being tested varied after accounting for age and gender differentials [59]. The differences were likely attributed to ready access to healthcare facilities, quality of healthcare services and health promotion services across the districts. Rural districts in Limpopo and Eastern Cape provinces reported the lowest HIV testing coverage (<80%) which was linked to limited geographical and financial accessibility [70]. In Tanzania, GIS was used to identify and effectively strategize the prioritization of VMMC service delivery [66]. The introduction of mobile and outreach services in rural healthcare facilities and non-healthcare facilities after identification of underserved areas increased VMMC rates from 48% in 2012 to 93% by the end of 2014 [66]. A recent modelling study on HIV prevention and treatment progress found that of all the five largest metropolitans in South Africa, Ekurhuleni failed to reach the 90% viral load suppression target in 2020 [71]. The barriers to and facilitators of optimal delivery and uptake of HIV services including virological failure are discussed in sub-sections 2.3 and 2.4 respectively.

2.3. Barriers to HIV services delivery and uptake

To optimize individual health outcomes and prevent onward transmission of HIV, addressing barriers along the HIV care cascade is needed to achieve the 95-95-95 UNAIDS [72]. Qualitative studies in SSA have highlighted several individual and structural barriers to engagement in care and revealed differences according to gender, age group and key population [72-82]. HIV-related stigma in the form of anticipated, internalized or felt is the most commonly reported barrier to optimal engagement in care [72, 73, 78, 82]. Most of this stigma emanates from unintentional disclosure of HIV status and manifests differently in men and women. Men are less likely to engage in care for fear of being shamed and blamed for the HIV infection whereas women engage in care despite any negative consequences including abandonment and violence [80, 83]. Owing to their role in the family set-up, men are also likely to disengage in care due to the competing demands care-seeking has on money and time spent outside work [72].

Worldwide, healthcare systems have not prioritized adolescents and young people health and in many countries in SSA, HIV services are not tailored to the needs for this population [77, 84]. Adolescents are less likely to test, link to care, and subsequently do not achieve viral load suppression [85]. The lost to follow-up rate among adolescents is approximately 20% within the first 12 months of engagement in care [77, 84]. Most reported challenges young women face with adherence to lifelong ART include difficulties in disclosing their HIV status to intimate partners and families for fear of violence [85]. The health system barriers stated for this population are location of the clinic, opening hours and long waiting periods [81]. At an interpersonal level, stigma, fears around breaching of confidentiality and unintended exposure to community were cited as some of the persistent barriers to delivery and uptake of HIV services among young people [81, 85]. Economic barriers preventing transportation to clinics were identified by young people in Uganda [74, 77]. Legal barriers including child assent and parental consent hinder access to health services targeting adolescents [80, 82].

Despite significant unmet health needs, key populations continue to experience barriers to accessing HIV services. A review of literature in Africa conducted in 2021 by Jin et al, found that key populations including MSM, male and female commercial sex and people using drugs experience stigma and discrimination which prevents optimum engagement in HIV care [86].

As a result, the proportion of MSM testing HIV positive and linking to care was 24% and of those in care, 25% attained viral load suppression [87]. A study conducted in Tanzania highlighted the lack of integrated healthcare services at a facility level as a possible barrier to disengagement in care for female sex workers [79]. Having dedicated rooms or venues for HIV patients did little to minimize privacy for this key population, a finding contradicting previous findings in other settings in SSA [88].

2.4. Facilitators of HIV services delivery and uptake

Good quality health services and a robust social network are the most commonly reported factors facilitating engagement in HIV care [72-74, 76, 79, 82, 83]. Respectful and non-judgmental delivery of services, without unnecessary delays and constraints facilitate linkage to and retention in care of HIV patients. A study with female sex workers showed that in this population, providing an all-inclusive package of health services could minimize stigma around accessing HIV services [79]. Better inclusion of HIV with sexual and reproductive health services, and antenatal services is necessary for continued engagement in care for mainly female key populations [79, 83, 84].

Spatial accessibility using differentiated service delivery models has encouraged access to healthcare [47] including male participation during ART delivery. In Uganda, a community client led ART delivery group where a group leader collected ART and distributed to other group members was favoured [75]. This was due to guaranteed confidentiality and money was used for other household expenses other than transportation to the clinic [75]. A project, The Score4Life, launched in 2016 in Johannesburg district, South Africa offered HIV testing and ART initiation services to men 21 years and older through pop-up clinics/stores located in areas of increased traffic such as taxi ranks and malls in local communities, across Johannesburg [43]. Since men face several accessibility barriers at individual, interpersonal, community and structural levels, non-traditional interventions and offering services in unconventional settings potentially increased HIV testing and treatment uptake [43]. The flexible working hours, convenient locations, short waiting times, privacy and confidentiality improve uptake [78, 80, 89]. For MSM, a systematic review and meta-analysis showed that expanding community-led services, access to rapid and home-based testing, increased treatment support or counselling from lesbian, gay, bisexual and transexual (LGBT)-friendly organisations, improved engagement in HIV care [89].

Strong social support from family and peers has facilitated engagement in HIV care across all populations [73]. FSWs identified peer-educators as their primary source of HIV information, and support through peer-escorted referrals essential for linkage to and retention in care [79]. Community education and mobilization as well as support structures for retention are key health system strategies that improve the uptake of HIV services for this population [72]. Peers provide important information to communities and follow-up on those who at risk of defaulting on treatment reducing health workers workload and further, strengthen community involvement. Family support for adolescent and young people improves their engagement in HIV services [73]. At a facility level, awareness of and willingness to support relevant HIV policies facilitated the normalization of services such as provider-initiated HIV counselling and testing which are seen to improve uptake of HIV testing [76].

2.5. Geographical "high-risk" spaces

High-risk spaces are prioritized geographic areas in which susceptible populations at high risk of HIV concentrated. These high-risk spaces often present an opportunity to apply spatially targeted interventions to most at risk populations which is likely to augment the impact of interventions on the epidemic in SSA [90]. These sub-populations including FSWs, MSM and IDU among others have certain behavioural characteristics that increase their HIV risk. The sub-populations, usually micro-epidemics in certain geographical areas can be identified through cluster analysis or integrated bio-behavioural surveillance surveys. These spaces have interlinked connections in the HIV transmission network, and spatially-targeted interventions for these geographical key populations could not only reduce incident HIV cases in these sub-populations, but also significantly interrupt HIV transmission in the general community [63]. A successful intervention with the potential of generating a great impact would be realised if the level of connectivity between the geographical key populations and people in the community is high. [58, 63]. Local cluster detection also known as hotspots analysis is the most common analytical technique for evaluating geographical risk spaces in space. This analysis assumes the random distribution of events/cases although clusters are often areas with elevated numbers of observed than expected events [91-93]. In a recent scoping review, hotspots of high and/or low HIV prevalence were detected, in 20 out of 22 countries using the Kulldorff spatial scan statistic [67]. Studies that compared clusters over time found that they tended to persist with little change in location [55]. In one study, findings

showed temporal persistent high HIV prevalence despite a decreasing prevalence outside the clusters [94].

Examples in which geospatial research has identified such high-risk communities and the importance of connectivity are as follows. In South Africa, a geographical high-risk location was identified in a peri-urban community in KwaZulu Natal to which 70% of the HIV transmission was linked to [63]. Although HIV prevalence is high in the fishing communities in Rakai, Uganda, there was little evidence of connectivity with inland communities of low HIV prevalence [95]. High-risk spaces were identified through spatial epidemiology. In Kenya, a population-based survey conducted between 2012 and 2013 showed high prevalence clusters of HIV in a generalized epidemic [96]. These clusters were associated with a higher proportion of the population inconsistently using condoms and having many lifetime sexual partners [96]. The presence of localized geographic clustering associated with various sociodemographic and behavioural factors, often suggest disproportionate exposure to higher HIV risk [97]. Many times, policymakers are likely to use these identified areas for targeted priority-tailored HIV interventions.

2.6. Facility level HIV program data use for approximation of community level HIV patterns

Population-based surveys such as the National Household HIV and Antenatal Sentinel HIV and Prevalence surveys have provided data to South African policy makers every two to three years. This creates a gap in evidence generation for decision making at lower administrative levels where rapid and timely decisions are needed [98]. In low- and middle-income countries (LMICs), the district health information systems (DHIS) were developed to collect aggregated routine data from all primary healthcare facilities. DHIS data generates HIV disease burden estimates and is a powerful tool for decision makers to prioritize resource allocation [69]. In 2019, the HIV disease burden in KwaZulu Natal province was estimated using the HIV testing data from routine clinic visits and revealed high disease burden areas in eThekwini, iLembe and uMngundgudlovu municipalities; and around major cities and national routes [99]. In addition to DHIS data, LMICs are using laboratory surveillance data to monitor several health outcomes reported from routine health visits for decision making. In 2020, changes in maternal viral load control were described using NHLS data and revealed low levels of viral load

suppression (<50 copies/mL) among pregnant women living with HIV, highlighting the prioritization of maternal health in PMTCT programmes in South Africa [100, 101]. CD4 recovery to 200 cells/μl among PLHIV on ART was described using laboratory data from the South Africa national HIV treatment programme[102]. The findings from this study revealed patterns in CD4 recovery for different population groups and recommended the monitoring of CD4 for 12 months post ART initiation until recovery of >200 cells/μl is achieved [102]. In Cape Town, routinely collected viral load data from ART programmes were extrapolated to estimate population viral load suppression using mixed methods estimation techniques highlighting the gaps in viral load monitoring to identify populations and areas which may require additional support for HIV testing, linkage, ART roll-out strategies and adherence/retention [101]. Routine data was used to assess the implementation of same-day ART initiation in two South African districts and findings revealed that although same-day ART initiation was increasing, retention rate in young people reduced highlighting the strengthening of the available ART support programmes [103]. Since routine data sources are interlinked, there may be variations in the findings for similar health outcomes. For instance, a study in Cape Town used three different interlinked data sources from the laboratory, pharmacy, and clinic to estimate retention in HIV care of women 24 months starting ART in pregnancy [104]. Retention from the three data sources ranged from 41% to 72% and most of the data being abstracted from clinical files [104]. Techniques that account such variations are needed to draw meaningful inferences from such datasets.

2.7. Application of space and time modelling techniques in HIV research

To understand variations of HIV prevalence and coverage of HIV prevention and treatment programmes at a district-level, on-going evaluations should employ methodologies that consider the existing time and space heterogeneity. Application of a broad range of spatial and temporal analysis techniques is on the rise in HIV-related research in SSA to characterize HIV geography, spatial risk factors and service implementation [61, 67]. Geospatial techniques produce maps with spatial and temporal data to visualize the relevant to health planning, implementation, and research. Time-series techniques evaluate the population impact of an intervention over an interval of time. The most commonly used techniques which include spatial cluster analysis, spatial interpolation, spatial regression and modelling and interrupted time series (ITS) are being described below.

2.7.1. Spatial cluster analysis

Spatial cluster analysis is the most commonly used analytical technique to identify 'hotspots' or 'coldspots' of HIV disease and outcomes. Most studies applied the Kulldorff spatial scan statistics in the SatScan software to systematically scan circular windows across the study area [62, 67]. This identified areas of increased risk and further compared the characteristics inside and outside the identified clusters. Studies that compared clusters temporally observed little change in their locations- across the study areas [55, 57, 58, 65]. The less commonly used is the Moran index, a global clustering application that determines the spatial autocorrelation of health outcomes for instance whether PLHIV lived closer to each other by chance [105].

2.7.2. Spatial interpolation

Interpolation techniques create continuous surface maps of various outcomes/disease events over space by using data collected in sampled locations to predict values in unsampled locations [106, 107]. Interpolation includes simpler methods such as inverse distance weighted estimates to more complex techniques including Kriging and Bayesian hierarchical modelling [107]. The resultant is a smoothed map that enables a visual comparison of geospatial patterns temporally or between different demographic characteristics of the population under study.

2.7.3. Spatial regression and modelling

Classical risk factor analysis assesses the hypothesis that data is not associated with geography. To test this assumption, spatial regressions with random effects assess correlations within and between study areas sharing boundaries [108]. Afterwards, outputs from spatial regression models provide more accurate estimates after accounting for confounding factors that are geographically determined. A recent spatial regression of HIV in South Africa revealed several factors common in high prevalence districts including poverty, intergenerational sex and gender disparity [98]. These findings were important for guiding context-specific programs and illuminating the need for more granular data collection and analysis [98].

2.7.4. Time series analysis and forecasting

Time-series analysis use historical values observed over time to extrapolate forecasts which help the health system prepare for the future [109, 110]. The Autoregressive Integrated Moving Average (ARIMA) is useful in evaluating and creating a forecasting model by modelling correlations in the datasets [111]. ARIMA regression is suitable for short term forecasting and non-stationary data. When a population-level intervention is introduced at a known time-point, the effect is evaluated using an interrupted time series (ITS) analysis. The result of this analysis is an assumed state under which the intervention had not taken place and the trend continues unchanged. This counterfactual state provides an opportunity to compare the impact of the intervention pre-intervention by examining any change occurring in the post-intervention period [111].

2.8. Summary of literature review

Chapter 2 examined the current literature on space and time analysis of HIV which is gaining traction, and the barriers to and facilitators of engaging in HIV care in SSA. This was done in line with the objectives of the study that were to assess the link between space and selected HIV services in routine settings. The literature review discussed the use of routine health data from the HIV or ART programmes in clinics or laboratory across South Africa to approximate the underlying patterns in HIV response. The literature review highlighted the most commonly used geospatial techniques and the heterogeneity of HIV and HIV services by age-group, gender, and key population. None of the studies investigated heterogeneity of characteristics defined by differences in geographical settings. The review revealed that space and time heterogeneity at a local level is rarely investigated due to access to available data at a community level. The various analytical techniques which consider the geographical and time differences, and trends were described in this chapter. A few examples on these applications were provided from previous studies and further highlighted the relevance of advancing this field in SSA. Of more importance is the focus on small area analysis to understand at a granular level the spatial and temporal associations between the health events in study with the spaces in which people reside in. In conclusion, it is important to first identify areas where disproportionately large numbers of disease events (transmissions, low uptake) are located. Second, is to characterize these risk-spaces using methodologies that highlight where

targeted prevention approaches are needed as part of an overall combination approach. The next chapter (Chapter 3) explores into detail the integrated methodologies used in this study.

3. CHAPTER THREE: METHODS

> *"The power of statistics and the clean lines of quantitative research appealed to me, but I fell in love with the richness and depth of qualitative research*." (Brené Brown) *Therefore, I applied both methods.*

3.1. Introduction

This chapter presents the methodology used to achieve this PhD thesis objectives. The ecological study design employed a series of data cross-sectionally collected. This study utilised an explanatory sequential mixed-methods approach which combined quantitative and qualitative data collection and analysis. A meta-inference was performed to confirm or dispute the quantitative with the qualitative findings. It is at this stage that conclusions are made, and a deeper understanding of the topic is realised. The meta-inference was incorporated in the discussion of the findings in Chapter Eight.

3.2. Data Sources

The data used for this PhD work were obtained from a combination of five data sources, namely: i) A National HIV survey from the Human Sciences Research Council (HSRC), ii) routinely collected clinical data from the District Health Information system (DHIS), iii) routinely collected laboratory data from the Central Data Warehouse (CDW) of the National Health Laboratory Services (NHLS), iv) the 2001 and 2011 South African National Census and v) clinic attendees and healthcare providers in selected PHCs. An overview of the PhD objectives and their respective data sources is outlined Table 3-1.

Table 3-1: Overview of PhD objectives and data sources

PhD paper and title	PhD Objective	Data type and source	Techniques used
1 - Assessing spatial patterns of HIV prevalence and interventions in semi-urban settings in South Africa: Implications for spatially targeted interventions	To establish pre-existing patterns of HIV prevalence, coverage, and uptake of HIV interventions in the study area.	**Secondary quantitative** • HSRC • DHIS • 2001 Census	Descriptive analysis Bayesian non-spatial regression Bayesian spatial regression Spatial interpolation (kriging)
2 – Small area analysis of HIV Viral load suppression patterns in a high priority district (2012-2016), South Africa	To examine the predictors of viral load suppression in Ekurhuleni while adjusting for non-spatial and spatial effects.	**Secondary quantitative** • DHIS • NHLS • 2011 Census	Spatial autocorrelation Bayesian and non-Bayesian spatio-temporal regression Spatial interpolation Cluster analysis
3 - Understanding factors influencing utilization of HIV prevention and treatment services among patients and providers in a heterogeneous setting: a qualitative study from South Africa	To investigate facilitators of and barriers to optimal uptake of HIV interventions at an individual and clinic level.	**Primary qualitative** • Patients • Healthcare workers	Inductive and deductive coding Thematic analysis
4 – Forecasting viral load suppression using routinely collected data from a high priority district in South Africa	To estimate the impact of interventions on HIV risk in Ekurhuleni post study period.	**Secondary quantitative** • DHIS • NHLS • 2011 Census	Geographical weighted regression Forecasting

HSRC-Human Sciences Research Council National HIV survey; DHIS – District Health Information Systems; NHLS – National Health Laboratory services

Retrospective data for this study were acquired from publicly available datasets. The 2012 South African National HIV Prevalence, Incidence and Behaviour Survey by the HSRC was used to provide data on HIV infection and socio-demographic information in the different sub-districts at a national level. Data on the uptake of HIV interventions at the clinic level in Ekurhuleni was abstracted from the DHIS hosted by the South Africa National Department of Health, which routinely collects individual-level data from all South African public health facilities at a local level. Census data was used to extrapolate demographic estimates at a ward level including income, literacy levels, population size and density.

3.2.1. South African National HIV Prevalence, Incidence and Behaviour Survey, 2012

From a database of 86 000 enumeration areas (EAs), 1 000 EAs were delineated from the previous population census (2001) stratified by province, locality type and race were randomly selected using probability proportional to size [112]. These EAs were mapped in 2007 using aerial photography to develop a sample for selecting households which formed primary sampling units. In each sampled EA, a total of 15 households were used as secondary sampling units and within each household selected for the survey, all household members made up the final sampling unit [112]. In Ekurhuleni, 57 EAs over 33 wards were sampled. Three outcomes from the national survey were generated: (i) HIV infection, defined as reported HIV positive test result, (ii) sub-optimal condom use, defined as reporting not consistently using condoms in the past month while sexually active and (iii) non-ART use defined as reporting not using ART despite a positive HIV status. HIV prevalence was defined as the proportion of individuals testing HIV-positive over the total population sampled per ward during the survey.

3.2.2. District Health Information System (DHIS)

The DHIS was introduced in 1996 to collect aggregated routine data from all public health facilities in South Africa [113]. The DHIS allows HCWs to analyse their levels of service provision, predict service needs, and assess performance in meeting health service targets. The DHIS consists of two parts: paper-based system of registers, tally sheets, and monthly data collation forms and analysis occurring at the facility-level; and DHIS software to processes the data. Routinely collected data on all services provided by a facility, or occasionally on infrastructure and human resources during clinic surveys is collated data and sent monthly to the sub-district or district level. These data are captured into a computer using DHIS software, analysed, and a report is submitted to district, provincial and national health departments [113].

Routine data for EMM from April 2012 to March 2016 fiscal years were used to determine aggregate male condom coverage calculated as the number of condoms distributed by the clinic over the number of males ≥15 years attending each clinic. ART initiation rate was calculated by estimating the total HIV patients remaining on ART at end of the month per the approximated number of PLHIV attending routine clinic visits in each clinic. An arithmetic mean by ward for both measures was calculated for each year.

3.2.3. *National Health Laboratory Services*

Monitoring of laboratory test results is done in the South Africa NHLS database which provided data on HIV viral loads from PLHIV. NHLS which conducts all laboratory monitoring for the national HIV program. The test results are placed in long-term storage as laboratory specimen in the NHLS CDW. For this study, I utilized data from all facilities in Ekurhuleni and the resulting study population included information of all PLHIV with valid viral loads test results from 88 wards in Ekurhuleni. The outcomes measured were viral load suppression (VLS) using, two of the thresholds (<1000 copies /mL and <400 copies/mL) in South Africa to determine treatment success. The annualized mean $_{log}10$ viral load was summarized and ward-level VLS proportion was calculated by taking the number of virally suppressed PLHIV per the total number of PLHIV in care per year.

3.2.4. *Qualitative in-depth interviews*

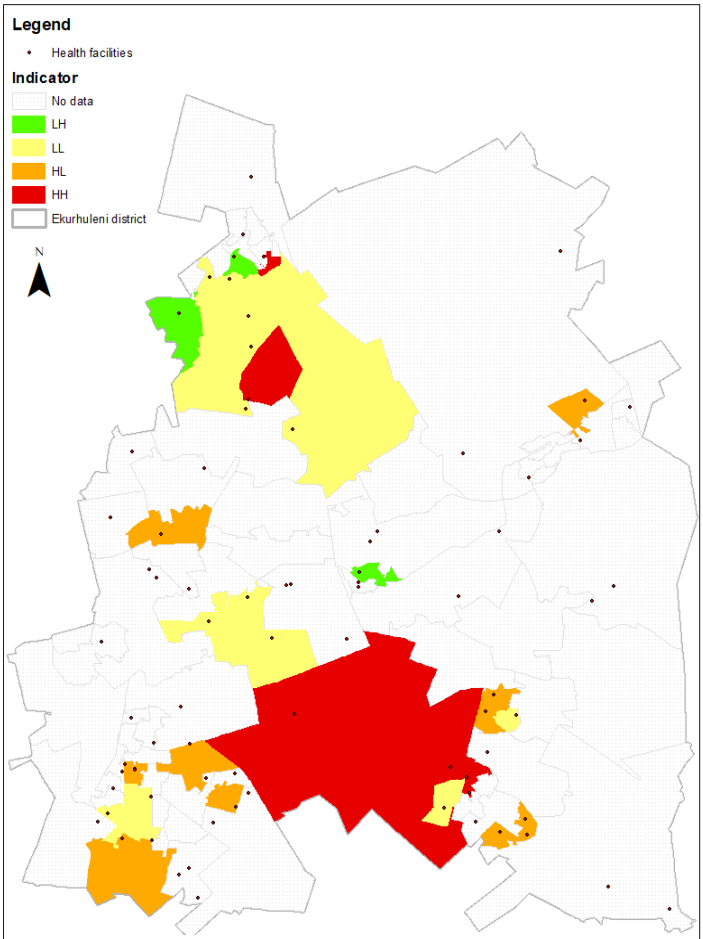


Figure 3-1: Areas for recruitment of qualitative participants

Qualitative in-depth interviews (IDIs) were conducted from areas categorized by HIV prevalence and uptake of two HIV services. This was done by generating four codes from the distribution of HIV prevalence and coverage of male condom use and ART initiation rates in 2012 and mapping them as shown in Figure 3-1.

Participants were enrolled from one clinic in each of the identified areas (Figure 3-1). Areas with low levels of HIV prevalence and high levels of uptake of services were considered as ideal. Similarly, areas with low levels of uptake of services were considered non ideal areas.

Data were collected using IDI guides between July 4 and July 27, 2020, by trained field staff experienced in qualitative research and with fluency in the study languages (see section 6.2 and Appendix H). These field staff visited the clinics daily in the morning (7am-12noon) to recruit willing participants. All participants were either adult (≥18 years) patients or staff from the sampled clinics, willing to voluntary participate having their conversations recorded digitally. At the end of the recruitment process, 30 male and female PLHIV and healthcare providers (HCP) consented to participate. The sample included HCP providing different HIV services at the clinic and community-level and PLHIV stable on ART, or newly initiating and HIV-negative patients. The diversity of the final sample provided a reasonably comprehensive detail about barriers and facilitators affecting uptake and delivery of HIV services in Ekurhuleni [114]. The recruitment and enrolment of qualitative participants is summarized in Figure 3-2.

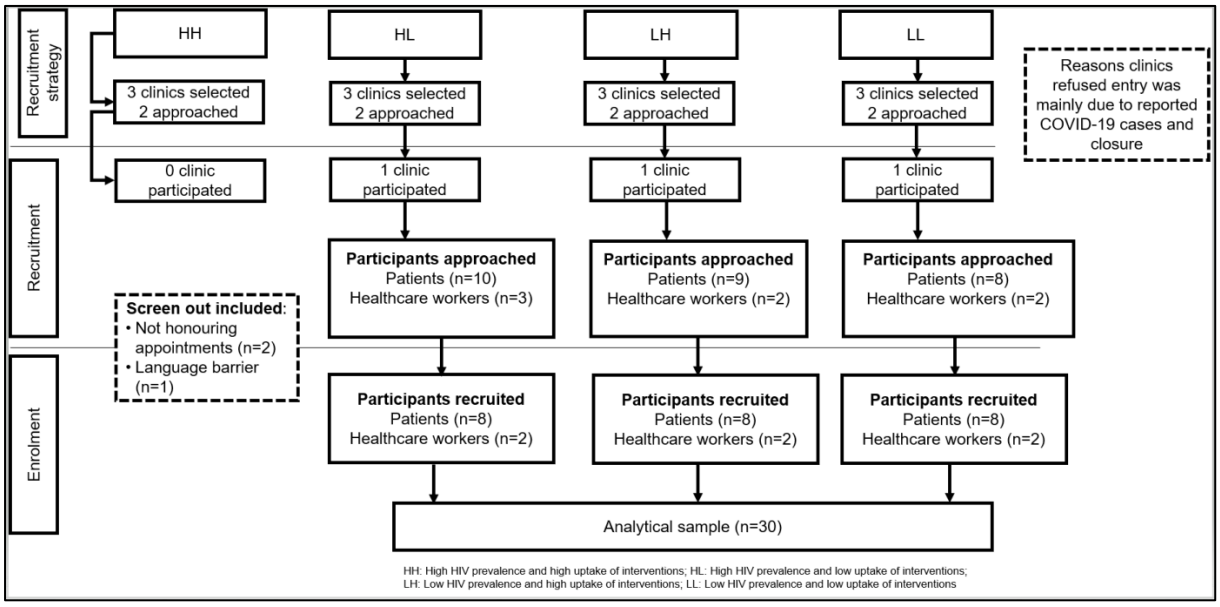


Figure 3-2: Recruitment and enrolment of qualitative study participants [73].

3.2.5. South African National Census data, 2001 and 2011

Two sets of census data were used. The 2001 census data was used to extrapolate the ward level population to estimate the HIV prevalence for each ward from the HIV data reported in the 2012 HSRC survey. During the 2012 HSRC survey, wards were sampled using the 2001 national census geographical data. The 2011 census provided ward-level data on level of

education, gender, household income level and populations at ward level in Ekurhuleni from 2013 to 2016.

3.3. Study setting

Ekurhuleni Metropolitan Municipality (EMM) is an urban and semi-urban district in Gauteng province, South Africa. It borders the cities of Johannesburg and Tshwane, and Sedibeng District Municipality (Figure 3-3). The population is over 3 million and the population density is 1 718 people per square kilometre according to the 2011 census, a densely population district in South Africa. Slightly over 50% of population is unemployed and 18.7% live in informal settlements with no electricity and, proper water and sanitation [115]. The informal settlements are characterised by extreme poverty, gender inequality, limited employment prospects and generalised violence.

The HIV prevalence in 2012 was 12% and increased to 14% in 2017 [116, 117]. EMM is sub-divided into three sub-districts (North, South and East) and 101 wards (Figure 3-2). There is a district hospital, seven community health centres and 87 primary health clinics (PHCs) across the wards. PHCs are entry-level facilities in communities providing free HIV care and treatment [118]. These facilities are staffed by clinical personnel and offer healthcare services, including HIV prevention and care, with no out-of-pocket payments required from patients. Also, various non-governmental organisations, through support and collaboration with PEPFAR and CDC South Africa, work in coordination with the NDoH to increase services such as direct service delivery and health systems strengthening [119]. PHCs in EMM collect a venous blood specimen from PLHIV at six and 12 months after newly initiating on ART and thereafter annually. The blood specimen are sent to NICD for centrifuging and viral load testing. The results are entered into the NHLS database to provide potential important and strategic information on the ART programme in EMM. Similarly, the DHIS reports on the information collected by HCWs in the PHCs to evaluate the HIV prevention and treatment programmes. Data including number of patients assessed for HIV, initiated on ART, and remaining on ART is collected and recorded daily.

EMM is identified as a high priority district according to the 2017- 2022 NSP due to its sizeable population (3.3 million) [120] and high HIV burden (15%) [121]. The population in EMM is mainly black male (51.2%), and almost a quarter are living in poverty (monthly earnings < ZAR

992). Most of the population live in congested informal settlements on the fringes of urban areas with limited access to employment prospects and satisfactory public services [122].

Throughout this thesis, the words Ekurhuleni district, Ekurhuleni and Ekurhuleni Metropolitan Municipality are used interchangeably.

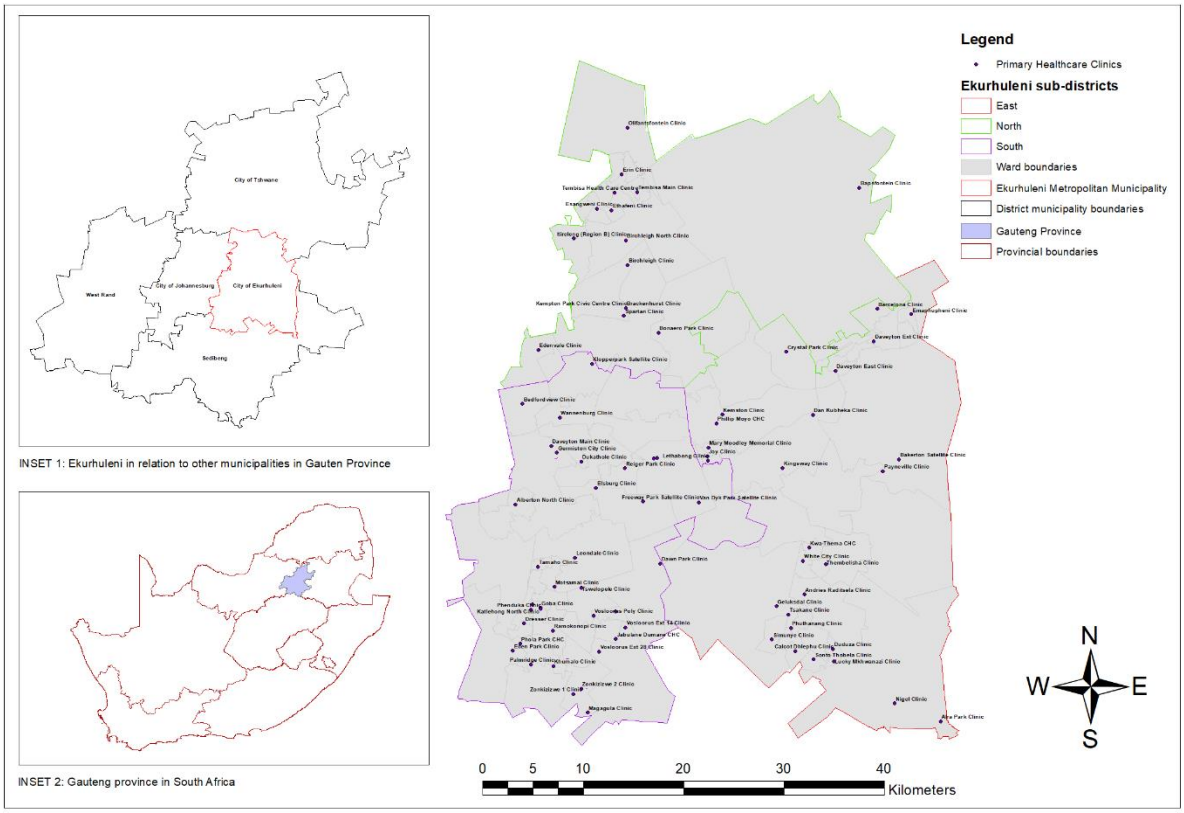


Figure 3-3: The study area and inset maps showing study area in relation to South Africa and Gauteng province

3.4. Study outcomes

This PhD work investigated different study outcomes for each objective. Table 3-2 describes the outcomes for each objective and their initial measurement.

Table 3-2: Study outcomes, the source, and their initial measurement

Objective	Source	Outcome(s)	Measurement
To establish pre-existing patterns of HIV prevalence, coverage, and uptake of HIV interventions in the study area.	HSRC database	HIV infected	Any respondent who reported testing HIV positive at time of survey
		HIV prevalence	HIV prevalence defined as the proportion of individuals testing HIV-positive over the total population sampled per ward at the time of the survey.
		Sub-optimal condom use	Participants who reported inconsistent or lack of condom use during their last sexual act.
		Non-ART use	PLHIV not ART at the time of the survey.
	DHIS (HIV prevention and treatment programme)	Male condom use coverage	Aggregated male condom coverage was calculated as the total number of condoms distributed by the clinic and other non-medical sites divided by the total reported number of males ≥15 years in 2012. An annual average per ward was calculated.
		ART initiation rate	ART initiation rate was calculated by estimating the total HIV patients remaining on ART at end of the month over the estimated number of PLHIV. An annual average by ward was calculated.
To examine the predictors of viral load suppression in Ekurhuleni while adjusting for non-spatial and spatial effects.	NHLS/NICD database (ART programme)	Proportion virally suppressed. (<1000 copies/mL)	Number of those with VL<1000 or <400 cp/ml divided by total number of patients reporting a viral load aggregated at ward level per year
		Proportion virally suppressed. (<400 copies/mL)	

Objective	Source	Outcome(s)	Measurement
To investigate facilitators of and barriers to optimal uptake of HIV interventions at an individual and clinic level.	Qualitative interviews with patients and providers	Facilitators of uptake of HIV services	Any mention of a reason why patients seek, or providers provide HIV services in primary healthcare clinics
		Barriers to uptake of HIV services	Any mention of why patients are reluctant to seek, or providers are reluctant to provide HIV services.
To estimate the impact of interventions on HIV risk in Ekurhuleni.	NHLS/NICD database (HIV programme)	Viral load suppression (<1000 copies/mL) Viral load suppression (<400 copies/mL)	Number of those with VL<1000 or <400 copies/ml divided by total viral load reported aggregated at ward level per year
		High viral load suppression rate (<1000 copies/mL) High viral load suppression rate (<400 copies/mL)	According to the 90-90-90 strategy, proportion of wards with high viral load suppression was considered to be those with above 74% of the HIV positive population virally suppressed.

3.5. Study methodology

Mixed-methods research designs are important for triangulating findings between qualitative and quantitative data [123]. For this study, the two approaches complemented each other and were adopted to provide an understanding of the uptake and delivery of HIV services is a high priority district. This PhD study adopted an explanatory sequential mixed-methods approach incorporating quantitative and qualitative methods of data collection and analysis (Figure 3-4). The quantitative component comprising of data retrieved from pre-existing datasets preceded the qualitative and the findings informed the purposive sampling for data collection for the qualitative component [124]. The data analysis for the different components was performed separately but overall interpretation and integration of the findings was combined [125].

Results of data analysed from publicly available national databases were interpreted together with findings from in-depth interviews. The process of explanatory sequential mixed methods is illustrated in Figure 3-4 and the results from this approach are used to validate the findings from one component to another. This mixed methods approach applied a meta-inference

technique where findings from the different types of analyses are validated and integrated according to the research question [126]. It is at this stage that conclusions are made, and a deeper understanding of a topic is determined.

3.6. Study design

The overarching study design was ecological where the unit of analysis was the ward level in EMM. This PhD study employed multiple study designs including cross-sectional and repeated cross sectional to answer the research objectives as outlined in Figure 3-4.

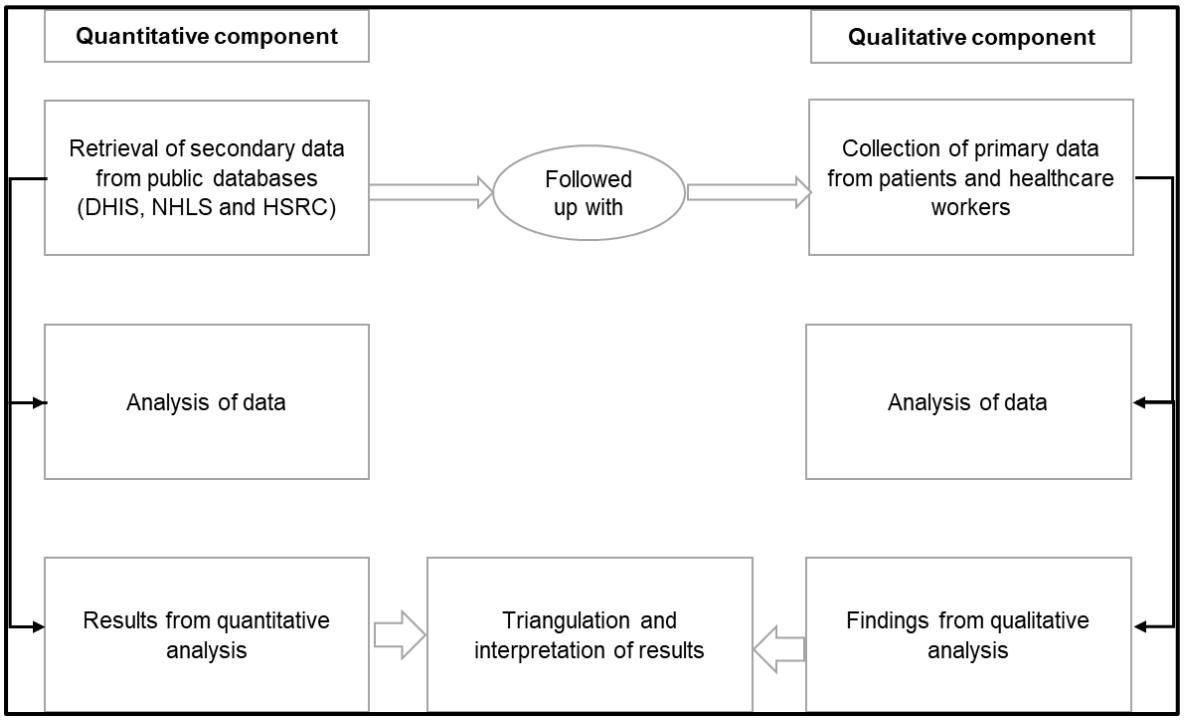


Figure 3-4: Explanatory sequential mixed-methods study design

3.7. Spatial and Bayesian modelling

3.7.1. Cross-sectional data

For the spatial regression models, each regression model fitted was a Bernoulli model since the outcome variables were binary. To explicitly understand the model: Y_{is} is the outcome (HIV infection, sub-optimal condom use and non-ART use) which takes values $Y_i = 1$ if the outcome occurs and if an individual i residing in ward $s = 1, 2, ..., 33$. Therefore, Y_{is} follows a Bernoulli

distribution with a probability of experiencing an outcome p_{is}, that is, $Y_{is} \sim Ber(p_{is})$. The probability density function of the outcome variables is $P(Y_{is}) = p_{is}^{Y_{is}}(1-p_{is})^{1-Y_{is}}$. Using the generalised linear model for a binary outcome, the probability can be modelled using logistic regression as:

$$\text{logit}(p_{is}) = P(Y_{is} - 1|x_{is}) = \beta_0 + X_{is}^T\beta_{is} + G_{is} \quad (1)$$

where β_0 is the intercept terms, $\boldsymbol{\beta}_i$ is the vector of regression coefficients of fixed effects, $\boldsymbol{X}_i$ denotes the vector of subject-level covariates and G_{is} are the spatial random effects corresponding to the binary response of an individual i residing in ward s. Since it is assumed that the outcome variables are spatially correlated, and the independence assumption in the response variables is questionable; hence, we introduced a spatial structure. The spatial random-effects (G_{is}) were decomposed into subject–specific uncorrelated (U_{is}) and spatially correlated random effects; hence, the following convolutional model was fitted:

$$\text{logit}(p_{is}) = \beta_0 + X_{is}^T\beta + U_{is} + H_{is} \quad (2)$$

A fully Bayesian inference approach whereby i assigned priors to all unknown random and fixed parameters and variance parameters (hyperparameters). Parameters of the fixed effects were assigned diffuse priors, $\beta \propto \text{constant}$. The uncorrelated spatial effects U_{is} were assumed to be independent and identically distributed Gaussian priors, that is, $U_{is} \overset{iid}{\sim} N(0, \tau_u^2)$ where the unknown hyperparameters of the variance components, τ_u^2 was assigned highly dispersed gamma priors $\left(\tau_u \sim G\left(a_{\tau_u}, b_{\tau_u}\right)\right)$ with known parameter values $\mathrm{a}_u = \mathrm{b}_u = 0.01$. The $S = 33$ structured spatial wards modelled in this study; these were assumed to follow a conditional autoregressive (CAR) prior. In the full conditional distribution, each H_{is} is conditional on the sum of the weighted values of its neighbours $\left(w_{jk \in s} H_s\right)$ and has an unknown variance:

$$H_j \mid H_k, j \neq k, \sim N\left(\sum_{j=1}^{n} W_{jk} H_s, \tau_h\right) \quad (3)$$

The W is an $S \times S$ adjacency weighting matrix that defines the relationship of $S \times S$ areal units(wards). For two adjacency neighbour wards polygons, $j \sim k, j \neq k$ the W matrix entries take values 1 if the wards are neighbours or 0 otherwise. In the CAR model, the neighbour relationship is symmetric but not reflective and a ward/polygon cannot be its neighbour. The hyperprior for the variance parameter was assumed to follow an inverse Gamma distribution, $\tau_h \sim G\left(a_{\tau_h}, b_{\tau_h}\right)$. Since this posterior function had no closed form, we used the Gibbs sampling to estimate the posterior parameters or Markov Chain Monte Carlo (MCMC) with Metropolis-Hastings algorithms.

The Bayesian models were fitted with 15, 000 MCMC iterations, and prior sensitivity was done by varying parameter values. Model convergency was assessed using trace plots and autocorrelations plots. Model comparisons for no spatial model, unstructured spatial random effects only model, structured spatial random effects only model and convolutional model were done using the deviance information criteria (DIC) defined as:

$$DIC = D\left(\bar{\theta}\right) + 2p_D = \bar{D} + p_D \quad (4)$$

where $D\left(\bar{\theta}\right)$ is the deviance statistic evaluated at $\bar{\theta}$, which is the posterior means of mean of the deviance statistic. The lower the DIC the better the model.

3.7.2. Longitudinal data

The Bayesian hierarchical spatio-temporal joint component model was used to concurrently measure the viral load suppression rates in EMM from 2012-2016. To improve the accuracy of estimates from spatio-temporal techniques, information was shared across the different and similar exposures and the outcome-specific components considering the underlying spatio-temporal interactions [32].

Let Y_{ij} be the observed proportion of viral load suppression (outcome), where i represents a given ward (1–33) and j represents the years (2012–2016) and $Y_{ij} \sim binomial\left(n_{ij}, \pi ij\right)$.

Here, π_{ij} represents the true, unknown viral load suppression rate in wards i and time j. The proportionate rate of viral load suppression specified on the logit scale is described in Equation 5 as:

$$logit(\pi_{ij}) = \alpha + X_i\beta_i + X_{ij}\beta_{ij} + \mu_{ij}. \quad (5)$$

The parameter α is the baseline relative risk for a given viral load suppression outcome. X_i and X_{ij} are the time-invariant spatial and spatio-temporal varying covariates (ART initiation rate, proportion diagnosed with TB, proportion of female patients, proportion with low literacy and with no income) respectively. The parameters β are the regression coefficients that account for the wide-ranging risk graduations of the joint spatial and temporal elements. The spatio-temporal structure, defined by μ_{ij} accounts for the variations of relative risk in the logit scale. The shared spatial-temporal structure was specified as follows in Equation 6:

$$\mu_{ij} = \gamma_k^s \mu_i^s + \mu_{ik}^s + \gamma_k^t \mu_j^t + \mu_{jk}^t + \nu_{ij} \quad (6)$$

μ_i^s are a set of common random effects associated with space, i.e., conditional autoregressive (CAR), $\mu_{ik}^s$is the outcome-specific random effects associated with space μ_j^t are a set of common random effects associated with time, i.e., random walk of order 1 (RW1), μ_{jk}^t are outcome-specific random effects associated with time (RW1). The space-time interaction term/heterogeneity of order two is represented by ν_{ij} which are the possible variations not explained by the spatial and temporal effects in the model.

A descriptive summary of the overall proportion of viral suppression at the municipality level and sub-district level using tables and line graphs was done. The predictors of the proportion of viral load suppression at ward level was determined by fitting spatial and spatio-temporal mixed-effects regression model using R integrated Nested Laplace Approximation (INLA) package in R version V.3.6.1 (R Foundation for statistical Computing). The mixed-effects model for viral load suppression accounted for fixed effects as well as ward specific random intercepts to account for over dispersion or correlation in viral load suppression within and between wards over five years. The hierarchical Bayesian model incorporating time varying covariates and several time and ward random effects for VLS rates is outlined in Equation 7:

$$\text{logit}\,(p_{it}) = \alpha_0 + u_i + v_i + \varphi 1_t + \psi_{it} + X_i'\beta, \text{ where} \quad (7)$$

- logit link function log ($P_{it}/(\underline{1-p_{it}})$); where P_{it} is the probability of VLS in ward $_i$ at year $_t$.

- an overall intercept term α_0. The intercept, α_0 was assigned a flat prior: $P(\alpha_0) \propto$ constant, (where, P indicates probability).
- $\boldsymbol{X_{it}'\beta}$ where, $\boldsymbol{X_{it}}$: is the i^{th} row and t^{th} column of the covariates matrix $\boldsymbol{X}$ and $\boldsymbol{\beta}$ is a vector of regression parameters. The $\boldsymbol{\beta}$ for fixed effects ($\boldsymbol{X_{it}'\beta}$) were assigned Normal priors. $\boldsymbol{\beta} \sim N(0,100)$
- the spatial effects, u_i, by ward to account for strong spatial autocorrelation, and were modelled via normal conditionally autoregressive priors (CAR) [127] where weights were assigned to each ward according to adjacency; neighbouring wards receive a weight of one while non-neighbouring wards receive a weight of zero. Specifically, for i = 1, …, m, wards, and j = 1,…, T, years.
- non-spatial random effects v_i by ward, to model residual spatial variation not dealt with by our spatial random effects and were assigned a Normal prior, $vi \sim N(0,1\tau v)$, with precision, τ_v. The conditional precision of the unstructured random effect was assigned $\tau_v \sim$ Gamma (1, 0.001) prior.
- correlated random time effects, φ_{1t}, to account for time dependence, were modelled via first order random walk [128, 129]. This component assumes that the values for a given ward in a given year depend upon the values observed for that ward in the prior year plus a residual. The correlated temporal random effect, φ_{1t}, which has a random walk prior distribution, with precision, $\tau_{\varphi 1}$; where $\varphi 1t \sim N(\varphi 1, t-1, 1\tau\varphi 1)$. The conditional precision of the unstructured random effect was assigned $\tau_{\varphi 1} \sim$ Gamma (1, 0.001) prior.
- an uncorrelated time dependent random effect φ_{2t}, to account for independent time effects, which were modelled as normal distributed with precision, $\tau_{\varphi 2}$; $\varphi 2t \sim N(0,1\tau\varphi 2)$. The conditional precision of the unstructured random effect was assigned $\tau_{\varphi 2} \sim$ Gamma (1, 0.001) prior.
- the space time interaction term, ψ_{it}, to account for any residual spatiotemporal variation that was not captured by the spatial or temporal main effects and were assumed to be independently and identically distributed [129]; $\psi it \sim N(0,1\tau\psi)$. The conditional precision of the unstructured random effect was assigned $\tau_\psi \sim$ Gamma (1, 0.001) prior.

(The precisions for the intercept, fixed effects and the random effects are assigned priors that are default in R-INLA. INLA assigns log (precisions) ~log-gamma (1, 0.001) priors) [130-133].

The adjusted viral load suppression rates were mapped using ArcGIS version 10.7.1 (Environmental Systems Research Institute, USA). To assess spatial autocorrelation of viral load suppression in Ekurhuleni, I used the Moran index and to map clusters of high and low viral load suppression, i used the Anselin Local Indicator Spatial Autocorrelation (LISA) function in ArcGIS. To test for trend of viral load suppression and ART initiation rate across the five years the Cochran-Mantel-Haenszel stratified test of association and Kruskal-Wallis equality of populations were applied in Stata version 14 (StataCorp, Texas, USA). Significance level was determined at 5%.

3.8. Spatial interpolation

Kriging, a geostatistical method that creates smoothed surfaces from point data, is often used in public health research to produce choropleth maps of risk or disease events [107]. Kriging requires very large datasets for precision of estimates, a limitation of a small area analysis of district data such as EMM. This PhD study applies a more advanced statistical technique, Bayesian kriging, which provides more accurate estimates for smaller datasets which in this study, come from incorporating prior information (see sub-section 3.7.1) since the observed data was fixed. Kriging, a spatial interpolation technique, was done on previously Bayesian generated prediction for 2012 by calculating an average value for the wards where no data was collected using values from nearby sampled wards to predict clusters of high HIV infections, sub-optimal condom use coverage and low ART initiation rates [106]. The value of the outcome (z) at a specific location (s_i) is modelled as the sum of the regional mean (m) and a spatially correlated random component ($e(s_i)$) (Equation 8).

$$Z(s_i) = m + e(s_i) \tag{8}$$

For the locations with no data (X_0), estimating the unknown mean required prediction. Each point (X_0) was predicted as the weighted average of the values at all sampled points and the weights assigned to each sampled point summed up to 1 making the prediction unbiased [107] (Equation 9).

$$\mathrm{E}\left[\hat{\mathrm{Z}}\left(\overrightarrow{\chi_0}\right) - \mathrm{Z}\left(\overrightarrow{\chi_0}\right)\right] = 0\Big] \tag{9}$$

Two sets of maps were produced: firstly, interpolated maps describing the patterns of HIV prevalence, coverage of male condom use and ART initiation rates across the district.

Secondly, smoothed maps showing the likelihood of HIV infection, suboptimal condom use and non-ART use from the spatial regression analyses were produced. The maps revealed areas with increased likelihood of poor outcomes (red colour) and as green in those whose likelihood was lower.

3.9. Statistical modelling

In this sub-section, various statistical techniques employed in this PhD thesis for longitudinal data are discussed. These techniques are linked to Table 3.1. where the underlying proposed analysis is linked to the overall study design.

3.9.1. Descriptive analysis

Initial summary statistics and plots such as line graphs over time were drawn to familiarize with the data. This was done for the overall district and then stratified across the three sub-districts. This identified the underlying trends and patterns in the viral load suppression in EMM over a period of five years. In addition, the more traditional descriptive analyses, such as summaries and bivariate comparisons between the viral load suppression and the potential time-varying confounders were done.

3.9.2. Regression analysis: Interrupted time series regression

To evaluate the effectiveness of universal test and treat post September 2016, an interrupted time series (ITS) regression was performed using these three variables namely:

i. T: the time passed since the start of the intervention used in this study (January – December 2016) with the units (months) representing the frequency with which observations were taken.

ii. X_t: a mock variable indicating the pre-intervention period (January-August 2016 coded as 0) or the post-intervention period (September-December 2016 coded as 1).

iii. Y_t: the outcome at time t.

The standard ITS analyses in this study used the following longitudinal series regression model illustrated in Equation 10:

$$Y = \beta_0 + \beta_1 T + \beta_2 X_t + \beta_3 TX_t \quad (10)$$

β_0 represented the baseline level the time elapsed = 0, β_1 and is interpreted as the change in outcome associated with a monthly increase (representing the original pre-intervention trend), β_2 is the baseline change following the intervention and β_3 is the gradual change after implementation of the intervention incorporating the time TX_t).

3.9.3. Regression analysis: non-spatial Bayesian regression

Sub-section 3.7.1 described the spatial Bayesian model used to model the risk factors for HIV prevalence, sub-optimal condom use and non-ART use. To account for non-spatial risk factors, a similar equation to Equation 1 was applied without including the spatial components as outlined in Equation 11.

$$\text{logit}(p_{is}) = P(Y_{is} - 1|x_{is}) = \beta_0 + X_{is}^T \beta_{is} \quad (11)$$

3.9.4. Ordinary least squares and geographical weighted regression

An ordinary least squares (OLS) and geographically weighted regression (GWR) were used to explore the spatial variation of viral load suppression across five years and model the relationship the two predictors had on high viral load suppression in Ekurhuleni [134]. Unlike the OLS regression, the coefficients from GWR are drawn from each ward and take different values. The GWR model [32] can be written as shown in Equation 12:

$$VLS_i(\boldsymbol{z}) = \beta_{0i}(\boldsymbol{z}) + \beta_{1i} PropFemale_i(\boldsymbol{z}) + \beta_{2i} PropART_i(\boldsymbol{z}) + \boldsymbol{\varepsilon_i} \quad (12)$$

Where VLS_i are observations of viral load suppression, $(\boldsymbol{z})$ are the parameters, β, estimated at each ward with centroids given by vector $\boldsymbol{z}$; i represents each ward ($i = 1,2, \ldots .88$), and $\boldsymbol{\varepsilon_i}$ the estimation residual in each ward. Mapping the two predictors and the association with change in viral load suppression was done in ArcGIS version 10 [135]. Smoothed maps for each year and parameter were produced.

3.9.5. Forecasting

To predict the performance of HIV inputs on HIV viral load suppression, a time-series approach in forecasting was employed. An auto-regressive integrated moving average (ARIMA) model forecasting approach is different because it is prediction is independent from the historical data trend. The moving average (MA) is a random process where the error term of the historical data has a linear relationship with the biased sum of the white noise error of the future model. The chosen model is subsequently tested against future data to confirm the correct representation of the time series. An ARIMA model is defined as ARIMA (p, d, q): where p is the order of the autoregressive segment (AR), d is the degree of first differencing involved and q, the order of the MA segment. The underlying time series approach is summarized in Figure 3-4.

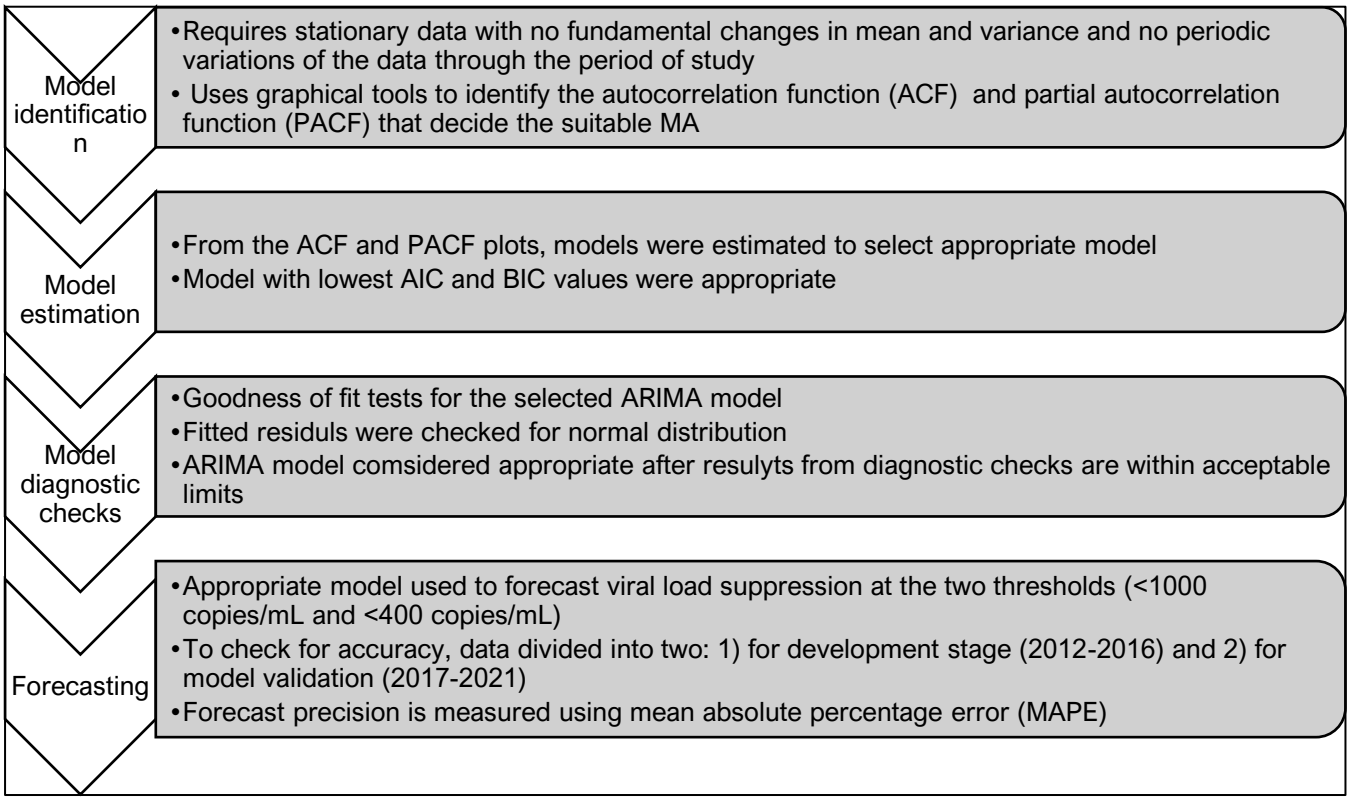


Figure 3-5: A summarized Box-Jenkins methodology for forecasting viral load suppression

3.9.6. Sensitivity analysis

A sensitivity analysis was conducted using:

i. viral load suppression of <400copies/mL as the outcome and

ii. viral load suppression rates reported before 1st September 2016 due to the national roll-out of UTT in clinic-level HIV programmes in South Africa

3.10. Summary of Chapter

Chapter three provided an in-depth look at the PhD study methodology. Initially beginning with the different data sources providing both quantitative and qualitative data for analysis of study objectives (section 3.2). A look at the study setting was introduced in this chapter highlighting the different socio-demographic characteristics of Ekurhuleni and the social infrastructure present in EMM (section 3.3). Next, a tabulated summary of the different study outcomes from the objectives and their respective measurements was outlined in section 3.4. This transitioned into the different methodological approaches to be used to answer the four objectives of this PhD study (section 3.5). An overall study design in line with the PhD objectives was discussed in detail in section 3.6. In Chapter two, the different statistical and modelling techniques were briefly introduced. However, Chapter three provides a more detailed explanation of the different modelling techniques used including the mathematical equations behind these techniques. To explain the importance of accounting for spatio-temporal and random effects of the study data, Bayesian modelling was explained in detail (section 3.7). This technique were applied to both cross-sectional (sub-section 3.7.1) and longitudinally collected data (sub-section 3.7.2). Spatial techniques to account for unmeasured data from unsampled locations were explained in section 3.8. Spatial modelling techniques were analysed in powerful software including WINBUGS and R with the capacity to handle unseen random and spatial effects. Traditional descriptive analysis (sub-section 3.9.1) were done to profile the study populations. OLS and GWR (sub-section 3.9.) were performed to show the change in viral load suppression in relation to ART coverage and population of women in each ward over the study period. Thereafter, other regression techniques such as ITS (sub-section 3.9.2), ARIMA (sub-section 3.9.3) were applied to provide accurate estimates of the routine data collected over five years. The models from these analyses were validated (sub-section 3.9.4). To predict the outcome five years post 2016, forecasting in Stata version 16.0 [136] was performed (section 3.9.5). Finally, a sensitivity analysis was performed to check for robustness of the findings and establish credible conclusions after different assumptions are made.

The next chapters (Chapters Four-Seven) discuss the methods used to analyse each of the four objectives which are outlined in the form of a manuscript submitted or prepared to be

submitted to a peer-reviewed journal. The corresponding detailed manuscripts of published and unpublished findings are attached in the appendices (Appendices F-I).

4. CHAPTER FOUR: KNOWING YOUR EPIDEMIC

"Paper 1: Assessing spatial patterns of HIV prevalence and interventions in semi-urban settings in South Africa: Implications for spatially targeted interventions"

In order to establish the patterns of HIV prevalence, and uptake of selected HIV services in Ekurhuleni, a secondary analysis of data collected during a previous National Survey and routinely collected data in 2012 was conducted. In this chapter, the methodology, results, and discussion for paper one of this PhD study are presented. The detailed published manuscript is found in Appendix F.

4.1. Introduction

Previously, the HIV epidemic in sub-Saharan Africa (SSA) was thought to be generalised but more recently, research is showing the presence of concentrated epidemics [57, 137, 138]. In South Africa, HIV prevalence varies significantly at the sub-national and district levels [139] due to complex economic and localised social, behavioural and cultural factors [140]. Similar to other countries in SSA, South Africa reports substantial numbers of incident HIV cases from at-risk populations including FSWs and their clients, IDU, MSM, and inmates in correctional institutions [48, 58, 139]. The presence of key populations at higher risk of HIV leads to concentrated epidemics [58, 65]. In response, significant resources are being invested in the expansion of prevention and treatment programmes to address these concentrated epidemics [141].

Interventions such as condoms effectively prevent sexual transmission of HIV provided, they are consistently and correctly used when targeting high-risk individuals [18, 48]. In addition, ART programmes have been scaled up in South Africa to prevent onward transmission of HIV [8, 142]. To improve the efficiency of the limited resource allocation, funding agencies shifted away from homogenous distribution of interventions towards optimizing the resources allocated in areas where they are needed [58, 61, 65, 139]. The implementation of spatially targeted interventions requires finding areas with concentrated HIV epidemics and utilisation

of interventions is low [61, 139]. This strategy is challenging due to the scarcity of spatial data caused by the costly implementation of population-based surveys in resource-limited settings [90]. Having data on HIV spatial distribution patterns at a local level may prevent new HIV infections and by targeted scale-up of treatment and prevention [50]. This may be achieved through prioritized allocation of resources to high burden areas and alignment of service delivery models as per the population requirements [50].

In SSA, spatial analysis of health data is gaining traction and has established variations in HIV prevalence, service use and risk factors. Using population-based survey data from demographic health surveys describing spatial clusters and geographical variation at a district-level revealed hot spots of HIV infection in Uganda and revealed non-condom use and non-circumcision that was driving HIV infection [62]. Similarly, spatial analysis at a district level identified high-risk populations and regions in Malawi where targeted interventions for HIV prevention and treatment programs are needed [143]. Nutor et al (2020) mapped the spatial distribution of HIV infection at the provincial level which highlighted associations of high-risk sexual behaviour with HIV infection in high-burden provinces [144].

Focusing progress at a sub-national level addresses the gaps national or provincial level analysis introduces due to masked local heterogeneities which negatively affects resource allocation [65]. Development of spatial analysis at a lower spatial unit such as ward-level is likely to improve accuracy in health estimates [67]. Spatial cluster techniques at a local level in Zimbabwe identified patterns of HIV prevalence, high HTS and ART uptake which improved resource allocation of HIV prevention and treatment interventions in two towns [50].

In the absence of costly population-based surveys, clinic-based routinely collected data on HIV services from different health facilities at a ward or sub-district level can be explored [65] and applied to monitor progress and provide scientific evidence to guide targeted resource allocation in areas with the greatest need [61]. In KwaZulu Natal, South Africa, Cuadros et al 2013 demonstrated the use of readily available programmatic data to map the heterogeneity of the HIV epidemic in a hyperendemic setting [65]. The authors demonstrated the feasibility of using these sources to identify areas for the implementation of spatially targeted interventions [65].

The current study combined data from a national survey and routinely collected HIV programme data to identify the heterogeneity of HIV infection, condom use and ART initiation

in EMM, South Africa. EMM, a hyperendemic district, which is described above (sub-section 3.3) is considered a high priority district characterised by a high population and a high HIV prevalence [2]. Resources to control HIV have been allocated to the district however, the HIV prevalence remains high at 14% [117, 145]. The objective of this study is to understand the underlying geographical patterns of HIV prevalence, coverage of male condom use and ART initiation rates in EMM using spatial techniques. Further, we sought to understand the drivers of the negative health outcomes in the study area using statistical techniques accounting for spatial random effects.

4.2. Methods

4.2.1. Description of study outcomes

Of the 88 wards delineated from the 2001 South African National Census, available data for the six outcomes of this study were calculated for 33 wards. These outcomes from the National HIV survey were namely:

(i) HIV infection, defined as reported HIV positive test result.

(ii) HIV prevalence, defined as the proportion of individuals testing HIV-positive over the total population sampled per ward during the survey.

(iii) Sub-optimal condom use, defined as reporting not consistently using condoms in the past month at the last sexual act.

(iv) Non-ART use, defined as reporting not using ART despite a positive HIV status.

Further, data on the coverage of male condom use and ART initiation rates were abstracted from DHIS (April – Dec 2012) and an annual average by ward was calculated.

(v) The aggregated male condom coverage was calculated as the number of condoms distributed by clinic over the number of males ≥15 years in each of the 33 wards in Ekurhuleni.

(vi) ART initiation rate was calculated by estimating the monthly total HIV patients remaining on ART per the estimated number of people living with HIV in each of the sampled wards in Ekurhuleni.

4.2.2. Spatial and non-spatial risk factor analysis

First, using WINBUGS [146], a Bayesian analysis of spatial and non-spatial risk factors associated with HIV infection, sub-optimal condom use and non-ART use in Ekurhuleni was performed using data from a national survey and routinely collected data from primary healthcare facilities in 2012. The study employed three models and the final model was selected based on the lowest deviation information criteria statistic. Detailed methodology is explained in section 3.7.1 and 3.9.3.

4.2.3. Geospatial mapping of risk factor analysis estimates

The estimates from the Bayesian analysis were mapped in ArcGIS v.10.7.1 [135] and produced smoothed maps showing the geospatial patterns of HIV infection, sub-optimal condom use and non-ART use. These maps were used to identify four distinct geographical areas characterized by the level of HIV prevalence and uptake of selected HIV prevention and treatment services. The areas were HL (high HIV prevalence and low uptake); HH (high HIV prevalence and high uptake); LH (low HIV prevalence and high uptake) and LL (low HIV prevalence and low uptake) (see Figure 3-2).

4.3. Findings

4.3.1. Characteristics of survey population

One thousand, one hundred and eighty-nine respondents participated in the 2012 HSRC survey from 33 of 101 wards in the study area (Table 4-1). The respondents' mean age was 37.6 years, and there were significant differences across the subdistricts (p-value=0.003) (Table 4-1). Slightly more than half of respondents were female (51.2%; 95% CI: 49.3%-53.0%). However, more respondents were male (50.3%; 95% CI: 48.4%-52.3%) in the South subdistrict. High levels of unemployment were reported in the study area (45.9%; 95% CI: 43.1%-48.7%), especially in the East (53.0%; 95% CI: 51.6%-54.4%) followed by the North (46.3%; 95% CI: 44.0%-48.7%) and South (41.5%; 95% CI: 36.1%-47.0%). The mean age at sexual debut was 18.3 years (SD: 18.1-18.6), and the mean number of lifetime sexual partners was 4.87 (SD: 4.6-5.1); this was significantly different across the three sub-districts. The overall consistent condom uptake was low across the district (26.4%; 95% CI: 24.2%-28.8%) and even

lower for those living in the North sub-district (19.4%; 95% CI: 15.9%-23.7%). The reported drug use was lowest in the East (12.3%; 95% CI: 7.2%-20.2%) and highest in North (27.4%; 95% CI: 24.6%-30.3%) subdistrict. ART use was reported at 28.7% (95% CI: 27.5%-29.9%) with differences observed across the subdistrict (Table 4-1).

Table 4-1: Survey weighted population profile of 2012 HSRC survey participants by subdistrict in Ekurhuleni, South Africa

	Overall (N=1189) Proportion estimate (95% CI)	**East (n=402) Proportion estimate (95% CI)**	**North (n=259) Proportion estimate (95% CI)**	**South (n=528) Proportion estimate (95% CI)**	**p-value**
Mean age (years)	37.6 (36.6-38.6)	40.9 (36.7-45.1)	38.8 (36.7-40.8)	35.0 (34.2-35.8)	0.003
Gender					
Male	48.8 (47.1-50.7)	45.7 (44.9-46.6)	49.6 (43.3-56.0)	50.3 (48.4-52.3)	0.004
Female	51.2 (49.3-53.0)	54.3 (53.4-55.1)	50.4 (44.0-56.7)	49.9 (47.7-51.6)	
Race					
Black	79.1 (71.3-85.1)	77.9 (51.8-92.0)	71.2 (61.0-79.7)	83.7 (72.7-90.9)	0.167
Non-Black	20.9 (14.9-28.6)	22.1 (8.0-48.1)	28.8 (20.3-39.0)	16.3 (9.1-27.3)	
Relationship status					<0.0001
Married	63.6 (62.4-64.8)	61.5 (58.0-64.9)	74.3 (73.0-75.5)	59.8 (58.4-61.2)	
Divorced	12.1 (11.3-12.9)	15.9 (13.5-18.7)	7.4 (7.2-7.6)	12.0 (10.9-13.3)	
Never Married	24.3 (22.9-25.7)	22.6 (18.027.9)	18.3 (17.0-19.8)	28.2 (26.5-29.9)	
Education level					
Primary school	8.2 (7.3-9.2)	11.4 (9.4-13.8)	5.2 (4.3-6.2)	7.8 (6.4-1.0)	0.004
Secondary school	78.7 (77.1-80.3)	83.0 (81.7-84.2)	78.5 (71.9-83.9)	76.6 (75.2-77.9)	
Post-secondary	13.0 (11.3-15.0)	5.6 (3.0-10.1)	16.3 (11.6-22.5)	15.4 (12.9-18.3)	
Employment status					0.0002
Unemployed n (%)	45.9 (43.1-48.7)	53.0 (51.6-54.4)	46.3 (44.0-48.7)	41.5 (36.1-47.0)	
Unemployed, student n (%)	16.9 (15.8-18.1)	14.6 (12.6-16.9)	10.0 (9.9-10.2)	21.6 (19.7-23.6)	
Employed n (%)	37.2 (34.1-40.3)	32.4 (30.5-34.3)	43.6 (41.1-46.2)	36.9 (31.0-43.3)	
Mean age at coital debut	18.3 (18.1-18.6)	18.4 (17.6-19.3)	18.9 (18.4-19.5)	18.0 (17.9-18.1)	0.024
Mean number of lifetime partners (IQR)	4.87 (4.6-5.1)	4.2 (3.2-5.3)	4.7 (4.1-5.3)	5.3 (5.1-5.6)	0.024
Condom use					
Yes n (%)	26.4 (24.2-28.8)	24.4 (20.4-28.9)	19.4 (15.9-23.7)	31.0 (27.0-35.4)	0.003
Sometimes n (%)	21.7 (19.6-24.0)	28.5 (23.6-34.0)	13.6 (11.1-16.5)	21.7 (20.7-22.7)	
No n (%)	51.9 (19.6-24.0)	47.1 (42.8-51.8)	66.9 (60.1-73.2)	47.3 (42.8-51.8)	
Circumcised					0.048
Yes n (%)	51.5 (48.3-54.6)	54.0 (48.8-59.0)	46.5 (44.4-48.7)	52.3 (47.1-57.4)	
No n (%)	48.5 (45.4-51.7)	46.0 (41.0-51.2)	53.4 951.3-55.6)	47.6 (42.6-52.9)	
Alcohol use (ever)					0.527
Yes n (%)	50.7 (47.5-54.2)	52.7 (46.7-57.8)	52.8 (49.1-56.5)	48.8 (41.9-55.7)	
No n (%)	49.3 (45.8-52.7)	47.7 (42.2-53.3)	47.2 (43.5-50.9)	51.2 (44.3-58.1)	
Drug use (past 3 months)	19.3 (17.3-21.3)	12.3 (7.2-20.2)	27.4 (24.6-30.3)	19.6 (16.6-23.1)	0.001

	Overall (N=1189) Proportion estimate (95% CI)	East (n=402) Proportion estimate (95% CI)	North (n=259) Proportion estimate (95% CI)	South (n=528) Proportion estimate (95% CI)	p-value
Yes n (%)	80.7 (78.7-82.7)	87.7 (79.8-92.8)	72.7 (69.7-75.4)	80.4 (76.9-83.4)	
No n (%)					
HIV status*					0.126
Positive n (%)	16.6 (15.1-18.1)	18.9 (16.5-21.6)	13.6 (11.3-16.4)	15.8 (12.9-19.2)	
Negative n (%)	83.4 (81.9-84.9)	81.1 (78.4-83.5)	86.4 (83.6-88.7)	84.2 (80.8-87.1)	
On ART**					
Yes n (%)	28.7 (27.5-29.9)	43.3 (-)	7.0 (-)	21.6 (-)	0.001
No n (%)	71.3 (70.1-72.5)	56.7 (-)	93.0 (-)	78.4 (-)	

*Almost 50% missing HIV status; ** sub-districts confidence intervals not calculated due to small sample

4.3.2. HIV prevalence and factors associated with HIV infection

Overall, HIV prevalence was estimated at 16.6% (95% CI: 15.1%-18.1%) and no observed differences across the subdistricts were reported. The highest HIV prevalence was reported in the East sub-district (18.9%; 95%CI: 16.5%-21.6%) (Table 4-1) and observed in wards within Clayville, Kempton Park areas (North), Katlehong and Germiston (South) and Kwa Thema, Etwatwa and Brakpan (East) (Figure 4-1). HIV infection in these areas was associated with being a student (POR:12.74: 95%CI:3.29-95.01) (Table 4-2). Upon adjusting for spatial random effects, the likelihood increased (POR: 19.53: 95%CI:3.22-84.93) (Table 4-2). The probability of increased odds of HIV infection was seen in Thokoza, Katlehong, Kempton Park, Edenvale, Tembisa and Brakpan areas (Figure 4-2). In wards with high odds of HIV infection, consistent condoms use was likely to lower HIV infection by 52% (POR:0.48: 95%CI:0.24-0.87) and if some protected sexual acts were reported, the likelihood of HIV infection decreased by 66% (POR:0.34: 95%CI:0.18-0.63) (Table 4-2).

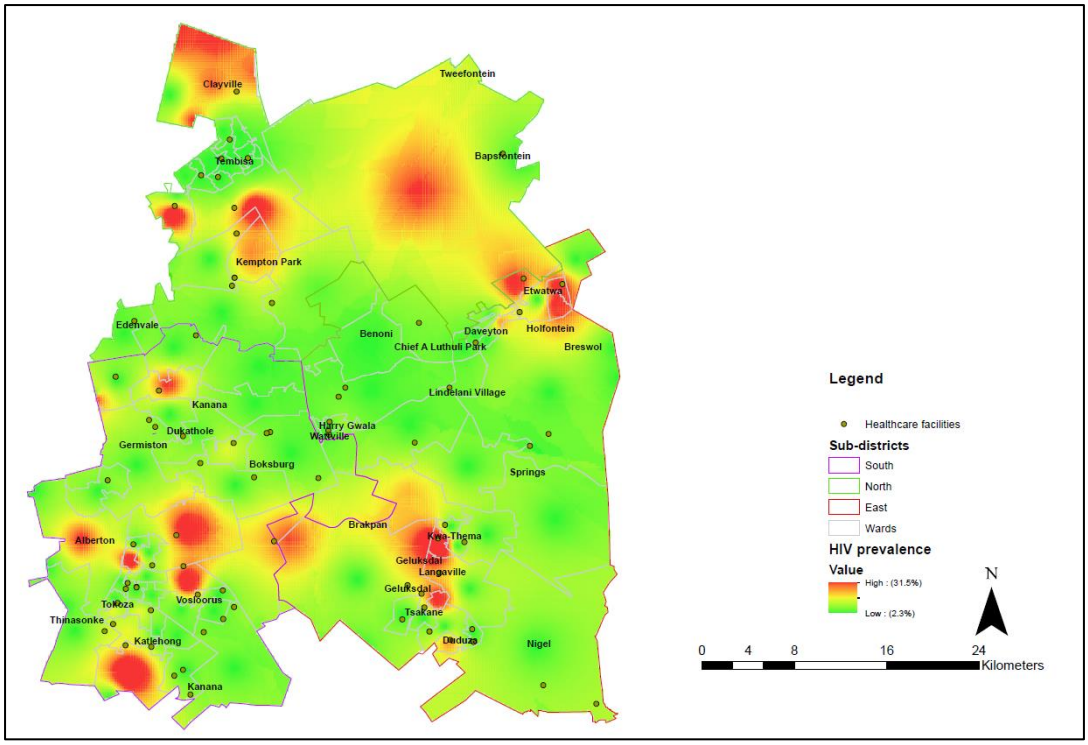


Figure 4-1: A smoothed HIV prevalence map of Ekurhuleni Metropolitan Municipality using 2012 HSRC national survey

Table 4-2: Posterior summaries of Odds Ratio for HIV infection in Ekurhuleni

Factor		**Standard logistic regression model POR (95%CrI)**	**Random effects logistic regression model POR (95%CrI)**	**Spatial effects logistic regression model POR (95%CrI)**
Employment status	Unemployed	1	1	1
	Employed	1.26 (0.76-2.08)	1.32 (0.78-2.17)	1.33 (0.73 - 2.12)
	Student	**12.74 (3.29-95.01)**	**19.37 (3.39-81.70)**	**19.53 (3.22- 84.93)**
Level of education	Primary	1	1	1
	Secondary	0.55 (0.24-1.42)	0.66 (0.24-1.52)	0.65 (0.25-1.52)
	Tertiary	0.67 (0.37-1.20)	0.68 (0.34-1.16)	0.70 (0.35-1.19)
Condom use in past one month	No	1	1	1
	Yes	**0.46 (0.25-0.85)**	**0.48 (0.25-0.87)**	**0.48 (0.24-0.87)**
	Sometimes	**0.31 (0.17-0.56)**	**0.34 (0.17-0.67)**	**0.34 (0.18-0.63)**
Number of lifetime sexual partners		0.97 (0.94-1.01)	0.97 (0.94-1.00)	0.97 (0.94 – 1.01)
Deviance information criteria		480.3	457.7	456.7

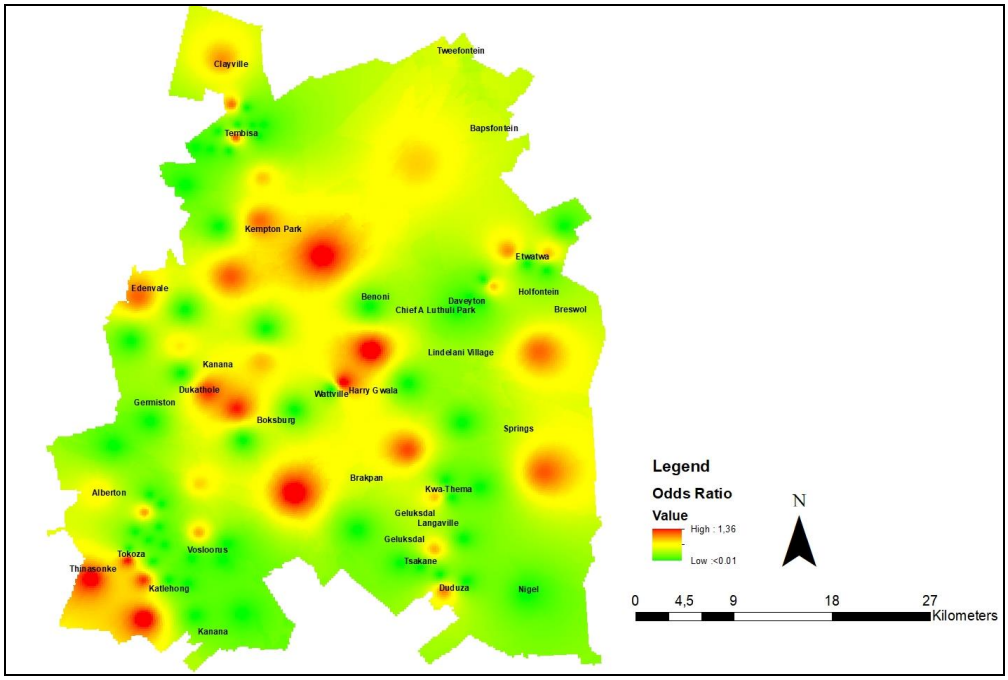


Figure 4-2: A smoothed map showing the expected posterior OR of HIV infection in Ekurhuleni Metropolitan Municipality using 2012 HSRC national survey

4.3.3. Male condom use coverage and factors associated with sub-optimal condom use

In 2012, the average male condom use coverage as reported from routine clinics across the wards ranged between 1% and 21% (Figure 4-3). Sub-optimal male condom use coverage was observed in Tembisa and Kempton Park (North), Springs, Brakpan and Kwa Thema (South), and Dukathole, Boksburg, Alberton and Katlehong (East). The proportion of those who reported consistent condom use during the 2012 National survey was 26.4% (Table 4-1). The odds of sub-optimal condom use increased by age (POR:1.09; 95%CI:1.06-1.12) and in those married (POR:3.19; 95%CI:1.23-4.12), before and after adjusting for spatial random effects (Table 4-3), The likelihood of sub-optimal condom use decreased by 5% after adjusting for spatial effects. Increased likelihood of sub-optimal condom use was seen in wards within Kempton Park, Springs, Etwatwa, Brakpan, Alberton, Thokoza, Katlehong and Edenvale areas (Figure 4-4). Males in these areas are less likely not engage in unprotected sexual acts (POR:0.52: 95%CI:0.33-0.80) (Table 4-3).

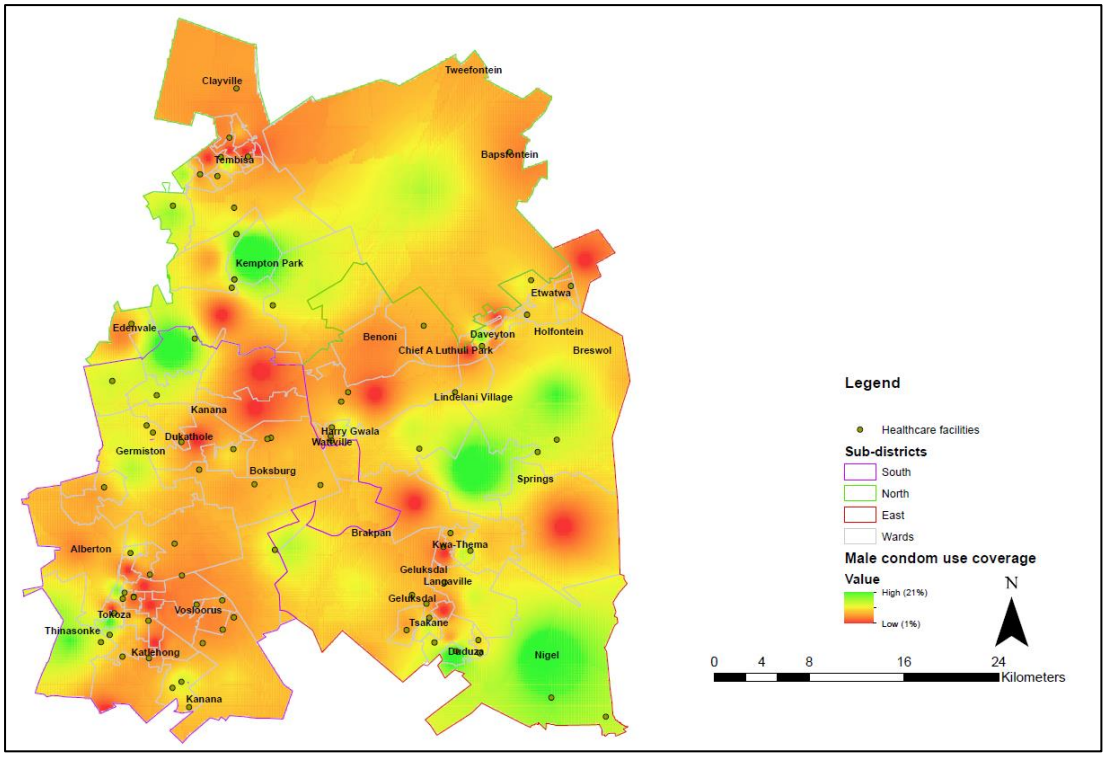


Figure 4-3: A smoothed distribution of male condom coverage in Ekurhuleni Metropolitan Municipality using routinely collected programmatic data

Table 4-3: Posterior summaries of Odds Ratio for sub-optimal condom use in Ekurhuleni

Factor		**Standard logistic regression model POR (95%CrI)**	**Random effects logistic regression model POR (95%CrI)**	**Spatial effects logistic regression model POR (95%CrI)**
Age (years)		**1.09 (1.06-1.12)**	**1.09 (1.06-1.11)**	**1.09 (1.06-1.11)**
Sex	Female	1	1	1
	Male	**0.52 (0.32-0.78)**	**0.51 (0.32-0.78)**	**0.53 (0.33-0.80)**
Marital status	Not married	1	1	1
	Currently married	**3.19 (1.23-4.12)**	**3.78 (1.24-4.06)**	**4.14 (1.23 - 4.28)**
	Previously married	**0.27 (0.07-0.76)**	**0.28 (0.07-0.79)**	**0.28 (0.07 - 0.79)**
Media exposure	Frequent	1	1	1
	Not frequent	1.90 (0.95-3.57)	1.95 (0.95-3.49)	1.97 (0.95 - 3.49)
Deviance information criteria		523.7	530.8	528.5

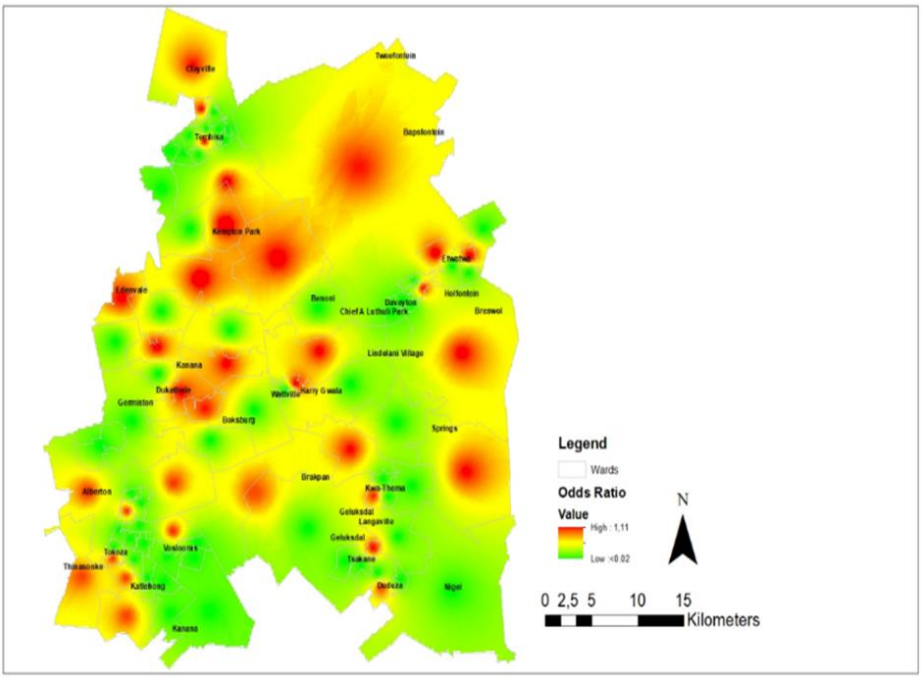


Figure 4-4: A smoothed map showing the expected posterior OR for sub-optimal condom use in Ekurhuleni Metropolitan Municipality using 2012 HSRC national survey

4.3.4. ART initiation and factors associated with non-ART use

In 2012, the ART initiation rate as reported from routine clinics across the wards averaged between 1% and 75%. Lower ART initiation rates were observed in Tembisa (North), Katlehong, Germiston and Boksburg (South), and Springs, Brakpan and Kwa Thema (Figure 4-5). The percentage of those not starting ART during the 2012 National survey was 71.3% (70.1%-72.5%) (Table 4-1). The odds of non-ART initiation increased in those married (POR:6.79; 95%CI:1.43-22.43) (Table 4-4). Wards within Vosloorus, Springs, Etwatwa, Brakpan, Alberton, Thokoza, Katlehong and Harry Gwala areas reported an increased likelihood of non-ART use (Figure 4-6).

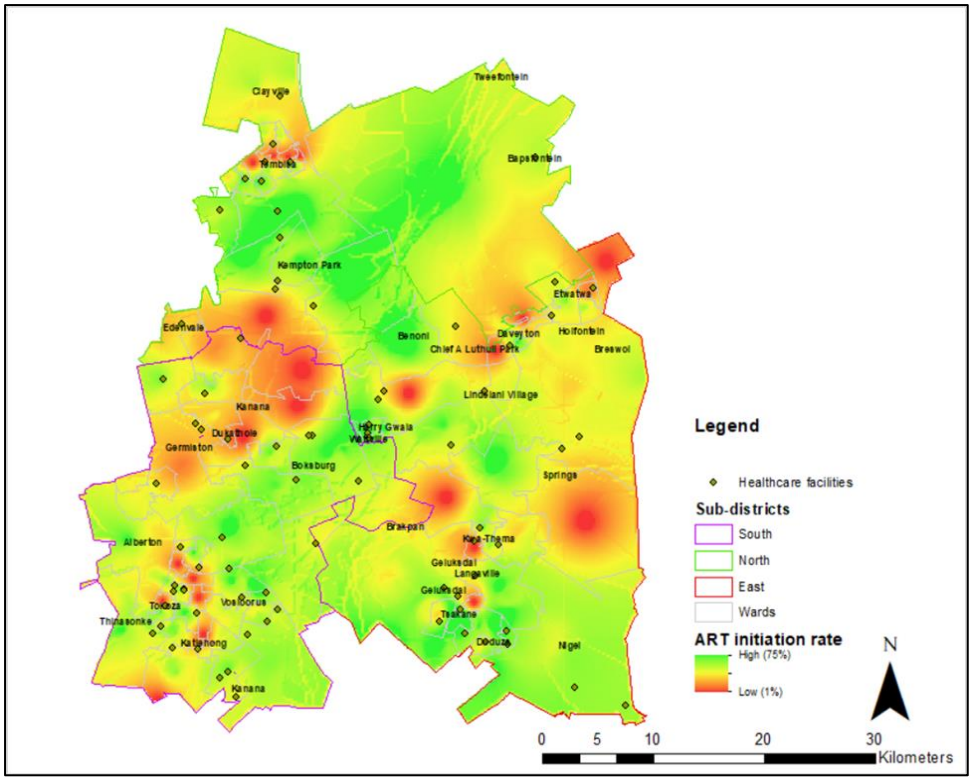


Figure 4-5: A smoothed map showing the distribution of ART initiation rates in Ekurhuleni Metropolitan Municipality using routinely collected programmatic data

Table 4-4: Posterior summaries of Odds Ratio for non-ART initiation in Ekurhuleni

Factor		**Standard logistic regression model POR (95%CrI)**	**Random effects logistic regression model POR (95%CrI)**	**Spatial effects logistic regression model POR (95%CrI)**
Age (years)		0.94 (0.88-1.00)	0.95 (0.88-1.01)	0.95 (0.90-1.00)
Drug use in past	No	1	1	1
3 months	Yes	6.72 (0.69-32.01)	7.03 (0.71-34.91)	7.17 (0.74-32.21)
Marital status	Not married	1	1	1
	Currently married	**6.12 (1.37-20.28)**	**7.18 (1.57-22.75)**	**6.79 (1.43-22.43)**
	Previously married	5.37 (0.38-28.71)	6.19 (0.37-33.96)	5.68 (0.33-25.98)
Media exposure	Frequent	1	1	1
	Not frequent	2.14 (0.52-6.39)	2.44 (0.54-7.98)	2.45 (0.59-8.24)
Deviance information criteria		107.4	109.0	107.8

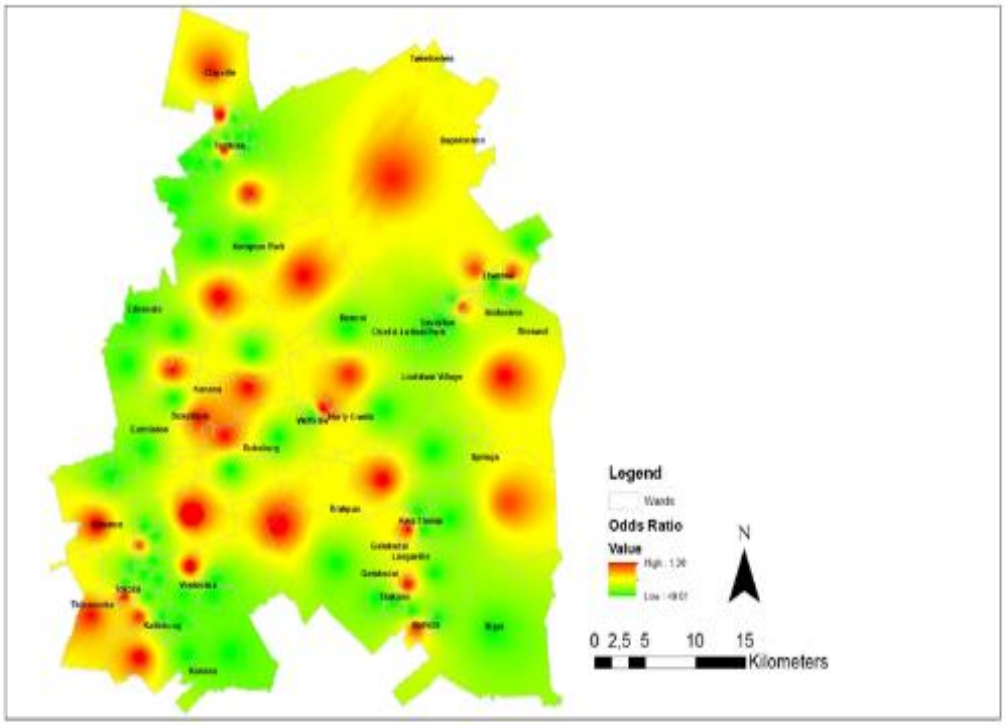


Figure 4-6: A smoothed map of showing expected posterior OR for non-ART use in Ekurhuleni Metropolitan Municipality using 2012 HSRC national survey

4.4. Summary of findings

The study highlighted geographical variations in HIV prevalence, coverage of male condom use and ART initiation rates in EMM. Findings revealed four distinct scenarios. A) In wards within Kempton Park, HIV prevalence was high and distribution of male condom use and ART initiation rates were high. B) In Kwa Thema and Brakpan, the HIV prevalence was high, but the uptake of condoms and ART was low. C) Wards within Tembisa showed low prevalence of HIV and similarly low uptake of HIV services. D) In Nigel, the observed HIV prevalence was low whereas the uptake of condoms and ART was high. Findings further showed an increased differences after adjusting for spatial effects signifying the importance of including space for targeted interventions. The wards within the areas with increased odds of HIV infection are likely to have a considerable proportion of younger people (<35 years) and mostly female, and other key populations including MSM, IDU and female sex workers living in informal dwellings,

high levels of unemployment (>30%) and a small proportion of the population with tertiary education (<3%).

HIV infection was associated with being a student. This finding showed that the likelihood of the strong association between being a student and HIV positive was heterogenous across the wards in Ekurhuleni. A report by HSRC written for Higher Education and training HIV/AIDS programme showed that alcohol consumption and age-disparate relationships are the commonly reported risks for HIV infection among students [147]. Alcohol consumption increases the risk of unprotected sexual acts by lowering sexual inhibition [148] where as a greater chance of exposure to HIV occurs when young people are in relationships of an age gap ≥5 years [149-151]. Consistent with many studies was the finding of condoms providing a protective effect against HIV infection [152, 153]. A spatial effect was observed suggesting that this likelihood was observed in some areas in Ekurhuleni. Further, findings also showed that HIV infection was reduced by inconsistent condom use in Ekurhuleni. A study in Rustenburg, South Africa showed that men with more than one steady female partners were unlikely to use condoms but would use condoms with new sexual partners [154] reducing exposure to HIV.

Findings showed a consistent use of condoms among males than females. The spatial effect was not observed implying that this likelihood was homogenous across the wards. Consistent with previous studies, females were less likely to use condoms [155, 156]. More in particular unemployed married women who, due to financial dependence on their male partners, and the expectation to bear children are unlikely to use condoms. Men on the other hand, were more likely to use condoms with partners considered casual or unexpected [154]. Findings from this PhD study associated marriage with sub-optimal condom use and no heterogeneity across the wards was observed. Globally, sub-optimal male condom use among married and cohabiting women has been widely reported [157-159]. The perceptions of marital infidelity, lack of relationship power and fear or intimate partner violence have contributed to lack of condom use among women [159]. Although being in a marital relationship was associated with sub-optimal condom use, previously married individuals in Ekurhuleni were less likely to report sub-optimal condom use. Those divorced/separated were likely seeking new relationships and therefore, use condoms with their new partners for protection from unplanned pregnancies or sexually transmitted infections [152].

Being married was associated with non-linkage to ART in this study area and this finding was homogenous across the study area. This association was contradicted by a systematic review

of several studies in SSA which showed that married (a potential proxy for social support) PLHIV were more likely to initiate ART than unmarried PLHIV [160]. Similarly, a recently conducted study on same-day ART initiation in Johannesburg revealed that men and women living with friends and relatives were more likely to defer ART initiation compare to those living with a spouse [161].

4.5. Strength and limitations

The limitations of this study include the inability to fully link the 2001 census enumeration areas data with what was provided by the HSRC as not all wards were sampled. As a result, underestimation, or overestimation of study outcomes was likely. However, condom use and ART initiation estimates from the national survey data were almost similar to the estimates from the DHIS which validates these findings. Another limitation was that data from DHIS may have been incomplete as clinics may not have submitted all their clinical data timeously. Despite these limitations, the use of interpolation allowed for the calculation of predicted values from areas not sampled using observations from nearby locations. The use of individual-level data rather than aggregated data is advantageous as more robust estimates are produced from the regression analysis. Although outcomes were derived from two different data sources, there were comparable findings between outcomes from the population-based survey routinely collected data. The comparisons revealed similar geospatial patterns supporting the continued use of inexpensive routine data over expensive surveys to evaluate HIV programmes.

4.6. Summary of chapter

This study adds valuable information to the growing body of knowledge prevention of HIV in South Africa at far lower administrative levels. Our findings have important public health implications to program planners on the use of maps to visualize HIV prevalence and coverage of HIV services. The maps produced from this study were used to identify four distinct areas based on HIV prevalence and uptake of selected HIV services. These maps were used for purposely selecting clinics for recruitment of participants to participate in qualitative interviews. Applying geostatistical modelling revealed the heterogeneity of study outcomes at a ward level which can assist programme planners to focus allocation of limited resources to where they are needed. From this study, it would be recommended to scale up condom uptake

and reinforce ART programmes according to the need to prevent HIV transmission. For instance, wards in Kwa Thema and Alberton where HIV prevalence was high and the uptake of condoms and ART initiation low, addressing the drivers for the sub-optimal male condom use and ART initiation identified in this study are encouraged. This may mean strengthening partner counselling and expanding access to condoms in existing HIV prevention and treatment programmes.

This chapter reveals suggestions for future work that may consider a shared component model that links HIV prevalence, sub-optimal use and non-ART use and estimate the explicit shared components across the domains discussed in this chapter at small area resolution.

5. CHAPTER FIVE: EXPLORING THE HETEROGENEITY OF VIRAL LOAD SUPPRESSION ACROSS SPACE AND TIME

Paper 2: Small area analysis of HIV viral load suppression patterns in a high priority district (2012-2016), South Africa

To assess the spatio-temporal predictors of high viral load suppression rates in Ekurhuleni over a five-year period, a secondary analysis of routinely collected clinical and laboratory data from 2012-2016 was conducted. In this chapter, the methodology, results, and discussion for paper two of this PhD study are presented. The detailed manuscript is found in Appendix G.

5.1. Introduction

Evaluating the effectiveness of HIV treatment programmes in a population through viral load monitoring is widely used in many HIV high-burden countries. There has been a massive scale-up of viral load monitoring since 2013 to meet the third 95 of the 95-95-95 targets by 2030 and achieve ultimate HIV control [2]. HIV control can be attained when PLHIV are identified, initiated on ART, and retained in HIV care. Therefore, high ART coverage and elevated viral load suppression rates reduce HIV transmission and ultimately reduce HIV incident cases [3].

In South Africa, HIV treatment initiation is done primarily at primary healthcare facilities and viral load is performed at six months, and thereafter annually [162]. If the viral load is greater than 1 000 copies/mL, a repeat testing is required according to World Health Organization guidelines [163]. The 2020 UNAIDS data for South Africa shows that >90% of people were aware of their HIV status, slightly above 70% were on treatment and 66% were virally suppressed [3]. Since tangible evidence has demonstrated the significant impact treatment has on the reduction of HIV transmission at a population level, monitoring viral load using the population viral load has been commonly done in resource constrained settings [3, 163].

Heterogeneity of HIV prevalence has been widely demonstrated [48, 57, 58, 65, 143]. Similarly, viral load suppression rates are likely to vary spatially. In order to curb HIV transmission, it may be important to monitor the viral load differences across geographical spaces. The 2020

UNAIDS Global report showed that 92% of people on HIV treatment achieved viral suppression [3] but this is likely to differ at a sub-national levels. Locally, little is also known about the estimates of viral load suppression and their association with related health outcomes. Exploring the association between viral load suppression and geographical location is important for spatially targeted interventions. Differences in viral load suppression across space may be attributed to the multifaceted interaction of risk factors that remain inadequately characterized in the spatio-temporal domain [106]. Studies utilizing the Bayesian techniques in mapping diseases/health outcomes are increasingly recognized [108]. Bayesian spatio-temporal techniques in this study will allow for the use of existing information in evaluating viral load suppression to study the persistent and unusual viral load suppression rate trends in the study area [164].

Five years of HIV program data for EMM in South Africa was used to assess the trends in viral load suppression rates and explore spatio-temporal autocorrelation of high viral load suppression rates at a ward-level. Further, predictors of high viral load suppression and the immediate impact of UTT roll-out, where all HIV-infected persons were started on antiretrovirals regardless of CD4 count, on viral load suppression in 2016 were assessed.

5.2. Methods

5.2.1. Data sources

NHLS conducts all laboratory monitoring for the national HIV program which are archived at the level of the laboratory specimen in the NHLS corporate data warehouse (CDW). The NHLS dataset contained viral load results from 1st January 2012 to 31st December 2016, from public health facilities in South Africa. From the same data source, data on age and tuberculosis (TB) diagnosis was obtained. Data on the ART uptake at the clinic level in Ekurhuleni was abstracted from the DHIS. Data on literacy levels, income levels, gender and population was obtained from the 2011 National Census.

5.2.2. Viral load measures

The South African national guidelines state that routine viral load monitoring for individuals receiving ART should be done at 6 and 12 months after ART initiation and then annually

thereafter [162]. During each routine visit, a standard request laboratory form containing patient identifiers are manually captured into the laboratory information system at the receiving laboratory, before the blood sample is centrifuged and tested using the Abbott Realtime HIV (Abbott Molecular Des Plaines, USA) or Roche Cobas Ampliprep/Cobas TaqMan HIV-1 (Roche Diagnostics, Branchburg, USA) assays. All viral load results from each patient the time period were used. The total number of patients with a viral load test in the time period was calculated.

5.2.3. Viral load suppression

Viral load suppression (VLS) was assessed using <1000 copies /mL (main outcome) and <400 copies/mL as two of the thresholds used in South Africa to determine treatment success. VLS was summarized using the mean $\log_{10}$ viral load per year. Ward-level VLS was estimated by taking the number of virally suppressed patients and dividing by the total number in care per year. Wards with ≥ 75% of PLHIV reporting viral load suppression were considered to have high VLS whereas wards those with <75% were considered as having low VLS.

5.2.4. Ward-level measures

Population-level characteristics at the ward level were estimated from 2011 Census data. Eight-eight wards were identified using geographical information provided in the 2011 Census data. The measures for each ward were calculated as follows: proportion of female respondents; proportion of low literacy levels; proportion reporting no income; and population density per ward from the 2011 Census data and performed standardization. Interpolation of estimates from midyear population estimates produced by Statistics South Africa from 2012-2016 [115] was done. The assumption that the population was growing at a constant rate using the exponential growth model was made. ART initiation rate per ward was calculated by estimating the total HIV patients in each ward remaining on ART at end of the month over the estimated number of people living with HIV. An arithmetic mean by ward was calculated for each year (see sub-section 4.2.1).

5.2.5. Space and time analysis of high viral load suppression

Using routinely collected laboratory data from NHLS, spatio-temporal predictors of viral load suppression (<1 000 copies/mL) were estimated by Markov Chain Monte Carlo methods using Bayesian techniques in RStudio [165]. Spatial exploratory analysis to assess spatial autocorrelation of high viral load suppression rates using Moran Index were done. Subsequently, identification of hotspots of high and low viral load suppression via the Anselin Local Indicator Spatial Autocorrelation was performed. Estimates from the mixed-effects Bayesian model were used to map viral load suppression rates between 2012 and 2016 in Ekurhuleni in ArcGIS v.10.7.1 [135]. GWR was used to show the changes in the relationships between the two selected predictors and high viral load suppression over five years. Smoothed maps were produced in ArcGIS v.10.7.1 [135]. Lastly, a sensitivity analysis using viral load suppression of <400copies/mL an additional outcome was done. In a separate analysis, all viral load suppression rates reported before 1st September 2016 national roll-out of UTT programmes in South Africa were analysed and an interrupted time series was done in Stata version 16 for 2016 as follows: pre-intervention (January–August 2016) — eight months before roll-out of UTT, excluding the month of September 2016 when UTT was rolled out nationally; and post-intervention (September 2016–December 2016) — four months of UTT implementation.

5.3. Results

5.3.1. Summary of HIV indicators in Ekurhuleni

From January 2012 to December 2016, 41 644 blood samples mostly male patients (n=25 631; 61.5%) and of median age 39 (IQR: 14) years visited 99 routine clinics in EMM. From these samples, 62.9% (n=26 222) HIV viral load tests were conducted. Table 5-1 shows an increase in the number of viral load tests conducted over a five-year period.

Table 5-1: Characteristics of samples collected from primary health care facilities in Ekurhuleni (2012-2016)

Indicator	2012	2013	2014	2015	2016	p-value
Number of patients	1,001	1,371	1,871	2,125	2,296	0.001
Median (IQR) age	36 (13)	36 (12)	39 (13)	42 (16)	39 (14)	<0.0001
Total viral load samples	2, 031	2, 509	4, 451	7, 741	9, 490	0.002
Mean (SD) (log_{10}) viral load	7.56 (2.9)	7.11 (3.2)	6.14 (3.3)	5.74 (3.2)	6.75 (3.2)	<0.0001

Proportion virally suppressed (<1000cp/mL)	55.8%	58.5%	69.0%	70.8%	61.1%	<0.0001
Proportion virally suppressed (<400cp/mL)	41.0%	49.0%	56.0%	62.0%	53.0%	<0.001

The HIV prevalence in EMM increased from 32.3% to 36.9% from 2012 to 2016. In the same time period, the proportion of PLHIV initiating on ART coverage steadily increased from 32.2% to 81.2% (Table 5-2).

Table 5-2: Estimated ART coverage for female PLHIV (2012-2016) in antenatal care in Ekurhuleni Metropolitan Municipality

Year	Estimated population*	Total HIV prevalence†	ART coverage‡
2012	3 219 000	32.3%	32.2%
2013	3 301 000	33.5%	56.4%
2014	3 385 000	30.2%	81.9%
2015	3 470 000	31.6%	88.0%
2016	3 559 000	36.9%	81.2%

*Interpolated from Statistic South Africa mid-year estimates

†Estimated obtained from National Antenatal Sentinel HIV and Syphilis Survey

‡Estimates obtained from District Health Information System

5.3.2. Five-year viral load suppression rates in Ekurhuleni

Overall, the proportion virally suppressed at <1 000 copies/mL increased from 55.8% in 2012 to 70.8% in 2015 and decreased in 2016 to slightly above 60% (Figure 5-1). A similar pattern was observed with viral load suppression of <400copies/mL (Figure 5-2).

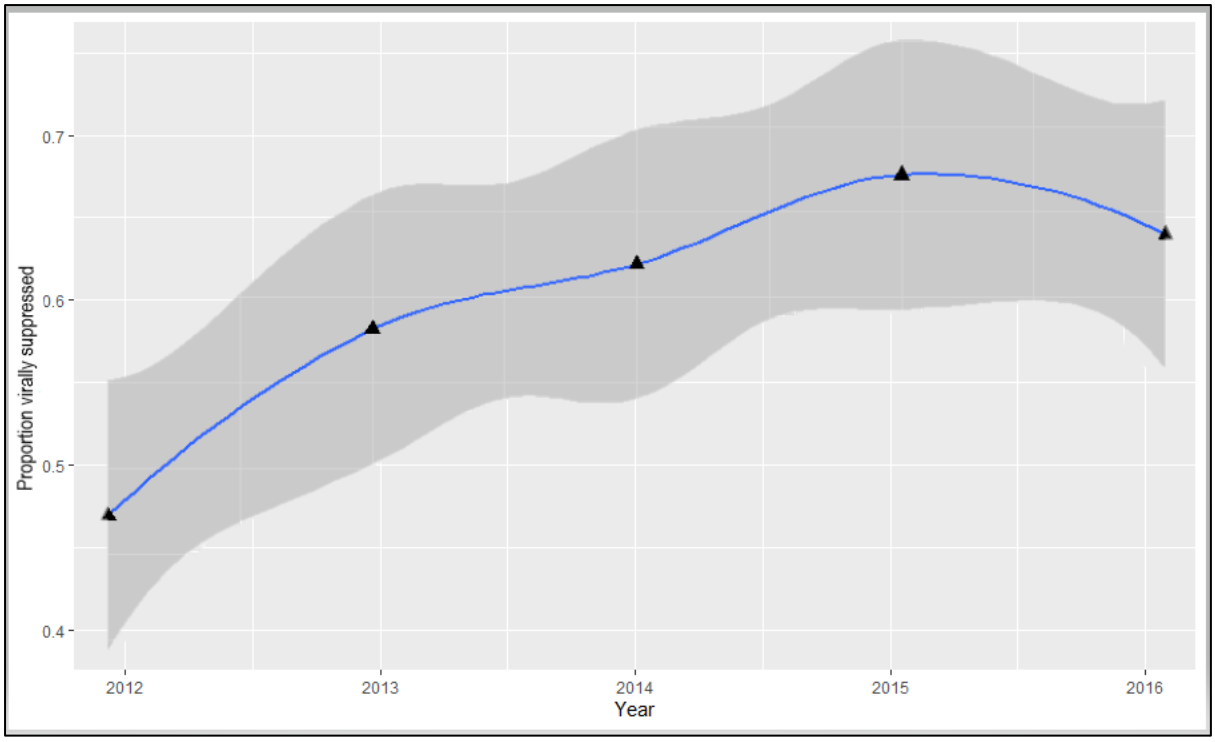


Figure 5-1: Overall proportion of viral load suppression (<1 000 copies/mL) Ekurhuleni Metropolitan Municipality (2012-2016). 95% confidence interval bands are shown.

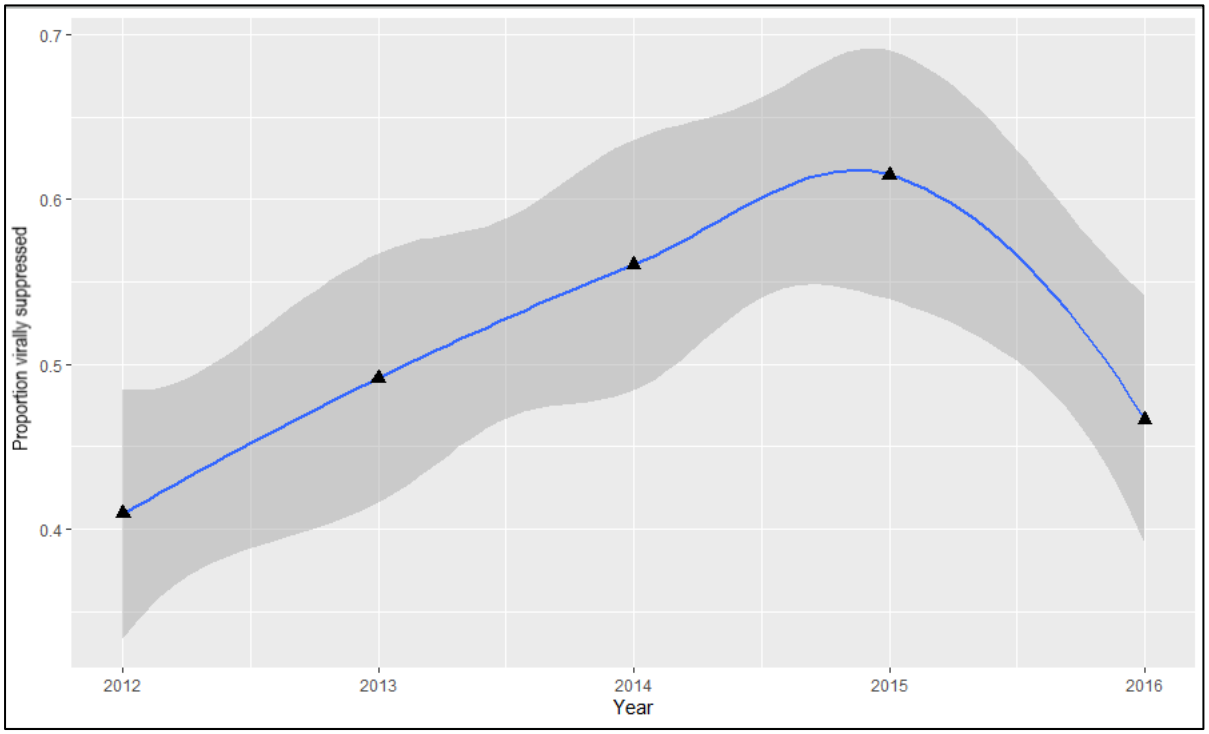


Figure 5-2: Overall proportion of viral load suppression (<400 copies/mL) by sub-district in Ekurhuleni Metropolitan Municipality (2012-2016). 95% confidence interval bands are shown.

5.3.3. Viral load suppression rates in 2016

Figure 5-3 further displays the pre-intervention trend of monthly proportions of viral load suppression (continuous line), and the counterfactual scenario (dashed line). The <400 copies/mL trend suggests that there was a decrease in the proportion of those virally suppressed in the post UTT phase given that most points lie below the counterfactual line which was also observed in the <1 000 copies/mL trend. Figure 5-3 further shows that the reported proportion of viral load suppression (<400 copies/mL) increased from February to May 2016 and began decreasing thereafter.

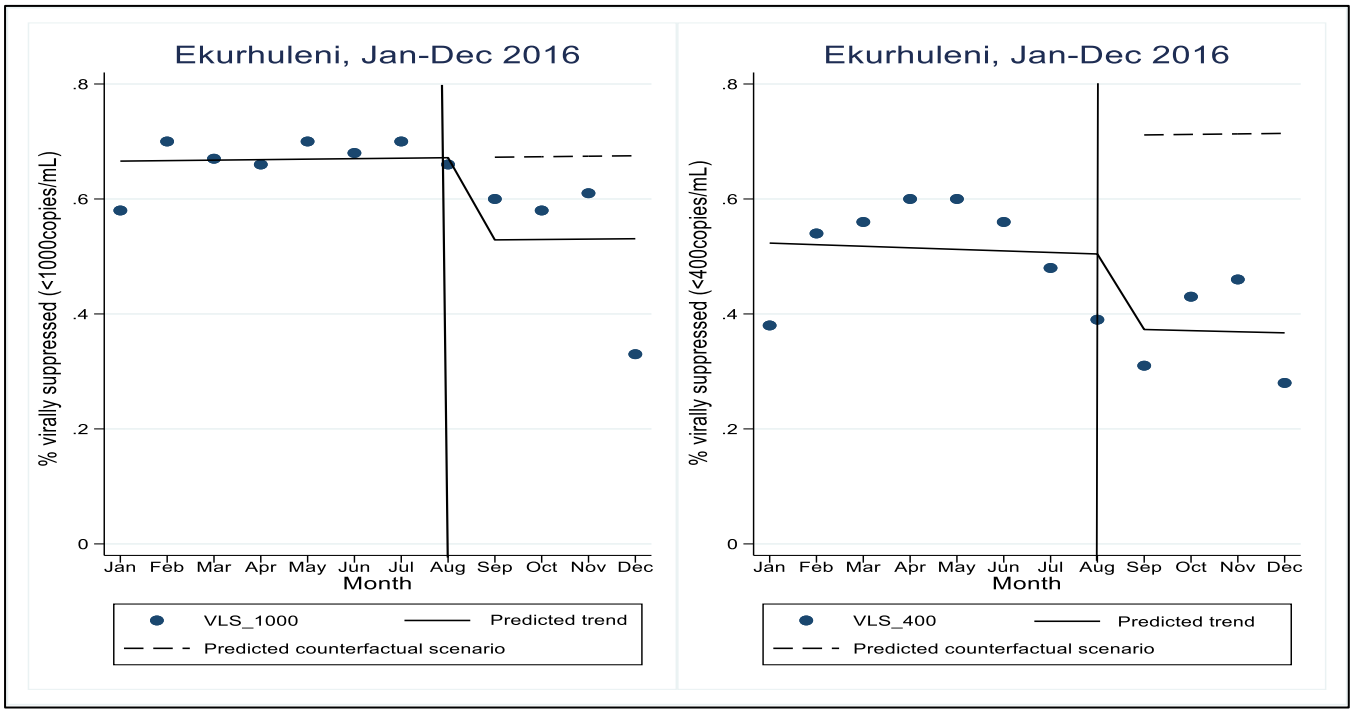


Figure 5-3: Proportions of viral load suppression rates in EMM before and after roll-out of universal test and treat (2016)

5.3.4. Spatial autocorrelation of viral load suppression

There were clusters of high and low viral load suppression in EMM as shown by the significant Moran index values of 0.51 and 0.10 for 1 000 copies/mL and 400 copies/mL thresholds. The local indicator spatial autocorrelation statistic (LISA) revealed clusters of areas with high (light blue colour) proportion of viral load suppression in the South district around Kempton Park, Alberton, Benoni and Boksburg areas. The areas with low (red colour) proportions of viral load suppression were observed in most wards in the East sub-district in the Thokoza, Brakpan and

Langaville areas (Figure 5-4). Some areas in the map are considered outliers, for instance the dark blue areas are clusters of high viral load suppression are surrounded by clusters of low viral load suppression and the pink areas are those where clusters of low viral load suppression are surrounded by clusters of high viral load suppression. There was an increase in the proportion of virally suppressed patients from 2012 to 2015 across the wards as depicted in green and a decrease in 2016 (Figure 5-5).

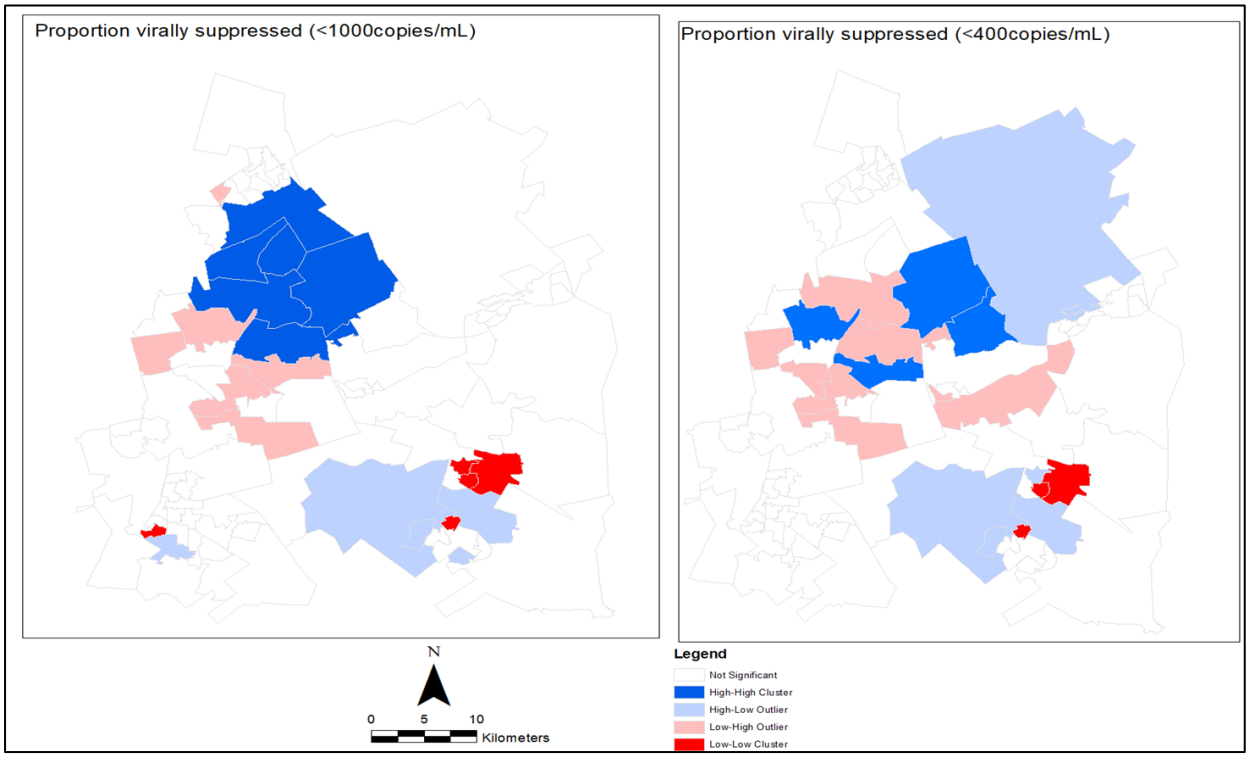


Figure 5-4: Location of clusters of high and low proportions of viral load suppression in Ekurhuleni Metropolitan Municipality

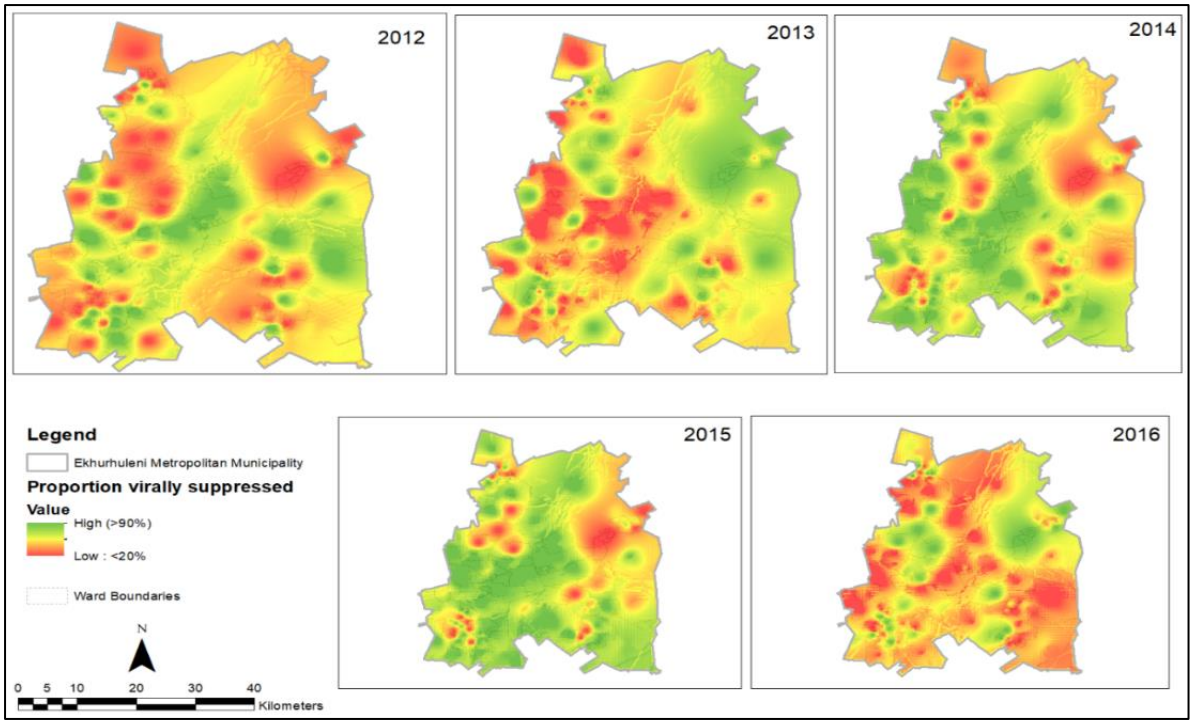


Figure 5-5: The spatio-temporal trend of viral load suppression (<1 000 copies/mL) from 2012 to 2016.

5.3.5. Spatio-temporal distribution of viral load suppression

The viral load suppression (<1 000 copies/mL) in January 2016 was 65% and increased to 70% by the end of August 2016. Immediately following the roll-out of UTT in Ekurhuleni, viral load suppression decreased to 58% between September and December 2016. A similar trend was observed when the 400 copies/mL threshold was applied (Figure 5-5).

5.3.6. Spatio-temporal predictors for viral load suppression

The spatio-temporal predictors of viral load suppression were an increasing proportion of PLHIV initiating on ART in a ward, increasing the viral load suppression rate by 35% (OR: 1.345; 95% CrI 1.221-1.492). In addition, the viral load suppression rate increased by 44% with an increasing proportion of females in a ward (OR: 1.442; 95%CrI: 1.056-1.962).

Table 5-3: Spatio-temporal predictors of high viral load suppression

	<1 000 copies/mL		**<400 copies/mL**	
Predictor	**Beta co-efficient Mean (95%CrI)**	**Exponentiated co-efficient OR (95%CrI)**	**Beta co-efficient Mean (95%CrI)**	**Exponentiated co-efficient OR (95%CrI)**
Population density	0.012 (0.001-0.024)	1.008 (0.993-1.023)	0.001 (-0.009-0.012)	1.001 (0.991-1.012)
% Diagnosed with TB	-0.600 (-0.17-0.500)	0.549 (0.843-2.729)	-0.600 (-0.16-0.400)	0.549 (0.843-1.492)
% Initiated on ART	**0.300 (0.200-0.400)**	**1.345 (1.221-1.492)**	**0.200 (0.100-0.300)**	**1.221 (1.052-1.350)**
% Female	**0.335 (0.085-0.585)**	**1.442 (1.056-1.961)**	0.302 (-0.024-0.626)	1.352 (0.976-1.870)
% Low literacy	-0.325 (-1.559-0.907)	0.563 (0.104-3.027)	0.527 (-1.163-2.198)	1.693 (0.312-9.003)
% No income	1.066 (-0.852 – 2.983)	3.835 (0.440-33.630)	0.297 (-1.873-2.452)	1.346 (0.154-11.614)
Constant	0.166 (-0.013-0.346)	1.194 (0.964-1.486)	0.186 (-0.043-0.420)	1.204 (0.958-1.523)

Table 5-3 shows that the higher the proportion of PLHIV initiating on ART in a ward, the higher viral load suppression rate increases by 35% (OR: 1.345; 95% CrI 1.221-1.492). The viral load suppression rate (<1 000 copies/mL) increased by 44% with an increasing proportion of female PLHIV in a ward (OR: 1.442; 95%CrI: 1.056-1.962).

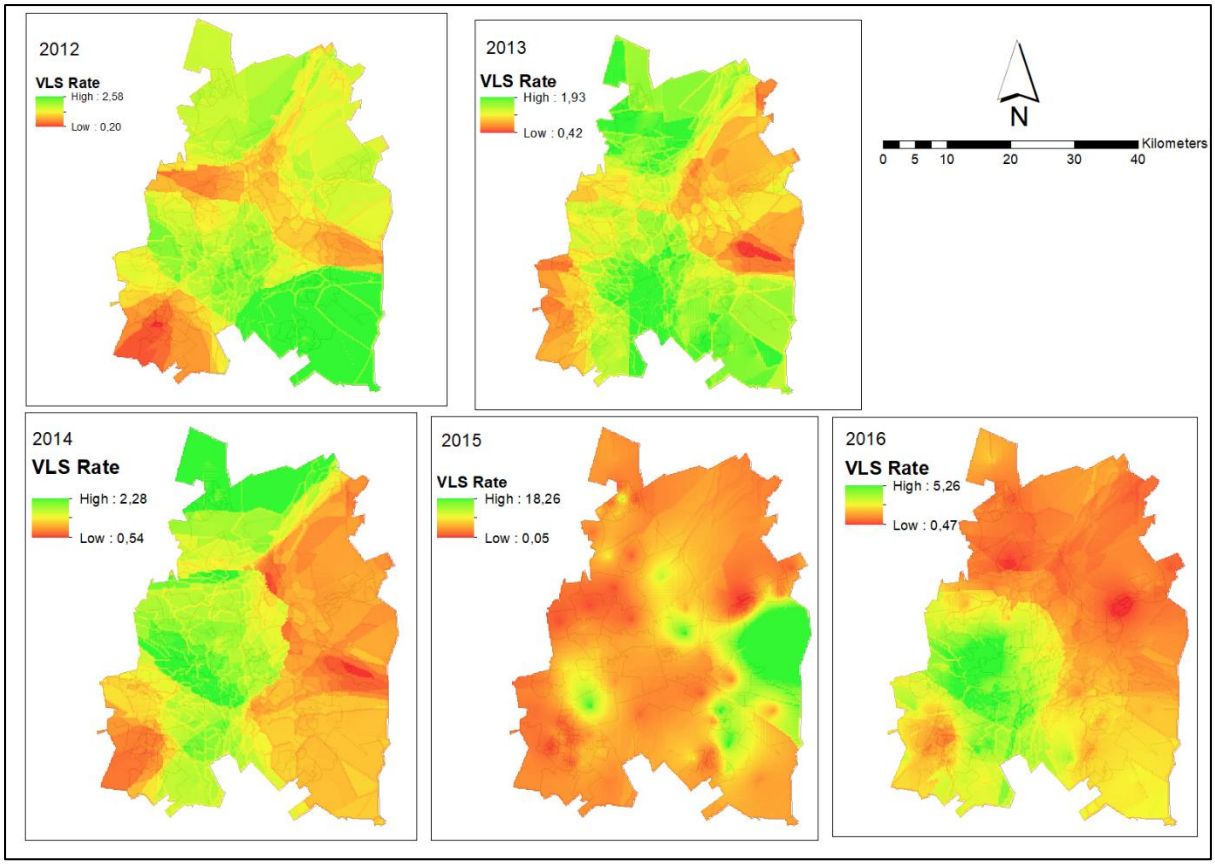


Figure 5-6: Heterogeneity of predicted viral load suppression (<1 000 cp/mL) rates in Ekurhuleni Metropolitan Municipality (2012-2016)

Figure 5-6 shows the spatio-temporal trend of predicted viral load suppression rates from 2012 to 2016. Over the five-year period, there was heterogeneity of viral load suppression rates in Ekurhuleni. The areas with high rates of viral load suppression are seen in the green colour, whereas those in red colour have low rates of virally suppressed PLHIV. Over the years, figure 5-6 shows that wards in the south-Western part of Ekurhuleni (Thokoza and Katlehong areas) have consistently reported low viral load suppression rates.

5.3.7. Temporal changes in predictors associated with viral load suppression

Female population and ART initiation are two important predictors of viral load suppression in Ekurhuleni but their relationship was stronger in some wards and weaker in some. The patterns of these two explanatory variables were randomly distributed for all years except 2014 (Moran index=0.077, p-value=0.040) whose distribution was clustered. However, after adjusting for spatial effects, the pattern showed a random distribution. The relationship between the proportion of female population and high viral load suppression in Ekurhuleni changed between 2012 and 2016 (Table 5-4). In 2013 (β=0.776; p-value <0.001), 2014 (β=0.523; p-value 0.009), and 2015 (β=0.561; p-value 0.015) this relationship was statistically significant. Spatially, the red areas were wards in Ekurhuleni where an increase in the proportion of women was a strong predictor of high viral load suppression. The dark blue areas were wards where an increasing female population is not a very strong predictor (Figure 5-7).

Table 5-4: Spatio-temporal changes of parameters associated with high viral load suppression

	2012 **Estimate** ***P-Value***	**2013** **Estimate** ***P-Value***	**2014** **Estimate** ***P-Value***	**2015** **Estimate** ***P-Value***	**2016** **Estimate** ***P-Value***
Regression results					
Intercept	0.034 *0.240*	0.023 *0.219*	0.006 *0.776*	0.032 *0.118*	0.031 *0.091*
Prop Female	0.374 *0.053*	0.776 *<0.001**	0.523 *0.009**	0.561 *0.015**	0.254 *0.092*
Prop ART initiation	0.713 *0.004**	0.258 *0.032**	0.424 *0.001**	0.409 *0.002**	0.530 *<0.001**
Ordinary least squares diagnostics					
Adjusted R^2	0.253	0.434	0.527	0.601	0.606
Koenker statistic†	17.117 *<0.001**	9.151 *0.010**	7.225 *0.027**	8.429 *0.016**	10.532 *0.005**
Moran index	-0.047 *0.415*	0.005 *0.701*	0.077 *0.040**	0.042 *0.209*	0.042 *0.204*
Geographically weighted regression diagnostics					
Adjusted R^2	0.294	0.482	0.541	0.596	0.612
Moran index	-0.050 *0.367*	-0.017 *0.910*	0.034 *0.289*	0.019 *0.467*	0.007 *0.662*

†- a statistically significant p-value indicates relationship between the explanatory variables and viral load suppression is non-stationary

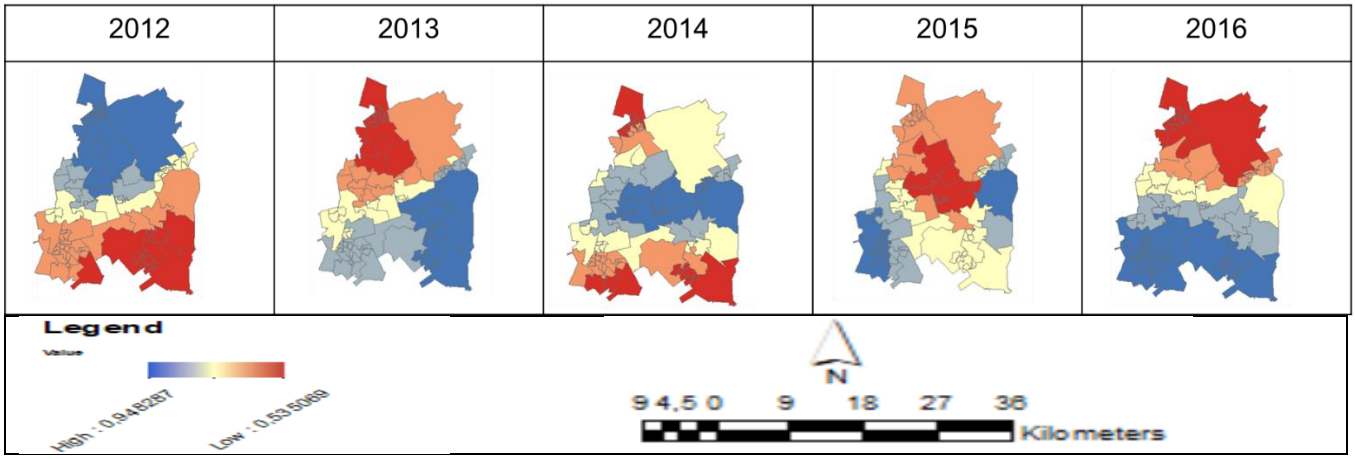


Figure 5-7: Spatial-temporal changes in the proportion of female population and viral load suppression (<1 000 cp/mL) rates in Ekurhuleni Metropolitan Municipality (2012-2016)

Similarly, the relationship between the proportion ART initiation and high viral load suppression in Ekurhuleni changed between 2012 and 2016 (Table 5-4). The relationship was statistically significant across all the years, namely: In 2012 (β=0.713; p-value <0.004), 2013 (β=0.258; p-value 0.032), 2014 (β=00.424; p-value 0.001), 2015 (β=0.409; p-value 0.002), and 2016 (β=0.530; p-value <0.001). Spatial patterns reveal that the red areas were those wards in Ekurhuleni where an increase in the proportion of PLHIV initiating on ART was a strong predictor of high viral load suppression. The dark blue areas were those wards where an increasing ART population was not a very strong predictor (Figure 5-8).

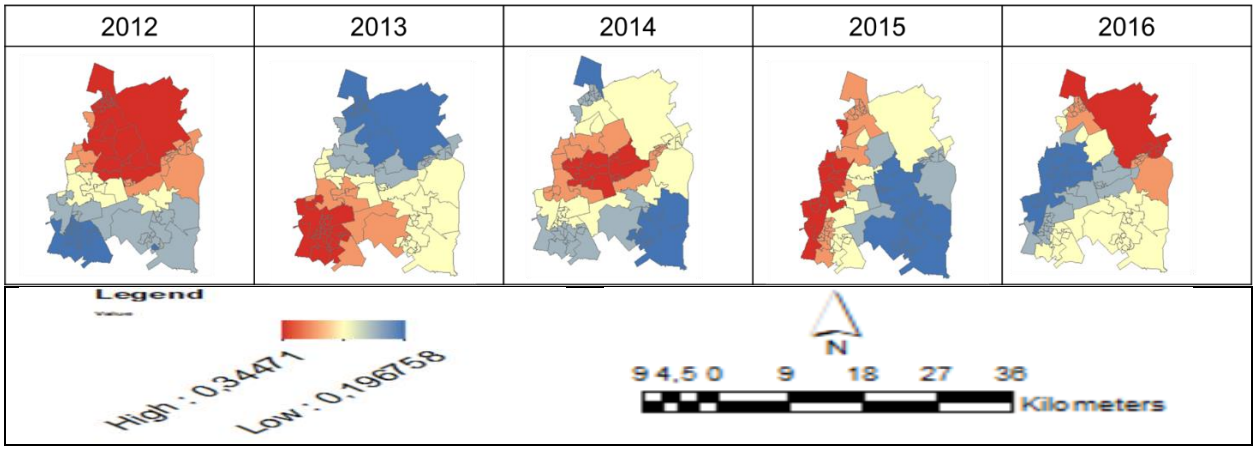


Figure 5-8: Spatial-temporal changes in the proportion initiating ART and viral load suppression (<1 000 cp/mL) rates in Ekurhuleni Metropolitan Municipality (2012-2016)

5.4. Summary of findings

This study used Bayesian statistical techniques to evaluate the ART programme in EMM and introduced a spatio-temporal techniques to account for heterogeneities in space and time using data collected from laboratory monitoring of viral load between 2012 and 2016.

These findings show presence of spatial and temporal heterogeneity in viral load suppression in EMM using routinely collected laboratory data. Findings further provide valuable insights into the HIV programmes in the study area by identifying wards needing additional support to link and retain PLHIV in care. Although the proportion of virally suppressed PLHIV steadily increased from 2012 to 2015, the spatial maps revealed ward-level differences and evidence that high and low levels of viral load suppression rates were clustered geographically across space and time. This study found that wards in the highest quartile, 86% of the PLHIV achieved viral suppression and whereas those in the lowest quartile, only 35% were virally suppressed. To ensure that the overall viral load suppression in EMM improves, an increase of 51% in wards in the lowest quartile is required.

An additional interrupted time series analysis showed an immediate impact on viral load suppression rates after roll-out of UTT from September to December 2016 in EMM. This decrease in the proportion of those reporting viral load suppression was likely attributed by the large number of PLHIV starting ART each month. Those newly initiated would have to wait for six months to receive their first viral load test.

The relationship between ART coverage and viral load suppression rates has been established by previous findings in other settings where ART coverage has led to improved viral load suppression rates [166]. These findings show gains in the HIV program in EMM which however need to be maintained. Services, such as same-day initiations and differentiated delivery of care are to be consistently provided [167, 168]. Reducing interruptions in ART initiation and retention increases the proportion of those on treatment and subsequently reduces incident HIV cases [71]. Interruptions at an individual level are likely to introduce resistance and the recent introduction of dolutegravir, an integrase strand-transfer inhibitor is likely to increase overall virological suppression rates [169]. However, more needs to be done to alleviate concerns regarding management of viremia and other side effects associated with the use of dolutegravir. Mapping such outcomes is likely to unearth priority areas for targeted interventions. These findings showed the areas that required targeted resource allocation and the variations across space and time.

After adjusting for space and time, findings showed that as the proportion of women increased at ward-level, viral load suppression increased. This finding is consistent with previous research that has shown that women are likely to reach viral load suppression faster and remain suppressed than men [169, 170]. The implications of this finding are two-fold: firstly, it is important for current and future HIV programmes to continue tracing women who may fall out of care to prevent treatment failure [171]. Secondly, there is evidence from this analysis for the need to tailor ART programmes to men who are likely to fail at retaining in HIV care thus failing at treatment [172, 173]. This can be done in areas where findings showed that a high proportion of women was not a strong predictor of viral load suppression.

5.5. Strengths and limitations

This analysis makes several contributions to the literature. Firstly, we demonstrated that the use of existing routinely collected laboratory data to monitor viral load in EMM is feasible. Secondly, we used Bayesian analytical techniques which incorporated the longitudinal design to assess the spatio-temporal predictors of viral load suppression over time rather than cross-sectional estimates which showed heterogeneity [174]. Lastly, we used geospatial techniques to identify areas of high and low clustering of viral load suppression, and strong predictors of high viral load suppression in EMM. These findings highlighted areas where focused interventions are needed. This analysis had some limitations, and the findings should be interpreted with caution. First, some variation in the ward-level viral load suppression measure may reflect random fluctuations. However, by averaging over the five years of data, a measure with high reliability was attained, indicating evidence of a persistent ward effect. Second, since laboratory data through to December 2016 four months after the start UTT was used, post-implementation for comparison was limited due to lack of enough data. In addition, there were potential missing laboratory data that may have originated from lack of adequate capturing. Also observed was the almost 37% of missing samples despite a large number of samples collected during the time-period. The missing results may imply lost to follow-up which may have underestimated the viral load test results. Lastly, we used data from patients who are in HIV care, and we may have missed to include data from those who do not frequently attend clinic visits or pharmacy pickups through decanting programmes.

5.6. Summary of chapter

This analysis demonstrates the feasibility of using routinely collected programme data and applying spatial techniques to describe outcomes associated with HIV epidemic control. The value of this analysis lies in HIV planning and includes forming a baseline for targeted interventions during district/sub-district operational plans. There was an improved ART coverage in EMM and a decline in HIV positivity rates among women between 2012 and 2014. To assess the impact of scaling up HIV services and the gaps in implementation, spatial-temporal analyses highlighted geographic areas that need greater attention and the underlying characteristics that affect viral load suppression in Ekurhuleni.

6. CHAPTER SIX: UNDERSTANDING THE UNDERLYING INFLUENCES FOR HETEROGENOUS DELIVERY AND UPTAKE OF HIV SERVICES

"Paper 3: Understanding factors influencing utilization of HIV prevention and treatment services among patients and providers in a heterogeneous setting: a qualitative study from South Africa."

In order to understand the reasons driving uptake and delivery of HIV services, in-depth interviews with patients attending primary health centres and their providers were conducted. In this chapter, the methodology, results, and discussion for paper three of this PhD study are presented. The detailed published manuscript is found in Appendix H.

6.1. Introduction

There is a less than optimal uptake and coverage of HIV services including HTS and ART in South Africa [38, 39]. Previous studies have cited several factors facilitating this sub-optimal uptake mainly, stigma, HIV status non-disclosure, ART side effects, and low perceived risk of HIV infection [38, 40]. Violent reactions from intimate partners has reduced female engagement in HIV care [41, 42]. Men on the other hand, report poorer health outcomes and higher AIDS-related morbidity and mortality from underutilization of healthcare services [44-46]. Most men fail to know their HIV status, access, and adhere to HIV care due to a variety of reasons. Some of these include lack of private consultation spaces, medication stock-outs, long queues, and negative patient-provider interactions [38, 40]. Additionally, the unawareness on available services at community-level and limited human resources prevents male patients from accessing HIV care [40].

A comprehensive package of services including HTS and ART initiation for PLHIV are a game-changer in the HIV response with promising results [175]. In South Africa, PHCs provide this package through vigorous HTS, linkage to care, prevention of onward transmission by providing male and female condoms, PrEP, post-exposure prophylaxis (PEP), PMTCT and UTT

[176]. The 2017–2022 South Africa NSP on HIV, STIs and TB supports for the adoption of these available HIV prevention or treatment services which may likely lead to a 60% reduction in HIV incidence by 2022 [2].

Heterogeneity in both HIV prevalence [58, 65, 68] and uptake of available HIV services [50]. exists in many high HIV burden settings in SSA. This uneven distribution of events suggests that the underlying dynamics associated with uptake or delivery of HIV services is uneven across geographical areas. The limited understanding of these dynamics is evident in diverse settings and having a target-specific understanding of these variations is necessary to allow targeted interventions for optimal uptake and delivery of existing HIV services [177].

Qualitative research with participants guided by a social cognitive theory (SCT) was conducted to examine in in-depth the barriers and facilitators of optimal uptake and delivery of HIV services in diverse settings in South Africa. The main aim of this study is for informed targeted and contextualised implementation of HIV services for improved uptake.

6.2. Methods

This study employed qualitative techniques to understand the factors influencing uptake and delivery of HIV prevention and treatment services at a facility-level in EMM. A framework built around the SCT guided the thematic analysis to describe behavioural, individual, and social/environmental factors motivating the use of HIV services in patients attending selected PHCs in EMM [73] (Figure 6-1).

Qualitative in-depth interviews (IDIs) were conducted using an IDI guide in July 2020 with patients and providers in selected clinics within the four identified geographical areas. Trained research assistants approached and provided detailed information to patients as they queued for their clinic visit. After obtaining written consent, trained research assistants conducted 30-45 minute-IDIs with 24 patients attending their routine clinic visits and 6 healthcare workers providing different HIV services at a clinic and community level. After the interviews, participants were reimbursed with a food voucher valued at R50 (~USD 6) for their time. Audio-recordings were transcribed verbatim and where necessary, translated to English language. Transcripts were read multiple times to capture context and manually code guided by the social cognitive theory constructs. Thematic analysis was performed in NVIVO version 10 ™ (QSR International Pty Ltd., Melbourne, Australia, Version 10, 2012) – a qualitative data

management and analysis software package that captured salient differences on the uptake and delivery of HIV services across the geographical settings.

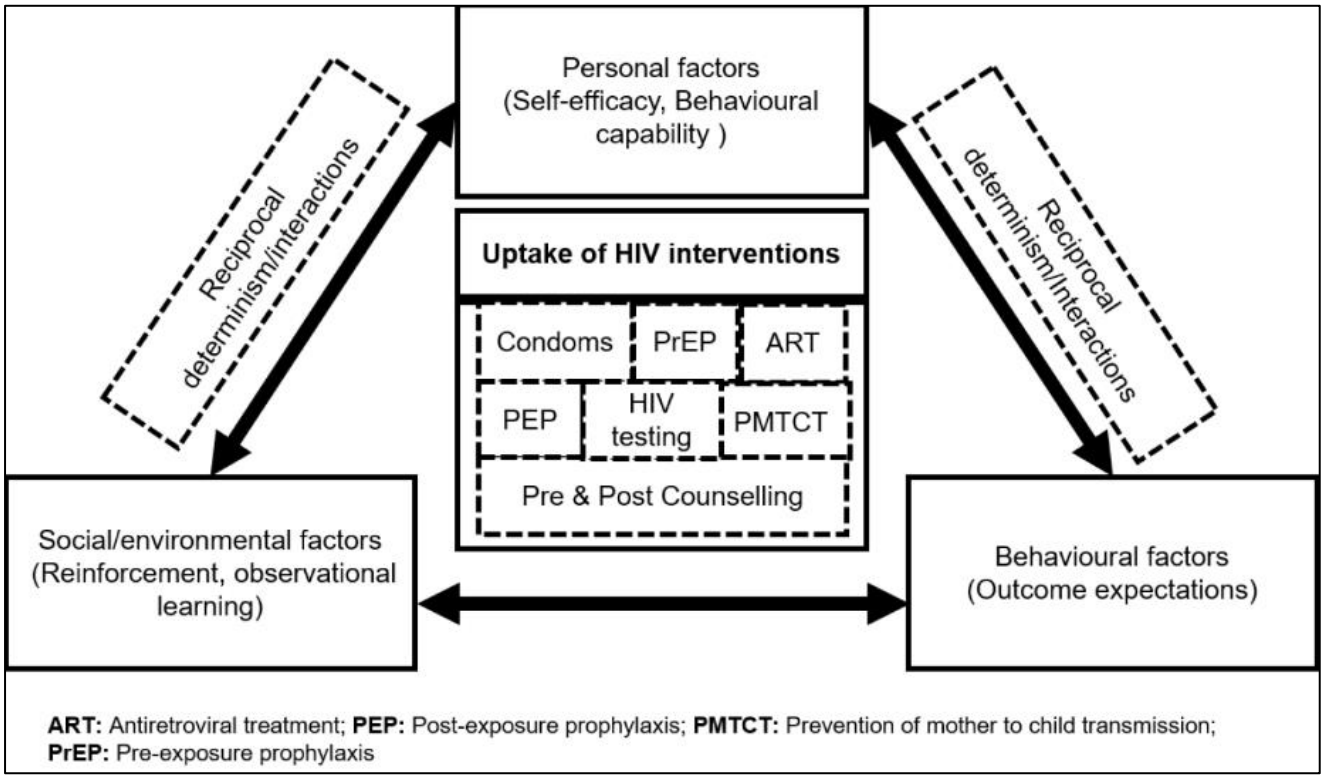


Figure 6-1: Adaptation of the social cognitive theory in uptake and delivery of HIV services in EMM

After completion of transcription, myself, and a junior researcher, read and summarised all interview transcripts to familiarise ourselves with the data. Following the initial reading of all transcripts, all participants were categorised according to the setting using information obtained from the mapping exercise explained in Section 4.2. We classified participants in this manner to contextualise identified themes with different geographical settings. Broad coding definitions were assigned to each transcript to ensure coding consistency. Participant's transcripts were coded separately for each interview conducted. Next, using an inductive and deductive approach to qualitative data analysis, 'fine' codes were developed by reviewing all coded excerpts to create a list of themes and sub-themes emerging from the data. All sub-themes were constantly compared to the definition of the broader code to ensure that they remained relevant to the coding framework.

6.3. Results and discussion

6.3.1. Characteristics of study participants

Twenty-four patients, majority female (66.7%), unmarried (66.7%), living with HIV (66.7%), and of median age of 37 (IQR: 31-40) years were interviewed. The median duration on ART by HIV-positive patients was 84 (IQR: 21-144) months. Two newly diagnosed PLHIV who started ART on the same day of the interviews were enrolled. The study also enrolled a HIV-positive MSM and a pregnant HIV-positive female patient. Six female HCWs involved in HTS provision, health promotion, HIV prevention and treatment, and HIV awareness and education (see Table 6-1) participated in the study.

Table 6-1: Socio-demographic characteristics of qualitative IDI participants

Patients	**n (%)**
Sex at birth	
Female	16 (66.7)
Male	8 (33.3)
Median age and IQR	37 (31-40)
Self-reported HIV-positive status	
Yes	16 (66.7)
No	8 (33.3)
Median duration on ART in months and IQR	84 (21-144)
Married	
No	16 (66.7)
Yes	8 (33.3)
Years lived in current residence	
< 1 year	1 (4.2)
1-5 years	8 (33.3)
>5 years	15 (62.5)
Years visiting the current clinic	
< 1 year	13 (54.2)
1-5 years	5 (20.8)
>5 years	6 (25.0)
Healthcare workers	**n (%)**
Skill level	
Clinician	1 (16.7)
Professional nurse	1 (16.7)
Primary health worker	1 (16.7)
HIV counsellor	2 (33.3)
Care facilitator	1 (16.7)
Overall years of experience	
≤ 5 years	2 (33.3)
>5 years	4 (66.7)
Overall years of experience in current clinic	
≤ 5 years	3 (50.0)
>5 years	3 (50.0)

6.3.2. Themes and sub-themes from thematic analysis

Five themes emerged from the analysis. Table 6-2 summarizes the thematic parallels and contrasts in the diverse settings. Quotes from participants were included to support the findings

Table 6-2: Themes and sub-themes from IDIs and their relevant social cognitive theory (SCT) constructs and domains

Theme and sub-themes*	Relevant SCT construct and *operational definition***	Relevant SCT domain**
Theme 1: Benefits from engaging in HIV care *Sub-themes* • Maintaining HIV negative status by using HIV prevention (PrEP or PEP) in case of unprotected sexual acts and protected sexual acts by condom use • Maintaining a suppressed viral load by consistently being on ART • Remaining in PMTCT programmes while pregnant for positive pregnancy outcomes including for both mother and child	**Outcome expectations** *"Expectations of positive health outcomes that are likely from a sustained action when utilising HIV prevention or treatment services"*	Behavioural factors
Theme 2: Possible negative consequences from engagement in HIV prevention or treatment care *Sub-themes* • Experienced or internalized stigma as a result of testing HIV positive • Intimate partner violence or condemnation from community for access and condom use especially for female patients. • Lack of support from providers to patients choosing PrEP over condoms. • Spending prolonged times in the clinics at the expense of their day-to-day jobs • Avoid attending clinics within the area of residence for fear of victimization from neighbours about one HIV positive status	**Reciprocal determinism** *"Interactions between personal and social/environmental factors that causes behaviour change that negatively influences utilization of HIV prevention or treatment services"*	
Theme 3: Good knowledge of existing HIV prevention or treatment services *Sub-themes* • Knowledgeable about HIV and existing HIV prevention services encouraging uptake PrEP and PEP services.	**Behavioural capability** *"Having and using the acquired knowledge and skills on HIV prevention or treatment to utilize the available services"*	Personal factors

Theme and sub-themes*	Relevant SCT construct and *operational definition***	Relevant SCT domain**
• Applying information and skills obtained from HTS, health promotion activities or campaigns to remain in HIV care • Maintaining positive attitudes when using HIV prevention or treatment services		
Theme 4: Ability to correctly use the available HIV prevention or treatment services *Sub-themes* • Correctly and consistent condom use for HIV prevention • Sustainable undetectable viral load to improve quality of life prevent death by life-long ART use	**Self-efficacy** *"Having a good understanding of the importance of HIV prevention or treatment services and persistently using them to monitor and control behaviour"*	
Theme 5: Interpersonal or environmental dynamics supporting use of HIV prevention or treatment services *Sub-themes* • Peer support • Family support • Structural support through well stocked facilities and interactions with friendly clinic staff to general and key populations • Presence of decanting programmes for differentiated delivery of HIV care for stable ART patients to overcome barriers associated with prolonged waiting times in the facility	**Observational learning** *"Observing from peers and performing desired behaviours from likening their experiences from utilizing HIV prevention or treatment services"* **Reinforcements** *"Encouraging positive changes through interpersonal and structural support"*	Social or Environmental factors

*From the data in the study; **well-defined and adopted from the SCT framework

Table 6-3: Overview of similarities and differences in themes across heterogenous settings and selected quotes

Theme and key dimensions	HL	LH	LL	Selected quote(s)
Theme 1: Benefits from engaging in HIV care				
Remaining in HIV care while pregnant for favourable pregnancy outcomes.	✓	✓	✓	*"By me taking my treatment, I gave birth to a HIV-negative baby. Although I was stressed about it (my HIV status), I learnt that I needed to consult the nurses and doctors at the clinic if I wanted to deliver a HIV-negative baby." (Female participant, 36 years, HIV positive, LH)*
Consistent ART use and sustained viral load suppression	✓	✓	✓	*"Since I have been on this treatment, I do not see anything wrong with it. My viral load is undetectable, and I see that I am gaining weight." (Female participant, 32 years, HIV positive, LL)*
Ensuring one maintains the HIV negative status by using the correct prevention method in case of accidental exposure	✓	✓	✓	*"Before marriage, I always used to check my HIV status every three months to know about myself and to avoid infecting my sexual partners." (Male participant, 45 years, HIV negative, HL)*
Theme 2: Possible negative consequences from engagement in HIV prevention or treatment care				
Anticipated or enacted stigma as a result of testing HIV positive	✓		✓	*"Most clients visit the clinic, look at how they are welcomed. Someone from a different area comes to this clinic to get help, either because of not wanting to disclose their status at their nearest facility to a lot of people that they may know that side. These people come but provide fake addresses which is a bit challenging when you want to trace them after they have defaulted." (NGO direct service delivery staff, HIV counsellor, HL)*
Inability to freely access or use condoms by female patients as a HIV prevention method for fear of condemnation from the community	✓		✓	*"If you are coming to the clinic as a lady and you want to collect condoms for protection, it's very hard because people are looking at you, judging and asking you why you need them. It is better to buy them in a shop, but the sales person also thinks that when a lady buys condoms, she is promiscuous." (Female participant, unknown age, HIV positive, LL)*
Judgemental connotations from service providers for preference of PrEP over condom use	✓		✓	*"My opinion is that we are encouraging clients to not use condoms by providing PrEP. People will start engaging in unprotected sexual intercourse with HIV-positive sexual partners and will not use condoms knowing that PrEP is available. This is not good. It's my personal opinion." (Department of Health Staff, Professional Nurse, LL)*

Theme and key dimensions	HL	LH	LL	Selected quote(s)
Interruption of ART use due to side effects	✓		✓	*"I started taking my medication and experienced drowsiness. But after three to four months, everything went back to normal as the nurse had advised." (Male participant, 38 years, HIV positive, HL)*
Theme 3: Good knowledge of existing HIV prevention or treatment services				
Knowledgeable on HIV and the available services at a clinic level facilitating uptake of HIV prevention interventions.		✓	✓	*"PrEP is a pill and condom is a condom. With a condom, there is a lower chance of getting HIV while you are having sex with HIV infected person. Likewise, with PrEP, when you are having sex without a condom you are still protected. Although using condom is much safer, there are chances that it may break, and you get infected." (Male participant, 40 years, HIV negative, LH)*
Application of robust information and skills obtained during HTS, health promotion activities or campaigns to remain in HIV care		✓		*"I usually come to this clinic, for PrEP. Before they give you PrEP, you test for HIV. If negative, the nurses give you pills that you will take for a period to prevent you from being infected. It does not actually motivate you to engage in unprotected sex but if you sometimes have unprotected sex, that pill will protect you." (Male participant, 26 years, HIV negative, LL)*
Maintaining positive towards seeking knowledge on how to seek HIV care for the patient and their sexual partner		✓		*"I'm not sure about PEP but probably immediately after finding out that you had intercourse with an infected person, you go the nearest clinic where they give you something. What I don't know is for how many hours, minutes, or days." (Female participant, 25 years, HIV positive, HL)*
Theme 4: Ability to correctly use the available HIV prevention or treatment services				
To prevent HIV transmission or acquisition by correct and consistent condom use		✓		*"Yes, I use condoms all the time because I don't want to get re-infected. My viral load is undetectable, and I would like it to stay like that." (Female participant, 30 years, HIV positive, LH)*
Sustainable undetectable viral load to improve quality of life prevent death by life-long ART use	✓	✓	✓	*"ART to me is like a battery, when it's flat you must charge and if you don't charge, it will shut down. I cannot stop taking treatment because I will lose my body, I am going to be sick and maybe after 2 or 3 years, I will be gone." (Male participant, 40 years, HIV positive, HL)*
Theme 5: Interpersonal or environmental dynamics supporting use of HIV prevention or treatment services				
Peer support on living positively with HIV		✓		*"This person was born HIV-positive, and I didn't know I will end up like him. I started reading his story while in school and when I discovered that I am HIV-positive, I was motivated to take my medication as we were born the same way." (Male participant, 40 years, HIV positive, LH)*

Theme and key dimensions	HL	LH	LL	Selected quote(s)
Social support from family members to adhere to HIV treatment	✓	✓	✓	*"At home, my parents and siblings remind me to take my medication. When I decide to sleep away from home, I don't bring my medication with me and skip my dose because I don't want anyone apart from my family to know my condition." (Female participant, 25 years, HIV positive, HL)*
Structural support by consistent supply of condoms in healthcare facilities and providing counselling services for those who chose this method of HIV prevention	✓	✓	✓	*"Every day in the morning, we issue out a new box of condoms which patients take them but do not utilize. The married ones say that their husbands are refusing to use condoms. We counsel the couple, they agree to use them but after a week, their story changes and they tell you that they cannot be told how to manage their bedroom issues." (Department of Health Staff, Professional Nurse, LH)*
Structural support by friendly clinic interactions with healthcare providers encouraging uptake of HIV services		✓		*"In this clinic, I've never experienced shortage of ART. I always get my medication on time and the nurses always remind me a week before my visit date. If I am unavailable, someone I trust will collect on my behalf." (Female participant, 35 years, HIV positive, LH)*
Decanting of stable ART patients to overcome barriers associated with constrained staffing levels at a clinic level and frequent clinic visits		✓		*"We can decant the patient for six months. The patient's viral load should be less than 50 copies/ml. We refer to the central chronic medicine dispensing and distribution (CCMDD) program where they get their medication delivered in a box every two months avoiding unnecessary clinic visits." (Department of Health Staff, Professional Nurse, LH)*

✓ Represents parallels across settings **Key**: **HL** = High HIV burden and Low uptake of interventions; **LH** = Low HIV burden and High uptake of interventions; **LL** = Low HIV burden and Low uptake of interventions

6.4. Benefits from HIV care engagement

The expected positive outcomes associated with HIV treatment were mentioned by all participants and emerged across the diverse geographical settings. Viral load suppression was widely mentioned. Some favourable health outcomes cited were HIV-negative children from HIV-positive expectant mothers, overall excellent health seen as weight gain and not transmitting HIV to sexual partners by most PLHIV and maintaining a HIV-negative status (See Table 6-3). Those using PrEP as a HIV prevention option require further education on prevention of STIs as mentioned by one male participant.

> *"PrEP is a very good thing; a very good initiative that helps you prevent yourself from getting infected, and it also helps you to know your status. You start the process by going through testing and after you find the result you act on the result regardless of what kind of result. PrEP is preventing you from getting infected. Though I am quite not sure whether it protects you from other STIs but from HIV I'm quite sure." (Male participant, 26 years, HIV negative, LH)*

6.5. Possible negative consequences from engagement in HIV prevention or treatment care

Most participants who reported negative consequences from engagement in HIV care resided in areas of low uptake of HIV services. Owing to self-stigma, HCWs revealed that PLHIVs avoided unintended disclosure of HIV status by providing incorrect physical addresses. As a result, health tracers high HIV prevalence and low uptake areas faced challenges during tracing and follow-up of PLHIVs that have defaulted on ART (see Table 6-3). Another reason is the fear of knowing their HIV status as reported by this one participant.

> *"I think the hardest thing in preventing HIV it is in a question of testing, many people don't want to test because they are afraid of the result, they are afraid of what they might find. So, it's very difficult to convince someone to go and test, it needs someone who is talkative someone with a good approach, you just can't come and tell me that I must go and test and then start the PrEP, you just have to tell me why I should start this and that". (Male participant, 26 years, HIV negative, LH)*

Further, experienced, and felt stigma was particularly reported by female patients. This occurred when negatively judged as promiscuous by retailers selling condoms to female customers. This barrier led to sub-optimal engagement in HIV care (see table 6-3). Male patients specifically reported prolonged waiting times caused by long queues from strained

human resources in facilities which likely impacted patients' livelihoods by interfering with working hours. This male participant highlighted this issue as quoted below:

> *"The only thing that I have a problem with this clinic is time. You come early around five o`clock in the morning but wait until 12 o`clock to see the nurse. Maybe it is because there are very many people. You finally miss work and some nurses do not provide you with a letter to explain why I missed work." (Male participant, 35 years, HIV positive, HL)*

HCWs in low uptake areas were concerned about the increasing PrEP use by patients seeking to prevent HIV infection in case of unprotected sexual acts. Unfortunately, these concerns are likely to perpetuate professional stigmatization of patients who choose using PrEP over condoms for HIV prevention and negatively affect PrEP uptake (see Table 6-3). On the contrary, the HCWs who provided condoms in their consulting rooms reported that many of their patients did not fully use them for protection due to the increased pregnancy cases as reported by this clinic staff from a low uptake area:

> *"There is not a lot of condom use reported in this clinic. We give them each and every patient in the consulting room condoms but then when they get home, they don`t use those condoms. You can decant the patient for six months, before they come back after six months, most of them are pregnant, so they don't use condoms. They just say they do but then in actions it's not happening." (DOH Staff, Clinician, LL)*

The last sub-theme from this theme is about experiencing side effects from ART use which was mentioned across all the geographical areas. This was mostly reported at the beginning of treatment but HCWs encouraged the continued ART use. The need to achieve a suppressed viral load facilitated continuous engagement in HIV care (See Table 6-3).

6.6. Good knowledge of existing HIV prevention or treatment services

Participants from all settings had the necessary knowledge and skills for using HIV prevention or treatment services obtained during HTS in healthcare facilities, health promotion activities and outreach campaigns in communities. The commonly accessible HIV prevention method was the condom use which all participants stated that they freely accessed from healthcare facilities or purchased from retail establishments in the communities. The use and importance of PrEP in HIV prevention was understood by participants who appeared to view it superior in preventing HIV infection than condoms (Table 6-3).

The HIV-negative participants were knowledgeable about PrEP which they acquired from counsellors and other HCWs in the facilities during HTS sessions. Campaigns and outreach programmes by NGOs provided an avenue that created PrEP awareness in the communities. (see Table 6-3).

Knowledge of and access to PEP services was explored. Many of the participants understood when to use this HIV prevention method and how to access PEP in event of an unintentional exposure from a HIV-infected sexual partner or needle pricks, cuts (Table 6-3).

Upon exploration of UTT knowledge, findings revealed that most participants knowledge across the geographical settings was limited. HIV-negative participants in particular, had limited understanding of the UTT benefit of reducing the risk of onward HIV transmission by supressing viral load to undetectable levels. HIV-positive participants misconstrued the benefits of UTT as an opportunity to disclose their HIV status to closed family members or friends.

> *"The advantages of UTT are for people to know their HIV status but if you are afraid of telling each other, try to tell one person you trust so that he can be the support. To remind you when to take your treatment and when to go collect them." (Female participant, 35 years, HIV positive, LL)*

Despite the good knowledge on the available HIV services, discussions showed that their uptake was dependent on a person's attitude and their perception of HIV risk.

> *"Using these interventions depends on my attitude towards HIV. As I said, I always use protection. If you are HIV-negative and do not take precautionary measures, you will become infected with HIV." (Female participant, 40 years, HIV negative, LH)*

6.7. Ability to correctly use the available HIV prevention or treatment services

The ability to correctly use the available HIV prevention or treatment services was assessed. To examine self-efficacy, participants showed that there were aware of the potential the barriers preventing uptake of these services and in addition, applied strategies to overcome the identified barriers. Commonly mentioned was the consistent use of condoms to protect accidental exposure or transmission.

Across all geographical settings, PLHIV understanding of the poor outcomes from non-adherence to ART was evident. Poor outcomes such as wasting, morbidity and mortality were

mostly cited. Participants opted to adhere to ART to prevent experiencing these negative outcomes (Table 6-3).

In low uptake settings HCWs were instrumental in ensuring that patients received information that will enable the correct use of the available prevention and treatment services. Mostly mentioned was education on the correct use and storage of condoms to maintain their effectiveness and quality.

> *"We teach patients how to use condoms. There are many cases where condoms have burst and upon investigation, you find, it's because of poor storage, using expired condoms or reusing them. Our people need education on proper use or storage of condoms. They should not put them in the pocket, walk around the mall or keep the packet in the sun." (Department of Health Staff, Clinician, HL)*

HCWs also encouraged newly initiated PLHIVs to adhere to ART despite experiencing any side effects. Many patients were aware that the side effects would resolve after a few days.

6.8. Interpersonal or environmental dynamics supporting use of HIV prevention or treatment services

Peer support motivated high uptake of the available HIV treatment services. One participant decided to engage in HIV care upon learning from and observing a peer's way of living positively despite a positive HIV status (see Table 6-3).

A strong family background with good relationships with parents and siblings encouraged engagement in HIV care for many participants living with HIV. These good relationships were a source of support, for young HIV-positive participants. Despite this, unintended disclosure of HIV status to other family members and friends leads to ART interruption when young PLHIVs are away from home (see Table 6-3).

Although family support was shown to increase uptake of HIV services, some HCWs reported the challenges female patients faced from intimate male partners over their choice of condom use.

> *"Every day in the morning, we issue out a new box of condoms which patients take them but do not utilize. The married ones say that their husbands are refusing to use condoms. We counsel the couple, they agree to use them but after a week, their story changes and*

they tell you that they cannot be told how to manage their bedroom issues." (Department of Health staff, Professional Nurse, LH)

At a facility level, positive interactions between patients and HCWs encouraged uptake of HIV services. Through these positive interactions, most PLHIV understood that ART was lifelong. Key populations such as MSM visited facilities that were friendly and upheld their privacy. These positive interactions reduce fear of institutional stigmatization from HCWs, which encourages uptake of HIV services by this key population.

"I like this clinic because it provides me comfort as a "deputy person" (MSM). I come here to express myself and I like that whenever I talk about confidential things, the staff respect my privacy and I do not hear of our conversation in the community." (Male, 40 years, HIV positive, LH).

Facilities ensure that no stock-outs of condoms or ART occur. In high uptake areas, an adequate delivery of HIV services evident by the structural support through consistent supply of ART and condoms at clinic-level encouraging continuous uptake (See Table 6-3).

Decanting programmes for stable ART patients facilitated constant engagement in care where PLHIV would collect their medications from a non-clinic setting. This addressed the challenges around staff shortage and long waiting periods (See Table 6-3). In high uptake settings, presence of ward-based outreach teams (WBOTS) to expand the existing HTS programmes at community level. This was done by setting up mobile testing clinics or distribution of self-testing kits to reach patients in the community for HIV testing who were unable to access the PHCs.

"We have WBOTS that serve in the community and mobile clinics that deliver HTS. They conduct HIV testing while WBOTS distribute HIV test kits to people in the community unable to visit the clinic for HIV services to test at home." (NGO direct service delivery staff, HIV counsellor, LH)

Additional structural support included the use of case-facilitators to link patients to HIV prevention services at community level. Case-facilitators organized created awareness about HIV prevention and the available services such as PrEP and HTS through campaigns. However, delivery of these services in the community was disrupted time of the study due to the national COVID-19 response.

"Before COVID-19, we were conducting campaigns in the community, giving health talks, and issuing condoms. Because of COVID-19 we are no longer campaigning but when a

patient comes to the clinic and asks for a test, we will ask for the reasons for HIV testing. For those testing negative and have had unprotected sex, we offer PrEP for prevention." (NGO direct service delivery staff, Case-facilitator, HL)

6.9. Summary of findings

The social cognitive theory provided a framework through which the perceptions about self-efficacy and outcome expectations were understood. PLHIV's engagement in HIV care was influenced by personal, interpersonal, and environmental factors, as well as behaviour capability. The interactions between the factors was very important for understanding the heterogenous utilization of HIV services in EMM.

Women of child bearing age across the heterogenous settings, living with HIV, were highly motivated to have good pregnancy outcomes (HIV-negative children) as observed in the Option B+ study conducted in four SSA countries [178]. This may be due to the widespread effective messaging and education that encourages women to initiate and retain on ART through PMTCT programmes. However, it is also important to note that young pregnant women delay presentation for antenatal care to healthcare facilities since they are dependent on older guardians such as mothers, aunts, grandmothers, or older siblings [156]. Young pregnant women living with HIV fail to enrol early in HIV care due to the stigma associated with adolescent pregnancy which may result into adverse pregnancy outcomes contrary to what this PhD study found [179]. Findings also showed that most patients not infected with HIV were likely to use condoms, PrEP, and PEP for prevention. The acceptability of these prevention services and willingness to use them was mostly reported by men. Findings from this PhD study showed that men were willing to consistently use HIV prevention options however, previous studies have reported that their responses, especially on condom use, are normatively biased [158, 180]. Structurally, educating HCWs to avoid the perpetuation of professional stigma associated when patients choose to use PrEP over condoms is required. Such training should encourage HCWs to view PrEP as an aid that allows control over one's sexual health rather than a reason to engage in reckless sexual behaviour [181]. Uptake of condoms among women was limited as most choose maintaining their relationships with their intimate partners over their sexual and reproductive health [180]. Such women are reluctant to use condoms to avoid unfounded accusations of infidelity from male partners which sometimes lead to abandonment or violence [159]. In addition, fear of victimization from the community was a major barrier to condom use in this population [180].

Stigma was manifested in many ways by both patients and HCWs. Mainly female patients reported reluctance in using condoms as a HIV prevention method due to negative attitudes they experienced at a community level and from intimate partners [79]. This finding is commonly reported in many studies investigating uptake of condom use by women [72, 77, 79, 82]. At a community level, women were perceived promiscuous whereas with their male partners, marital infidelity is implied [73]. To address stigma from such experiences, more discreet HIV prevention methods such as oral and injectable PrEP have been made available and dapivirine vaginal rings recently introduced. However, HCWs in this study perpetuated stigma over their preference condoms over PrEP. Training of HCWs on the benefits of PrEP as a discreet alternative choice of HIV prevention is necessary [73].

Increasing mobile clinic services in the communities was done to address challenges associated with lack of finances for transport to healthcare facilities. However, stigma from the fear of breach of confidentiality or inadvertent disclosure of HIV status was reported leading to patients seeking care from clinics far away from their homes [83]. In some cases, patients provided incorrect physical addresses which hinder tracing efforts. Differentiated delivery of care is addressing a multitude of barriers to retention in care. Stable ART patients pick their medication from pick up points in the community, or a member of an adherence group collects and distributes ART to group members [182]. These approaches reduce the known negative consequences associated with seeking HIV care, and in turn optimizes HIV care engagement [183].

The findings show that PrEP and PEP knowledge was limited among HIV-positive participants and UTT was not well understood by many patients. Low levels of knowledge of these services reduces optimal engagement in HIV care [74].

6.10. Strengths and limitations

The main strength of this study is the use of SCT constructs to amplify the experiences of patients' engagement in HIV care across different geographical settings. The findings are likely to encourage targeted delivery of existing HIV prevention or treatment services across the settings. Furthermore, the findings emphasize the relevance of applying SCT in the implementation of HIV prevention and treatment programs. Interpretation of findings should be done with caution due to existing study limitations. To begin with, the sample population comprising of clinic attendees in select clinics in Ekurhuleni District limited generalizability of findings to populations that did not attend PHCs or reside outside EMM. The fact that the study

was conducted in a frequently researched area, it is my belief that participants may have had increased exposure to HIV information and health services. However, during these IDIs participants narration of real experiences while seeking HIV care it emerged that these findings were comparable to other qualitative data collected in other settings examining the same topics validating my findings and further attenuating this concern. The final limitation was the lack of access to some selected facilities as a result of COVID restrictions. Due to closure of clinics after reports of possible COVID exposure, permission to conduct non-essential activities such as research was denied. However, I believe that the findings reflect the delivery and uptake of HIV services in a heterogeneous setting.

6.11. Summary of chapter

This chapter presented the findings from the analysis of semi-structured interviews conducted with patients and providers in selected clinics. The interviews explored barriers to the delivery and uptake of selected HIV services within routine settings. Patients reported utilizing the available HIV services however, the study noted a few barriers lead to underutilization of these services. The most commonly reported barrier is stigma and discrimination emanating from breach of confidentiality, unintended disclosure, experiences from social harms. If not consistently addressed, progress on HIV testing, disclosure, treatment initiation and adherence will be negatively affected [38, 184, 185]. Strategies addressing stigma and discrimination are required to prevent attrition of patients in HIV care. At a personal level, PLHIV protect themselves from the impact of self or enacted stigma and discrimination by non-disclosure of status or attending distant clinics [186]. This leads to a negative effect on their retention in care

Providing all-inclusive health packages integrated with HIV services in existing programs can address the adverse consequences from engaging in HIV care and reduce stigma. At a community level, sensitization of these services by community healthcare or peer workers and is likely to improve uptake of HIV services [187, 188]. The use of community outreach programmes, adherence support groups and decanting programmes have facilitated engagement in HIV care in EMM.

7. CHAPTER SEVEN: EVALUATING IMPACT OF IMPROVING COVERAGE OF ART ON VIRAL LOAD SUPPRESSION

Evaluating the impact of a programme is necessary to estimate progress and plan for the future. Using secondary data from NHLS, a forecast of viral load suppression post December 2016 was conducted. In this chapter, the methodology, results, and discussion for paper four of this PhD study are presented. The detailed manuscript is found in Appendix I.

7.1. Introduction

Viral load suppression monitoring in people living with HIV (PLHIV) and on antiretroviral treatment (ART) is important for improving individual patients' health and reducing HIV transmission [172, 173, 189]. At a population level, there is a reduction in morbidity and mortality rates as well as HIV incidence [8, 190]. To optimize the HIV response in South Africa and reach the target of 95% of virally suppressed ART patients by 2030, numbers of patients initiating and successfully retaining in care must increase [191]. South Africa has the largest HIV treatment program worldwide with more than seven million adults reported in 2020 according to the Global AIDS 2021 report [1]. Since September 2016, the South Africa NDoH extended the ART to all people testing positive for HIV [2]. The policy, UTT offers promised to enhance the efforts to initiate and retain 95% of PLHIV on treatment as part of the UNAIDS global 95-95-95 strategy [192]. In 2020, about 62% of PLHIV were virally suppressed an increase of 8% from 2018 but below the minimum threshold of 75% [1]. Real-time viral load suppression monitoring relies on programmatic data from routinely collected clinical data rather than infrequent household-based surveys which were once considered the gold standard in evaluating HIV patterns and trends [193].

Routinely collected clinical data for clinical care have increased the availability of longitudinal, individual level data at both facility and national level. In South Africa, clinical and laboratory HIV records are electronically captured through various platforms including Three Interlinked Electronic Register (Tier.Net) [194], DHIS and CDW in NHLS. WHO in 2013 recommended that clinicians in primary health care use viral load test results to diagnose treatment failure

and viral load suppression [195]. These tests are typically conducted six and twelve months post-ART initiation and every year [196].

UTT studies in sub-Saharan Africa have associated lower HIV incidence with lower population-level HIV viremia [197]. Individual viral load suppression predictors in adults identified in previous research are mainly female sex, older age, early and timely ART initiation [26, 198]. However, improved understanding of population-level viral suppression and its extent to reduce HIV incidence is needed. Given the variety of these individual predictors, addressing heterogeneities in viral load suppression by using predictive models could facilitate targeted prevention interventions while focusing on delivery of these interventions [199]. To augment findings from predictive modelling, forecasting through time-series approach can be used for particularly short-term time series prediction. The ARIMA model is useful for evaluating and creating a forecasting model by modelling correlations in the datasets and has been used in non-healthcare sectors. In the healthcare sector, the model has been used in forecasting diseases such as future incident malaria cases deaths in Ethiopia [110], and the prevalence of opportunistic infections in PLHIV in Uganda [200]. ARIMA models could be used to forecast precise trends of events which provide early warnings for the future disease state for appropriate allocation of limited resources to effective interventions at a ward or facility level.

All HIV programs in resource constrained settings have used viral load suppression as a proxy for reduced HIV incident cases. In this study we have used predictive modelling on routinely collected data in EMM to identify predictors for viral load suppression, evaluated the extent to which the validated model can differentiate between wards with optimal and sub-optimal viral load suppression rates and assessed the agreement between the predicted and actual estimates of viral load suppression. In addition, a model was developed from January 2012 to December 2016 and forecasted viral load suppression from January 2017 to December 2021.

7.2. Methods

This study used predictive modelling through a time-series forecasting approach on routinely collected viral load data to evaluate viral load suppression rates in EMM and predict future viral load suppression rates. In addition, an OLS model was fitted to explain the relationship between proportion of women and ART initiation with high viral load suppression at a global level. The geographically weighted regression (GWR) was used to show the relationship between viral load suppression with the proportion of females and ART initiation at a local level. A map of the local parameters and the association with change in viral load suppression

was produced using ArcGIS version 10. Model performance was evaluated using OLS and GWR diagnostics. Data was collapsed into quarters and forecasting techniques through ARIMA to predict and forecast viral load suppression five years post-2016 were employed.

7.2.1. Data sources

Series cross sectional data between January 2012 and December 2016 from EMM with information on gender, age, ART start date and viral load count records were used as explained in Table 3-1. Ward-level data on gender and age was sourced from the 2011 National Census, ART initiation (ART start date) was abstracted from DHIS and viral load counts from the NHLS database.

7.2.2. Measures of viral load suppression

The outcome viral load suppression (VLS) using <1000 copies /mL (WHO guidelines) and <400 copies/mL (South African National guidelines), two of the thresholds used in South Africa to determine treatment success was assessed. The mean $\log_{10}$ viral load per month was summarized and VLS proportion was estimated by taking the number of virally suppressed patients and dividing by the overall number in HIV care per month. According to the 90-90-90 strategy high viral load suppression was considered above 74% [1]. We used this cut-off to generate a dichotomous variable (high VLS=1 and low VLS=0).

7.2.3. Statistical analysis

All statistical analysis were performed in Stata version 16.1 [136]. *P*-values <0.05 were considered statistically significant. Geographical weighted analysis was performed in ArcGIS v.10.7.1 [135]. For OLS, the variance inflation factor (VIF) assessed multicollinearity where a value >10 indicated presence of multicollinearity. The Moran index was used to assess the spatial independence of the residuals. The Moran index values range from -1 (negative autocorrelation) to +1(positive autocorrelation). Negative autocorrelation mean nearby locations have dissimilar values while positive autocorrelation mean similar values tend to occur in adjacent locations. A significant Moran Index indicate that clustering of residuals is not chance.

7.2.4. Model validation

7.2.5. Forecasting viral load suppression post 2016

To forecast aggregated viral load suppression rates from 2017 to 2021, a time series approach was used. To ensure accuracy, the data was divided the data into two groups: first, one for model development (January 2012 to December 2016) and the second for model validation (January 2017 to December 2021). I collapsed the monthly data into quarters and smoothed out the series using a centred moving average to understand the underlying growth component. Using ARIMA's Box and Jenkins methodology the assessment of autocorrelation within the time series of equally spaced time intervals was applied. The model's construction was done on data with a constant mean and variance over time. The best model was identified by having the highest value of parameters shown in Table 7-4.

7.3. Results and discussion

7.3.1. Sample characteristics

Between 2012 and 2016, 65.5% and 56.9% of the viral load test results from 26, 222 samples of PLHIV in routine care were virally suppressed at <1 000 copies/mL and <400 copies/mL thresholds, respectively. Most PLHIV were of average age 38.5 (SD: 7.5) years. The average proportion of female patients was 47.3% (SD:40.7%) and the average proportion of patients initiated on ART was 39.8% (SD: 30.1%).

7.3.2. Global and local predictors of high viral load suppression

The OLS confirms that the two variables (proportion of females and PLHIV initiating ART) are important predictors of VLS as shown by the VIF (<7.5). Using proportion of female and ART initiation at ward level, the OLS model is explaining 75% of the viral load suppression rates in Ekurhuleni. There is a significant positive relationship between an increasing proportion of women and ART initiation at ward level and increased rates of VLS in Ekurhuleni (Table 7-4). Every one percent single female population increase was associated with 0.36 increase in viral load suppression, while a one percent increase in ART initiation in the population was significantly associated with 0.54 increases in viral load suppression.

Table 7-1*:* Overall estimates from GWR including model diagnostic checks

Variable	Coefficient	Standard Error	P-value	VIF
Intercept	0,013	0,031	0.168	-
Proportion of females	0,361	0,113	0.007*	2.811

Proportion on ART	0,543	0,078	<0.001*	2.811
OLS diagnostics				
Adjusted R^2	0,752	-	-	
Moran Index	0,051	-	0,148	
Koenker statistic	10,687	-	0,005*	
GWR diagnostics				
Adjusted R^2	0,731	-	-	
Moran Index	0,003	-	0,737	

The Moran index of 0.05, p-value 0.148, the pattern does not appear to be significantly different than random. This means that the explanatory variables are good predictors of viral load suppression in Ekurhuleni as the residuals from the OLS are randomly distributed (Table 7-4). The relationship between the explanatory variables and viral load suppression is non-stationary as indicated by a significant Koenker test (p-value= 0,005). This means that proportion of women may be a strong predictor in some wards and weak in other wards. Similarly, ART initiation maybe a strong predictor in some wards and weak in other wards.

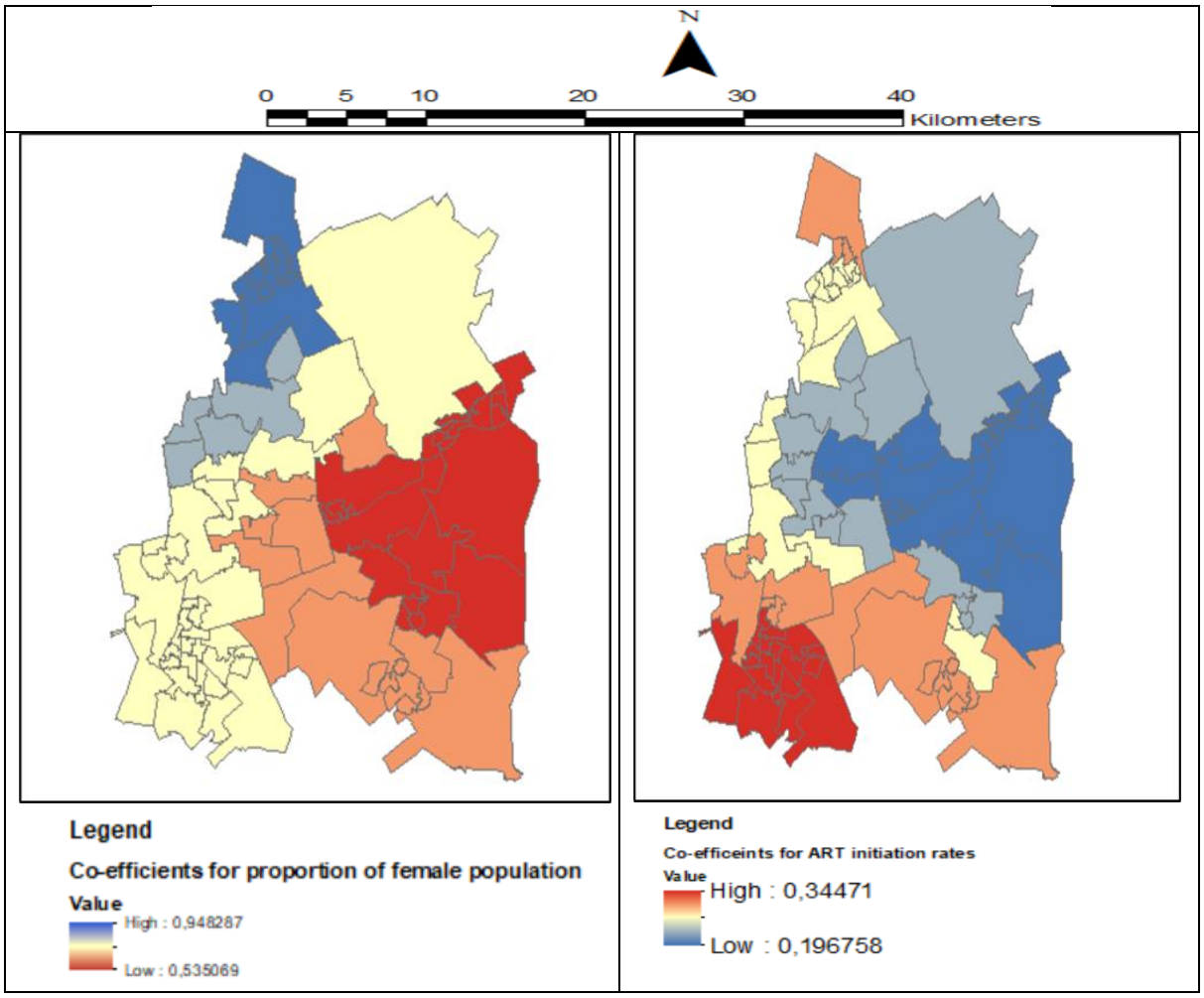


Figure 7-1: The overall relationship between proportion of females (A) and ART initiation (B) per ward and viral load suppression

The wards in red colour show where an increasing proportion of women is a strong predictor of increased VLS rates. The wards in dark blue colour show where an increasing female proportion is not a very strong predictor (Figure 7-1a). The wards in red colour show where an increasing proportion of PLHIV on ART is a strong predictor of increased VLS rates in Ekurhuleni. The dark blue areas show where ART initiation is not a very strong predictor (Figure 7-1b).

7.3.3. Forecasting viral load suppression

The ARIMA models (1, 0, 2) and (2, 0, 2) were identified as the most ideal models for forecasting (Table 7-5). The predicted viral load suppression rate values matched well with the actual historical rates as seen in Figure 7-2. The out of sample forecast of viral load suppression rate for the 1000 copies/mL threshold increased in 2017 before decreasing from 2018. As observed in Figure 7-2, the out of sample forecast for viral load suppression rates for the 400 copies/mL threshold increased from 2017-2019 and started to decrease beyond the second quarter of 2019. As expected, the confidence intervals show increasing uncertainty as one moves further into the forecast window (Figure 7-3).

Table 7-2: Model fit for viral load suppression rates in Ekurhuleni using <1000 copies/mL and <400 copies/mL thresholds

VLS < 1 000 copies/mL			
Fit statistic	**ARIMA (1, 0, 2)**	**ARIMA (1, 0, 1)**	**ARIMA (1, 0, 0)**
Log likelihood	24.1622	23.8233	23.7181
Sigma-squared	-0.00580	0.0735	0.0739
Normalized AIC	-38.3245	-39.647	-41.436
Normalized BIC	-33.346	-35.664	-38.449
VLS < 400 copies/mL			
	ARIMA (2, 0, 2)	**ARIMA (2, 0, 1)**	**ARIMA (2, 0, 0)**
Log likelihood	21.5849	20.3110	19.6776
Sigma-squared	0.07548	0.0846	0.0902
Normalized AIC	-31.1698	-32.622	-31.355
Normalized BIC	-25.1954	-28.639	-27.372

In Ekurhuleni, applying the <1 000copies/mL and <400 copies/mL thresholds, the study found that 65.5% and 56.9% of the viral load test results were virally suppressed. Most patients were of average age 38.5 (SD: 7.5) years. The average proportion of female patients was 47.3% (SD:40.7%) and the average proportion of patients initiated on ART was 39.8% (SD: 30.1%).

The predictors of high viral load suppression (both thresholds) in EMM were increased ART coverage [<1 000 copies/mL: 0.52 (95% CI: 0.12-0.93)]. An increasing female population decreased high viral load suppression by 0.35 [<1 000 copies/mL: -0.35 (95% CI: -0.65, -0.04)]. A similar observation was made for the <400 copies/mL threshold.

Time-series forecasting approach used the ARIMA model and predicted the viral load suppression rate values between (2012-2016) matched well with the out of sample forecast (2017-2022). This observation was similar in the two thresholds (Figure 7-4).

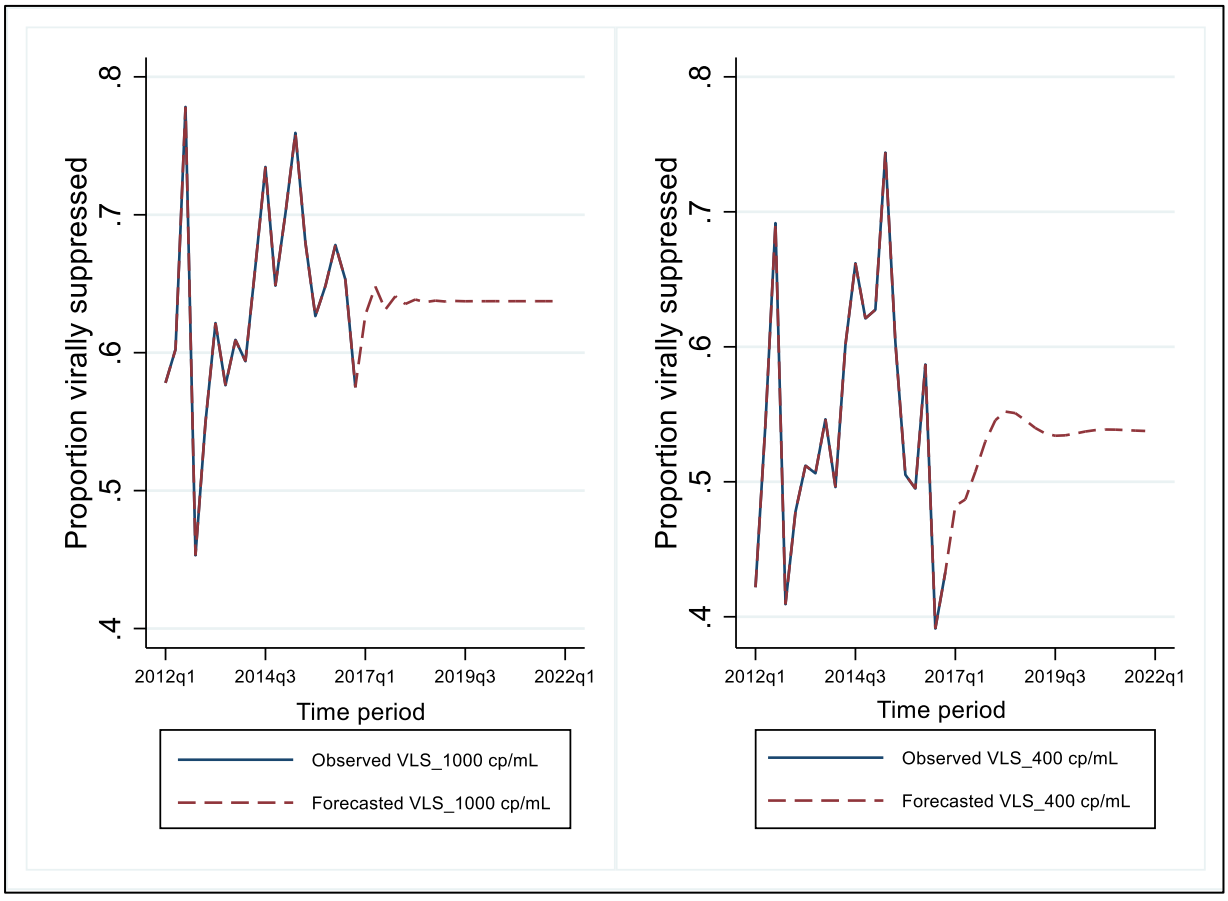


Figure 7-2: Observed (2012-2016) and forecasted (2017-2021) viral load suppression rates by ARIMA modelling technique

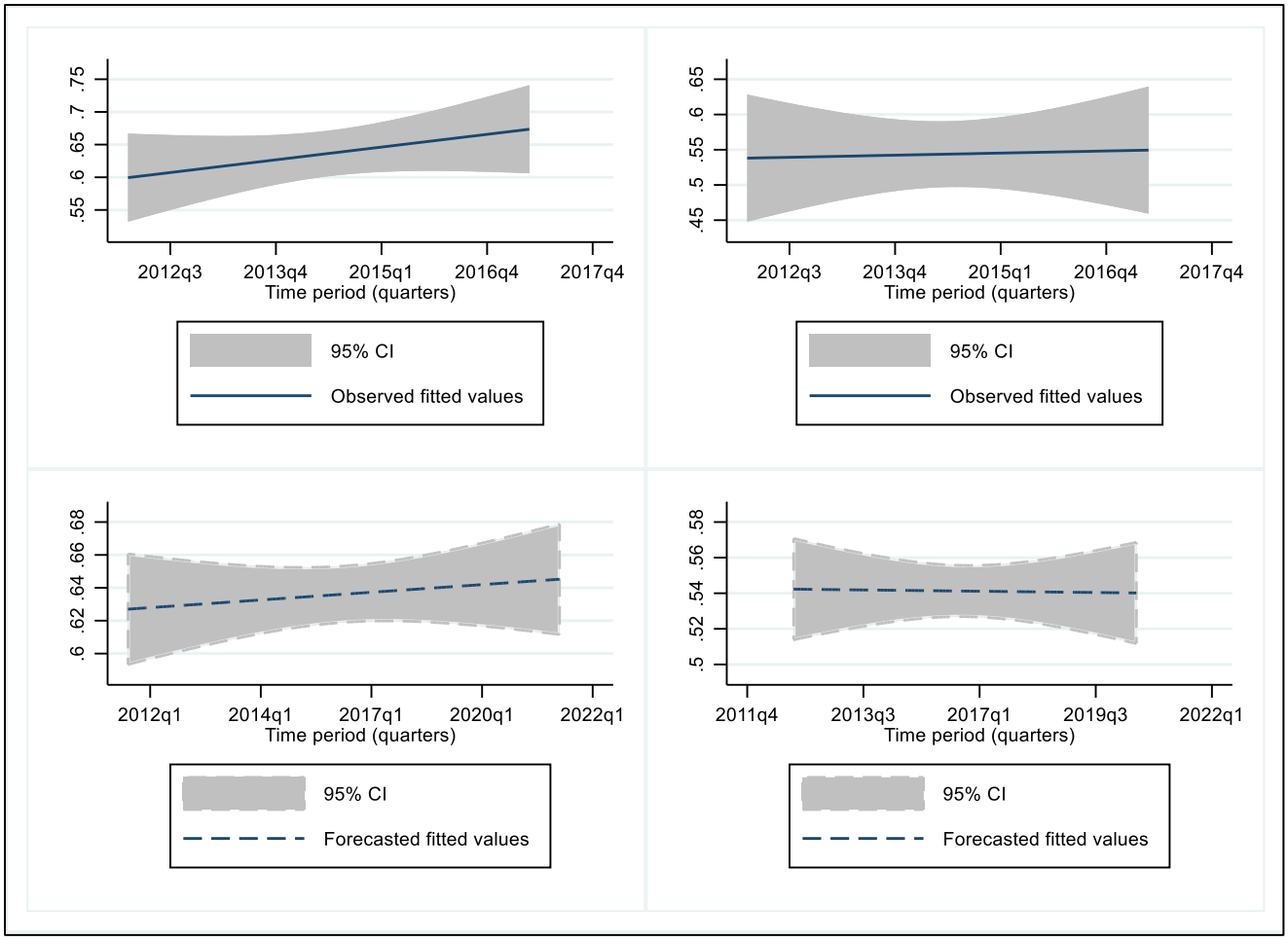


Figure 7-3: Observed (2012-2016) and forecasted (2017-2021) viral load suppression rates by ARIMA modelling technique

7.4. Summary of findings

Forecasting revealed that the viral load suppression rates in Ekurhuleni were lower than the targeted 90%. The proportion virally suppressed in 2018 ranged between 40% and 50%. These findings were corroborated by a recent study assessing district level targets for 90-90-90 in 2018, which showed that viral load suppression in Ekurhuleni was still low at 41.3% [71]. The findings highlight the urgent need to improve viral load monitoring through more nuanced approaches.

Confirming previous findings in Chapter five, the findings showed that an increasing female population in Ekurhuleni was likely to increase viral load suppression rate at a ward level. In South Africa, studies have shown that at an individual level, being female is a predictor of viral load suppression. A multi-centre study in KwaZulu Natal, Johannesburg and Cape Town showed that adult women were 26% more likely to report greater viral load suppression rates [201]. Our findings showed that an increasing female population in Ekurhuleni was likely to

increase viral load suppression rate at a ward level and this was observed in certain wards. In such wards, focusing on reaching women and strengthening retention strategies is important. A study on pregnant women using the 2017 national antenatal survey, highlighted the failure to achieve viral load suppression by the third trimester [171]. Pregnancy is a known predictor of poor viral load suppression [202]. Delayed entry into antenatal care, delayed initiation, poor adherence, and infrequent clinic visits during the 3rd trimester were the main reasons cited for a viral load >50 copies/mL [171, 203]. Although this study was not specific to Ekurhuleni, it underscores the importance of improving early antenatal care and ART initiation among pregnant women and improving HIV care to women living with HIV.

The findings also highlight the need to continually increase access of HIV services to women and men. In areas where an increasing female proportion was not a strong predictor of viral load suppression, focus on finding men living with HIV would be an important strategy as this may be where the greatest impact on viral load suppression would be felt. As efforts towards achieving 95-95-95 UNAIDS targets intensify, South Africa needs to implement additional interventions along the HIV care continuum. A similar intensity will be observed as data systems expand and more robust methodologies are used to mine the data.

The findings from this analysis showed increased treatment initiation rates as a predictor of high viral load suppression rates of <1 000 copies/mL only. This finding is consistent with the previous findings of this PhD which accounted for space and time (sub-section 5.3.6). As discussed previously in section 5.4, continuous provision of services, such as same-day initiations and differentiated delivery of care are necessary to ensure proper linkage to care [167, 168] would be beneficial in wards where increasing proportions of ART initiation was a strong predictor of high viral load suppression. Therefore, identifying challenges such as lack of client and clinic readiness, that hinder same-day initiation and address them to reduce interruptions in ART initiation is important [103]. Various differentiated service delivery models from individual to group-based care and facility to community-based health delivery systems have the potential of streamlining retention efforts reducing treatment interruptions [71, 182]. Interruptions at an individual level are likely to introduce resistance and the recent introduction of dolutegravir, an integrase strand-transfer inhibitor is likely to increase overall virological suppression rates [169]. However, more needs to be done to alleviate concerns regarding management of viremia and other side effects associated with the use of dolutegravir. In the wards where increasing ART initiation was not a strong predictor, strengthened retention strategies are recommended. Proper follow-up of PLHIV, monitoring

and evaluation data is needed to identify patients defaulting from care. Tracing, referral, and tracking programmes are therefore required to maintain retention in HIV care.

7.5. Strengths and limitations

This study combined two rapidly increasing statistical techniques: OLS, GWR approaches and forecasting through the time-series approach to make predictions related to HIV programmes in Ekurhuleni. Interpretation of these findings should be done with caution in consideration of study limitations. Firstly, forecast accuracy may have been affected by unmeasured confounders. Further work that involves more covariates is suggested to improve accuracy. Secondly, our model may not be generalizable to other settings but may be representative of other high priority districts. Lastly, routine data maybe incomplete with missing laboratory results of viral load counts and lacked sufficient data time points obtained after implementation of universal test and treat. Nevertheless, using forecasting, we predicted the viral load suppression in Ekurhuleni between 2017 and 2021.

7.6. Summary of chapter

This PhD research work has implications for applying data analytics for healthcare data. The findings support the use of prediction modelling and forecasting techniques as useful methods that can be leveraged in eliminating HIV in Ekurhuleni. Expanding ART coverage and improving the quality of HIV care in women living with HIV at a ward level is likely to increase viral load suppression rates in some wards in EMM. On the other hand finding men to link to and retain in HIV care will increase viral load suppression in those wards where the relationship between VLS and an increase in the proportion of women was weak .

8. CHAPTER EIGHT: DISCUSSION AND POLICY IMPLICATIONS

8.1. Introduction

A meta-inference through the process of integration and triangulation was made to confirm or dispute quantitative findings with qualitative findings. Conclusions after a deeper understanding of the findings were made. Policy implications were inferred from these findings.

8.2. Key findings

Understanding the variations in HIV prevalence and uptake of the available HIV services is the first step for optimum implementation of targeted HIV programs at a district level. Targeting focus through the identification and addressing of gaps in the HIV cascade of care for optimal engagement in HIV care at facility, ward or community level is necessary to achieve 90-90-90 targets. This PhD study sought to identify the context-specific factors that hinder or optimal uptake of HIV services at a clinic-level and explored how accounting for space and time plays a role in evaluating HIV programmes in at a district level. The key findings are discussed in detail in the following sub-sections.

8.2.1. Heterogenous factors for sub-optimal uptake of available HIV services

Findings from conducting geospatial analysis of 1 189 participants sampled from 33 wards in Ekurhuleni showed variations in ART initiation and male condom use which existed in 2012. Wards in Springs, Thokoza, Germiston, Edenvale, Daveyton, Kwa Thema and Tembisa areas showed low proportions of PLHIV initiating on ART. Sub-optimal male condom use was associated with an increasing age. It appears that the older people get, the more likely they are to form stable sexual relationships, start families and therefore inconsistently use condoms.

Since these findings showed that males were less likely to inconsistently use condoms than women in Ekurhuleni, it is important to understand some of the reasons behind this. Studies have revealed that young men have showed positive attitudes and expressed acceptance in using condoms as a HIV prevention tool with new and casual partners. However, condom use

becomes inconsistent as the relationship matures increasing their HIV risk [204]. Multiple factors affect condom use in women increasing their HIV risk. The disproportionate distribution of female compared to male condoms in many public places, inability to use the female condom, and traditional gender norms and imbalanced power between men and women [157, 158, 204]. A systematic review of multiple studies across SSA which highlighted the limitations women faced when making decisions to mitigate their HIV risk [205]. A lower relationship power meant choosing relationship maintenance with their intimate partners over their sexual health. The qualitative findings revealed that perceptions of marital infidelity from intimate partners and promiscuity from the community prevented women from accessing condoms for HIV prevention in low uptake areas as women will more likely comply for unprotected sexual intercourse to avoid violence [206, 207]. Gender discrimination in the context of violence, poverty and insecurity continues to heighten HIV risk and block access to services for women [42, 208]. At clinic-level, although this PhD study found that healthcare workers provided counselling to intimate partners on using condoms to reduce HIV risk, this is not followed through. This finding was consistent with a study that showed women in long-term relationships viewed non-condom use as proof of commitment to male partners [41]. This verifies the unbalanced gendered power dynamics women face when trying to negotiate condom use [41]. A meta-analysis showed that increased condom use frequency among intimate sexual partners is likely improved through communication [209].

Findings also showed that at the time of the survey, being married was a risk factor for non-ART use. Marriage is considered a proxy for social support. However, from the qualitative findings across all settings, most of the PLHIV in stable relationships did not mention any encouragement from partners in adherence to ART. Many of them were aware of the benefits of having a suppressed viral load such as weight gain, longevity, and good pregnancy outcomes. Therefore, findings from this PhD study contradicted what has been widely reported about marriage and its positive influence on engagement in care. Nevertheless, strengthening partner counselling in HIV treatment programmes is important.

Since students in this PhD study were more likely to acquire HIV in Ekurhuleni, it is important to identify barriers that lead to sub-optimal uptake of HIV services. Young people undergo various psychological and behavioural changes that put them at risk for HIV infection [210, 211]. Globally, several studies globally have highlighted barriers to engagement in care to include having to attend a clinic during school hours, fear of disclosure to others, social isolation, and conflict with clinical staff [212, 213]. As the HIV prevention model shifts to

treatment-as-prevention strategies, identifying drivers that promote adherence to and retention in care to antiretroviral regimens among HIV-positive young people is necessary [213]. High self-efficacy of HIV prevention services such as condom use is often associated with those with secondary school education, and it is assumed that with this level of education, knowledge of HIV transmission and prevention is high [214, 215]. A study conducted in Kwa Zulu Natal, South Africa among university students reported low condom use and a lack of confidence in using condoms at sexual debut due to poor negotiation with a partner and were likely to form negative attitudes about condom use [216]. Expanding existing HIV treatment and prevention programmes in communities and educational facilities to include youth-centred interventions through innovative technologically driven platforms is recommended. Qualitative findings revealed the improper storage of condoms may decrease their quality and increase breaks during intercourse heightening HIV risk. Because of this perception that the quality provided by the government is poor, uptake becomes low. In many poor settings, there is shared spaces and very limited private places to store condoms or HIV prevention or treatment medicines. Young men and women will walk around with condoms in their pockets, which are not ideal storage places. Healthcare workers, provide education on the storage of condoms to prevent deterioration of quality but acknowledging that this may be impossible in poor households where privacy is not guaranteed is important. Distribution of condoms that can withstand non-ideal storage conditions may be the best alternative to people living in poor communities.

8.2.2. Intersectional stigma: Identifying and addressing stigma to improving the delivery and uptake of HIV services

Findings from reviewing interview transcripts of patients and healthcare workers revealed on-going HIV-related stigma in Ekurhuleni. The social stigma around women when seeking condoms is concerning because the perception of promiscuity is a major barrier to utilize this HIV prevention method in South Africa [217]. Due to victimisation from community or fear of abandonment and intimate partner violence, women were unlikely to use condoms as a HIV prevention method [41, 42]. Providing discreet options such as PEP or PrEP could significantly facilitate uptake of these services. Findings from this study revealed PrEP demand among HIV negative participants. Similar to condom use, addressing misconceptions towards PrEP use is needed to curb stigma from intimate sexual partners and community. While offering these alternatives, healthcare workers require training to avoid perpetuating prejudice associated with one's choice of PrEP over condom use. Such training should encourage healthcare

workers to view PrEP as an aid that allows control over one's sexual health rather than encourage reckless sexual behaviour [181]. At a facility level, integration of HIV services into existing programs can address the negative sequalae and reduce stigma. At a community level, sensitization efforts by community healthcare or peer workers are likely to improve uptake of these integrated services [187, 188].

Stigma associated with breach of confidentiality, prejudiced attitudes, or lack of privacy from living closer to a healthcare facility prompted patients to seek HIV healthcare from far away PHCs and also provide incorrect physical addresses. The qualitative work further showed decanting programmes introduced at facility-level have addressed stigma that would be associated with patients visiting clinics to pick up their ART. LGBTQ-friendly staff encouraged engagement in HIV care for HIV-positive MSMs through respectful and private interactions at facility-level. Findings also revealed that young HIV-positive patients are likely to miss doses of ART during visits with friends and extended family. It is important to find ways where young people continuously adhere to ART whether they are in the company of people who provide social support or not.

8.2.3. Variations in viral load suppression pre-and post- UTT

Our analysis identified geographic variations in viral load suppression rates in Ekurhuleni over space and time. Over a five-year period (2012-2016), low rates of viral load suppression were observed in Thokoza, Brakpan and Kwa Thema. In addition to this variation, clusters of low viral load suppression were identified. These areas were close together implying that low viral load suppression rates was not random. For such poor performing wards, adjacent to each other, strengthening tracing programmes which track patients who do not link to care or default on ART requires collaboration. Facilities serving communities in Thokoza, Langaville and Brakpan need to intensify efforts to ensure that PLHIV are linked to and retained in care to achieve viral load suppression.

Between 2012 and 2015, the proportion reporting viral load suppression in Ekurhuleni steadily increased significantly. However, in 2016 a decrease as reported. In September of the same year, a national roll-out of UTT was conducted, and the reported proportion of viral load suppression decreased from about 63% to 54%. This could have been attributed by the increased number of newly initiated PLHIV who would need to wait for at least six months for

their first viral load test. The forecasting of viral load suppression (1 000 copies/mL) post-2016 showed that the proportion of viral load suppression by Q1 2017 which aligns with the first viral load post ART initiation increased to above 65%. However, reported viral load suppression (<400 copies/mL) decreased to less than 40% in the same year. A modelling study conducted in 2018 reported viral load suppression rates of 77% in Ekurhuleni[71], implying an increase in the number of stable ART patients triggered by successful HIV treatment programmes.

8.2.4. Sustaining ART coverage to achieve viral load suppression

Findings from this PhD have highlighted sustained ART coverage as a predictor for high viral load suppression. The estimated ART initiation rate in Ekurhuleni from DHIS has increased from 32.2% in 2012 to 81.2% in 2016. By 2018, a modelling study reported about 60% of PLHIV in Ekurhuleni initiated ART [71]. Qualitative findings revealed social support from family as one of the facilitators for ART adherence. This implies that over an 8-year period, there have been massive strides at a community and facility level to increase partner engagement in HIV programmes. For women living with HIV of childbearing age, the greatest motivation to initiate and retain on ART was for the positive pregnancy outcome of having a HIV-negative child [73]. Extensive effective messaging and proper education in PMTCT programmes in Ekurhuleni may have contributed to this. This result is further corroborated by findings from three high HIV burden South African districts which showed that ART initiation rates in pregnant women were higher compared to men and non-pregnant women [177]. In contrast, Ng'eno *et al* (2020) systematic review highlighted delayed entry in antenatal HIV care as a common reason for the adverse pregnant outcomes experienced by young women [84]. Sustained ART coverage in the UTT era comprises of regularly testing for HIV and of those testing positive, immediate initiation of ART. From September 2016, implementation of test and treat strategies was rolled-out nationally [2] with efforts to reach the third 90 of the UNAIDS 90-90-90. Facilities in Ekurhuleni are currently reporting ART coverage of 72% [71] and improvements are needed to reach the current 95% target. Services such as same-day initiations and differentiated delivery of care are to be consistently provided [167, 168]. Reducing interruptions in ART initiation and retention increases the proportion of those on treatment and subsequently reduces incident HIV cases [71]. Interruptions are likely to introduce resistance and the introduction of the integrase strand-transfer inhibitor dolutegravir, may increase overall virological suppression rates [169]. However, more needs to be done to alleviate concerns regarding management of viremia and other side effects. Proper education of UTT is one approach that may reduce interruptions and delayed initiation. This PhD's qualitative findings

revealed that patients attending routine visits did not have adequate knowledge on UTT. The counselling provided before and after HIV testing was not comprehensive enough to inform the patient. Although, at the time of this study, newly diagnosed patients were immediately initiated on ART. The post-linkage to care home-based and community-based services provided by the ward-based outreach teams need strengthening. Side-effects such as drowsiness were widely mentioned particularly at the beginning ART. Support from healthcare workers motivated PLHIV to remain in care to suppress their viral load for health reasons despite experiencing side effects [218]. This will be needed more as more PLHIV are switched to dolutegravir, which is known to contribute to weight gain [219, 220]. Integrated HIV and weight management or nutrition programmes at the facility level need to be considered with introduction of dolutegravir.

8.2.5. Finding missing women and men at a community level for sustained engagement in care

Findings from this PhD work showed that the viral load suppression at ward level decreased as the population of women increased without adjusting for spatial and random effects. Slightly above half (51%) of the South African population is female and in Ekurhuleni, women make 49% of the population, according to the latest 2020 mid-year census estimates [221]. Although the incident HIV cases are reducing, adolescent girls, young women and women are disproportionately affected by HIV and accounted for 59% of all new infections in 2018 [208]. Several barriers such as lack of social support hinder girls and young women from engaging in HIV care [208]. Moreover, studies in South Africa have shown that most HIV-positive pregnant women are likely to delay entry into HIV care in the first trimester and drop out of HIV care during the third semester therefor, reporting poor viral load suppression [171, 202]. Although these findings were not confirmed in this PhD study, it underscores the importance of strengthening early antenatal care, ART initiation and adherence among pregnant women.

Conversely, findings also showed that when space and random effects are taken into consideration, viral load suppression increased as the proportion of women at ward-level increased. This finding makes a case for finding missing men and encourage engagement in HIV care. Without interventions targeting this population, the district will fail to achieve its 95-95-95 targets. HIV programmes in addition to focusing on women who mostly access clinics compared to males, should find the missing men who disengage from health seeking [222]. Male-friendly HIV services in healthcare facilities is important to ensure that those living with

HIV are retained in care. Qualitative findings revealed that knowledge of UTT is inadequate across all geographical settings. At facility level, HCWs must ensure that good quality information is provided during counselling sessions. In the community, peer educators should be adequately trained to provide correct information on UTT and its importance.

8.3. Strengths and limitations

The strength of an explanatory sequential mixed-method study is that the findings obtained from the qualitative study informed and enrich the understanding of the uptake and delivery of HIV services at a patient and provider level. The qualitative sub-study employed the SCT whose constructs amplified the experiences of the patients as they engaged in care in a heterogenous setting.

Despite using secondary quantitative data, non-traditional regression techniques that accounted for multilevel factors and heterogeneity provided accurate estimates and revealed areas where focus for impact should be directed.

Interpretation of findings of this PhD should be done with caution considering the inherent limitations for ecological studies. Ecological fallacy does not support inferences on associations with individual from aggregated data. Despite this limitation, findings from this PhD study can generate interesting hypothesis for further work as described in section 8.2. The use of secondary datasets presented various problems including researcher bias which was difficult to mitigate. The HSRC dataset may have underestimated HIV prevalence due to the inability to fully link the 2001 census enumeration areas data with what was as not all wards were sampled during the survey in 2012. The routinely collected data was incomplete with missing laboratory results of viral load counts that may have originated from lack of adequate capturing and lacked sufficient data time points obtained after implementation of universal test and treat. The use of data from patients who are in HIV care excluded data from those who do not frequently attend clinic visits or pharmacy pickups.

As the study was conducted in a frequently researched setting, it is my belief that participants may have increased exposure to HIV information and health services. However, during these IDIs participants narration of real experiences while seeking HIV care it emerged that these findings were comparable to other qualitative data collected in other settings examining the same topics validating my findings and further attenuating this concern. The final limitation was the lack of access to some selected facilities as a result of COVID-19 restrictions. Due to closure of clinics after reports of possible COVID-19 exposure, permission to conduct non-

essential activities such as research was denied. However, I believe that the findings reflect the delivery and uptake of HIV services in a heterogeneous setting.

The qualitative IDIs were conducted between four and eight years after the quantitative data was collected. This is likely to have a bearing on the findings which could be irrelevant in explaining the current behaviours and choices in the uptake and delivery of HIV services. However, extensive literature review highlighted the areas with similar findings.

8.4. Methodological aspects to improve understanding of HIV dynamics at a local scale

Population surveys are an effective and reliable tool to collect data on different risk factors health outcomes, but their use to understand small area variation in such risk factors is limited [223]. There is growing demand for reliable small area statistics but sample sizes are usually too small to provide direct estimators with acceptable accuracy. More often, it is necessary to borrow strength from related areas through linking models based on auxiliary data such as recent census and administrative records. This leads to indirect estimators. Therefore, specialized knowledge and skills to conduct robust analyses, correctly interpret the results and translation into public health policies is required [224].

In addition to Bayesian models which have provided more stable estimates of disease patterns by smoothing underlying risk estimates across small areas, mixed-level study designs are needed to allow linkage of individual-level survey/cohort with small-area data [225]. This provides a better understanding of the associations between risk factors/exposures and health outcomes by overcoming confounding from ecological bias [226]. Recent work has included the imputation of missing information form large datasets that may lack full spatial coverage [227, 228]. The imputed data is then used in an ecological regression linking risk factors to health outcomes with the potential to reduce bias [227, 228]. Caution is needed in the implementation and interpretation of such models.

In the non-communicable diseases field, hybrid models have been used in small area epidemiological studies to allow for the modelling of previously understudied environmental exposures where the temporal resolution of exposure estimates are extrapolated at different levels while maintaining spatial granularity [229, 230]. These hybrid models could be adapted for use in the HIV field, particularly investigating HIV transmission.

Spatial data mining methods have been used to search for patterns in large health datasets such as cancer mortality using study census data in Mexico [231]. Such methods can be applied to NHLS and DHIS datasets in South Africa to identify emerging patterns in HIV outcomes. Applying spatial data mining techniques to analyse health outcomes associated with a common exposure may help validate previously reported associations and identify new combinations of health effects [231].

Introducing tools in routine surveillance such as *BaySTDetect* for the early detection of spatio-temporal signals that prompt the further investigation is needed [232]. The *BaySTDetect* tool includes a mixture of models that distinguish between areas with unusual temporal trends from those following a common trend [232]. This may be useful in identifying HIV drug resistant patterns that warrant further investigations.

Lastly, while introducing these innovative techniques for small area analysis, strict information governance and data security is important due to available personal identifiable information in these large datasets [224]. Dissemination of study findings needs careful attention by masking values or aggregating data to a avoid inadvertent disclosure.

8.5. Remaining gaps from the study for future research direction

Improving access to PrEP in wards with high HIV prevalence, but low uptake of services is recommended. The findings showed that the population in wards with increased likelihood of HIV infection was young, mostly female, and high unemployment levels. There is also presence of key populations at risk for HIV including FSW, IDUs and MSMs. Extensive PrEP options awareness and enhanced PrEP programmes is suggested to meet the demand. This study has also demonstrated the feasibility of using readily available programmatic data for program planning, without expensive research studies. A model for similar studies in other settings, which can potentially have a high impact on the HIV epidemic.

High viral load suppression rates were positively correlated by increasing ART coverage and being female. When the threshold of <400 copies/mL was applied, the viral load suppression declined by 15%. This highlights the gaps in monitoring, treatment, and availability of more effective ART drugs. Furthermore, HIV programmes in addition to focusing on women who mostly access clinics compared to men, should find the missing men who disengage from health seeking [222].

Despite roll-out of UTT, a recent study assessing district level targets for 90-90-90 in 2018, showed that viral load suppression in Ekurhuleni was still low at 41.3% [71]. This highlights the need to improve viral load monitoring in EMM as these recent estimates predict viral load suppression to 86% by 2030 [71]. The inclusion of the ITS showed the initial impact a new intervention has as it is initially rolled out. However, there is an opportunity to evaluate the impact of UTT as more robust data is collected in Ekurhuleni. In the era of UTT, more nuanced approaches are required to identify at a clinic and laboratory level, patients at risk for poor adherence. A clinic- level prediction score developed using routinely collected data showed better performance in correctly identifying patients with poor adherence outcome at 6 months post ART initiation [233]. Applying this an improved version of this score to patients will subsequently show who requires individualized treatment to prevent virologic failure as has been observed in developed countries [234, 235].

The spatio-temporal maps have shown areas with clusters of high and low viral load suppression in EMM over a five-year period (2012-2016). Moreover, these maps have highlighted the temporal changes in the predictors associated with high viral load suppression. Future work will involve utilizing such granular maps as a basis for targeted resource allocation. More importantly, maps showing the completeness of viral load data by determining the proportion of PLHIV with or without a viral load result at district level over time will be useful.

Our study did not include pregnant adolescents living with HIV and therefore, future studies including this population investigating the promotion of engagement in HIV care are needed. HIV-related stigma will continue reducing engagement in HIV care and stigma-reduction programmes which include increasing knowledge and encouraging adequate support network may be key to successful HIV prevention or treatment programs in Ekurhuleni. In areas with low uptake of HIV services, evaluating interventions targeting health system barriers including confidentiality concerns, stigma and staff shortage are needed.

The few variables available for selection in the predictive value of the model affected the accuracy and the model would be greatly improved by adding other factors including related information from the health system level and other clinical factors such as drug resistance. Forecast accuracy may have been affected by unmeasured confounders. Further work that includes more covariates is suggested to improve accuracy of findings.

8.6. Policy implications from PhD findings

Findings from the GWR are important for decision makers to use to better target programmes that are likely to have the biggest impact. Suppose HIV programme managers decide to increase the proportion of viral load suppression at ward level, strengthening the existing programmes will entail the following.

1. In areas where a high proportion of females is a strong predictor of high viral load suppression, programme managers need to find missing women and link them to care. Afterwards employ innovative retention strategies to monitor viral load. Antenatal programmes should ensure that pregnant women living with HIV are timeously engaged in PMTCT programmes for favourable pregnancy outcomes.
2. In areas where high proportion of females is not a strong predictor, the focus should be on finding missing men and encouraging linkage to and retention in care. Addressing known barriers to health seeking in this population is encouraged.
3. In areas where high ART initiation rates are strong predictors of high viral load suppression, strategies to increase HIV testing are needed, afterwards same-day ART initiation at any healthcare facilities including tertiary must be considered. In case ART initiation is not conducted at tertiary levels, improving down-referral to primary healthcare facilities is important. Addressing stigma related with HIV testing is an important strategy to increase ART initiation in these areas.
4. In areas where high ART initiation rates are not strong predictors of high viral load suppression, focus on retention in care is important. Differentiated care models for stable PLHIV require monitoring and evaluation to prevent attrition. Pharmacovigilance of effective drugs such as dolutegravir should be strengthened to manage unfavourable adverse events such as weight gain. Integration of weight management in HIV programmes is worth considering.

8.7. Conclusions

Successful implementation of HIV programmes in Ekurhuleni will require evidence-based targeted interventions to maximize the available human and financial resources for focused impact. This study confirms what is already known about the heterogeneity of HIV prevalence in South Africa. It has highlighted the heterogeneity of HIV prevalence and coverage or uptake of HIV services that occurs at lower administrative levels. This PhD thesis has highlighted the

important consideration to enable evidence-based targeted interventions to optimize HIV programmes in heterogenous settings, thus improving the uptake along the HIV care cascade.

Understanding the local epidemiology using available routinely collected data is the first step. Next is identifying geographical patterns by revealing the underlying heterogeneities in HIV prevalence, uptake/coverage of HIV prevention and treatment services. Lastly is to identify the risk factors for poor outcomes while adjusting for ward-level and spatial effects. The risk of HIV infection was greater in young school-going people and this finding was not homogenously seen across the wards. Although consistent condom use was protective against HIV infection, condom uptake was sub-optimal in the study area, particularly among women. For men consistent condom use was reported uniformly across the wards. Implementers, therefore, need to address context-specific differences to equitably increase access and uptake of available HIV services. From the findings, strengthening of condom distribution programmes is recommended. In instances where social stigma prevents access to condoms, discreet alternatives such as oral, injectables and recently introduced vaginal rings PrEP can be provided. Counselling and education of the use and delivery of PrEP at a facility level is important. Condom use was mostly observed in men. The most commonly mentioned barrier was the quality of government-provided condoms which tear easily thereby, reducing their effectiveness. Education on proper use and storage of condoms to maintain its quality is required for the end-user and distribution of superior quality condoms in communities is encouraged. In addition to this education, understanding that storage of condoms in poor households without privacy and storage space may be challenging. An alternative approach is for manufacturers of latex condoms to consider a more durable product that can withstand non-ideal conditions for this market.

In Ekurhuleni, most women understood the importance of ART use in the prevention of mother to child transmission. Despite this, findings also showed low levels of ART use in Ekurhuleni mostly by married individuals. Programmes on strengthening partner counselling programmes are required to ensure that couples remain on sustained ART for improved viral load suppression. The main predictors for viral load suppression in Ekurhuleni was increasing ART coverage. Ensuring that the ART coverage reaches 95% will take concerted efforts to identify and track patients at risk of defaulting and lost to follow-up and individualize their treatment. Although at an individual-level, women have better viral load suppression than men, this PhD showed that in Ekurhuleni, at a population-level, the higher the proportion of women in a ward, the lower the viral load suppression rates. This finding emphasizes the need to provide quality HIV care for women. It has been shown that pregnant women have poor viral load suppression

and early entry into antenatal care programmes at a ward level is important. This PhD identified areas such as Thokoza, Langaville and Brakpan where intensified efforts are needed to ensure that PLHIV are retained in care to achieve viral load suppression.

Finally, findings from the forecast showed that if the current status quo prevails, Ekurhuleni will not achieve the 95% target for viral load suppression. Increasing sustained ART coverage at ward level and expanding the quality of HIV care for women living with HIV, is likely to increase the viral load suppression. This means that PLHIV with undetectable viral loads are unable to transmit the HIV virus and in the long-term reduce cases of incident HIV cases. Structural interventions such as ART delivery through differentiated care models should be regularly monitored and evaluated. Therefore, constant monitoring and evaluation will be needed to plan for further improvements in implementation of integrated health programmes in areas of sub-optimal uptake and delivery.

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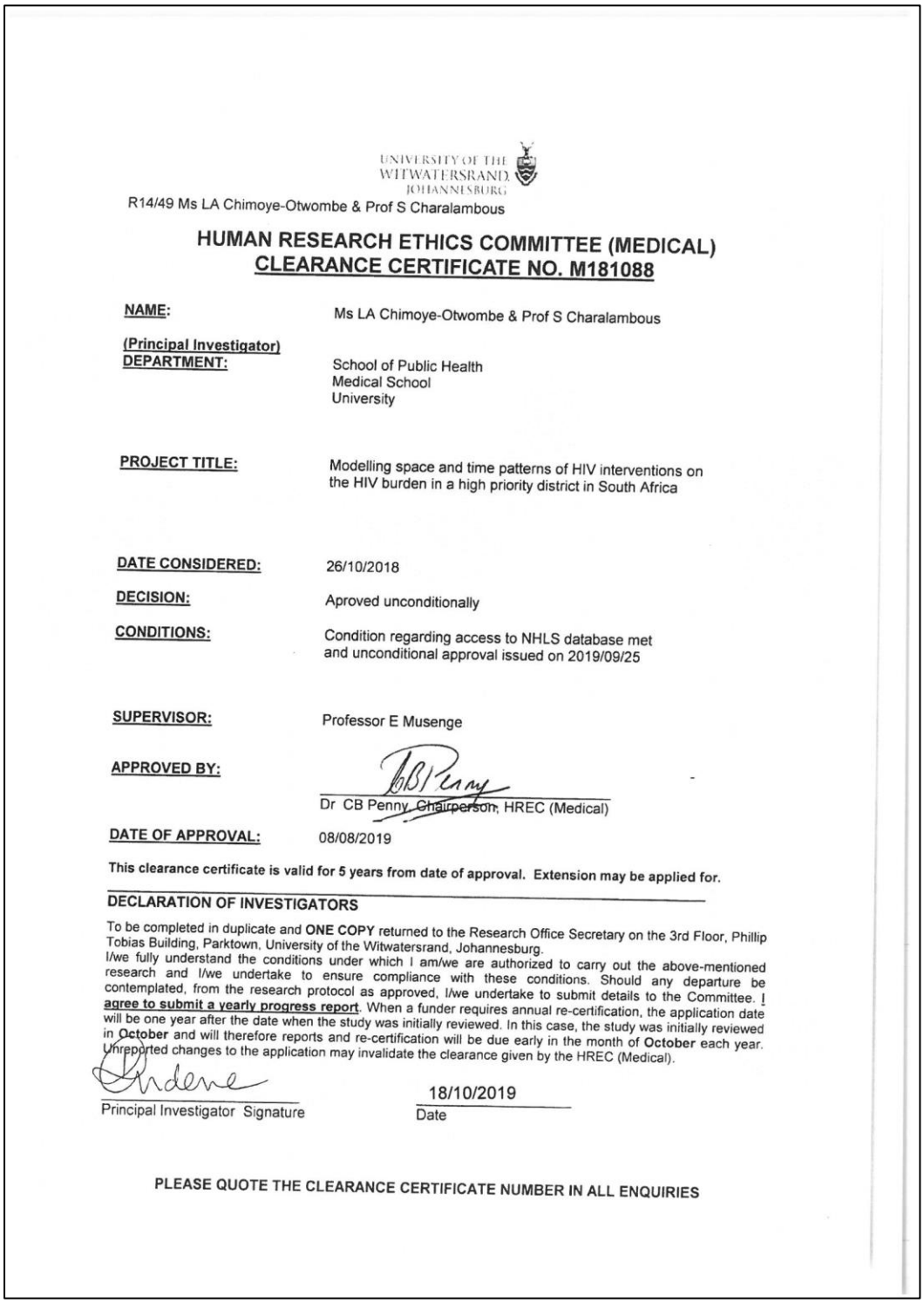
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10. APPENDICES

Appendix A: Ethics approval – Wits HREC



UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Ms LA Chimoye-Otwombe & Prof S Charalambous

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M181088

NAME: (Principal Investigator)	Ms LA Chimoye-Otwombe & Prof S Charalambous
DEPARTMENT:	School of Public Health Medical School University
PROJECT TITLE:	Modelling space and time patterns of HIV interventions on the HIV burden in a high priority district in South Africa
DATE CONSIDERED:	26/10/2018
DECISION:	Aproved unconditionally
CONDITIONS:	Condition regarding access to NHLS database met and unconditional approval issued on 2019/09/25
SUPERVISOR:	Professor E Musenge
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	08/08/2019

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 on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
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 submit details to the Committee. I **agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore reports and re-certification will be due early in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature — Date: 18/10/2019

PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix B: Ethics approval- NHLS CDW

NATIONAL HEALTH LABORATORY SERVICE

Academic Affairs and Research
Modderfontein Road, Sandringham, 2031
Tel: +27 (0)11 386 6142
Fax: +27 (0)11 386 6296
Email: babatyi.kgokong@nhls.ac.za
Web: www.nhls.ac.za

08 November 2019

Applicant: Lucy Chimoyi-Otwombe
Institution: Aurum Institute
Department: School of Public Health
Email: lchimoyi@auruminstitute.org
Tel: 010 590 1360

CC: Tendesayi Chakezha
HIV Epidemiologist
NHLS / NICD

Re: Approval to access National Health Laboratory Service (NHLS) Data

Your application to undertake a research project **"Modelling space and time patterns of HIV interventions on HIV burden in high priority districts in South Africa"** using data from the NHLS database has been reviewed. This letter serves to advise that the application has been approved and the required data will be made available to you ***without patient names*** to conduct the proposed study as outlined in the submitted application. Submissions should be made annually on the AARMS system – https://aarms.nhls.ac.za.

Please note that approval is granted on your compliance with the NHLS conditions of service and that the study can only be undertaken provided that the following conditions have been met.

- Processes are discussed with the relevant NHLS departments (i.e. Information Management Unit and Operations Office) and are agreed upon.
- Confidentiality is maintained at participant and institutional level and there is no disclosure of personal information or confidential information as described by the NHLS policy.
- NHLS Data cannot be used to track patients as no pre-approval/consent is obtained from Patients.
- CDW form is to be completed for the request with clear indications of the data required.
- All data requested should be in accordance with the research protocol submitted and approved by the relevant Ethics Committee.
- Request for the inclusion of the NHLS as a source of data in the original protocol to be approved by Ethics as NHLS does not have a Human Research Ethics Committee.
- A final report of the research study and any published paper resulting from this study are submitted and addressed to the NHLS Academic Affairs and Research office and the NHLS has been acknowledged appropriately.
- Tendesayi Chakezha is noted as NHLS collaborator for this research.

Please note that this letter constitutes approval by the NHLS Academic Affairs and Research Office. Any data related queries may be directed to NHLS Corporate Data Warehouse, contact number: 011 386 6074 email: zarina.sabat@nhls.ac.za

Dr Babatyi Malope-Kgokong
National Manager: Academic Affairs and Research

NATIONAL HEALTH LABORATORY SERVICE HELPDESK

Tel: (011) 386-6125/6/7/9 Fax: (011) 386-6308 email: helpdesk.1@nhls.ac.za

APPLICATION FOR DATA FROM NHLS INFORMATION SYSTEMS (Q-Pulse FMI0069)

Each application will be approved or rejected subject to the ability to extract this data and the availability of the data, and subject to the intended usage of the requested data. Applications that are incomplete and/or do not contain supporting documentation, will be rejected.

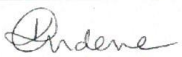
APPLICANT'S DETAILS

Applicant Name	Lucy Chimoyi - Otwombe	**Tel No**	(010)5901360	**Email**	LChimoyi@auruminstitute.org
Business Role / Designation			Senior Research Manager PhD Student (Public Health)		
Laboratory / Department / Branch / Region (Internal applicants)			Not Applicable		
Organisation (External applicants)			The Aurum Institute University of the Witwatersrand		
Supervisor Name	Prof Eustasius Musenge Prof Salome Charalambous	**Tel No**	(011) 798 1356 (010) 590 1389	**Email**	Eustasius.Musenge@wits.ac.za SCharalambous@auruminstitute.org
Supervisor Designation	**Associate Professor of Biostatistics (Prof Musenge)** **Deputy Chief Scientific Officer (Prof Charalambous)**				

CONDITIONS

- **Data / Information is not to be used in contravention of Sections 14, 15, 16 and 17 of the National Health Act 61 of 2004 and the Promotions of Access to information Act 2 of 2000.**
- **The applicant undertakes to ensure that the data supplied to it by the NHLS is used ethically and solely for the purposes for which it is provided as detailed in this application, and further acknowledges that it shall remain liable for any breaches of this clause by the end user.**
- **If the purpose for the data requested in this application is research or if patient identity linked data is required, ethics approval and a one-page summary of the protocol shall be attached to this application form. It is the responsibility of the applicant to ensure that their institutions' Human Ethics approval includes explicit authorisation to access the requested NHLS data.**
- **The applicant undertakes to store the NHLS data in a confidential manner by separating patient identifying details from laboratory data and storing the master list that links patient identifying details to study patient identifiers in a separate, secure location.**
- **The information is for the private use of the applicant only, unless further approval is obtained from the NHLS. In the event of this, the applicant shall give due credit, including affiliation, of the participation of the NHLS in any such publications or presentations.**
- **The applicant undertakes to provide the Executive Manager: Academic Affairs, Research and Quality Assurance at the NHLS with a copy of any report, presentation or publication emanating from the use of this data.**

ACCEPTANCE OF CONDITIONS

By signing this document, we accept the conditions stated above.			
Applicant Signature		**Date**	**22/03/2019**
Supervisor Signature		**Date**	**22/03/2019**

In the event of a dispute concerning this document, the electronic version stored on Q-Pulse will be deemed to be the correct version

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Appendix C: Ethics approval- Ekurhuleni District

City of Ekurhuleni

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

EKURHULENI HEALTH DISTRICT
RESEARCH PERMISSION

Research Project Title: : Modelling space and time patterns of HIV interventions on HIV burden in a high priority district in South Africa.

NHRD No: GP_201908_015

Research Project Number: 08/09/2019-03

Name of Researcher(s): Ms Lucy Chimoyi-Otwambe

Division/Institution/Company: University of Witwatersrand

Date of review by the EHDRC: 12 September 2019

DECISION TAKEN BY THE EKURHULENI HEALTH DISTRICT RESEARCH COMMITTEE (EHDRC)

- This document certifies that the above research project has been reviewed by the EHDRC and permission is granted for the researcher(s) to commence with the intended research project.
- Facilities approved for the research: All Ekurhuleni Health District clinics
- Participants' rights and confidentiality must be maintained throughout the study period and when disseminating the findings.
- No resources (financial, material and human resources) from the health facilities will be used for the study. Neither the district nor the health facilities will incur any additional cost for the study.
- The study will comply with Publicly Financed Research and Development Act 2008 (Act 51 of 2008) and its related regulations.

- The EHDRC must be informed in writing before publication or presentation of research findings and a copy of the report/publications/presentation must be submitted to the EHDRC
- The district must be acknowledged in all the reports/publications generated from the research.
- The researcher will be expected to provide the EHDRC with
  - Six monthly progress updates including any adverse events
  - The final study report in electronic format
  - Present the final research findings at the annual Ekurhuleni research conference if possible.
- The EDHRC reserves the right to withdraw the approval, if any of the conditions mentioned above have being breached
- The research committee wishes the researcher(s) the best of success.

DR. J. SEPUYA Jenny

DEPUTY CHAIRPERSON: CITY OF EKURHULENI

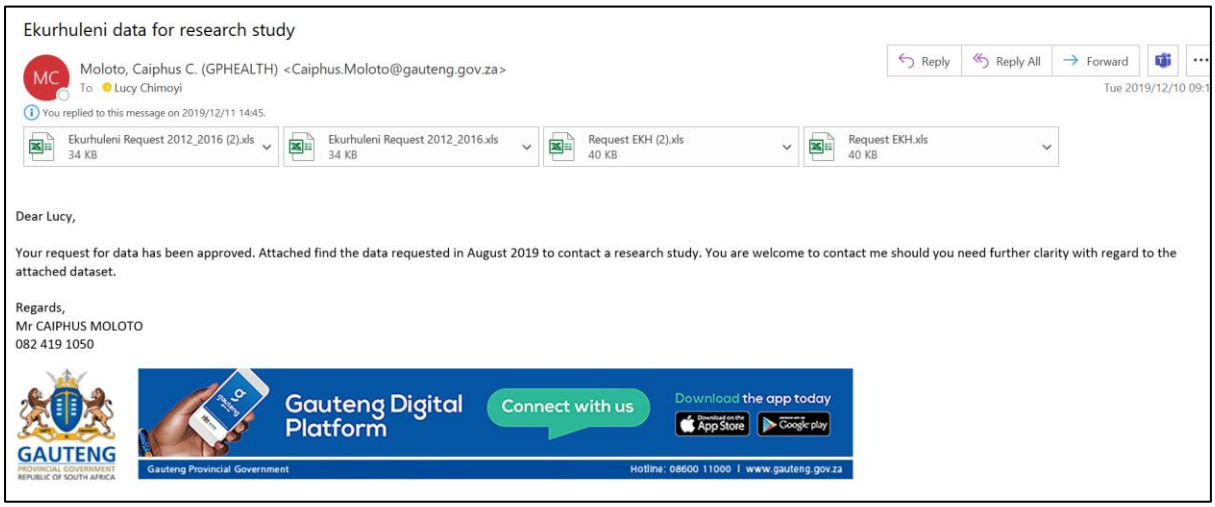
Dated: 12/09/2019.

Dr R Ngwenya

CHAIRPERSON: GAUTENG DEPARTMENT OF HEALTH (EKURHULENI HEALTH DISTRICT)

Dated: 12/09/2019.

Appendix D: Permission to use data from GDoH



Ekurhuleni data for research study

MC Moloto, Caiphus C. (GPHEALTH) <Caiphus.Moloto@gauteng.gov.za>
To Lucy Chimoyi

Reply | Reply All | Forward

Tue 2019/12/10 09:1

You replied to this message on 2019/12/11 14:45.

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Dear Lucy,

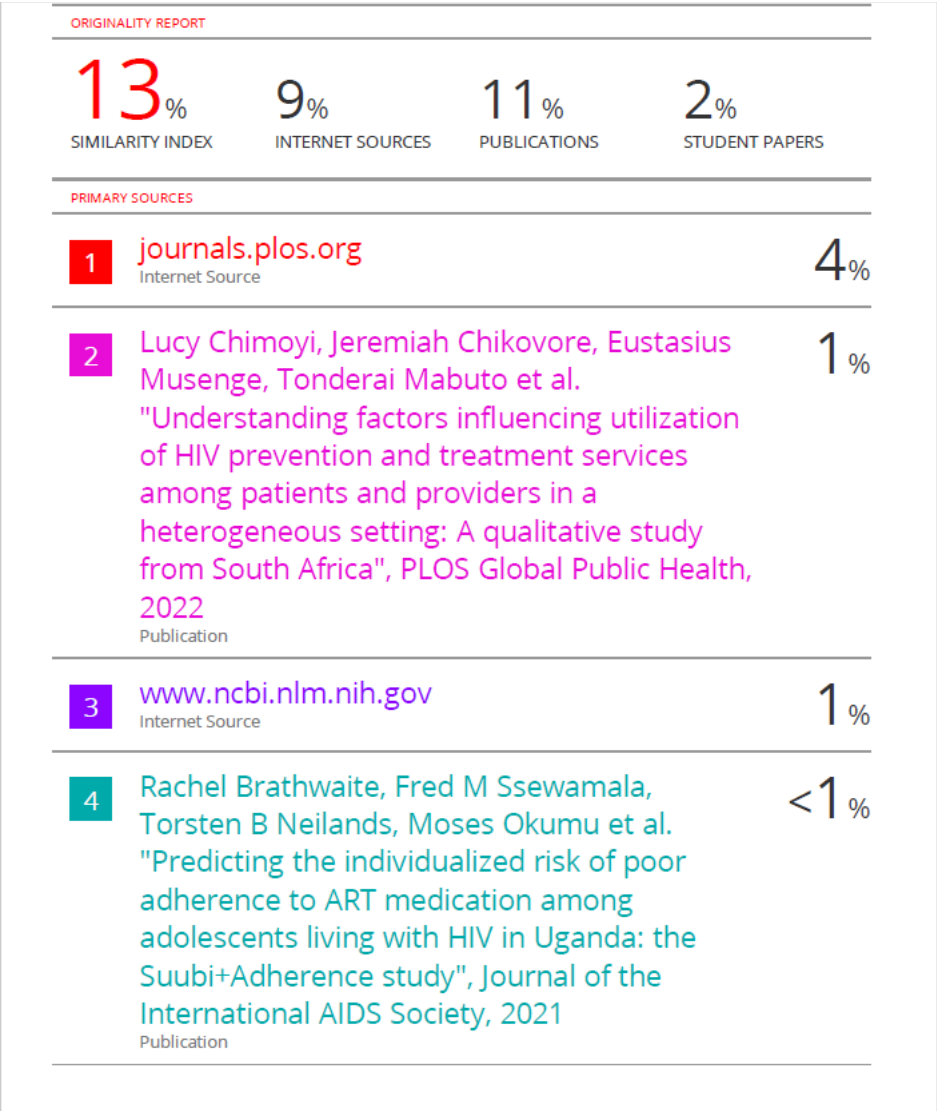
Your request for data has been approved. Attached find the data requested in August 2019 to contact a research study. You are welcome to contact me should you need further clarity with regard to the attached dataset.

Regards,
Mr CAIPHUS MOLOTO
082 419 1050

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Assessing spatial patterns of HIV prevalence and interventions in semi-urban settings in South Africa. Implications for spatially targeted interventions

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Data availability statement: the data presented in this study are available on request from the corresponding author. The data are not publicly available as permission from the gatekeepers is required for access.

See online Supplementary files for additional material.

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Abstract

Equitable allocation of resources targeting the human immunodeficiency virus (HIV) at the local level requires focusing interventions in areas of the greatest need. Understanding the geographical variation in the HIV epidemic and uptake of selected HIV prevention and treatment programmes are necessary to identify such areas. Individual-level HIV data were obtained from a 2012 national HIV survey in South Africa. Spatial regression models on each outcome measure (HIV infection, sub-optimal condom use or non-anti-retroviral treatment (ART) adjusted for spatial random effects at the ward level were fitted using WINBUGS software. In addition, ward-level data was utilized to estimate condom use coverage and ART initiation rates which were obtained from routinely collected data in 2012. Ordinary Kriging was used to produce smoothed maps of HIV infection, condom use coverage and ART initiation rates. HIV infection was associated with individuals undertaking tertiary education [posterior odds ratio (POR): 19.53; 95% credible intervals (CrI): 3.22-84.93]. Sub-optimal condom use increased with age (POR: 1.09; 95%CrI: 1.06-1.11) and was associated with being married (POR: 4.14; 95%CrI: 1.23-4.28). Non-ART use was associated with being married (POR: 6.79; 95%CrI: 1.43-22.43). There were clusters with high HIV infection, sub-optimal condom use, and non-ART use in Ekurhuleni, an urban and semi-urban district in Gauteng province, South Africa. Findings show the need for expanding condom programmes and/or strengthening other HIV prevention programmes such as pre-exposure prophylaxis and encouraging sustained engagement in HIV care and treatment in the identified areas with the greatest need in Ekurhuleni Metropolitan Municipality.

Introduction

Previously, the human immunodeficiency virus (HIV) epidemic in sub-Saharan Africa (SSA) was generalised but more recently, research is showing the presence of concentrated epidemics (Cuadros *et al*., 2013; Ramjee *et al*., 2019; Zulu *et al*., 2014). At the country level, the presence of key populations at higher risk of HIV leads to such concentrated epidemics (Cuadros *et al*., 2017; Cuadros *et al*., 2018). In South Africa, HIV prevalence varies significantly at the sub-national and district levels (Tanser *et al*., 2014) due to complex economic and localised

social, behavioural and cultural factors (Hallman, 2005). Similar to other countries in SSA, South Africa reports substantial numbers of HIV incidence from key populations at high risk including sex workers and their clients, people who inject drugs, men who have sex with men, and inmates in correctional institutions (Coburn *et al*., 2017; Cuadros *et al*., 2017; Tanser *et al*., 2014).

Significant resources are being invested in scaling up prevention and treatment programmes to address these concentrated epidemics (Grabowski *et al*., 2017). Condoms are highly effective in preventing sexual transmission of HIV as long as they are consistently and correctly used (Versteeg and Murray, 2008); they are most effective in high-risk individuals (Coburn *et al*., 2017). Antiretroviral treatment programmes have been scaled up in South Africa to prevent transmission of HIV (Granich *et al*., 2009; Wilson, 2012). Previously, homogenous distribution of such interventions was resource intensive. To improve the efficiency of the limited resource allocation, funding agencies shifted towards optimizing the resources allocated in areas where they are most needed (Boyda *et al*., 2019; Cuadros *et al*., 2017; Cuadros *et al*., 2018; Tanser *et al*., 2014). The implementation of spatially targeted interventions requires identifying areas where the burden of HIV infection is concentrated and utilisation of preventive techniques is low (Boyda *et al*., 2019; Tanser *et al*., 2014). This strategy is challenging due to the scarcity of spatial data caused by the costly implementation of population-based surveys in resource-limited settings. However, this strategy identifies populations at higher risk of infection as well as areas of high and low risk (Aral *et al*., 2015). Having such data on HIV spatial distribution patterns at the local level could help prevent new HIV infections and scale up treatment and prevention by prioritizing the allocation of resources to high-burden areas and aligning service delivery modalities to the needs of the population (Schaefer *et al*., 2017).

In SSA, spatial analysis of health data is gaining traction and has established variations in HIV prevalence, service use and risk factors. Using population-based survey data from demographic health surveys (DHS) spatial clusters and geographical variation at the district-level revealed hotspots of HIV infection in Uganda and revealed non-condom use and non-circumcision as factors driving HIV infection (Chimoyi and Musenge, 2014). Spatial analysis at the district level identified high-risk populations and regions in Malawi where targeted interventions for HIV prevention and treatment programs are needed (Nutor *et al*., 2020). These authors also mapped the spatial distribution of HIV infection at the provincial level which revealed associations of high-risk sexual behaviour with HIV infection in high-burden provinces.

Focusing progress at the sub-national level addresses gaps at the national or provincial levels, which negatively affects resource allocation due to masked local heterogeneities (Cuadros *et al*., 2018). Development of spatial analysis at lower spatial units, such as the ward-level is likely to improve accuracy in health estimates (Manda *et al*., 2020). Spatial epidemiologists have used spatial smoothing and spatial interpolation such as Kriging to improve the estimation of health outcomes and disease burdens by incorporating geographic information systems (GIS) allowing the use of values at observed locations to estimate values at unobserved locations (Manda *et al*., 2020). Spatial cluster techniques at the local level identified patterns of HIV prevalence, high HIV testing and counselling and anti-retroviral treatment (ART) uptake, which improved resource allocation of HIV prevention and treatment interventions in two towns in Zimbabwe (Schaefer *et al*., 2017).

In the absence of costly population-based surveys, clinic-based routinely collected data on HIV services from different health facilities at the ward or sub-district level can be explored (Cuadros *et al*., 2018) and applied to monitor progress and provide scientific evidence to guide targeted resources allocation in areas with the greatest need (Boyda *et al*., 2019). A study in KwaZulu Natal, South Africa illustrated the use of readily available programme data to map the heterogeneity of the HIV epidemic in a hyperendemic setting. The authors demonstrated the feasibility of using these sources to identify areas for the implementation of spatially targeted interventions (Cuadros *et al*., 2018).

The current study combined data from a national survey and routinely collected HIV programme data to identify the heterogeneity of HIV infection, condom use and ART initiation in Ekurhuleni Metropolitan Municipality (EMM), Gauteng Province, South Africa. EMM, a hyperendemic HIV district, is considered a high priority district as it is characterised by a high population and a high HIV prevalence (National Department of Health, 2017). Resources to control HIV have been allocated to the district however, the HIV prevalence remains high at 14% (Magege *et al*., 2009; Simbayi *et al*., 2019). The objective of this study was to understand the underlying geographical patterns of HIV prevalence, condom use coverage and ART initiation rates in EMM using spatial techniques. Further, we sought to understand the drivers of the negative health outcomes (sub-optimal condom use and lack of ART use) in the study area using statistical techniques accounting for spatial random effects.

Materials and methods

Study design and population

This study used national- and local-level data collected in 2012 from adults participating in a national survey and patients attending routine visits in primary health care clinics in EMM, South Africa.

Study area

EMM borders the city of Johannesburg, the city of Tshwane and the Sedibeng District Municipality. The population is over 3 million and its density is 1718 people per km^2 according to the 2011 census. The HIV prevalence in 2012 was 12% and increased to 14% in 2017 (Human Sciences Research Council, 2018; Simbayi *et al*., 2019). EMM is sub-divided into three sub-districts (North, South and East) and 101 wards. There is a district hospital, seven community health centres and 87 primary health clinics. These facilities are staffed by clinical personnel and offer health care services, including HIV prevention and care, with no out-of-pocket payments required from patients. Also, various non-governmental organisations, through support and collaboration with the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) and the U.S. Centres for Disease Control and Prevention (CDC) work in collaboration with the South Africa National Department of Health (NDoH) to increase services such as direct service delivery and health systems strengthening (Gaal *et al*., 2005).

Data sources

Retrospective data for this study were acquired from publicly available datasets. We used two datasets for this study namely: i) the 2012 South African National HIV Prevalence, Incidence and

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Behaviour Survey by the Human Research Sciences Council (HSRC). This was used to acquire data on HIV infection and socio-demographic information in the different sub-districts at a national level; ii) data on the uptake of HIV interventions at the clinic level in EMM was abstracted from the District Health Information System (DHIS) hosted by the NDoH, which routinely collects individual-level data from all South African public health facilities at the local level.

From a database of 86,000 enumeration areas (EAs), 1000 EAs from the 2001 population census stratified by province, locality type and race were randomly selected using probability proportional to size. These EAs were mapped in 2007 using aerial photography to develop the 2007-2011 HSRC primary sample for selecting households. The EAs formed the primary sampling units. Oversampling of smaller strata *e.g.*, racial groups was done to meet the required minimum sample size. In each sampled EA, a total of 15 households were used as secondary sampling units. Within each household selected for the survey, all household members (including consenting and non-consenting household members) constituted the ultimate sampling unit. In Ekurhuleni, 57 EAs over 33 wards were sampled.

Variables

Three outcomes from the national survey were: i) HIV infection, defined as reported HIV positive test; ii) sub-optimal condom use, defined as reporting not consistently using condoms in the past month; and iii) non-ART use, defined as reporting not using ART despite a positive HIV status. Data on the coverage of male condom use and ART initiation rates were provided by Gauteng DoH. The HIV interventions used were abstracted from DHIS (April-December 2012). Aggregated male condom coverage was calculated as the number of condoms distributed by the clinic and other non-medical sites per the number of males ≥15 years of age. The ART initiation rate was calculated by estimating the total number of HIV patients remaining on ART over the estimated number of PLHIV reporting to the clinic at the end of each month. An annual average by ward was calculated based on the HIV prevalence, defined as the proportion of individuals testing HIV-positive over the total population sampled per ward during the survey.

Other measures included socio-demographic (age, gender, and employment status) and high-risk behavioural variables such as number of lifetime sexual partners, age of coital debut and drug use.

Data analysis

The population profile was described using frequencies, percentages, median and interquartile ranges (IQR). A P-value <0.05 was considered significant. Model building was performed in Stata (https://www.stata.com/) through a stepwise binary logistic regression approach and the final model used for Bayesian analysis. The latter was carried out in WinBUGS, version 1.4 (MRC Biostatistics Unit, Cambridge, UK), which included fitting three models: standard, random-effects model and spatial effects logistic regression model that assessed the risk factors for HIV infection, sub-optimal condom use and non-ART and describe the heterogeneity of these outcomes in space. Bayesian methodology, using Markov Chain Monte Carlo (MCMC), estimated the parameters in the three models through 20,000 iterations with burn-in of 1000 iterations. Parameter estimates of each outcome at the ward level from this analysis were used to create interpolated maps in ArcGIS v.10.7.1 (Environmental Systems Research Institute, 2019). Posterior odds ratios (POR) and their corresponding 95% credible intervals (CI) were reported. A significant effect is observed when the CI does not contain 1. A deviance information criterion (DIC) was used to assess model fit and the model with the lowest DIC value was taken to be the best model. In addition, a difference >5 implied no differences in the models (Spiegelhalter *et al*., 2002).

Statistical modelling

Each regression model was fitted using a Bernoulli distribution for binary outcomes. The outcome with respect to HIV infection, sub-optimal condom use and non-ART use (Y_{is}) took values Y_i=1 when an event occurred or 0 otherwise with regard to an individual i residing in ward s= 1,2,…,33. Therefore, Y_{is} follows a Bernoulli distribution with a probability of experiencing an outcome p_{is}, that is, Y_{is}~$Ber(p_{is})$. The probability density function of the outcome variables is $P(Y_{is}) = p_{is}^{Y_{is}}\left(1-p_{is}\right)^{1-Y_{is}}$. Using the generalised linear model for a binary outcome, the probability can be modelled using logistic regression as:

$$\text{logit}(p_{is}) = P(Y_{is}=1|x_i) = \beta_0 + X_i^T\beta_i + G_{is} \quad (1)$$

where β_0 is the intercept terms; β_i the vector of regression coefficients of fixed effects; X_i the vector of subject-level covariates; and G_{is} the spatial random effects corresponding to the binary response of an individual i residing in ward s. Since we assumed that the outcome variables were spatially correlated and the independence assumption in the response variables questionable, we introduced a spatial structure. The spatial random-effects (G_{is}) were decomposed into subject-specific uncorrelated (U_{is}) and spatially correlated random effects; hence, the following convolutional model was fitted:

$$\text{logit}(p_{is}) = \beta_0 + \boldsymbol{X}_i^T\boldsymbol{\beta} + \mathrm{U}_{is} + H_{is} \quad (2)$$

We fitted a fully Bayesian inference approach whereby we assigned priors to all unknown random and fixed parameters and variance parameters (hyperparameters). Parameters of the fixed effects were assigned diffuse priors, $\beta \propto$ constant. The uncorrelated spatial effects U_{is} were assumed to be independent and identically distributed Gaussian priors, that is, $U_{is} \overset{iid}{\sim} N\left(0,\tau_u^2\right)$ where the unknown hyperparameters of the variance components, τ_u^2 was assigned highly dispersed gamma priors $\left(\tau_u \sim G\left(a_{\tau_u},b_{\tau_u}\right)\right)$ with known parameter values a_{τ_u}=b_{τ_u}=0.01. The structured spatial wards (S=33) modelled in this study were assumed to follow a conditional autoregressive (CAR) prior. In the full conditional distribution, each H_{is} is conditional on the sum of the weighted values of its neighbours $\left(w_{js\neq s},H_s\right)$ and has an unknown variance, which is:

$$H_j \mid H_k, j \neq k, \sim N\left(\sum_{j=1}^{n} W_{js}H_s, \tau_k\right) \quad (3)$$

where W is an $S\times S$ adjacency weighting matrix that defines the relationship of $S\times S$ areal units (wards). For two adjacency neighbour ward polygons, j–k, $j\neq k$ the W matrix entries take values 1 if

the wards are neighbours or otherwise 0. In the CAR model, the neighbour relationship is symmetric but not reflective and a ward/polygon cannot be its neighbour. The hyperprior for the variance parameter was assumed to follow an inverse Gamma distribution, $\tau_k \sim G(a_{\tau_k}, b_{\tau_k})$. Since this posterior function had no closed form, we used the Gibbs sampling (Hrycej, 1990) to estimate the posterior parameters or MCMC with Metropolis-Hastings algorithms (Chib and Greenberg, 1995).

The Bayesian models were fitted with 15,000 MCMC iterations, and the prior sensitivity was done by varying parameter values. Model convergency was assessed using trace plots and autocorrelations plots. We used DIC to identify the preferred model among the non-spatial 1, unstructured spatial random effects only, structured spatial random effects only and convolutional models DIC define as seen in Eq. 4:

$$DIC = D(\bar{\theta}) + 2p_D = \bar{D} + p_D \quad (4)$$

where $D(\bar{\theta})$ is the deviance statistic evaluated at $(\bar{\theta})$(which is the posterior means of the parameter of interest); p_D the effective number of parameters in the model; and $\bar{D}$ the posterior mean of the deviance statistic. The lower the DIC, the better the model.

Kriging analysis

Kriging was done to calculate an average value for locations with no data using values from nearby weighted locations and used to predict hotspots of clusters of high HIV infections, sub-optimal condom use coverage and low ART initiation rates (Cressie, 2015). The value of the outcome (z) at a specific location (s_i) is modelled as the sum of the regional mean (m) and a spatially correlated random component ($e(s_i)$) as follows:

$$Z(s_i) = m + e(s_i) \quad (5)$$

Aggregated data were available for 33 wards from the datasets collected. For the wards with no data (X_0), prediction is required to estimate the unknown mean. Each point (X_0) was predicted as the weighted average of the values at all sampled points and the weights assigned to each sampled point summed up to 1 making the prediction unbiased (Oliver and Webster, 1990) using the equation:

$$E[\hat{Z}(\overrightarrow{x_0}) - Z(\overrightarrow{x_0})] = 0 \quad (6)$$

Two sets of maps were produced; firstly, interpolated maps describing the patterns of HIV prevalence, male condom use coverage and ART initiation rates across the district from the national survey, and secondly, smoothed maps showing the likelihood of

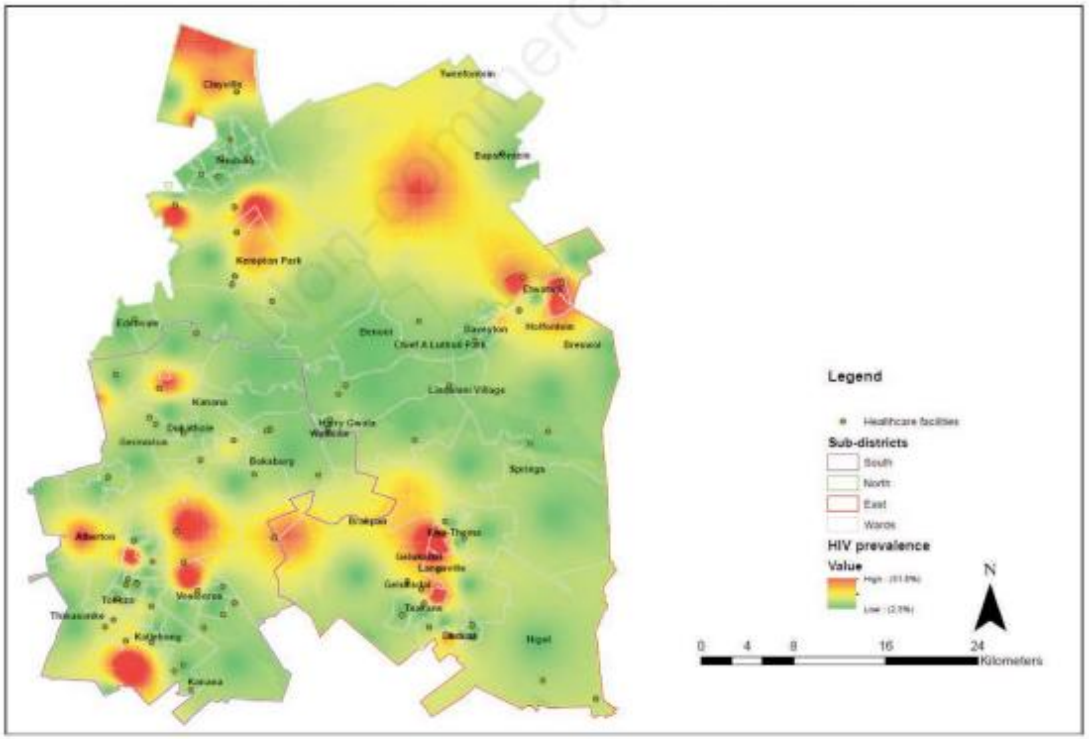


Figure 1. A smoothed HIV prevalence map of Ekurhuleni Metropolitan Municipality, South Africa. Based on 2012 HSRC national survey.

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HIV infection, suboptimal condom use and non-ART use using the routinely collected data from the regression analyses. The maps showed areas with increased proportions of poor outcomes (red colour) and those whose proportions were lower (green colour) (Figures 1-6).

Results

Characteristics of the study population

A total of 1189 respondents participated in the 2012 HSRC Survey from 32 of 101 wards in the study area (Supplementary file 1). The respondents' mean age was 37.6 years, and there were significant differences across the sub-districts (P=0.003) (Supplementary file 1). More than half of respondents were females (51.2%; 95%CrI: 49.3%-53.0%). In the South sub-district, more respondents were male (50.3%; 95%CrI: 48.4%-52.3%).

Unemployment was high in the study area (45.9%; 95%CrI: 43.1%-48.7%) and highest in the East sub-district (53.0%; 95%CrI: 51.6%-54.4%) compared to the North sub-district (46.3%; 95%CrI: 44.0%-48.7%) and the South sub-district (41.5%; 95%CrI: 36.1%-47.0%). The mean age of coital debut was 18.3 years (SD: 18.1-18.6), and the mean number of lifetime sexual partners was 4.87 (SD: 4.6-5.1); differences across the sub-districts were observed. The overall proportion of those reporting consistent condom use was low across the district (26.4%; 95%CrI: 24.2%-28.8%) and even lower for those living in the North sub-district (19.4%; 95%CrI: 15.9%-23.7%). The proportion reporting drug use was lowest in the East (12.3%; 95%CrI: 7.2%-20.2%) and highest in North (27.4%; 95%CrI: 24.6%-30.3%) sub-district.

HIV prevalence and factors associated with HIV infection

The overall HIV prevalence was estimated at 16.6% (95%CrI: 15.1%-18.1%). The highest HIV prevalence was reported in the East sub-district (18.9%; 95%CrI: 16.5%-21.6%) (Supplementary file 1) and observed in wards within Clayville, Kempton Park areas (North), in Katlehong and Germiston (South) and in Kwa Thema, Etwatwa and Brakpan (East) (Figure 1). HIV infection in these areas was associated with being a student (POR: 12.74; 95%CrI: 3.29-95.01) (Table 1). Upon adjusting for spatial random effects, the magnitude increased (POR: 19.53; 95%CrI: 3.22-84.93) (Table 1). A high proportion of HIV infection was seen in wards within Thokoza, Katlehong, Kempton Park, Edenvale, Tembisa and

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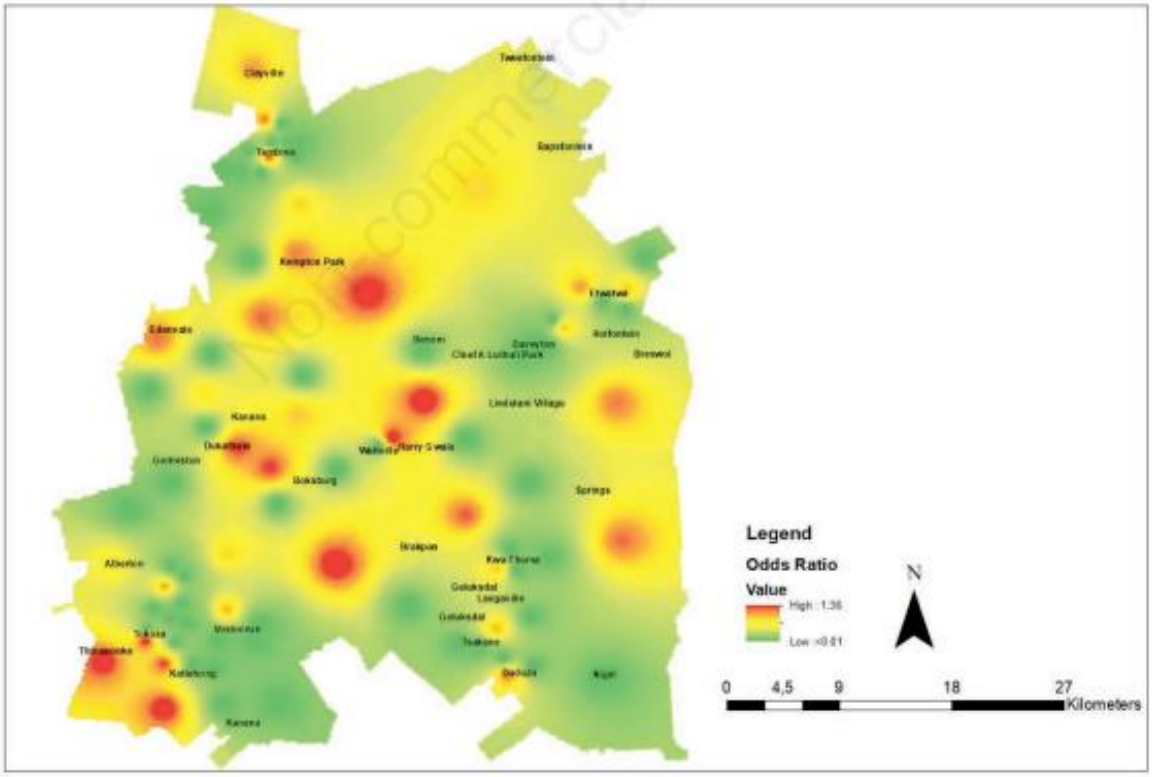


Figure 2. A smoothed map showing the expected posterior odds ratio HIV infection in Ekurhuleni Metropolitan Municipality, South Africa. Based on the 2012 HSRC national survey.

Brakpan areas (Figure 2). In these wards, inconsistent [66% (POR: 0.34; 95%CrI: 0.18-0.63)] and consistent [(52% (POR: 0.48 95%CrI: 0.24-0.87)] use of condoms was associated with lower HIV infection (Table 1).

Male condom use coverage and factors associated with sub-optimal condom use

In 2012, the average male condom use coverage as reported from routine clinics across the wards ranged between 1% and 21% (Figure 3). Sub-optimal male condom use coverage was observed in Tembisa and Kempton Park (North), in Springs, Brakpan and Kwa Thema (South) and in Dukathole, Boksburg, Alberton and Katlehong (East). The proportion of those who reported consistent condom use during the 2012 National survey was 26.4% (Supplementary file 1). The odds of sub-optimal condom use were associated with increased age (POR: 1.09;

Table 1. Posterior summaries of odds ratio for HIV infection in Ekurhuleni, South Africa.

Factor		Standard logistic regression model POR (95%CrI)	Random effects logistic regression model POR (95%CrI)	Spatial effects logistic regression model POR (95%CrI)
Employment status	Unemployed	1	1	1
	Employed	1.26 (0.76-2.08)	1.32 (0.78-2.17)	1.33 (0.73-2.12)
	Student	*12.74 (3.29-95.01)*	*19.37 (3.39-81.70)*	*19.53 (3.22-84.93)*
Level of education	Primary	1	1	1
	Secondary	0.55 (0.24-1.42)	0.66 (0.24-1.52)	0.65 (0.25-1.52)
	Tertiary	0.67 (0.37-1.20)	0.68 (0.34-1.16)	0.70 (0.35-1.19)
Condom use in past one month	No	1	1	1
	Yes	*0.46 (0.25-0.85)*	*0.48 (0.25-0.87)*	*0.48 (0.24-0.87)*
	Sometimes	*0.31 (0.17-0.56)*	*0.34 (0.17-0.67)*	*0.34 (0.18-0.63)*
Lifetime sexual partners (no.)		0.97 (0.94-1.01)	0.97 (0.94-1.00)	0.97 (0.94-1.01)
Deviance information criteria		480.3	457.7	456.7

POR, posterior odds ratio; CrI, credible intervals. Values in italics represent parameters estimates from Bayesian regression models and their corresponding 95%CrI).

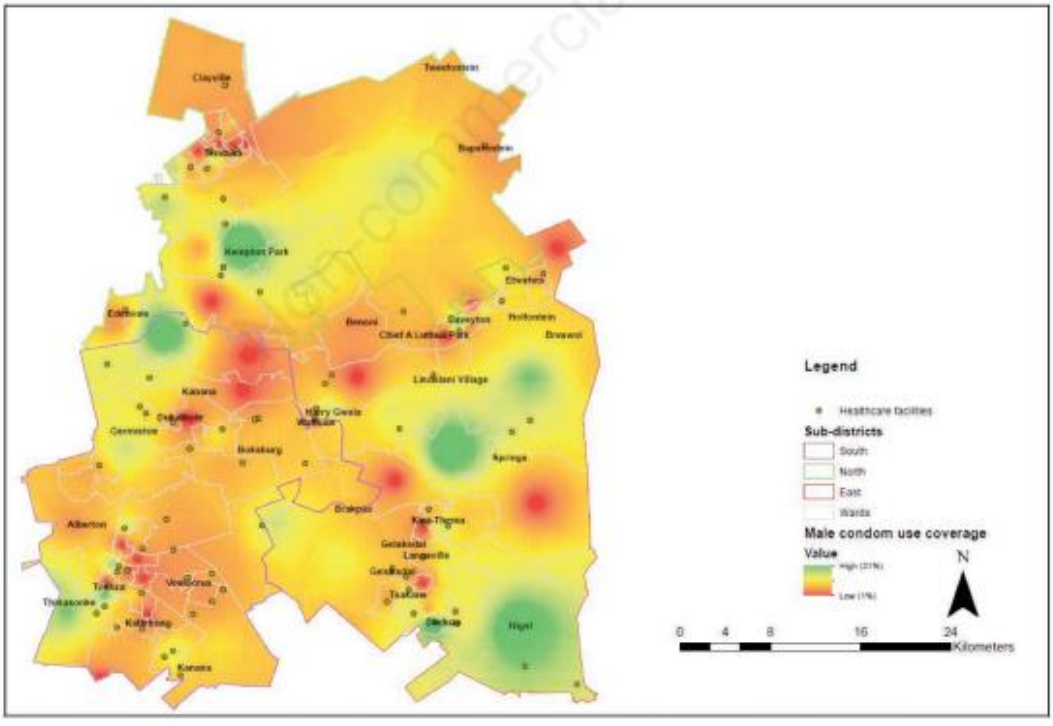


Figure 3. A smoothed distribution of male condom coverage in Ekurhuleni Metropolitan Municipality, South Africa. Based on routinely collected programmatic data.

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95%CrI: 1.06-1.12) and marriage (POR: 3.19; 95%CrI: 1.23-4.12) before and after adjusting for spatial random effects (Table 2). Increased likelihood of sub-optimal condom use was seen in wards within Kempton Park, Springs, Etwatwa, Brakpan, Alberton, Thokoza, Katlehong and Edenvale areas (Figure 4). In these wards, males were less likely not to have unprotected sexual acts (POR: 0.52; 95%CrI: 0.33-0.80).

Anti-retroviral treatment initiation and factors associated with non-anti-retroviral treatment initiation

In 2012, the average ART initiation rate as reported from routine clinics across the wards ranged between 1% and 75%. Lower ART initiation rates were observed in Tembisa (North), in Katlehong, Germiston and Boksburg (South) and in Springs, Brakpan and Kwa Thema (Figure 5). The proportion of those who reported not starting ART during the 2012 National survey was 71.3% (70.1%-72.5%) (Supplementary file 1). The odds of non-ART initiation increased in those married before (POR: 6.12; 95%CrI: 1.37-20.28) and after (POR: 6.79; 95%CrI: 1.43-22.43) adjusting for spatial random effects (Table 3). Increased likelihood of non-ART use was seen in wards within Valorous, Springs, Etwatwa, Brakpan, Alberton, Thokoza, Katlehong and Harry Gwala areas (Figure 6).

Table 2. Posterior summaries of odds ratio for sub-optimal condom use in Ekurhuleni, South Africa.

Factor		Standard logistic regression model POR (95%CrI)	Random effects logistic regression model POR (95%CrI)	Spatial effects logistic regression model POR (95%CrI)
Age (years)		1.09 (1.06-1.12)	1.09 (1.06-1.11)	*1.09 (1.06-1.11)*
Sex	Female	1	1	1
	Male	*0.52 (0.32-0.78)*	*0.51 (0.32-0.78)*	*0.53 (0.33-0.80)*
Marital status	Not married	1	1	1
	Currently married	*3.19 (1.23-4.12)*	*3.78 (1.24-4.06)*	*4.14 (1.23-4.28)*
	Previously married	*0.27 (0.07-0.76)*	*0.28 (0.07-0.79)*	*0.28 (0.07-0.79)*
Media exposure	Frequent	1	1	1
	Not frequent	1.90 (0.95-3.57)	1.95 (0.95-3.49)	*1.97 (0.95-3.49)*
Deviance information criteria		523.7	530.8	528.5

POR, posterior odds ratio; CI, confidence interval. CrI, credible intervals. Values in italics represent parameters estimates from Bayesian regression models and their corresponding 95%CrI).

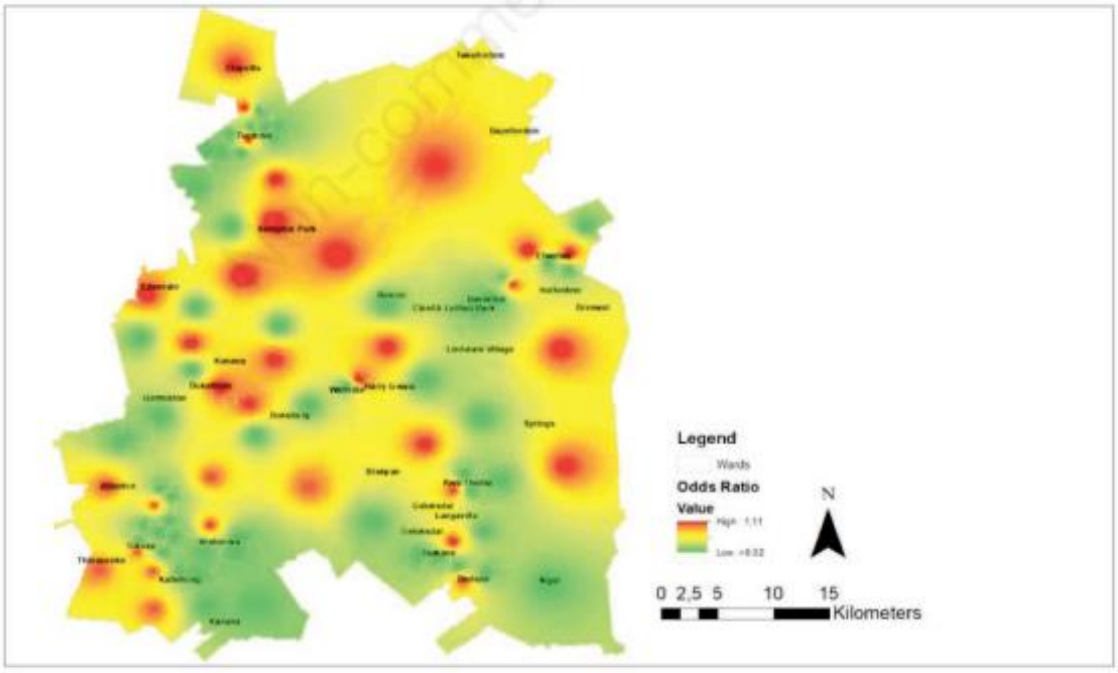


Figure 4. A smoothed map showing the expected posterior odds ratio sub-optimal condom use in Ekurhuleni Metropolitan Municipality, South Africa. Based on the 2012 HSRC national survey.

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Discussion

This study focuses on the heterogeneity of HIV prevalence and uptake of HIV interventions and has shown the feasibility of using routinely collected data from primary health care facilities to reveal areas for spatially targeted interventions. Findings from this data source corroborate the sub-optimal uptake of condoms and linkage to ART reported from the national population-based survey conducted in the same year in this setting. This is the first study to analyse geographical variations in HIV prevalence, coverage of condoms, and uptake of at the ward level which is often overlooked by national population-based surveys. The variation was considerable, *e.g.*, lower HIV prevalence was observed in certain wards, together with low ART initiation rates and condom use coverage, and in other areas HIV prevalence could be higher, also the reported HIV prevalence was higher in some areas with low uptake of HIV interventions. On the other hand, in other wards, as expect-

Table 3. Posterior summaries of odds ratio for non-anti-retroviral treatment initiation in Ekurhuleni, South Africa.

Factor		Standard logistic regression model POR (95%CrI)	Random effects logistic regression model POR (95%CrI)	Spatial effects logistic regression model POR (95%CrI)
Age (years)		0.94 (0.88-1.00)	0.95 (0.88-1.01)	*0.95 (0.90-1.00)*
Drug use in past 3 months	No	1	1	1
	Yes	6.72 (0.69-32.01)	7.03 (0.71-34.91)	*7.17 (0.74-32.21)*
Marital status	Not married	1	1	1
	Currently married	*6.12 (1.37-20.28)*	*7.18 (1.57-22.75)*	*6.79 (1.43-22.43)*
	Previously married	5.37 (0.38-28.71)	6.19 (0.37-33.96)	5.68 (0.33-25.98)
Media exposure	Frequent	1	1	1
	Not frequent	2.14 (0.52-6.39)	2.44 (0.54-7.98)	*2.45 (0.59-8.24)*
Deviance information criteria		107.4	109.0	107.8

POR, posterior odds ratio; CI, confidence interval. CrI, credible intervals. Values in italics represent parameters estimates from Bayesian regression models and their corresponding 95%CrI).

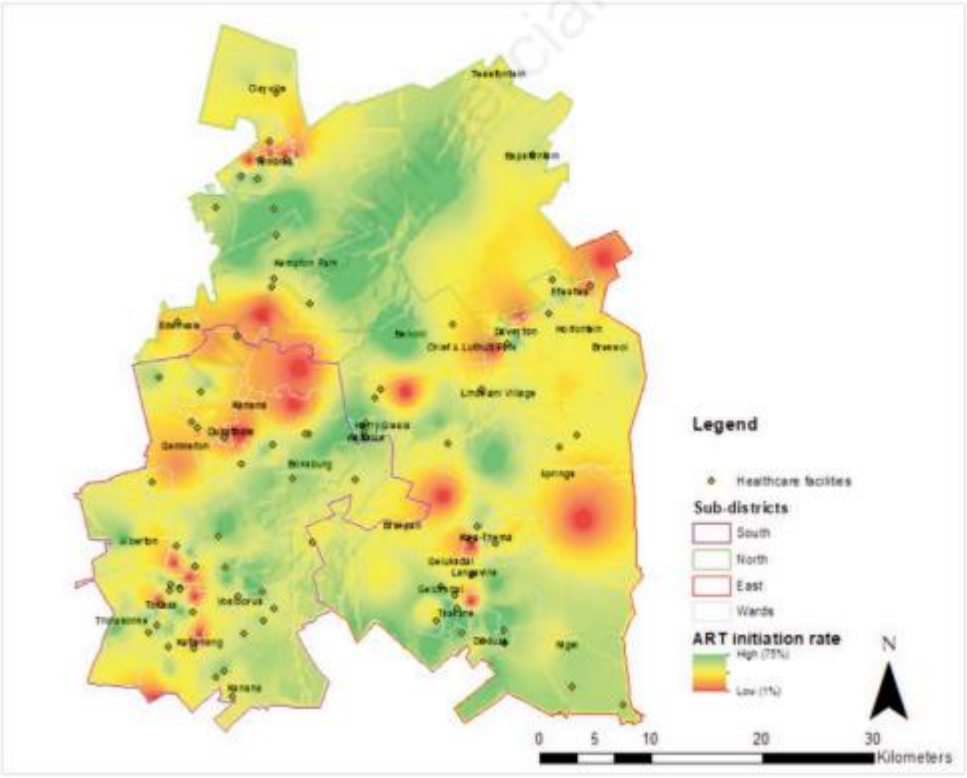


Figure 5. A smoothed map showing the distribution of anti-retroviral treatment (ART) initiation rates in Ekurhuleni Metropolitan Municipality, South Africa. Based on routinely collected programmatic data.

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ed, the observed HIV prevalence was low when the uptake of interventions was high.

The importance of using spatial data to visualize gaps in service coverage has been a recurring theme across many studies highlighting the critical role of geography in informing access to HIV-related health services in low-income settings (Boyda *et al*., 2019). GIS and spatial analysis allow for a more efficient allocation of resources and appropriate targeting (Aral *et al*., 2015; Coburn *et al*., 2017). Condom and ART program implementation could benefit from dynamic, interactive, and iteratively updated maps with verified health facility coordinates and infrastructure data, and simple mapping may be a good entry point for more advanced geospatial techniques (Cuadros *et al*., 2018). Also, our study further investigated the reasons driving these unfavourable health outcomes in this setting.

Our findings identified drivers of HIV infection, sub-optimal condom use and non-ART use. We found that HIV infection was associated with being in school. Students, usually young people undergo various psychological and behavioural changes that put them at risk for HIV infection (Bekker and Hosek, 2015; Dellar *et al*., 2015). Findings further showed an increased likelihood after adjusting for spatial effects signifying the importance of including space for targeted interventions. The wards within the areas with increased odds of HIV infection are likely to have a considerable proportion of younger people (<35 years) and mostly female, and other key populations including men who have sex with other men, injection drug users and female sex workers living in informal dwellings, high levels of unemployment (>30%) and a small proportion of the population with tertiary education (<3%). Although we did not find an association with being female, other studies have shown the disproportionate high HIV burden in young women compared to men. Indeed, a recent systematic review showed that the HIV incidence rates in young women far outweigh male counterparts (Birdthistle *et al*., 2019). Expanding existing HIV treatment and prevention programmes in communities and educational facilities to include youth-centred interventions through innovative technologically driven platforms is recommended.

This study found that males were more likely to consistently use preventive techniques compared to females. The spatial effect was not observed implying that the likelihood was homogenous across the wards. Consistent with previous studies, females were less likely to use technical prevention (Muchiri *et al*., 2017). Reasons for this from similar studies indicate the need to show faithfulness to a male partner, the ability to negotiate condom use as well as the perceived inefficacy of condoms (Jama Shai *et al*., 2010). Married unemployed women are less likely to use this kind of technical prevention due to financial dependence on their male partners and the expectation to bear children (Ayiga, 2012; Jama Shai *et al*., 2010; Versteeg and Murray, 2008). High self-efficacy of condom use is often associated with those with secondary school education, and it is assumed that with this level of education, knowledge of HIV transmission and prevention is high (Ayiga, 2012; Jama Shai *et al*., 2010). Our findings contrasted with

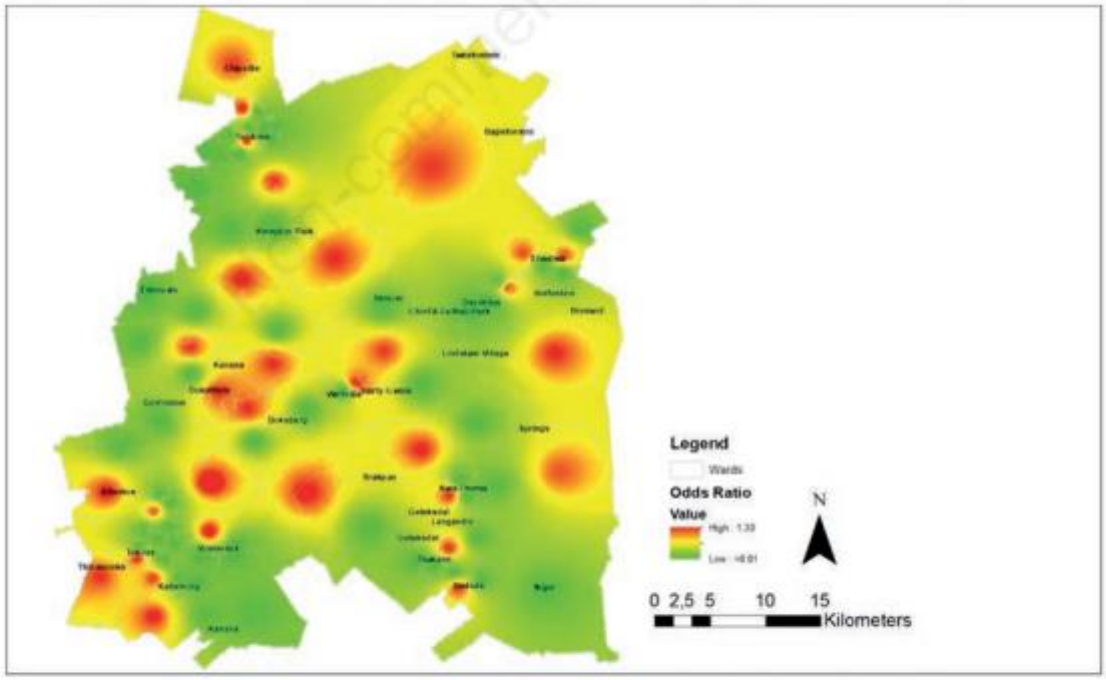


Figure 6. A smoothed map of showing expected posterior odds ratio for non-anti-retroviral treatment use in Ekurhuleni Metropolitan Municipality, South Africa. Based on the 2012 HSRC national survey.

what has been found in other settings where sub-optimal condom use was observed in those with secondary school education. A study conducted in Kwa Zulu Natal, South Africa among university students reported low condom use and a lack of confidence in using condoms at sexual debut due to poor negotiation with a partner and were likely to form negative attitudes about condom use (Haffejee *et al*., 2018).

Notably, sub-optimal ART uptake was associated with being in school. This is confirmed by several studies globally which have shown barriers to retention in care include having to attend a clinic during school hours, fear of disclosure to others, social isolation, and conflict with clinical staff (Zanoni *et al*., 2019; Lall *et al*., 2015). As the HIV prevention model shifts to treatment as prevention strategies, identifying drivers that promote adherence to and retention in care to antiretroviral regimens among HIV positive young people is necessary (Lall *et al*., 2015). At the ward level, drug use was a factor that may prevent optimal ART uptake and addressing these challenges may promote adherence in identified areas and subsequently improve HIV outcomes. However, this association was not observed in any of our models.

The limitations of this study include underestimation of HIV prevalence due to the inability to fully link the 2001 census enumeration areas data with what was provided by the HSRC as not all wards were sampled. As a result, underestimation, or overestimation of study outcomes from HSRC was likely. However, condom use and ART initiation estimates from the national survey data were almost similar to the estimates from the DHIS which validates these findings. Data from DHIS may have been incomplete as clinics may not have submitted all their clinical data timeously. Despite these limitations, the use of interpolation allowed the calculation of predicted values from areas not sampled using observations from nearby locations. Although outcomes were derived from two different data sources, we attempted to compare findings between outcomes from the population-based survey with those from the routinely collected data.

Conclusions

This study adds valuable information to the growing body of knowledge prevention of HIV in South Africa. It confirms what is already known about the heterogeneity of HIV prevalence in South Africa. The study utilized two data sources; a national survey and routinely collected data for a high priority district in 2012 with similar findings. Further, the study's novel contribution is conducting spatial modelling at a far higher spatial resolution than used before thereby visualizing patterns of poor HIV outputs and outcomes in the study area.

The use of maps to visualize HIV prevalence and interventions provides support how to apply limited resources to where they are most needed. Thus, our findings have important public health implications for program planners. Furthermore, modelling revealed the heterogeneity of outcomes at the ward level. From this study, it would be recommended to scale up condom uptake and reinforce ART programmes according to the need to prevent HIV transmission. Addressing the drivers for the sub-optimal condom use and ART initiation identified in this study is encouraged. This may mean strengthening partner counselling and expanding access to condoms in existing HIV prevention and treatment programmes. This study also demonstrates the feasibility of using readily available programme data for planning, without expensive research studies. This can be a model for similar studies in other settings, and potentially have a high impact on the HIV epidemic.

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Appendix G: Copies of PhD outputs – Manuscript 2

IN PREPARATION FOR IMMINENT JOURNAL SUBMISSION

Small area analysis of HIV viral load suppression patterns in a high priority district (2012-2016), South Africa

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Abstract

Introduction

South Africa has the largest HIV treatment programme worldwide and evaluation at sub-national or provincial levels is likely to highlight variations that are largely masked at national or provincial level. We used Bayesian statistical techniques to assess effectiveness of this programme and introduced spatio-temporal techniques to account for heterogeneities in space and time.

Methods

We extracted data from 2012-2016 on HIV in Ekurhuleni Metropolitan Municipality from routinely collected clinical and surveillance data, including ward-level characteristics such as proportion of females, low literacy levels, low-income levels, and population density from 2011 Census data. The proportion virally suppressed using two thresholds (<400 copies/mL and <1 000 copies/mL) per ward was calculated. A high proportion of viral load suppression was considered when ≥75% of the PLHIV in a ward were virally suppressed. The predictors of high viral load suppression were estimated by Markov Chain Monte Carlo methods and assessed using Bayesian techniques. Rate ratios with their corresponding 95% credible intervals (CrI) were reported. Spatial exploratory analysis was performed, and viral load suppression rates were mapped across the study period.

Results

From January 2012 to December 2016, 26 222 HIV viral load tests were conducted for 6 977 patients. Viral load suppression increased by 19% from 2012 to 2015 but decreased by 9.7% in 2016 after the roll-out of universal test and treat. The higher the proportion of PLHIV initiating on ART in a ward, the proportion of viral load suppression increased by 34% (RR: 1.345; 95% CrI 1.221-1.492). The proportion of viral load suppression (<1 000 copies/mL) increased by 44% with an increasing number of female PLHIV in a ward (RR: 1.442; 95%CrI: 1.056-1.962). There was evidence of clusters of high or low viral load suppression observed in wards in Ekurhuleni.

Conclusions

There was heterogeneity of high viral load suppression across wards in Ekurhuleni between 2012 and 2016. Addressing gaps that target the initiation to and retention in care for men is critical to achieve optimal viral load suppression. Measuring differences in viral load across wards and visualizing the variations is a critical step toward improving HIV treatment programmes through application of targeted interventions.

Key words

Bayesian analysis, viral load suppression, Ekurhuleni, spatio-temporal, spatial autocorrelation

Introduction

Evaluating the effectiveness of HIV treatment programmes in a population through viral load monitoring is widely used in many HIV high burden countries (1, 2). There has been a massive ART roll-out and scale-up of viral load monitoring since 2013 to meet the third 95 of the 95-95-95 targets by 2030 and achieve ultimate HIV control (1). HIV control can be attained when people living with HIV (PLHIV) are identified, initiated on ART, and retained in HIV care (2). Therefore, high ART coverage and high rates of viral load suppression are likely to reduce HIV transmission and ultimately reduce HIV prevalence (1, 3, 4).

In South Africa, HIV treatment initiation is done primarily at primary healthcare facilities and viral load is performed at six months, and thereafter annually (5). If the viral load is greater than 1000 copies/mL, a repeat testing is required according to World Health Organization (WHO) guidelines (3). The 2020 UNAIDS data for South Africa shows that 92% of people were aware of their HIV status, 72% were on treatment and 66% were virally suppressed (1). Since tangible evidence has demonstrated the significant impact that treatment has on the reduction of HIV transmission at a population level, population viral load is commonly monitored in resource constrained settings (1, 3).

Heterogeneity of HIV prevalence has been widely demonstrated (6-10). Similarly, viral load suppression rates are likely to vary spatially. In order to curb HIV transmission, there is a need to find other ways of monitoring the viral load while considering heterogeneity in across geographical spaces (11). The 2020 UNAIDS Global report showed that 92% of people on HIV treatment had viral suppression (1) but this is likely to differ at a sub-national level. Locally, little is known about the estimates of viral load suppression and their association with related health outcomes. This limited information may be attributed to the complex interplay of risk factors that remain inadequately characterised in the spatial and temporal domain.

Studies utilizing the Bayesian techniques in mapping health outcomes are increasing as they leverage information on the disease events across neighbouring geographical units and prior distribution of health outcomes. its framework allows for the analysis of health outcomes based on unknown area-specific relative risks It is often difficult to identify risk clusters in small areas such as Ekurhuleni given the dynamic population structure. Small area estimation using Bayesian methods overcomes this problem by integrating prior information to the underlying relative risk, making the predicted risk estimates robust. The statistical methodology for using Bayesian models to surveillance in space–time is still work in progress, but it is an attractive tool since it allows a proficient and local understanding of disease processes assimilated via the specification of prior distributions on model parameters.

Exploring the association between viral load suppression and geographical location is important for informing spatially targeted interventions. Research using space–time disease surveillance methods have developed dramatically over the last two decades and has provided new dimensions to disease mapping and shaping prevention intervention programs in public health. Applying Bayesian spatio-temporal techniques to analyse this heterogeneous data will allow for the incorporation of prior information in evaluating viral load suppression allowing for improvements in out of sample prediction (12). In addition, space-time disease mapping models allow for the concurrent study of persistent and unusual viral load suppression rate trends, providing added benefits over only spatial disease mapping models.

Bayesian models have been extensively used in disease mapping studies. The studies mapping viral load suppression in South Africa are limited. We used five years of HIV program data for Ekurhuleni, South Africa to assess the trends in viral load suppression rates and explored spatio-temporal autocorrelation at a ward-level.

Methods

Study setting

This ecological study utilized aggregated data on HIV indicators collected from primary health care facilities in Ekurhuleni Metropolitan Municipality (EMM) between 2012 and 2016. EMM is divided into three sub-districts (East, South and North) and 101 wards. Available spatial data was recorded for 88 wards. Most wards has one primary healthcare facility.

Data sources

Data on HIV viral loads from were obtained from the South Africa National Health Laboratory services (NHLS). NHLS conducts all laboratory monitoring for the national HIV program which are archived at the level of the laboratory specimen in the NHLS corporate data warehouse (CDW). The NHLS dataset contained viral load results from 1st January 2012 to 31st December 2016, from public health facilities in South Africa. From the same data source, data on age and tuberculosis (TB) diagnosis was obtained.

Data on the ART uptake at the clinic level in Ekurhuleni was abstracted from the District Health Information System (DHIS) hosted by the South Africa National Department of Health, which routinely collects individual-level data from all South African public health facilities at a local level.

Data on literacy levels, income levels, gender and population was obtained from the 2011 National Census.

Viral load measure

The South African national guidelines state that routine viral load monitoring for individuals receiving ART should be done at six and twelve months after ART initiation and then annually thereafter (5). During each routine visit, a standard request laboratory form containing patient identifiers are manually captured into the laboratory information system at the receiving laboratory, before the blood sample is centrifuged and tested using the Abbott Realtime HIV (Abbott Molecular Des Plaines, USA) or Roche Cobas Ampliprep/Cobas TaqMan HIV-1 (Roche Diagnostics, Branchburg, USA) assays. All viral load results from each patient the time period were used. The total number of patients with a viral load test in the time period was calculated. Additionally, the proportion of those patients with tests less than 400 copies/mL (virologically suppressed), and between 400 and 1 000 copies/mL (considered at risk for poor adherence). This analysis considered <1 000 copies/mL as the main outcome.

Viral load suppression

We assessed viral load suppression using <1000 copies /mL and <400 copies/mL as two of the thresholds used in South Africa to determine treatment success. We summarized the mean $\log_{10}$ viral load per year. Ward-level VLS was estimated by taking the number of virally suppressed patients and dividing by the total number in care per year. Wards with ≥ 75% of PLHIV reporting viral load suppression was considered high whereas wards with <75% were considered as having low viral load suppression rates.

Ward-level measures

We estimated the population characteristics at the ward level from 2011 Census data. Eight-eight wards were identified using geographical information provided in the 2011 Census data. We calculated the following measures for each ward: proportion of female respondents; proportion of low literacy levels; proportion with no income; and population density per ward from the 2011 Census data and performed standardization. We further interpolated subsequent estimates from midyear population estimates produced by Statistics South Africa from 2012-2016 (13) assuming that the population is growing at a constant rate using the exponential growth model. ART initiation rate per ward was calculated by estimating the total HIV patients in each ward remaining on ART at end of the month over the estimated number of people living with HIV. A geometric mean by ward was calculated for each year.

Statistical analyses

Spatio-temporal component model

The Bayesian hierarchical spatio-temporal component model was used to simultaneously quantify the viral load suppression rates in EMM from 2012-2016.

Let Y_{ij} be the observed proportion of viral load suppression (outcome), where i represents a given ward (1–88) and j represents different periods (2012–2016). Let η_{ij} be observed viral load suppression proportion for each ward *i* (*i*=1, …,88) and time period *j* (j=*1*, …, 5). A binomial model for observed proportion with a logit link function was used in the analysis. i.e., We assume that the observed proportion of viral load suppression Y_{ij}arises from a binomial distribution (Equation 1).

$$Y_{ij} \sim binomial(n_{ij}, \pi) i = 1, \cdots, 88\ j = 2012, \ldots, 2016 \quad \text{Equation (1)}$$

Here, π_{ij} represents the true, unknown viral load suppression rate in wards i and time *j*. The proportionate rate of viral load suppression is specified on the logit scale as shown in Equation 2:

$$logit(\pi_{ij}) = \alpha + X_i\beta_i + X_{ij}\beta_{ij} + \mu_{ij} \quad \text{Equation (2)}$$

The parameter α is the baseline relative risk for a given viral load suppression outcome, X_i and X_{ij} are the time invariant spatial covariates and space-time varying covariates (ART initiation rate, proportion diagnosed with TB, proportion of female patients, proportion with low literacy and with no income). The parameters β are the regression coefficients that account for the varied risk gradients of the shared spatial and temporal components. The spatio-temporal structure, defined by μ_{ij} accounts for the variations of relative risk in the logit scale. The joint spatial-temporal structure was specified as illustrated in Equation 3:

$$\mu_{ij} = \gamma_k^s\ \mu_i^s + \mu_{ik}^s + \gamma_k^t \mu_j^t + \mu_{jk}^t + \nu_{ij} \quad \text{Equation (3)}$$

μ_i^s are a set of common random effects associated with space, i.e., conditional autoregressive (CAR), $\mu_{ik}^s$is the outcome-specific random effects associated with space μ_j^t are a set of common random effects associated with time, i.e., random walk of order 1 (RW1), μ_{jk}^t are outcome-specific random effects associated with time (RW1). The space-time interaction term/heterogeneity of order two is represented by ν_{ij} i.e., it represents the possible variations not explained by the spatial and temporal effects in the model.

We summarized the overall proportion of viral suppression at the municipality level and sub-district level using tables and line graphs. We examined the predictors of the proportion of viral load suppression at ward level by fitting spatial and spatio-temporal mixed-effects regression model using R integrated Nested Laplace Approximation (INLA) package in R version V.3.6.1 (RStudio). The mixed-effects model accounted for viral load suppression as fixed effects with ward specific random intercepts to account for over dispersion or correlation in viral load suppression within and between wards over five years. The adjusted viral load suppression rates were mapped using ArcGIS version 10.7.1. To assess spatial autocorrelation of viral load suppression in Ekurhuleni, we used the Moran index and to map clusters of high and low viral load suppression, we used the Anselin Local Indicator Spatial Autocorrelation (LISA) function in ArcGIS. To test for trend of viral load suppression and ART initiation rate across the five years we used the Cochran-Mantel-Haenszel stratified test of association and Kruskal-Wallis's equality of populations in Stata version 14 (StataCorp, Texas, USA). Significance was determined at 5% level.

Sensitivity analysis

We conducted two sensitivity analyses. The first one used viral load suppression of <400copies/mL as an additional outcome. In the second one, we restricted the analysis to include all observations until August 2016 before the national roll-out of universal test and treat (UTT) begun.

Interrupted time series

Two periods were specified: The preintervention (January–August 2016)—8 months before roll-out of UTT, excluding the month of September 2016 when UTT was rolled out nationally; and the postintervention (September 2016–December 2016)—4 months of UTT implementation. In standard ITS analyses, the following segmented regression model in Equation 4 was used:

$$\mathrm{Y} = \beta_0 + \beta_1 \mathrm{T} + \beta_2 \mathrm{X_t} + \beta_3 \mathrm{TX_t} \quad \text{..... Equation (4)}$$

where β_0 represents the baseline level at $T = 0$, $\beta 1$ is interpreted as the change in outcome associated with a time unit increase (representing the underlying pre-intervention trend), β_2 is the level change following the intervention and β_3 indicates the slope change following the intervention (using the interaction between time and intervention: TX_t).

Ethical approval

Ethical clearance was sought from the Wits Human Research Ethics committee (HREC; M181088). Additional permission was sought and approved from the National and Gauteng Department of Health (to access DHIS data), NHLS ethics committee and the Ekurhuleni Metropolitan Municipality Research Committee. Due to the use of retrospective anonymized data, this study did not seek individual patient consent.

Results

Study area characteristics

From January 2012 to December 2016, 41 644 patients mostly male patients (n=25 631; 61.5%) and of median age 39 (IQR: 14) years visited 99 PHCs in EMM for their routine HIV

care. From these, 26 222 HIV viral load patients. The differences between the years were significant (Table 1). Table 1 shows a summary of selected characteristics of the laboratory data by year.

Table1: Characteristics of samples collected from primary health care facilities in Ekurhuleni (2012-2016)

Indicator	2012	2013	2014	2015	2016	p-value
Number of patients	1 001	1 371	1 871	2 125	2 296	0.001
Median (IQR) age	36 (13)	36 (12)	39 (13)	42 (16)	39 (14)	<0.0001
Total viral load samples	2 031	2 509	4 451	7 741	9 490	0.002
Mean (sd) (log_{10}) viral load	7.56 (2.9)	7.11 (3.2)	6.14 (3.3)	5.74 (3.2)	6.75 (3.2)	<0.0001
Proportion virally suppressed (<1000cp/mL)	55.8%	58.5%	69.0%	70.8%	61.1%	<0.0001
Proportion virally suppressed (<400cp/mL)	41.0%	49.0%	56.0%	62.0%	53.0%	<0.001

The HIV prevalence in EMM increased from 32.3% to 36.9% from 2012 to 2016. In the same time period, the proportion of PLHIV initiating on ART coverage steadily increased from 32.3% to 81.2% (Table 2).

Table 2: Estimated ART coverage for PLHIV (2012-2016) in antenatal care in Ekurhuleni Metropolitan Municipality

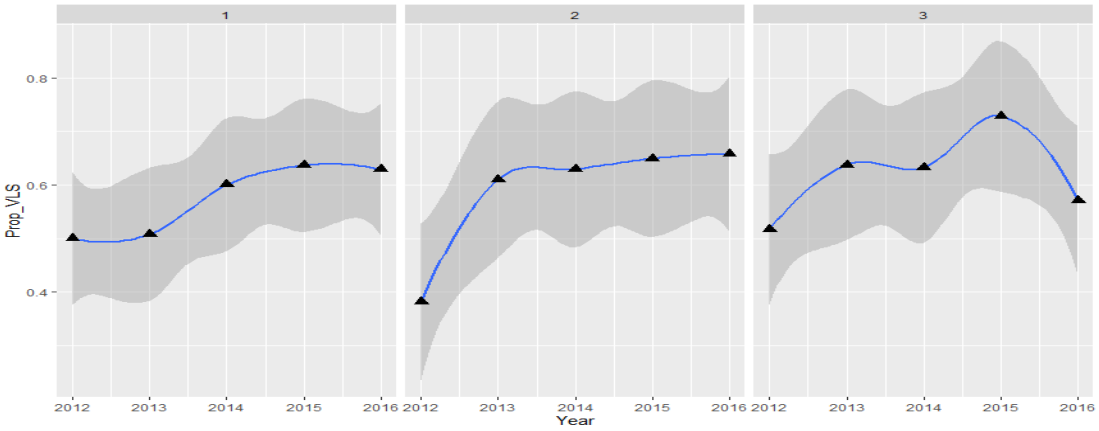
Year	Estimated population*	Total HIV prevalence†	ART coverage‡
2012	3,219,000	32.3%	32.2%
2013	3,301,000	33.5%	56.4%
2014	3,385,000	30.2%	81.9%
2015	3,470,000	31.6%	88.0%
2016	3,559,000	36.9%	81.2%

*Interpolated from Statistic South Africa mid-year estimates
†Estimated obtained from National Antenatal Sentinel HIV and Syphilis Survey
‡Estimates obtained from District Health Information System

Viral load suppression

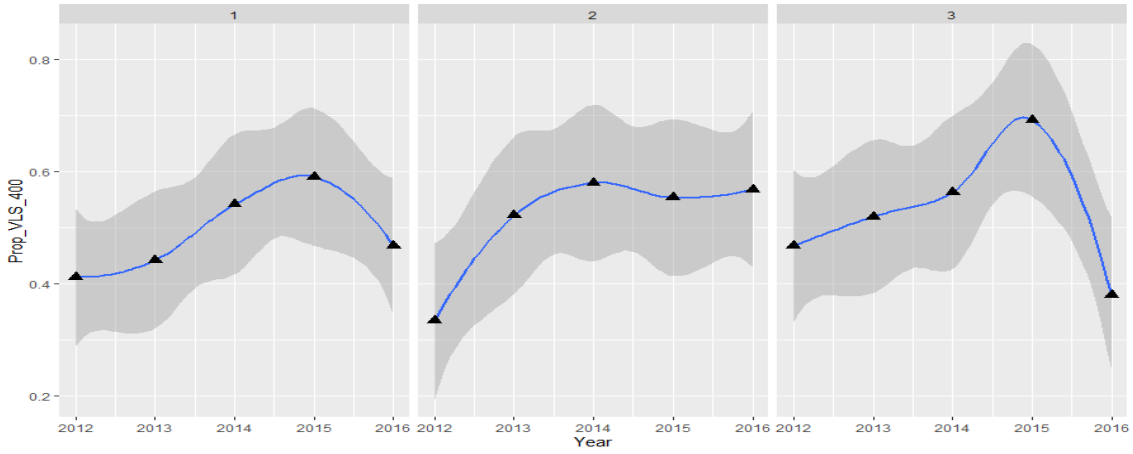
The proportion virally suppressed at <1 000 copies/mL increased from 55.8% in 2012 to 70.8% in 2015 and decreased in 2016 to slightly above 60.0%. However, across the subdistricts, this trend was observed in the East and South subdistricts (Figure 1). In the North subdistrict, the proportion of those virally suppressed increased in 2016. Overall, viral load suppression (<400 copies/mL) in Table 1 followed a similar pattern. The sensitivity analysis showed a similar trend of viral load suppression overall (Supplementary file 1) and at a sub-district level (Supplementary file 2). The differences at a subdistrict level were revealed in Figure 1. The North subdistrict showed the proportion of those virally suppressed increased from 2012 to 2014 and decreased in 2015 and increased in 2016 (Figure 2). Sensitivity analysis at subdistrict-level in Supplementary files 3 and 4 showed similar patterns.

Figure 1: Proportion of viral load suppression (<1000 copies/mL) by sub-district in Ekurhuleni Metropolitan Municipality (1st January 2012 - 31st December 2016)



Sub-district 1: South; sub-district 2: North and sub-district 3: East

Figure 2: Proportion of viral load suppression (<400 copies/mL) by sub-district in Ekurhuleni Metropolitan Municipality (1st January 2012 - 31st December 2016)



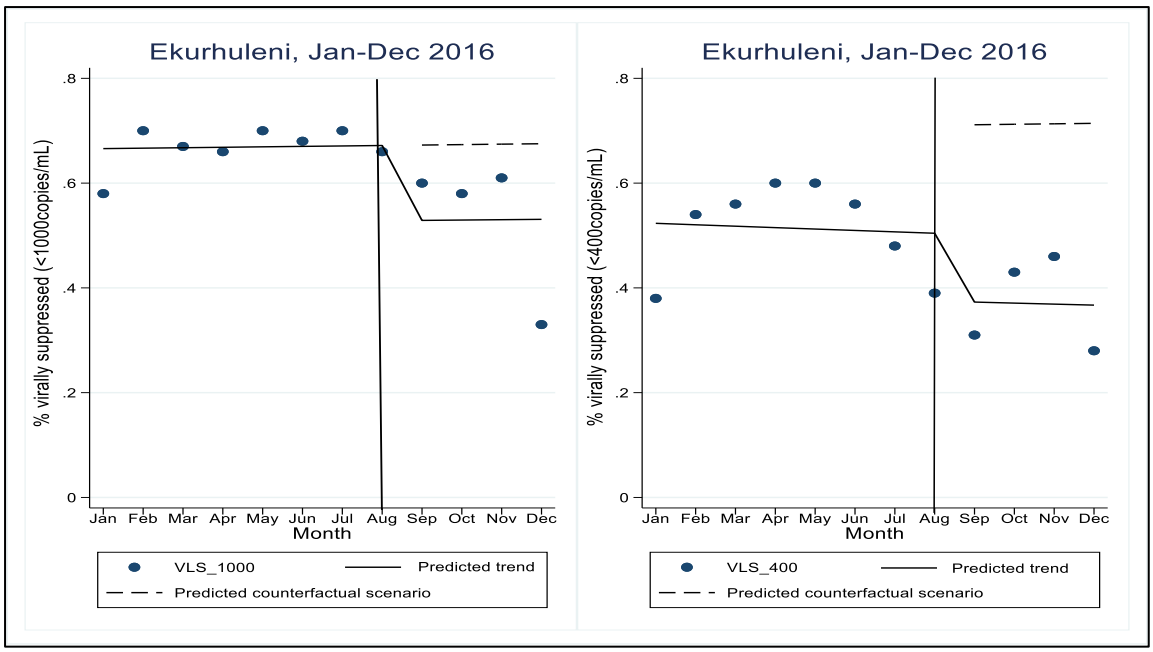
Sub-district 1: South; sub-district 2: North and sub-district 3: East

Viral load suppression in 2016

The proportions of those virally suppressed in EMM decreased immediately after the roll-out of UTT. Overall, the viral load suppression (<1 000copies/mL) ranged from 65.0% in January 2016 to 70.0% by the end of August 2016 and to 58.0% by end of December 2016. The proportion virally suppressed at <400 copies/mL was lower as shown in Figure 3 before and after UTT roll-out.

Figure 3 further displays the pre-intervention trend of monthly proportions of viral load suppression (continuous line), and the counterfactual scenario (dashed line). The proportion of those virally suppressed in the post UTT phase is reduced when looking at <400 copies/ml given that most of the points lie below the counterfactual line which is not observed in the <1 000 copies/mL trend.

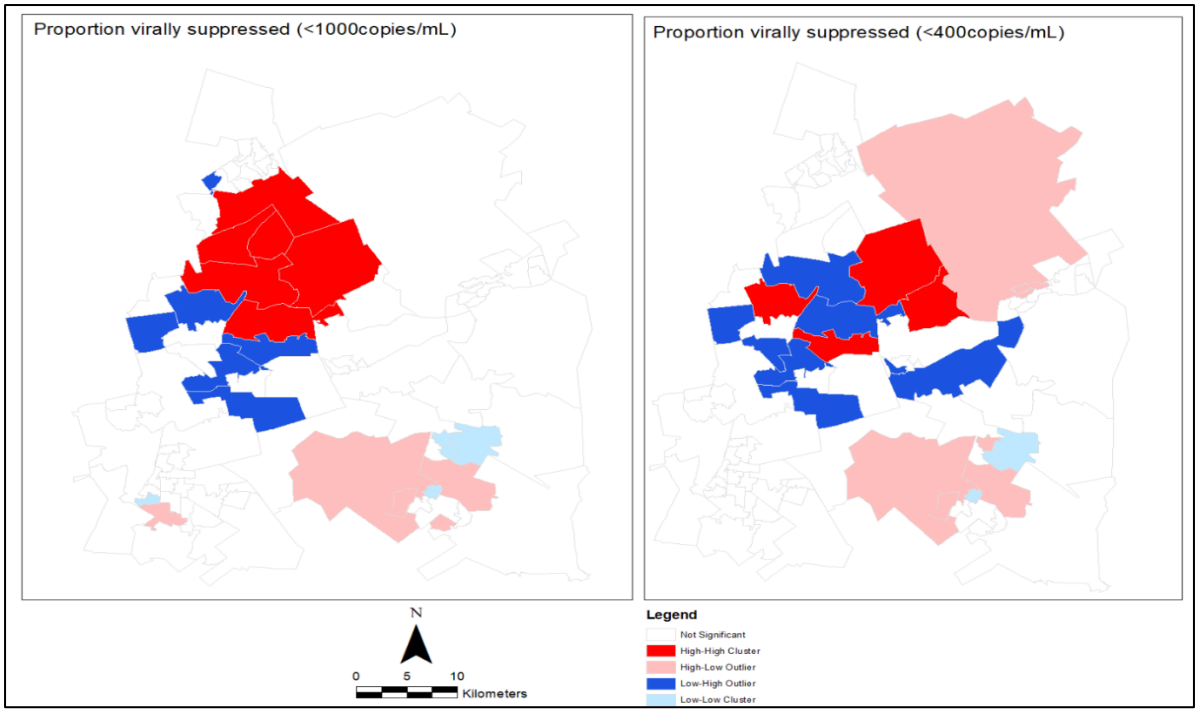
Figure 3: Proportions of viral load suppression rates in EMM before and after roll-out of universal test and treat (2016)



Spatial autocorrelation of viral load suppression

To assess spatial autocorrelation of viral load suppression (<1 000copies/mL) in EMM, an estimated Moran index value of 0.51 with a statistically significant p-value (<0.0001). Further, the estimated Moran index value of 0.10 was calculated from spatial autocorrelation of viral load suppression (<400 copies/mL) with a statistically significant p-value (<0.0001). This indicated the evidence of clusters of high or low viral load suppression in the study area. To identify the presence of these clusters, the local indicator spatial autocorrelation statistic (LISA) revealed clusters of areas with high (blue colour) proportion of viral load suppression in the South district around Kempton Park, Alberton, Benoni and Boksburg areas. The areas with low (red colour) proportions of viral load suppression were observed in most wards in the East subdistrict in areas such as Thokoza, Brakpan and Langaville (Figure 4).

Figure 4: Location of clusters of high and low proportions of viral load suppression in Ekurhuleni Metropolitan Municipality (1st January 2012 - 31st December 2016)



Spatio-temporal distribution of viral load suppression

Figure 5 shows the spatial-temporal distribution of viral load suppression (<1 000copies/mL) from 2012 to 2016. There was an increase in the proportion of virally suppressed patients from 2012 to 2015 across the wards as depicted in green and a decrease in 2016.

Figure 5: The spatio-temporal trend of viral load suppression (<1 000 copies/mL) from 1st January 2012 - 31st December 2016.

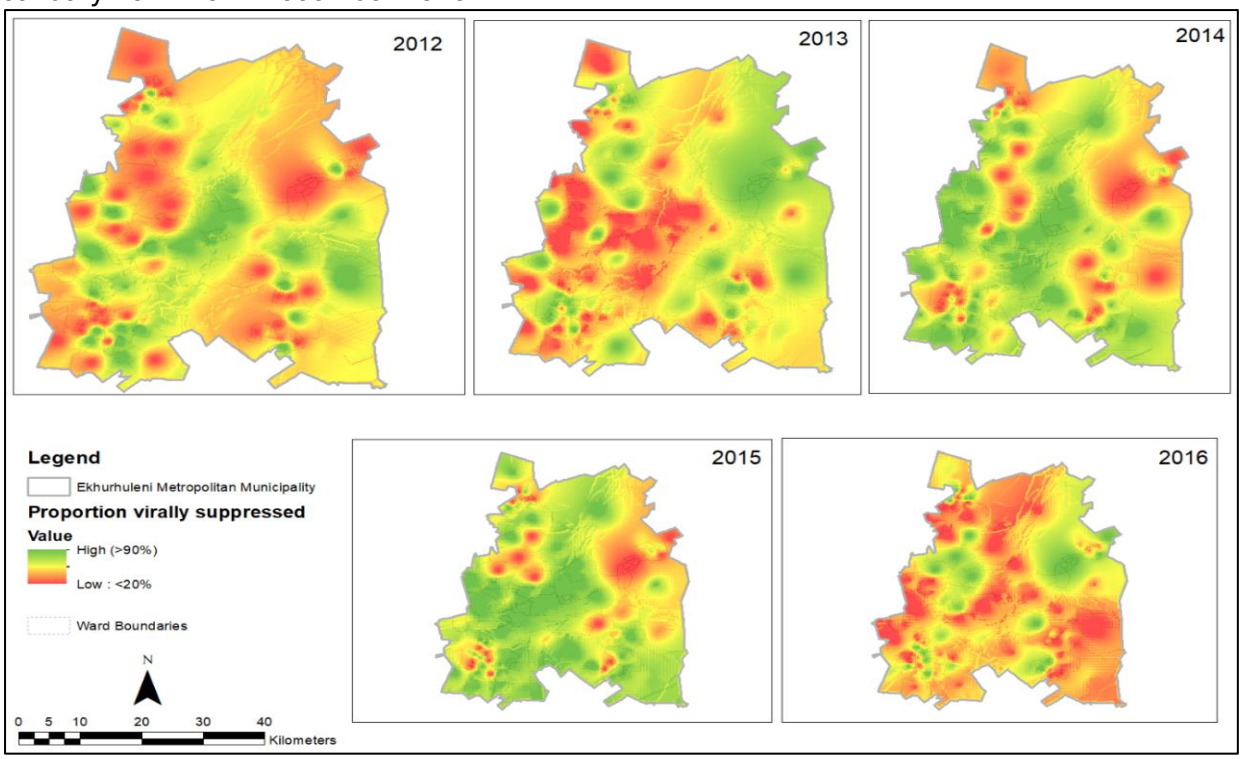


Table 3: Spatio-temporal predictors of higher viral load suppression

	<1000 cp/mL		<400 cp/mL	
Predictor	**Beta co-efficient Mean (95%CrI)**	**Exponentiated co-efficient) RR (95%CrI)**	**Beta co-efficient Mean (95%CrI)**	**Exponentiated (co-efficient) RR (95%CrI)**
Population density	0.012 (0.001-0.024)	1.008 (0.993-1.023)	0.001 (-0.009-0.012)	1.001 (0.991-1.012)
% Diagnosed with TB	-0.006 (-0.017-0.005)	0.994 (0.983-1.004)	-0.006 (-0.016-0.004)	0.994 (0.983-1.005)
% Initiated on ART	**0.300 (0.200-0.400)**	**1.345 (1.221-1.492)**	**0.200 (0.100-0.300)**	**1.221 (1.052-1.350)**
% Female	**0.335 (0.085-0.585)**	**1.442 (1.056-1.961)**	0.302 (-0.024-0.626)	1.352 (0.976-1.870)
% Low literacy	-0.325 (-1.559-0.907)	0.563 (0.104-3.027)	0.527 (-1.163-2.198)	1.693 (0.312-9.003)
% No income	1.066 (-0.852 – 2.983)	3.835 (0.440-33.630)	0.297 (-1.873-2.452)	1.346 (0.154-11.614)
Constant	0.166 (-0.013-0.346)	1.194 (0.964-1.486)	0.186 (-0.043-0.420)	1.204 (0.958-1.523)

Table 3 shows that the higher the proportion of PLHIV initiating on ART in a ward, the viral load suppression rate increases by 35% (RR: 1.345; 95% CrI 1.221-1.492). The viral load suppression rate (<1 000 copies/mL) increased by 44% with an increasing number of female PLHIV in a ward (RR: 1.442; 95%CrI: 1.056-1.962).

Figure 6: Heterogeneity of predicted viral load suppression (<1 000 cp/mL) rates in Ekurhuleni Metropolitan Municipality 2012-2016 (1st January 2012 - 31st December 2016)

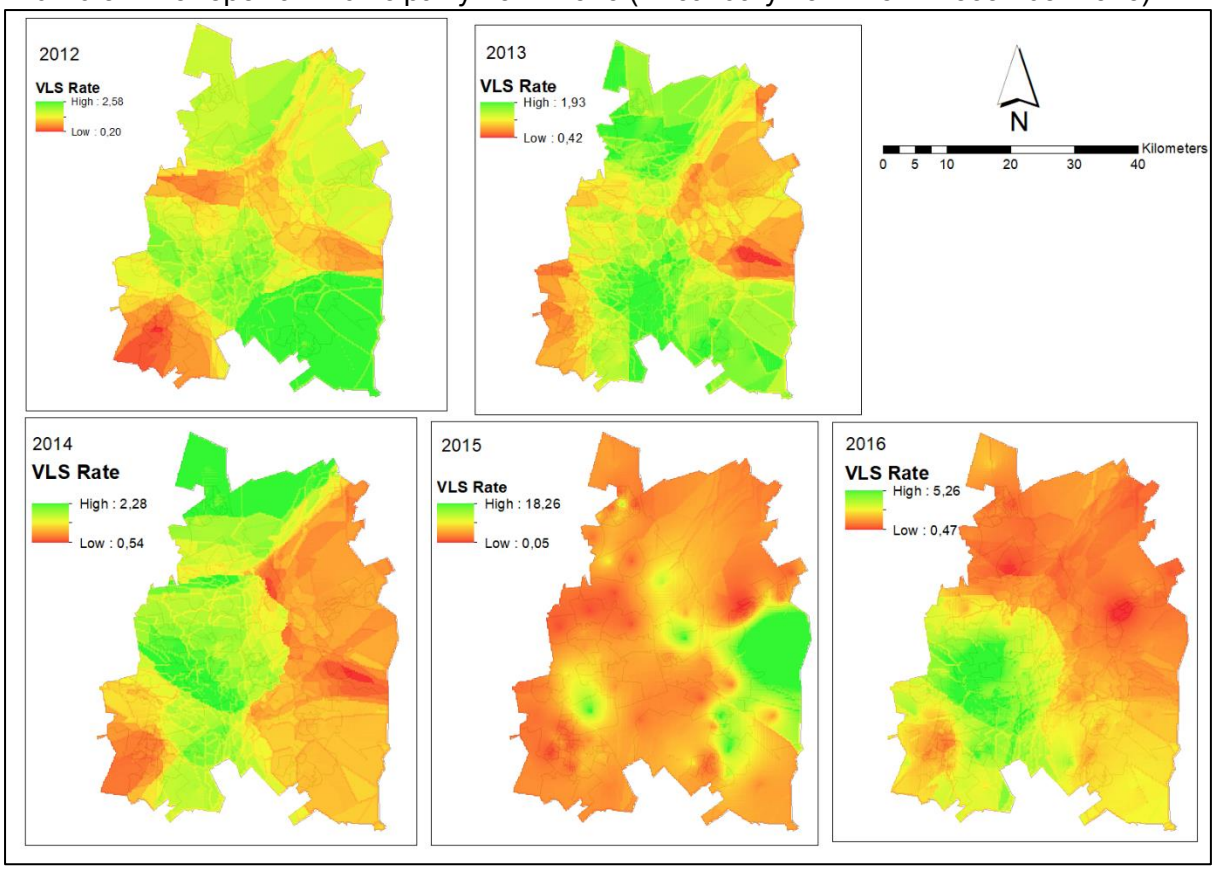


Figure 6 shows the spatial-temporal trend of viral load suppression rates from 2012 to 2016 highlighting the heterogeneity of viral load suppression rates in Ekurhuleni over the study period. The areas with high proportion of viral load suppression are seen in the green colour, whereas the red colour are areas where the proportion of those virally suppressed is low

Discussion

These findings show presence of spatial and temporal heterogeneity in viral load suppression in EMM using routinely collected laboratory data. These further provide valuable insights into the HIV programmes in the study area by identifying wards needing additional support for linkage to and retention in care. Although the proportion of virally suppressed PLHIV steadily increased from 2012 to 2015, the spatial maps revealed ward-level differences and evidence that high and low levels of viral load suppression rates were clustered geographically across space and time. High viral load suppression rates were positively correlated by increasing ART coverage and being female. When the threshold of <400 copies/mL was applied, the viral load suppression dropped by at most 15%. This highlights the gaps in monitoring, treatment, and availability of more effective ART drugs.

Understanding the variations in viral load suppression across space and time can guide interventions to improve programmes monitoring retention in care, which may ultimately lead to reduces HIV transmission and HIV incidence in EMM. Controlling the HIV epidemic in the age of universal test and treat, requires targeting individuals in the right areas. Areas with high and low performing healthcare facilities at a ward-level should be identified. In Ekurhuleni, the currently reported ART coverage is 72%. All facilities reporting less than 95% should expand community-level HIV programmes to improve the ART coverage. To reach

95% in addition to focusing on women who mostly access clinics compared to males, facilities should find the missing men in communities who largely disengage from health seeking (14). Mostly antenatal studies in South Africa have been used to evaluate viral load suppression in women (15-17). Across the studies, adolescent girls, and young women (AGYW) have reported lowest viral suppression rates (15-17) and findings suggest that this may be due to delayed ART initiation mostly occurring after pregnancy (15, 18). Viral load suppression is reported in married women, suggesting a presence of social support structures that encourage disclosure of HIV positive status to partners facilitating adherence to ART (16-18). These previous findings highlight the need for targeted approaches to reach different key groups of female individuals, specifically those in the younger age groups (15-18) to improve viral load suppression rates.

In our study, we found that for wards in the highest quartile, 86% of PLHIV achieved viral suppression and whereas those in the lowest quartile, only 35% were virally suppressed. To ensure that viral load suppression improves in Ekurhuleni, targeting wards with lower viral load suppression is necessary. Improving the performance along the care cascade is one key steps toward HIV elimination. At ward-level, facilities could improve their performance by improving the indicators in the care continuum. For instance, adherence counselling before ART initiation needs examining. Understanding the comprehension of counselling messages by patients' needs assessment. Our findings show that more than one viral load test was conducted for each patient per year suggesting alignment with national guidelines. The number of viral loads samples tested increased over the five-year period suggesting increased retention in care and viral load suppression. At an individual level, one study in South Africa showed that viral load suppression (<400 copies/mL) was associated with having a viral load measurement two months within the scheduled date in the facility (19). Although our study did not set out to investigate this association, the findings are necessary to improve viral load monitoring at facility or ward-level.

Our findings show that the proportion of viral load suppression increased between 2012 and 2015 but dropped in 2016. In 2016, universal test and treat was introduced for all people testing HIV positive. This may have led to an increase in the number of people presenting at healthcare facilities for HIV care decreasing the rate of viral load suppression as observed in 2016. In addition, the large number of patients initiated on immediate treatment may have stretched the existing constrained resources and reduced efforts on counselling and follow up. However, a recent study assessing district level targets for 90-90-90 in 2018, showed that viral load suppression in Ekurhuleni was still low at 41.3% (20). This highlights the need to improve viral load monitoring as these recent estimates predict viral load suppression to 86% by 2030 (20). In the era of UTT, more nuanced approaches are required to identify at a clinic and laboratory level, patients at risk for poor adherence. A clinic prediction score developed from a previous study using routinely collected data showed better performance over standard adherence measures in correctly identifying patients with poor adherence outcome at 6 months post ART initiation (21). These patients will subsequently require individualized treatment to prevent virologic failure as has been observed in some developed countries (22, 23).

Our findings showed a weak relationship between increasing the proportion initiating ART and viral load suppression rates at ward-level which confirmed previous findings in other settings which showed widely increasing ART initiation leads to improved viral load suppression rates (24). These show marginal gains in the HIV program in Ekurhuleni which however need improvement. Services such as same-day initiations and differentiated delivery of care to are needed (25, 26) to increases the proportion of those on treatment and

interruptions in ART initiation and retention (20). Interruptions are likely to introduce resistance and the introduction of the integrase strand-transfer inhibitor dolutegravir, may increase overall virological suppression rates (27). However, more needs to be done to alleviate concerns regarding management of viremia.

Our analysis has identified geographic disparities and recommends strengthening targeted adherence at ward-level by improving counselling and management of the patients to address ward inequalities. Continued exploration of the interaction of population dynamics and programmatic interventions such as viral load testing access or coverage and enhanced adherence for individuals on treatment and those with virologic failure are needed (28). For the poor performing wards, strengthening tracing programmes which track patients who default or those living in adjacent wards requires collaboration between wards. Facilities serving communities in Thokoza, Langaville and Brakpan need to intensify these efforts to ensure that PLHIV are retained in care to achieve viral load suppression.

This analysis makes several contributions to the literature. First, we used existing routinely collected laboratory data to monitor viral load in Ekurhuleni and used other readily available databases. Secondly, we used Bayesian analytical techniques which incorporated longitudinal design to assess the predictors of viral load suppression over time rather than cross-sectional estimates (29). Lastly, this study provided a robust approach to spatial analysis whereby geospatial data was used to evaluate underlying patterns of viral load suppression within a small area using local surveillance data Lastly, we used geospatial patterns of high and low clustering of viral load suppression were identified in Ekurhuleni. Our analysis had some limitations, and the findings should be interpreted with caution. First, some variation in our ward-level viral load suppression measure may reflect random fluctuations. However, by averaging over the five years of data, we attained a measure with high reliability, indicating evidence of a persistent ward effect. Secondly, we used laboratory data through December 2016 three months into UTT implementation and did not have enough data post-implementation for comparison. In addition, there were potential missing laboratory data that may have originated from lack of adequate capturing. Thirdly, we used data from patients in HIV care, and may have missed including data from those who do not frequently attend clinic visits or conduct pharmacy pickups. Lastly, the absence of health facility characteristics from this analysis limited accounting for the differences across the different health facilities. This must be considered in any future work where data on inputs, costs, outputs, and quality is obtained to measure provider efficiency. Furthermore, the determinants of and interrelationships between costs, efficiency, and quality across the health facilities is examined.

Conclusions

Wards with facilities that successfully monitor PLHIV for viral suppression are likely see a reduction in HIV incidence in the communities they serve. Wards with facilities reporting poorer performance will experience persistent transmission and other poor outcomes. Addressing gaps that target the adherence, and retention in care for men is critical to achieve optimal viral load suppression in Ekurhuleni. Measuring differences in viral load across wards and visualizing their variations is a critical step toward viral load suppression. Ekurhuleni's public health strategy should increase intensive implementation of retention programmes and wider efforts around HIV viral suppression in these geographic areas to achieve the goals of the 95-95-95 plan.

Competing interests

All authors declare no conflicts of interest.

Authors' contributions

LC conceptualized the study, acquired, and analysed the data. TK-C, SC and EM contributed to interpretation of the results. All authors read and approved the final manuscript.

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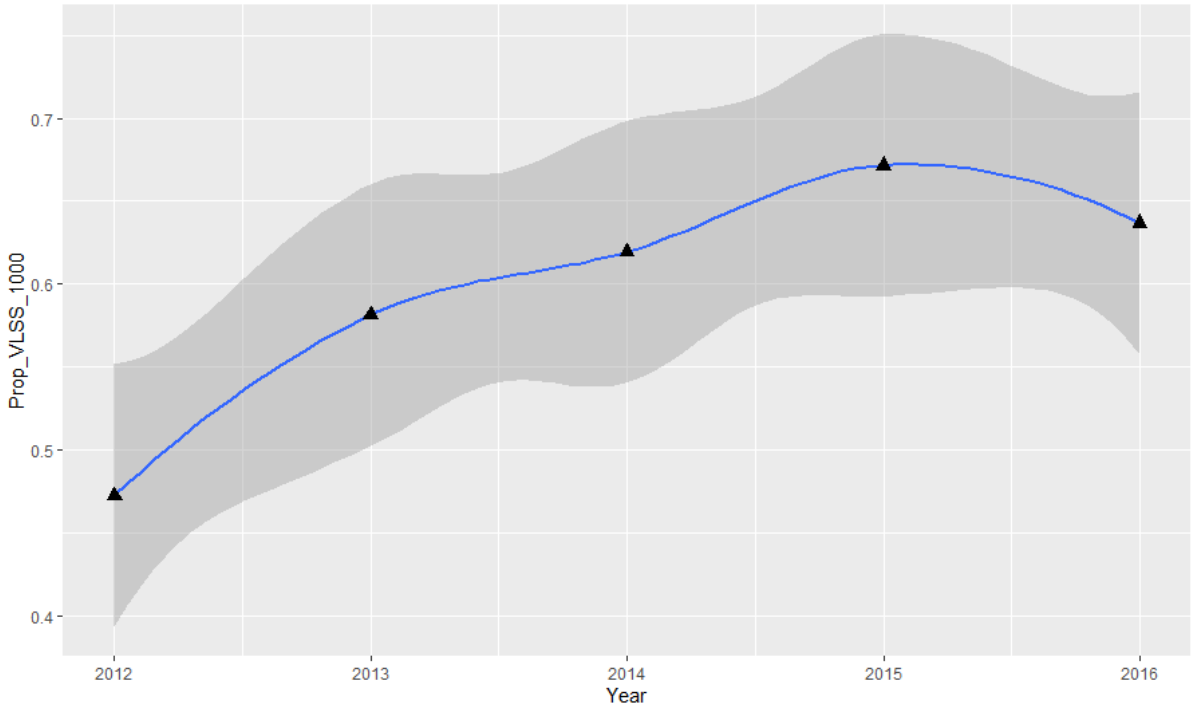
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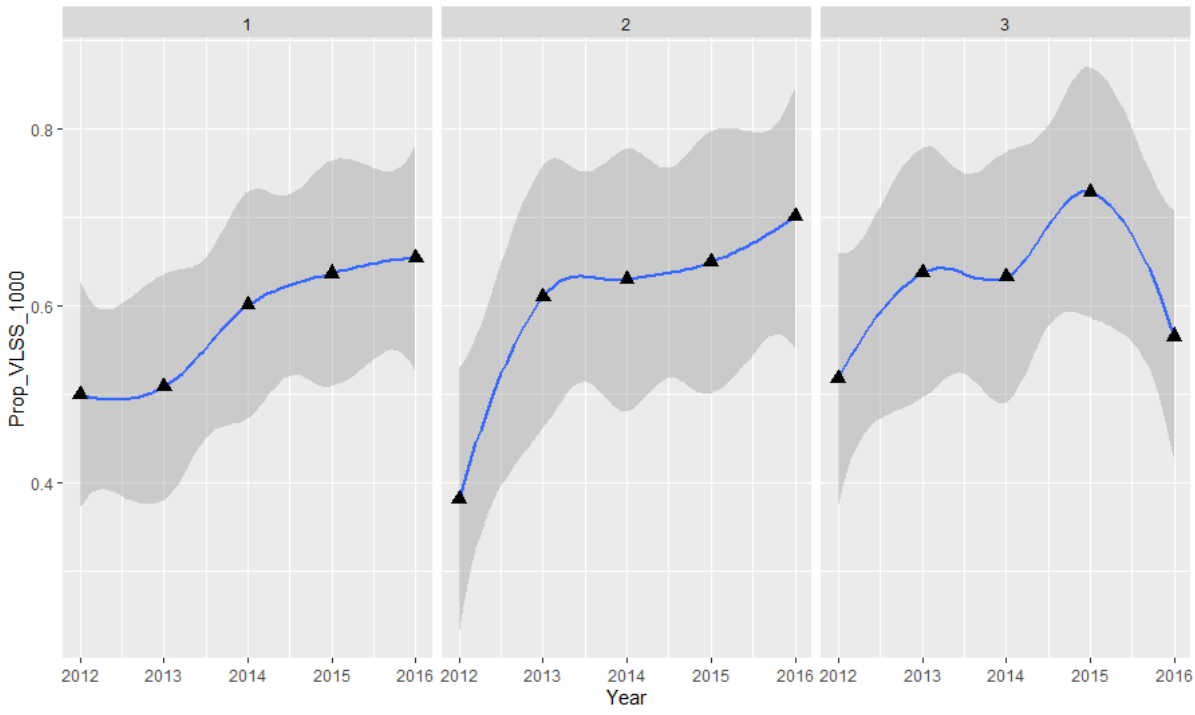
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Supporting information

Supplementary file 1: Overall proportion of viral load suppression (<1000 copies/mL) Ekurhuleni Metropolitan Municipality (1st January 2012 - 31st August 2016)

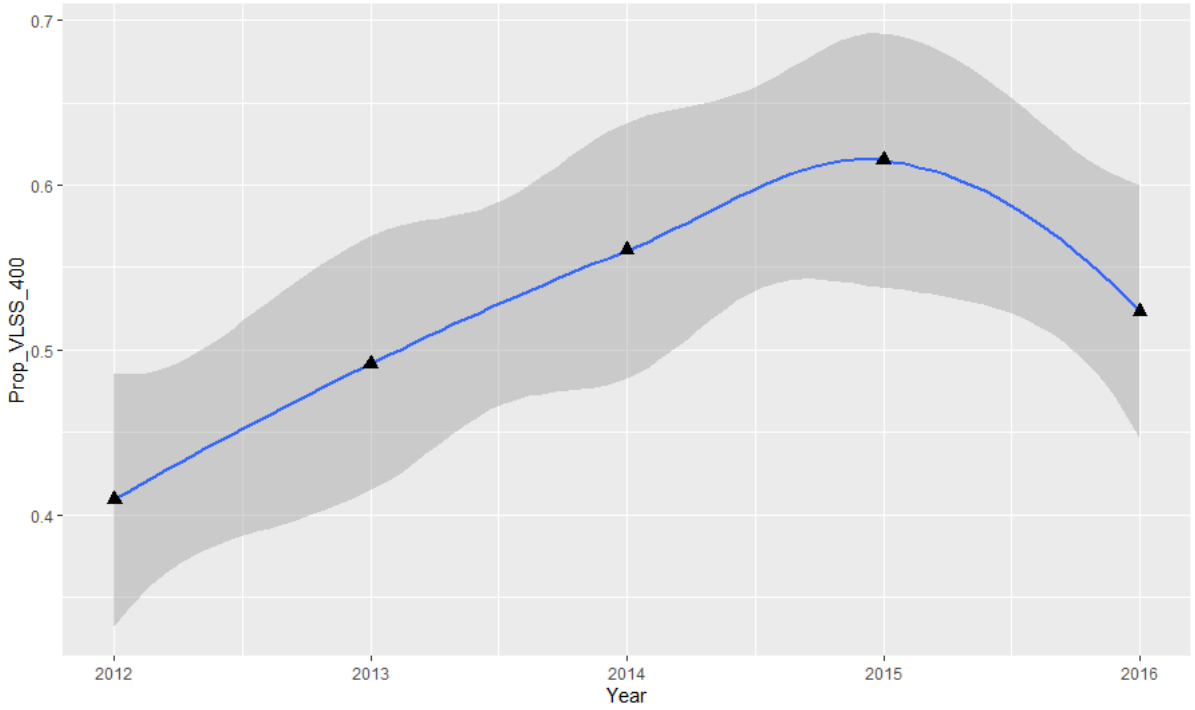


Supplementary file 2: Proportion of viral load suppression (<1000 copies/mL) by sub-district in Ekurhuleni Metropolitan Municipality (1st January 2012 - 31st August 2016)

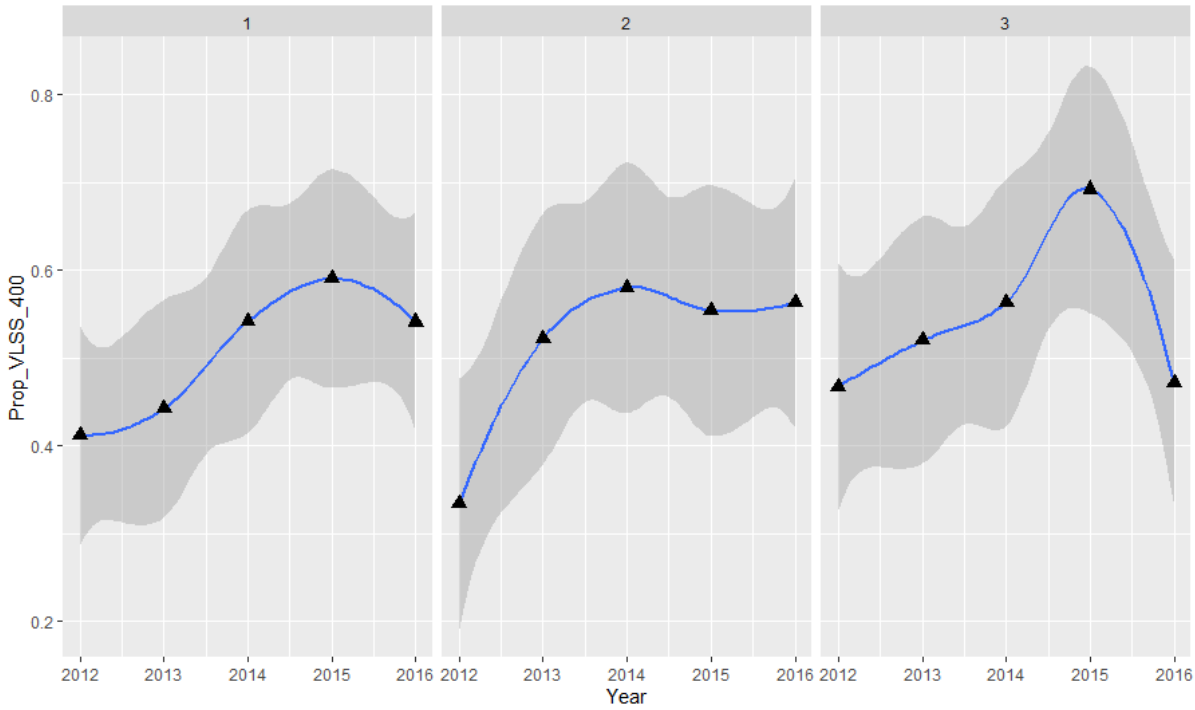


Sub-district 1: South; sub-district 2: North and sub-district 3: East

Supplementary file 3: Overall proportion of viral load suppression (<400 copies/mL) by sub-district in Ekurhuleni Metropolitan Municipality (1st January 2012 - 31st August 2016)



Supplementary file 4: Proportion of viral load suppression (<400 copies/mL) by sub-district in Ekurhuleni Metropolitan Municipality (1st January 2012 - 31st August 2016)



Sub-district 1: South; sub-district 2: North and sub-district 3: East

Appendix H: Copies of PhD outputs – Manuscript 3

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PLOS GLOBAL PUBLIC HEALTH

RESEARCH ARTICLE

Understanding factors influencing utilization of HIV prevention and treatment services among patients and providers in a heterogeneous setting: A qualitative study from South Africa

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Abstract

Despite advances made in HIV prevention and treatment interventions in South Africa, barriers to their utilization continue to exist. Understanding perspectives from patients and providers of healthcare can shed light on the necessary strategies to enhance uptake of HIV services. A cross-sectional qualitative study was conducted in July 2020 in Ekurhuleni District. Based on HIV prevalence estimates from a national survey, male condom use coverage and antiretroviral treatment (ART) initiation rates from routinely collected clinical data for 2012, we selected facilities from geographical areas with varying HIV prevalence and uptake of HIV services. In-depth interviews were conducted with adult (≥ 18 years) patients and healthcare workers in selected primary healthcare facilities. Thematic analysis was performed following a framework built around the social cognitive theory to describe behavioural, personal, and social/environmental factors influencing utilization of HIV services. Behavioural factors facilitating uptake of HIV services included awareness of the protective value of condoms, and the benefits of ART in suppressing viral load and preventing mother-to-child HIV transmission which was evident across geographical areas. Barriers in high prevalence areas included suboptimal condom use, fears of a positive HIV result, and anticipated HIV-related stigma while seeking healthcare services. Across the geographical areas, personal factors included ability to correctly use available services enhanced by knowledge acquired during counselling sessions and community-based health promotion activities. Further, social support from family reinforced engagement in care. Compared to low uptake areas, clinics in high uptake areas used care-facilitators, outreach teams and decanting programs to address the environmental barriers including staff shortages and long queues. Barriers at multiple levels prevent optimal utilization of HIV services, calling for strategies that

Data Availability Statement: Excerpts of the transcripts relevant to the study are available within the paper and data has been uploaded as supplementary information.

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target and address the different levels and tailored to needs of specific settings. Overall, improved delivery of HIV prevention or treatment interventions can be achieved through strengthening training of healthcare providers in facilities and communities and addressing negative sequelae from utilising services in low uptake areas.

Introduction

The HIV care cascade indicates sub-optimal uptake and coverage of HIV interventions including HIV testing and adherence to antiretroviral therapy (ART) [1,2]. Factors such as anticipated stigma, non-disclosure of HIV status, HIV medication side effects, and low HIV risk perception have been reported worldwide to prevent uptake of HIV interventions [1,3]. Among women, reduced engagement in care has also been noted due to actual or anticipated violent reaction from male partners [4,5]. Men have poorer health outcomes as they are less likely than women to know their HIV status, access and adhere to HIV treatment and more likely die as a result of AIDS-related illnesses due to underutilization of healthcare services [6–8]. Lack of confidential spaces, stock-outs, long queues and negative patient-provider relationship hinder uptake of these interventions [1,3]. Furthermore, lack of awareness on available interventions in the communities and constrained human resources prevent patients from accessing available interventions [3].

Services including HIV testing services (HTS) and ART initiation for those who test positive are a major response to the HIV epidemic, offering a comprehensive package with promising outcomes [9]. In South Africa, primary healthcare clinics (PHCs), often providers of this package, offer HIV pre-and post-test counselling, testing, linkage to care, prevention of onward transmission by providing condoms, pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), prevention of mother-to-child transmission (PMTCT) and universal test and treat (UTT) [10]. The South African National Strategic Plan (NSP) on HIV, STIs and TB 2017–2022 advocates for the adoption of these available HIV prevention or treatment services to reduce incident infections by more than 60% by 2022 [11].

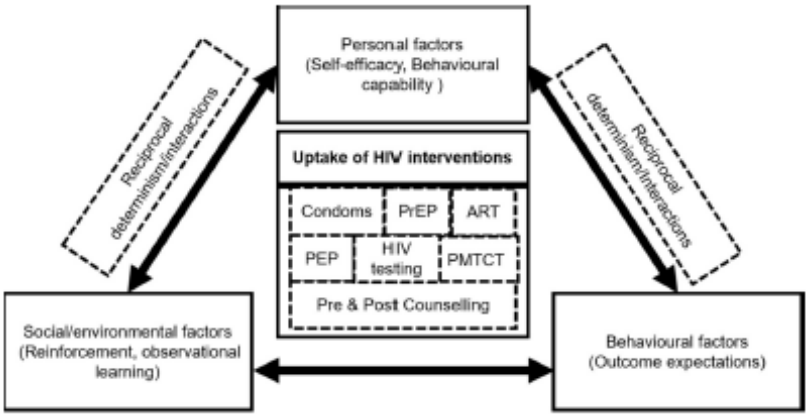
In many high HIV prevalence settings in Africa, there is heterogeneity in both HIV prevalence [12–14] and uptake of available HIV services [15]. Non-homogenous distribution of resources implies that the dynamics associated with utilization or delivery of HIV programmes may also differ across geographical areas. Limited insights exist regarding these dynamics as they manifest in different geographical areas. Having a context-specific understanding of these factors is necessary to allow realigning of interventions to enhance uptake and coverage of existing HIV programmes [16].

Using a qualitative research approach and drawing on perspectives from patients and providers, this study sought to generate an in-depth understanding of the factors that influence uptake of HIV interventions in a heterogeneous setting in South Africa. The goal is to inform targeted and contextualised implementation to improve uptake.

Materials and methods

Study design and theoretical framework

This cross-sectional qualitative study using in-depth interviews (IDIs) sought to understand and describe the factors that influence patients' and providers' utilization of HIV prevention or treatment services [17,18]. We adapted the social cognitive theory (SCT) framework to



ART: Antiretroviral treatment; **PEP:** Post-exposure prophylaxis; **PMTCT:** Prevention of mother to child transmission; **PrEP:** Pre-exposure prophylaxis

Fig 1. Adaptation of the social cognitive theory.

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describe patient and healthcare worker (HCW) experiences when utilizing and delivering HIV prevention or treatment services [19]. SCT identifies key determinants of health behaviours including outcome expectations (beliefs about consequences of behavioural choices), behavioural capability (actual ability to perform desired behaviours), self-efficacy (belief in one's ability to account for and check one's behaviours), observational learning (belief based on observing role models accomplish desired behaviours), and reinforcement (responding to external factors). A central concept within SCT is reciprocal determinism, where all factors operate as interacting determinants that influence each other [20]. The adaptation of the SCT theory, used in this study is illustrated in Fig 1 [19].

Study setting

The study was carried out in three PHCs in Ekurhuleni Metropolitan Municipality (EMM), Gauteng Province, of South Africa. The district is considered high priority in the NSP 2017–2022 due to its large population (3.1 million) [21] and high HIV prevalence (15%) [22]. Primary healthcare clinics serve as the first point of entry in communities where free HIV care and treatment is provided [23]. EMM has a predominantly black male population (51.2%), and almost 25% live below the poverty line (earn less than ZAR 992 per month ≈ US$64) in overcrowded informal settlements on the urban periphery with limited access to job opportunities and adequate social infrastructure [24].

Sampling, participant recruitment, and data collection

We created three maps showing the distribution of HIV prevalence (estimated from a national survey [25]), and male condom use coverage and ART initiation rates (from routinely collected data in clinics) in 2012. Four geographical areas were identified and categorized as follows: high HIV prevalence and high uptake of interventions (HH); high HIV prevalence and low uptake of interventions (HL); low HIV prevalence and high uptake of interventions (LH); and low HIV prevalence and low uptake of interventions (LL). Participants were enrolled from three clinics in LL, LH and HL areas (Fig 2). LH was further considered as ideal due to the combination of high uptake of interventions and low HIV prevalence whereas LL and HL

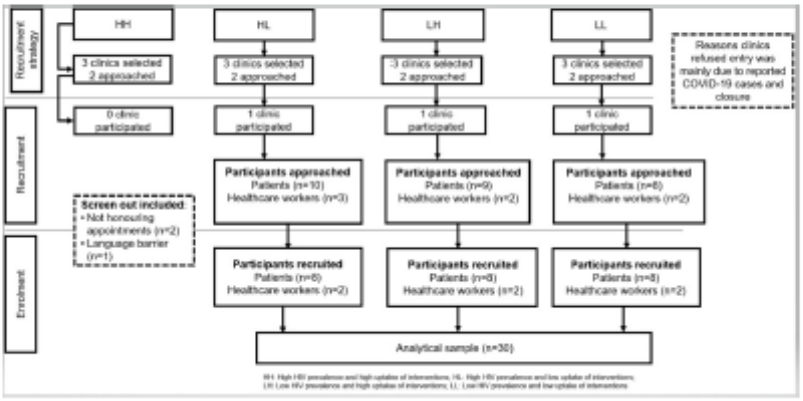


Fig 2. Flow diagram showing the recruitment strategy and enrolment of participants for the study.

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were considered non ideal areas due to low uptake of interventions. Due to restrictions imposed as a result of COVID-19 pandemic, participants from clinics in HH areas were not included.

Data were collected in July 2020 by four female and three male research assistants (RAs) with experience in conducting qualitative interviews. The RAs, fluent in the major languages used in the study area (English, IsiZulu, Sesotho and Setswana), visited the PHCs during the week between 7am and 12pm. They either approached patients for recruitment as they queued for their routine visits, or as referred by HCWs those newly initiating ART. RAs also made appointments with HCWs providing HIV prevention and treatment services for interviews, which were scheduled at the HCW's convenience. All participants were provided with detailed study information before giving their written informed consent. All participants were either working in or seeking treatment from the selected clinics, $\geq$18 years and willing to consent to audio recording of the interview. Consenting participants were assigned a unique study number for confidentiality. The final sample of 30 participants included male and female PLHIV, patients who were newly initiated on ART, HIV negative patients, and HCWs providing different HIV services at the clinic and community-level. The variedness of this ultimate sample would enable obtaining a fairly comprehensive picture about experiences and perceptions related to uptake and delivery of HIV services [26].

Interviews lasted 30–45 minutes and were carried out using a guide with open-ended questions. Topics covered in the guide included benefits of using available interventions; knowledge and awareness of HIV prevention and treatment interventions, where to access these and experiences in using them; barriers to and facilitators for uptake, and provider perceptions of regarding the utilization and delivery of HIV care. Interviews were conducted in quiet locations, mostly an open space or in vehicles outside the healthcare facilities, or in empty offices. Discussions were primarily conducted in English, but participants were free to express themselves in vernacular (Setswana, isiZulu or Sesotho) where they felt it helped them better articulate their lived experiences when utilising HIV interventions. RAs were trained to listen carefully and probe during interviews. The investigator (LC) reviewed the first five patient interviews and gave feedback to teams to enhance the questioning and probing. After the interviews, RAs thanked participants and presented a meal voucher of ZAR50≈US$3.3 for their time. Saturation of themes during data collection was achieved through regular debriefing discussions with the RAs on probing techniques [27]. Interviews were stopped when no new issues emerged.

Data analysis

All interviews were transcribed verbatim. Audio recordings with renderings of local languages were directly transcribed and translated to English by RAs. RM and TN, fluent in the study languages, checked the accuracy of the transcripts against digital recordings. Multiple reading of transcripts was done by LC to capture context, followed by manual coding and categorisation of recurring themes. Transcripts (S1 Data) were imported into QSR International NVivo version 10 software to group the initial codes into themes and subsequently organize into key dimensions and identify patterns across groups. [28]. Soft-copy transcripts were stored securely and safely on password-protected computers and audio recordings deleted from recorders. Transcripts were not returned to participants for comment.

Two members of the study team with Master's and Honours degree qualification (LC and RM) independently reviewed and coded the transcripts guided by the SCT constructs to explore the perceptions of participants on uptake and delivery of HIV services in routine settings. To analyse the qualitative data, we used thematic analysis and inductively and deductively developed codes. The codes were organized into three overarching domains of factors, namely behavioural, personal, and social/environmental. Five themes, aligned to these domains and partly adapted from the original SCT framework and emerging from the data, were defined. SCT constructs were used as initial guides to coding, and the subsequent themes emerging during iterative and deductive coding were therefore closely aligned with the six SCT constructs [29]. Collaboratively, LC and JC (qualitatively -oriented social scientist) reviewed and refined emerging key dimensions and themes The process of refining, reviewing key dimensions and emerging themes was repeatedly done until saturation was achieved when no additional themes or categories could be identified [27]. The analysis process identified salient differences in the geographical settings. Participant demographic characteristics were obtained from the qualitative interviews. We categorized gender based on the responses from the question: "Tell us more about yourself," when the participant explicitly and voluntarily mentioned their gender as either male or female without probing.

Ethical considerations

University of the Witwatersrand Human Research Ethics Committee (HREC; M181088) granted ethics approval and Ekurhuleni District Research Committee gave permission to access patients and staff in the primary healthcare clinics. All participants provided written consent for participation, audio recording of IDIs and use of their quotations. All participant records and information were anonymized and de-identified prior to analysis.

Results

Participants' characteristics

Patients (n = 24) were mostly female (n = 16, 66.7%), not married (n = 16, 66.7%) and HIV-positive (n = 16, 66.7%), and of median age of 37 (IQR: 31–40) years. Most reported having lived in the area for longer than 5 years (n = 15, 62.5%). Slightly above half had been seeking healthcare from the clinics for less than one year (n = 13, 54.2%). HIV-positive patients were on ART for at least 84 (IQR: 21–144) months, and two were newly diagnosed and initiated on ART at the time of the interviews (Table 1). One male patient self-identified as MSM and one HIV-positive female patient was pregnant. The HCWs (all female and employed by either Department of Health (DOH) or donor-funded NGOs working in the area) included a clinician, a professional nurse, a primary health worker, two HIV counsellors and a care facilitator. Most had more than 5 years of professional experience (Table 1). All described their roles as

Table 1. Socio-demographic characteristics of participants.

Patients	**N = 24**
Gender	
Female	16 (66.7)
Male	8 (33.3)
Age—median (interquartile range)	37 (31–40)
Self-reported HIV status	
Positive	16 (66.7)
Negative	8 (33.3)
Duration on ART in months—median (interquartile range)	84 (21–144)
Marital status	
Not married	16 (66.7)
Married	8 (33.3)
Years lived in area of residence	
< 1 year	1 (4.2)
1–5 years	8 (33.3)
>5 years	15 (62.5)
Years visiting the current clinic	
< 1 year	13 (54.2)
1–5 years	5 (20.8)
>5 years	6 (25.0)
Healthcare workers	**N = 6**
Professional category	
Clinician	1 (16.7)
Professional nurse	1 (16.7)
Primary health worker	1 (16.7)
HIV counsellor	2 (33.3)
Care facilitator	1 (16.7)
Professional years of experience	
≤ 5 years	2 (33.3)
>5 years	4 (66.7)
Years working in the current clinic	
≤ 5 years	3 (50.0)
>5 years	3 (50.0)

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involving HIV care and treatment services including counselling, ART services, health promotion, HIV prevention and HIV awareness and education.

We present five themes from the analysis (Table 2) supported with verbatim, minimally edited quotes. Table 3 provides a summary of the thematic similarities and differences across the three geographical settings

Benefits from adopting HIV prevention or treatment services

Participants anticipated positive outcomes associated with HIV treatment. The anticipation of improved health outcomes emerged across different geographical areas, particularly, in reference to viral load suppression. Other positive health outcomes included good pregnancy outcomes for HIV-positive mothers, general good health including weight gain for those living with HIV, and remaining HIV-negative or not transmitting HIV to sexual partners.

Table 2. Themes and key dimensions from in-depth interviews and their relevant SCT constructs and domains.

Theme and key dimensions*	Relevant SCT construct and *operational definition***	Relevant SCT domain**
Theme 1: Benefits from adopting HIV prevention or treatment services *Key dimensions* • Remaining HIV negative by using PrEP or PEP in case of unprotected sexual acts and protected sexual acts by condom use • Suppressed viral load as a result of consistently taking ART • Being in HIV care while pregnant for positive pregnancy outcomes including HIV negative children	**Outcome expectations** *"Expectations of positive health outcomes that are likely from a sustained action when utilising HIV prevention or treatment services"*	Behavioural factors
Theme 2: Potential negative sequelae from utilising HIV prevention or treatment services *Key dimensions* • Fear of testing HIV positive which may lead to anticipated or enacted stigma • Accessing and using condoms especially for female patients may lead to anticipated or enacted stigma or intimate partner violence • Concerns from providers when patients do not use condoms in favour of PrEP, or not seek healthcare due to distance from healthcare facilities or prolonged waiting times • Side effects from ART may interrupt or stop utilization of HIV treatment	**Reciprocal determinism** *"Interactions between personal and social/environmental factors that causes behaviour change that negatively influences utilization of HIV prevention or treatment services"*	
Theme 3: Well-informed about available HIV prevention or treatment services *Key dimensions* • Having knowledge on HIV and available interventions, which facilitates utilization of HIV prevention or treatment interventions such as PrEP and PEP. • Using information and skills obtained during pre- and post-test HIV counselling, health promotion activities or campaigns to remain in HIV care • Attitudes towards utilizing HIV prevention or treatment services	**Behavioural capability** *"Having and using the acquired knowledge and skills on HIV prevention or treatment to utilize the available services"*	Personal factors
Theme 4: Ability to correctly use the available HIV prevention or treatment services *Key dimensions* • To correctly and consistently use condoms for HIV prevention • Taking ARVs to sustain an undetectable viral load and prevent death	**Self-efficacy** *"Having a good understanding of the importance of HIV prevention or treatment services and persistently using them to monitor and control behaviour"*	
Theme 5: Social or environmental dynamics and conditions supporting utilization of HIV prevention or treatment services *Key dimensions* • Drawing inspiration from peers who have lived positively despite being HIV positive • Social support from family members to continue utilizing the available HIV prevention or treatment interventions • Ensuring supply of condoms in healthcare facilities and in the communities • Structural support by friendly clinic staff who encourage utilization of interventions including to key populations • Differentiated care delivery of interventions for stable ART patients to overcome barriers associated with staff shortages and lengthy queues	**Observational learning** *"Observing from peers and performing desired behaviours from likening their experiences from utilizing HIV prevention or treatment services"* **Reinforcements** *"Encouraging positive changes through interpersonal and structural support"*	Social or Environmental factors

* Emerged from the data in the study

** Pre-defined and adopted from the SCT framework.

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"By me taking my treatment, I gave birth to a HIV-negative baby. Although I was stressed about it (my HIV status), I learnt that I needed to consult the nurses and doctors at the clinic if I wanted to deliver a HIV-negative baby." (Female, 36 years, HIV positive, LH)

Table 3. Overview of similarities and differences in themes across geographical setting.

Theme and key dimensions	HL	LH	LL
Theme 1: Benefits from adopting HIV prevention or treatment services			
Being in HIV care while pregnant for positive pregnancy outcomes including HIV negative children	Ō	Ō	Ō
Suppressed viral load as a result of consistently taking ART	Ō	Ō	Ō
Remaining HIV negative by using PrEP or PEP in case of unprotected sexual acts and protected sexual acts by condom use	Ō	Ō	Ō
Theme 2: Potential negative sequelae from utilising HIV prevention or treatment services			
Fear of testing HIV positive which may lead to anticipated or enacted stigma	Ō		Ō
Accessing and using condoms especially for female patients which may lead to anticipated or enacted stigma or violence	Ō		Ō
Concerns from providers when patients do not use condoms in favour of PrEP or when patients fail to seek healthcare due to proximity to healthcare facilities or prolonged waiting times	Ō		Ō
Side effects from ART that may interrupt or stop utilization of HIV treatment	Ō		Ō
Theme 3: Well-informed about available HIV prevention or treatment services			
Having knowledge on HIV and available interventions, which affect utilization of HIV prevention or treatment interventions such as PrEP and PEP.		Ō	Ō
Using information and skills obtained during pre and post-test HIV counselling, health promotion activities or campaigns to remain in HIV care		Ō	
Attitudes towards utilizing HIV prevention or treatment services		Ō	
Theme 4: Ability to correctly use the available HIV prevention or treatment services			
To correctly and consistently use condoms for HIV prevention		Ō	
Taking ARVs to sustain an undetectable viral load/prevent death	Ō	Ō	Ō
Theme 5: Social or environmental dynamics and conditions supporting utilization of HIV prevention or treatment services			
Drawing inspiration from peers who have lived positively despite being HIV positive		Ō	
Social support from family members to continue utilizing the available HIV prevention or treatment interventions	Ō	Ō	Ō
Ensuring supply of condoms in healthcare facilities and in the communities	Ō	Ō	Ō
Structural support by friendly clinic staff who encourage utilization of interventions including to key populations		Ō	
Differentiated care delivery of interventions for stable ART patients to overcome barriers associated with staff shortages and lengthy queues		Ō	

Ō Denotes similarities across settings.

Key: **HL** = High HIV prevalence and Low uptake of interventions; **LH** = Low HIV prevalence and High uptake of interventions; **LL** = Low HIV prevalence and Low uptake of interventions.

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"Since I have been on this treatment, I do not see anything wrong with it. My viral load is undetectable and I see that I am gaining weight." (Female, 32 years, HIV positive, LL)

"Before marriage, I always used to check my HIV status every three months to know about myself and to avoid infecting my sexual partners." (Male, 45 years, HIV negative, HL)

Potential negative sequelae from utilising HIV prevention or treatment services

This theme was mostly observed in areas where uptake of HIV services was low. Due to anticipated stigma, HCWs revealed that patients avoided disclosure of HIV status by providing incorrect addresses. This led to challenges when tracing and following-up of patients who defaulted on treatment especially in high HIV prevalence and low uptake areas.

"Most clients visit the clinic, look at how they are welcomed or how the facility operates. Someone from a different area comes to this clinic to get help, either because of not wanting to disclose their status at their nearest facility to a lot of people that they may know that side. These people come but provide fake addresses which is a bit challenging when you want to trace them after they have defaulted." (NGO Staff, HIV counsellor, HL)

Further, anticipated and enacted stigma was particularly reported by female patients. This barrier prevented optimum engagement in care. Other barriers included long queues and prolonged waiting times in facilities which impacted patients' livelihoods.

"If you are coming to the clinic as a lady and you want to collect condoms for protection, it's very hard because people are looking at you, judging and asking you why you need them. It is better to buy them in a shop but the sales person also thinks that when a lady buys condoms, she is promiscuous." (Female, unknown age, HIV positive, LL)

"The only thing that I have a problem with this clinic is time. You come early around five o`clock in the morning but wait until 12 o`clock to see the nurse. Maybe it is because there are very many people. You finally miss work and some nurses do not provide you with a letter to explain why I missed work." (Male, 35 years, HIV positive, HL)

IDIs revealed concerns from HCWs in certain areas about delivery of interventions particularly PrEP to patients seeking protection in case of unprotected sexual acts. These concerns are likely to perpetuate stigmatization of patients who choose to use PrEP for HIV prevention.

"My opinion is that we are encouraging clients to not use condoms by providing PrEP. People will start engaging in unprotected sexual intercourse with HIV-positive sexual partners and will not use condoms knowing that PrEP is available. This is not good. It's my personal opinion." (DOH Staff, Professional Nurse, LL)

Lastly, side effects from treatment were mentioned across the geographical areas. Most participants reported experiencing side effects from ART at the beginning of treatment but were encouraged to continue taking their treatment by HCWs.

"I started taking my medication and experienced drowsiness. But after three to four months, everything went back to normal as the nurse had said." (Male, 38 years, HIV positive, HL)

Well-informed about available HIV prevention or treatment services

Participants across the geographical areas had the necessary knowledge and skills for HIV prevention or treatment from counselling sessions in healthcare facilities, health promotion activities and campaigns in communities. All participants, described condoms as the commonly accessible HIV prevention method either freely from healthcare facilities or pharmacies and shops in the communities. Participants understood the importance of PrEP in HIV prevention

and appeared to see it as having superior levels of safety in protecting against HIV than condoms.

"PrEP is a pill and condom is a condom. With a condom, there is a lower chance of getting HIV while you are having sex with HIV infected person. Likewise, with PrEP, when you are having sex without a condom you are still protected. Although using condom is much safer, there are chances that it may break and you get infected." (Male, 40 years, HIV negative, LH)

There seemed to be adequate knowledge of PrEP among study participants. Patients seeking PrEP services from clinics explained in detail the HIV testing and pre-and post-counselling sessions

"I usually come to this clinic, for PrEP. Before they give you PrEP, you test for HIV. If negative, the nurses give you pills that you will take for a period to prevent you from being infected. It does not actually motivate you to engage in unprotected sex but if you sometimes have unprotected sex, that pill will protect you." (Male, 26 years, HIV negative, LL)

Knowledge of PEP services and its access was explored. Most participants knew where to access these services in case of an accidental exposure from an infected partner. However, HIV-positive participants seemed to have limited knowledge on PEP.

"I'm not sure about PEP but probably immediately after finding out that you had intercourse with an infected person, you go the nearest clinic where they give you something. What I don't know is for how many hours, minutes or days." (Female, 25 years, HIV positive, HL)

There appeared to be lack of adequate knowledge on universal test and treat (UTT) among the participants. Across all geographical areas, HIV-negative participants showed limited understanding of UTT and its benefit to reduce the risk of onward transmission by supressing viral load whereas some HIV-positive participants misunderstood the benefits of UTT in promoting disclosure.

"The advantages of UTT is for people to know their HIV status but if you are afraid of telling each other, try to tell one person you trust so that he can be the support. To remind you when to take your treatment and when to go collect them." (Female, 35 years, HIV positive, LL)

Lastly, discussions revealed that utilization of available interventions was said to depend on attitude and HIV risk perception.

"Using these interventions depends on my attitude towards HIV. As I said, I always use protection. If you are HIV-negative and do not take precautionary measures, you will become infected with HIV." (Female, 40 years, HIV negative, LH)

Ability to correctly use the available HIV prevention or treatment services

Aligned to the self-efficacy construct, this theme focused on participant ability to utilize HIV prevention or treatment services, the barriers and the strategies that would be adopted to overcome identified barriers. Consistent use of condoms to protect oneself and partners from infection or re-infection was commonly mentioned.

"Yes, I use condoms all the time because I don't want to get re-infected. My viral load is undetectable and I would like it to stay like that." (Female, 30 years, HIV positive, LH)

HIV-positive participants across geographical settings understood that non-adherence to treatment could result in weight loss, severe sickness, or death. Discussions revealed that to avoid experiencing these negative outcomes, adherence to ART was important.

"ART to me is like a battery, when it's flat you must charge and if you don't charge, it will shut down. I cannot stop taking treatment because I will lose my body, I am going to be sick and maybe after 2 or 3 years, I will be gone." (Male, 40 years, HIV positive, HL)

To ensure that patients were correctly utilizing the prevention services, HCWs educated them on proper use and storage of condoms to prevent deterioration in effectiveness and quality.

"We teach patients how to use condoms. There are many cases where condoms have burst and upon investigation, you find, it's because of poor storage, using expired condoms or reusing them. Our people need education on proper use or storage of condoms. They should not put them in the pocket, walk around the mall or keep the packet in the sun." (DOH Staff, Clinician, HL)

Social or environmental dynamics and conditions supporting utilization of HIV prevention or treatment services

Participants were motivated to utilize the available HIV treatment services from learning from and observing peers, as explained in this quote.

"This person was born HIV-positive and I didn't know I will end up like him. I started reading his story while in school and when I discovered that I am HIV-positive, I was motivated to take my medication as we were born the same way." (Male, 40 years, HIV positive, LH)

Social support was associated with the successful engagement in HIV care. Family members, particularly parents and siblings emerged as a key source of support, for HIV-positive participants. However, due to fear of disclosure, treatment was interrupted when away from home as explained by one young participant.

"At home, my parents and siblings remind me to take my medication. When I decide to sleep away from home, I don't bring my medication with me and skip my dose because I don't want anyone apart from my family to know my condition." (Female, 25 years, HIV positive, HL)

Although there were concerns about enacted, anticipated stigma and discrimination, many participants found strength from the support of those with whom they had close and trustworthy relationships. Family and HCWs increased uptake. However, in some instances, intimate partners prevented utilization of certain services such as condoms despite knowledge of HIV status. HCWs reported the challenges female patients faced from male sexual partners regarding condom use.

"Every day in the morning, we issue out a new box of condoms which patients take them but do not utilize. The married ones say that their husbands are refusing to use condoms. We counsel the couple, they agree to use them but after a week, their story changes and they tell you that they cannot be told how to manage their bedroom issues." (DOH staff, Professional Nurse, LH)

Despite challenges in using condoms or ART due to relational dynamics or side effects, it emerged that at a structural level, a positive patient-provider relationship and consistent

supply of ART or condoms at clinic-level encouraged utilization of HIV services. Most HIV-positive patients understood that ART was lifelong and facilities have ensured that stock-outs were minimized. In high uptake areas, there was an adequate supply of ART to HIV patients and evidence of structural and social support.

"In this clinic, I've never experienced shortage of ART. I always get my medication on time and the nurses always remind me a week before my visit date. If I am unavailable, someone I trust will collect on my behalf." (Female, 35 years, HIV positive, LH)

In high uptake geographical areas there are MSM friendly clinics. There is no fear of stigmatization from HCWs, which encourages uptake of HIV servicess by this key population.

"I like this clinic because it provides me comfort as a "deputy person" (MSM). I come here to express myself and I like that whenever I talk about confidential things, the staff respect my privacy and I do not hear of our conversation in the community." (Male, 40 years, HIV positive, LH).

To address issues around small clinic spaces and staff shortage, clinics in high uptake geographical areas have utilized differentiated delivery of care programmes where patients stable on ART and virally suppressed collect medication every two months for six months from a specified location to ensure retention in care.

"We can decant the patient for six months. The patient's viral load should be less than 50 copies/ml. We refer to the central chronic medicine dispensing and distribution (CCMDD) program where they get their medication delivered in a box every two months." (DOH Staff, Professional Nurse, LH)

HCWs mentioned additional strengthening of existing system to expand HIV prevention services. Clinics in high uptake geographical areas have used ward-based outreach teams (WBOTS) to conduct HTS in the communities. The WBOTS work together with mobile testing clinics to link patients in the community for HIV testing. The WBOTS also distribute HIV self-testing kits.

"We have WBOTS that serve in the community and mobile clinics that deliver HTS. They conduct HIV testing while WBOTS distribute HIV test kits to people in the community unable to visit the clinic for HIV services to test at home." (NGO staff, HIV counsellor, LH)

In addition to mobile clinics and WBOTS, some clinics utilize case-facilitators to provide linkage to HIV prevention services. Case-facilitators held campaigns to create awareness about HIV and the available services such as PrEP and HTS. At the time of the study, these services were interrupted due to restriction measures put in place during the COVID-19 pandemic.

"Before COVID-19, we were conducting campaigns in the community, giving health talks, and issuing condoms. Because of COVID-19 we are no longer campaigning but when a patient comes to the clinic and asks for a test, we will ask for the reasons for HIV testing. For those testing negative and have had unprotected sex, we offer PrEP for prevention." (NGO staff, Case-facilitator, HL)

Discussion

These findings highlight the relevance of using SCT framework for strengthening utilization of HIV prevention and treatment services in high priority districts such as EMM. SCT provides a framework for understanding how perceptions about self-efficacy and outcome expectations, influenced by personal, interpersonal and environmental factors, as well as behaviour capability, ultimately affect engagement in care. The interactions between factors at each one of these levels is particularly important for understanding why patients utilize HIV services in heterogeneous settings. The construct of self-efficacy emphasized on overcoming barriers to utilization of the available interventions. The construct of behavioural capability emphasized the need for individuals seeking HIV care and treatment to have a desired target of being well informed and knowledgeable about the HIV interventions and their availability. Newer HIV prevention or treatment methods such as UTT were not well understood in settings with low uptake of services. The current study showed that newly diagnosed HIV patients had received immediate ART initiation but most did not show adequate understanding of UTT. Health promoters and counsellors should aim to increase factual knowledge of UTT. In high uptake settings, there was high HIV risk perception which seemed to motivate engagement in HIV services. Findings highlight examining personal and relational dynamics which are likely to influence disengagement along the HIV care continuum.

The various outcome expectations associated with utilizing HIV prorammes in this study have been widely reported elsewhere [16,30,31]. Implementers need to continually consider these factors when rolling out programs at facility level. For instance, HIV-positive women of child bearing age are more motivated to give birth to HIV-negative children as observed in the Option B+ study conducted in four sub-Saharan countries [31]. A similar finding was made in our study, and was observed across geographical settings. This points to widespread effective messaging and education which, in turn, likely encourages women to take up and be retained on ART for PMTCT and to protection of their infants [30]. Corroborating this finding, a study in three high HIV burden South African districts found ART initiation rates in pregnant women being higher compared to males and non-pregnant females [16]. HIV-positive men and women were more motivated to remain in care to suppress their viral load for health reasons despite experiencing side effects [30]. Although our study showed that pregnant mothers were adherent in PMTCT programs, a systematic review conducted by Ng'eno et al highlighted common reasons for the poor outcomes experienced by adolescent and young women. This population is often delayed into HIV care due to inadequate knowledge to navigate health system, and stigma from consequences of a positive HIV care result from healthcare workers, family and community [32]. Psychosocial support from healthcare workers and peer support is encouraged to increase engagement in HIV services [33].

Findings also showed that HIV-negative patients were likely to use HIV prevention services including condoms, PrEP and PEP to prevent infection. There was awareness and acceptability of PrEP and willingness to use was mostly reported in males. However, a recent study in South Africa with the youth revealed that there was low awareness of PrEP and males were not likely to use PrEP compared to females due to its daily pill burden [34]. Our study found no concerns about side effects from using PrEP as reported by other populations (MSM) in different settings (Europe) [35,36]. Although reports on the quality of government issued condoms were frequently cited, findings across all geographical settings showed that males mostly utilized condoms to prevent HIV infection. This was encouraging considering the declining proportions of condom use among men reported in the 2020 Global AIDS report [37]. This however was not consistent with findings on younger males in South Africa who have reported performing condomless sex acts for various reasons including impregnating a female partner

as a symbol of prestige and sexual maturity [38]. However, for females, there was evidence of lack of or inconsistent condom use. This finding was corroborated by a systematic review of multiple studies across sub-Saharan Africa that showed that a lower relationship power limits women's decision-making power to mitigate HIV risk [39]. Many females choose relationship maintenance over their sexual health and are reluctant to suggest using condoms to avoid perceptions of infidelity from male partners which may lead to violent reactions [38]. Furthermore, those in long-term relationships see lack of condom use as proof of commitment to male partners, an assertion that corroborates the gendered power dynamics influencing inability by females to negotiate condom use. A meta-analysis showed improved partner communication was likely to increase condom use frequency among sexual partners [40]. In addition, good quality and desirable condoms to the end-user should be distributed in government healthcare facilities.

Peer support encouraged uptake of HIV interventions as shown across all settings in our study. Implementers need to encourage patients to explore potential sources of social support continuously, as they are likely to evolve. Newly diagnosed HIV patients entering care are likely to have varying level of support which may increase their vulnerability to disengaging in care [41]. Expanding programs that address the lack of social support from a psychosocial perspective are likely to improve health outcomes. Individual and family-centred counselling, and peer support while implementing mental health services have improved linkage to and retention in care among PLHIV [42]. Studies in South Africa on healthcare utilization highlight structural factors that continue to challenge uptake of HIV services [43,44]. Factors such as long queues at clinics, shortage of staff, and lack of privacy in clinics have been widely mentioned [45]. In Ekurhuleni, structural support is improving HIV outcomes. Our study identified the use of WBOTs and care-facilitators who are expanding HIV testing, a critical entry for linkage and retention [46]. Linkage to HIV prevention services such as PEP, PrEP and condoms are offered to HIV-negative whereas treatment programs to patients living with HIV. Some clinics in Ekurhuleni provide decanting services to stable ART patients, following the differentiated care model to encouraged retention in care. Most of these structural interventions were reported in high uptake areas.

The fear of HIV-related stigma has been well document in existing literature and is shown in this study as a barrier to engaging in HIV care [47,48]. Some patients in low uptake areas provide incorrect contact details and have disengaged from care due to stigma [49]. Other studies found that due to victimisation from community or fear of violence from partners, women were less likely to use condoms for protection from HIV [4,5]. The social stigma around women who seek condoms as a means of HIV prevention is concerning because the perception of promiscuity is a major barrier to utilize this method of HIV prevention which has been reported in HIV prevention studies in South Africa [50]. Offering alternatives such as PEP or PrEP is a significant facilitator for uptake of HIV prevention. Similar to condom use, misconceptions towards PrEP use needs to be addressed to curb stigma from partners and community. While offering these alternatives, HCWs should also be trained to avoid perpetuation of social stigma associated with choosing to use PrEP over condoms. Such training should encourage HCWs to view PrEP as an aid that allows control over one's sexual health [51]. Incorrect and inadequate knowledge is a significant barrier to the uptake of interventions, has been linked to perceived stigma and discrimination which likely influences attitudes that may deter engagement in HIV care [52]. Stigma and discrimination influences negatively on testing, disclosure, treatment initiation and adherence [1,52,53]. Community-based interventions including integration of HIV services into existing programs can address the negative sequelae and reduce stigma through sensitization by community healthcare or peer workers and is likely to improve uptake of HIV services, thus leading to higher ART coverage and viral load

suppression [54,55]. Most PLHIV protect themselves from the impact of stigma and discrimination by non-disclosure of status or attending clinics far away from where they live which affects retention in care [56]. Strategies that reduce stigma and discrimination are required for continuous engagement in care. Robust education campaigns are needed for both patients and providers to demystify misconceptions about existing HIV prevention strategies and are necessary for a successful demand-creation strategy.

Limitations of the study include the sample comprising of patients already seeking care at selected clinics in Ekurhuleni District. The findings may have limited generalizability to populations that did not attend clinic visits and outside Ekurhuleni. We also acknowledge that the study was conducted in an area where research is frequently conducted, and participants may have increased exposure to HIV information and health services. Nevertheless, we believe participants provided real experiences that validated our findings, as the qualitative data collected was comparable to data provided in other settings examining the same topics, which further attenuated this concern. The study was conducted four months into the COVID-19 lockdown and some clinics did not provide access to participants due to closure after reports of possible exposure or not permitting non-essential activities including research. However, we believe that the findings are a reflection of a heterogeneous setting. Despite these limitations, the strength of this study is that it is one of few studies to explore how SCT constructs amplify the experiences of patients as they engaged in HIV care while looking at geographical differences. The findings are likely to reinforce and expand the existing programmes that encourage utilization of HIV prevention or treatment services and emphasize the relevance of the SCT in the implementation of HIV prevention and treatment programs.

Conclusions

Firstly, negative sequelae such as HIV-related stigma is a significant problem for implementers of programs because it reduces engagement in care. Decreasing stigma by increasing knowledge and encouraging adequate support network are key to successful HIV prevention or treatment programs in Ekurhuleni. Secondly, mass campaigns and health talks on proper storage, consistent and correct condom use are strongly encouraged to increase self-efficacy. Thirdly, gender-transformative approaches addressing low relationship power in females are useful in encouraging decision-making in improving protective sexual behaviours. Lastly, to address context-specific differences in uptake of HIV care in Ekurhuleni, we should take into account the contextual environment in which these services are to be implemented. High uptake areas showed a comprehensive approach to increasing access and uptake of available services. Interventions targeting health system barriers including confidentiality concerns, stigma and staff shortage seen in low uptake areas can increase uptake and delivery. We acknowledge that there was adequate supply of HIV services in the study area. However, in settings where supplies may be irregular, we highlight the need for the healthcare system to include HIV prevention supplies as part of their essential commodity security plans to expanding access. Furthermore, on-going monitoring and evaluation will be needed to plan for further improvements in implementation of HIV and other health services.

Supporting information

S1 Data.
(ZIP)

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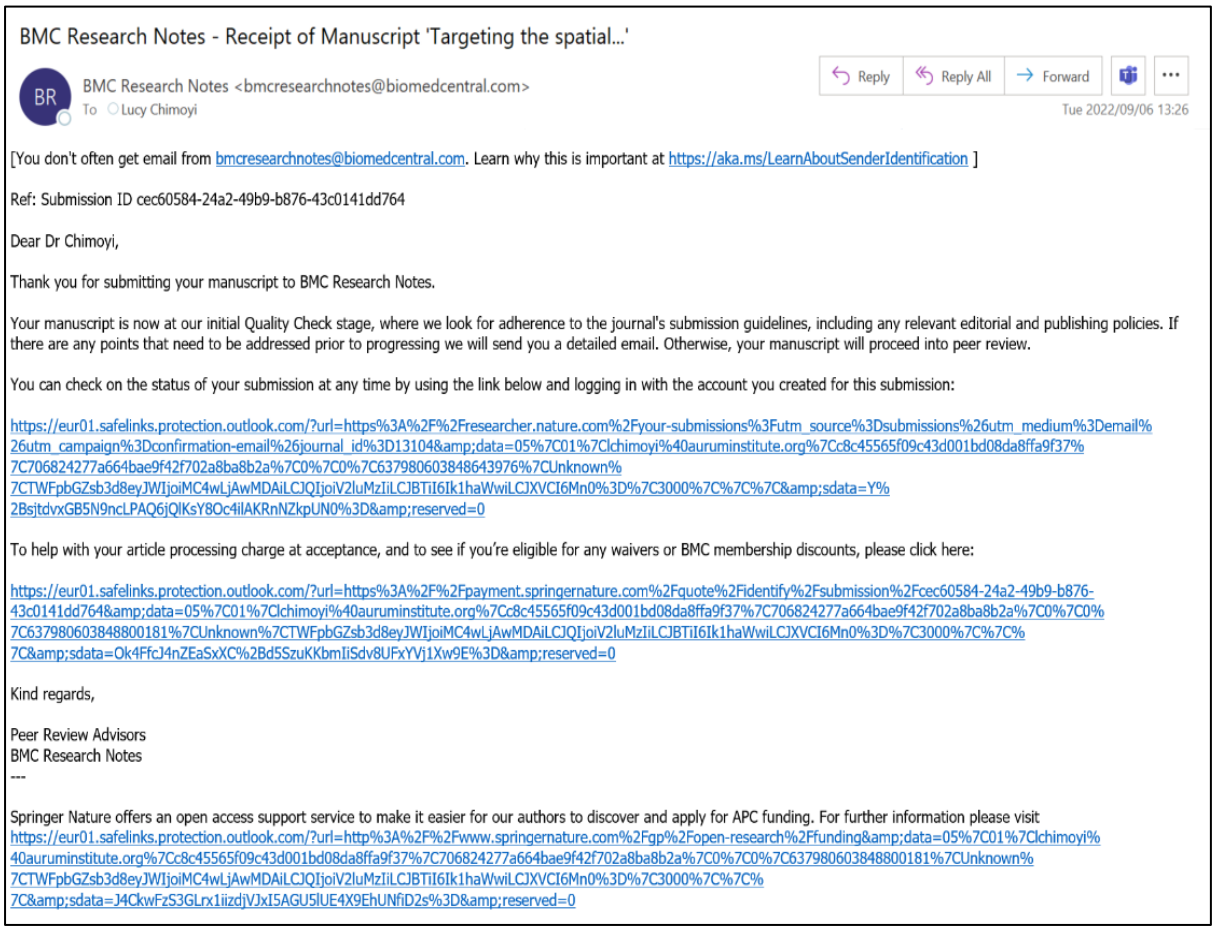
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Targeting the spatial patterns of HIV viral load suppression in Ekurhuleni, South Africa: A geographically weighted regression analysis

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Abstract

Objective

Little is known about the relationship between viral load suppression rates and selected covariates at local levels. The objective of this study was to identify important predictors of viral load suppression and areas where targeted effective resource allocation can successfully improve viral load suppression in Ekurhuleni.

Results

The study highlighted the heterogeneity of viral load suppression rates and the selected predictors in Ekurhuleni. An increasing proportion of a female population and ART initiation rates were important predictors of high viral load suppression. We observed that this relationship was strong in some areas and weak in others. A percentage increase in the proportion of females in some areas increased viral load suppression by 36% (β=0.361, p-value=0.007). Similarly, an increase in ART initiation increased viral load suppression by 54% (β=0.543, p-value=<0.001) in some areas. These findings are aligned with the need by policy makers for more localized analysis to inform targeted strategies for resource allocation in heterogenous settings.

Keywords: Targeted interventions, viral load suppression, geographically weighted regression, spatial autocorrelation, South Africa

Introduction

Viral load suppression is likely to follow the same heterogenous spatial pattern as HIV prevalence in South Africa. South Africa has the largest HIV treatment program worldwide with more than 7 million adults reported to be on ART in 2020 according to the Global AIDS 2021 report (1). Since September 2016, the National Department of Health extended the availability of antiretroviral treatment (ART) to all people testing positive for HIV regardless of CD4 count (2). The policy , universal test and treat (UTT) offers promise to enhance the efforts to initiate and retain 95% of PLHIV on treatment as part of the UNAIDS global 95-95-95 strategy (3). In 2020, about 62% of all people living with HIV and on treatment were virally suppressed an increase of 8% from 2018 but below the minimum threshold of 75% (1). Efforts to explore the global relationship between viral load suppression and known predictors has mostly been at national or provincial levels. Such findings obscure the local heterogeneity causing misinterpretation of the predictors of high viral load suppression. Understanding localized relationships is critical in strengthening retention in care efforts in especially in resource-constrained settings. In Ekurhuleni, a high priority district with a heterogenous HIV profile (4), viral load suppression monitoring in people living with HIV (PLHIV) and on antiretroviral treatment (ART) is important for improving individual patients' health (5-7). At a population level, there is a reduction in morbidity and mortality rates (8, 9). To optimize the HIV response in Ekurhuleni and reach the target of 95% of virally suppressed ART patients by 2030, proportions of patients initiating and successfully retaining in care must increase (10).

UTT studies in sub-Saharan Africa have associated lower HIV incidence with lower population-level HIV viremia (11). Individual predictors of viral load suppression in adults identified in previous research are mainly female sex, older age, early and timely ART initiation (12, 13). Given the variety of these individual predictors, addressing heterogeneities in viral load suppression by using predictive models could facilitate targeted prevention interventions while focusing on delivery of these interventions (14). In this study we assessed the relationship between viral load suppression and further investigated the association between the observed local patterns and known variables from routinely collected data.

Main text

Methods

Survey design, sites, population, and outcome measurement

We conducted an ecological study using secondary laboratory data collected from routine clinic visits from 2012 to 2016 in Ekurhuleni Metropolitan Municipality. The outcome, viral load suppression (VLS) using <1 000 copies /mL (World Health Organization guidelines) and <400 copies/mL (South African National guidelines), two of the thresholds used in South Africa to determine treatment success, was assessed. The mean $\log_{10}$ viral load per month per ward was summarized and VLS proportion was estimated by taking the number of virally suppressed patients in each ward and dividing by the total number in care per month in the same ward. The potential predictors of VLS were obtained from available routine clinical data (ART) and 2011 National census data (female gender). A geometric mean of the VLS proportion per ward was calculated. The final analytical dataset contained ward-level proportions of the viral load suppression, female population, and ART initiation (see Supplementary 1).

Data management and analysis

Data was captured on a Microsoft Excel programme and manipulation and analyses were conducted in STATA 14 software (StataCorp, Texas, USA) (15). Population-level demographic and clinical data were summarized using frequencies and percentages and means and standard deviations (SD). We used the spatial statistics function in ArcGIS (Environmental Systems Research Institute, Redlands, USA) to i) explain the global relationship between high viral load suppression and the two covariates (female population, and ART initiation) using ordinary least squares regression (OLS), ii) show how the two covariates changed from one region to another using geographically weighted regression (GWR) and iii) assess the spatial independence of the regression residuals (Moran index) and multicollinearity (variance inflation factor(VIF)). A VIF value >10 indicated presence of multicollinearity, a significant Moran Index, indicated clustering of residuals (non-random). Lastly, a significant Koenker Statistic indicated non-stationary relationships between explanatory variables and viral load suppression. Two models were fitted (Equation 1 and 2). The OLS model was fitted using 88 observations where proportion of viral load suppression was estimated at each ward, ($i = 1,2, \ldots .88$), β_0, is the global intercept and β_1 and β_2, the regression coefficients of the explanatory variables (Equation 1)

$$VLS_i = \beta_0 + \beta_1 PropFemale_i + \beta_2 PropART_i + \boldsymbol{\varepsilon_i} \quad (1)$$

Similarly, the GWR model was fitted, where VLS_i are observations of viral load suppression, $(\boldsymbol{z})$ are the parameters, β, estimated at each ward with centroids given by vector $\boldsymbol{z}$; i represents each ward, ($i = 1,2, \ldots .88$), and $\boldsymbol{\varepsilon_i}$ the estimation residual in each ward (Equation 2).

$$VLS_i(\boldsymbol{z}) = \beta_{0i}(\boldsymbol{z}) + \beta_{1i} PropFemale_i(\boldsymbol{z}) + \beta_{2i} PropART_i(\boldsymbol{z}) + \boldsymbol{\varepsilon_i} \quad (2)$$

Smoothed maps were produced using ArcGIS software v.10.7.1 (16).

Results

Sample characteristics

Between 2012 and 2016, the 65.5% and 56.9% of the viral load test results from 26, 222 samples of PLHIV in routine care were virally suppressed at <1 000copies/mL and <400 copies/mL thresholds, respectively. Most PLHIV were of average age 38.5 (SD: 7.5) years. The average proportion of female patients was 47.3% (SD:40.7%) and the average proportion of patients initiated on ART was 39.8% (SD: 30.1%).

Global and local predictors of high viral load suppression in Ekurhuleni

The OLS confirms that the two variables (proportion of females and PLHIV initiating ART) are important predictors of VLS as shown by the VIF (<2.7). The VIF values for the explanatory variables indicate no biasness in the OLS estimates from multicollinearity (Table 2 and 3). Using proportions of female and ART initiation at ward level, the OLS model explained 75% (<1000 copies/mL) and 65% (<400 copies/mL) of the viral load suppression rates in Ekurhuleni. There was a significant positive relationship between an increasing proportion of women and ART initiation at ward level and increased rates of VLS (<1000 copies/mL) in Ekurhuleni (Table 1). A one percent increase in the proportion of females was associated with 36% increase in viral load suppression (<1000 copies/mL), while a one percent increase in proportion of HIV positives who have initiated on ART, was significantly associated with 54% increases in viral load suppression (Table 1). The relationship between the proportion of female population and <400 copies/mL viral load suppression was not significant (Table 1).

Table 1*:* Estimates from OLS and GWR results)

	<1 000 copies/mL				**<400 copies/mL**			
Variable	**Coefficient**	**Standard Error**	**P-value**	**VIF**	**Coefficient**	**Standard Error**	**P-value**	**VIF**
Intercept	0,013	0,031	0.168	-	0.023	0.034	0.128	-
Proportion of females	0,361	0,113	0.007*	2.811	0.085	0.113	0.507	2.728
Proportion on ART	0,543	0,078	<0.001*	2.811	0.638	0.082	<0.001*	2.728
OLS diagnostics								
Adjusted R^2	0.752	-	-		0.684	-	-	
Moran Index	0.051	-	0.148		0.104	-	0.007	
Koenker statistic	10.687	-	0.005*		20.329	-	<0.001*	
GWR diagnostics								
Adjusted R^2	0.731	-	-		0,760	-	-	
Moran Index	0.003	-	0.737		-0.007	-	0.947	

The Moran index of 0.05, p-value 0.148, indicates that the patterns of residuals do not appear to be significantly different than random explanatory variables are good predictors of viral load suppression (<1000 copies/mL) in Ekurhuleni as the residuals from the OLS are randomly distributed (Table 2). There is a clustered distribution of residuals for the viral load suppression (<400 copies/mL) threshold. The relationship between the explanatory variables and viral load suppression from the two models is non-stationary as indicated by a significant Koenker test (p-value= 0,005 and <0.001) respectively. This means that proportion of women may be a strong predictor for high viral load suppression (<1000 copies/mL) in some areas or weak in others. Similarly, ART initiation maybe a strong predictor in some areas and weak in others.

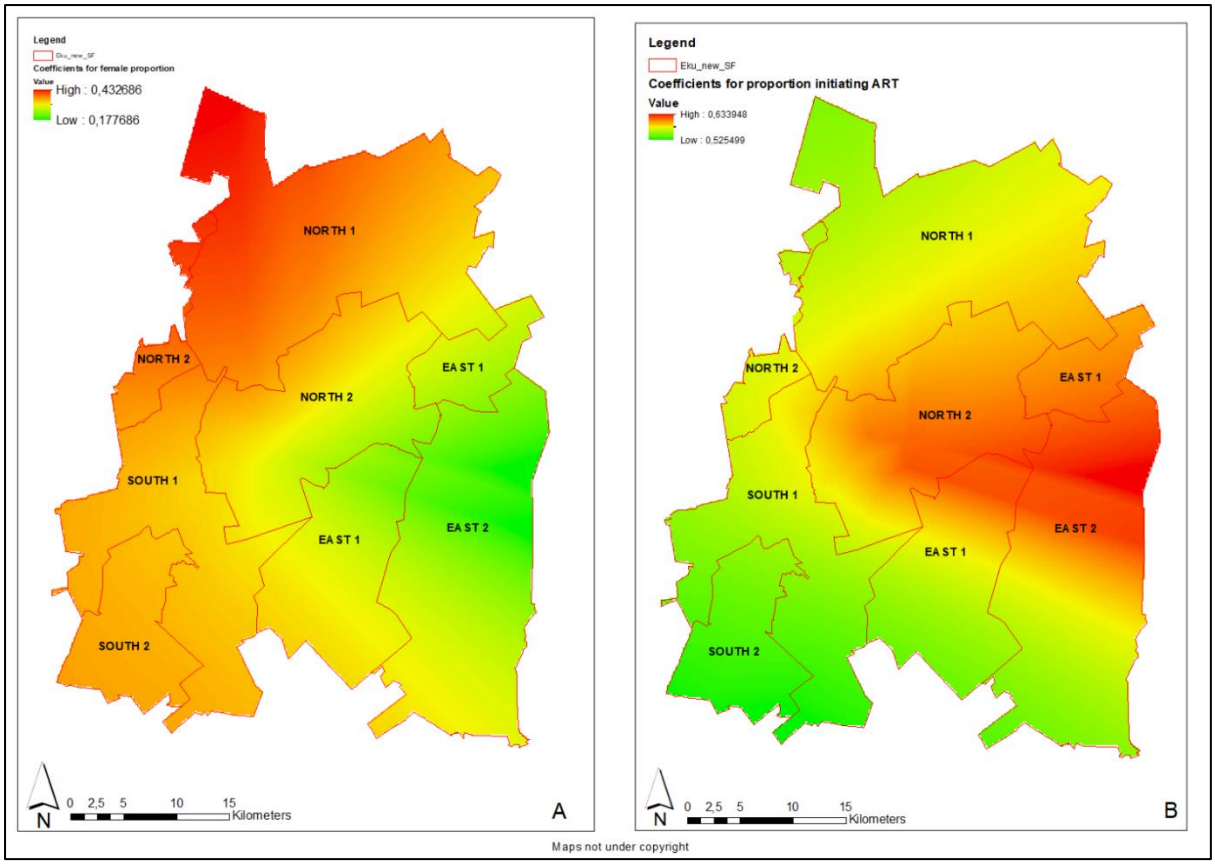


Figure 1: The relationship between proportion of females and ART initiation per ward and high viral load suppression (<1000 copies/ml)

Figures 1A and B show smoothed maps of explanatory variables and illustrate how the percent female population (Figure 1A) and ART initiation (Figure 1B) associates with viral load suppression (<1 000 copies/mL). The areas in red/orange colour (North1 and North 2) show where an increasing proportion of women is a strong predictor of increased VLS threshold (Figure 1A). The wards in green colour show where an increasing female proportion is not a strong predictor (Figure 1A). Similarly, the areas in red/orange colour (East1, East 2 and North 2) show where an increasing proportion of PLHIV on ART is a strong predictor of increased VLS rates in Ekurhuleni. The green areas show where ART initiation is not a strong predictor (Figure 1B).

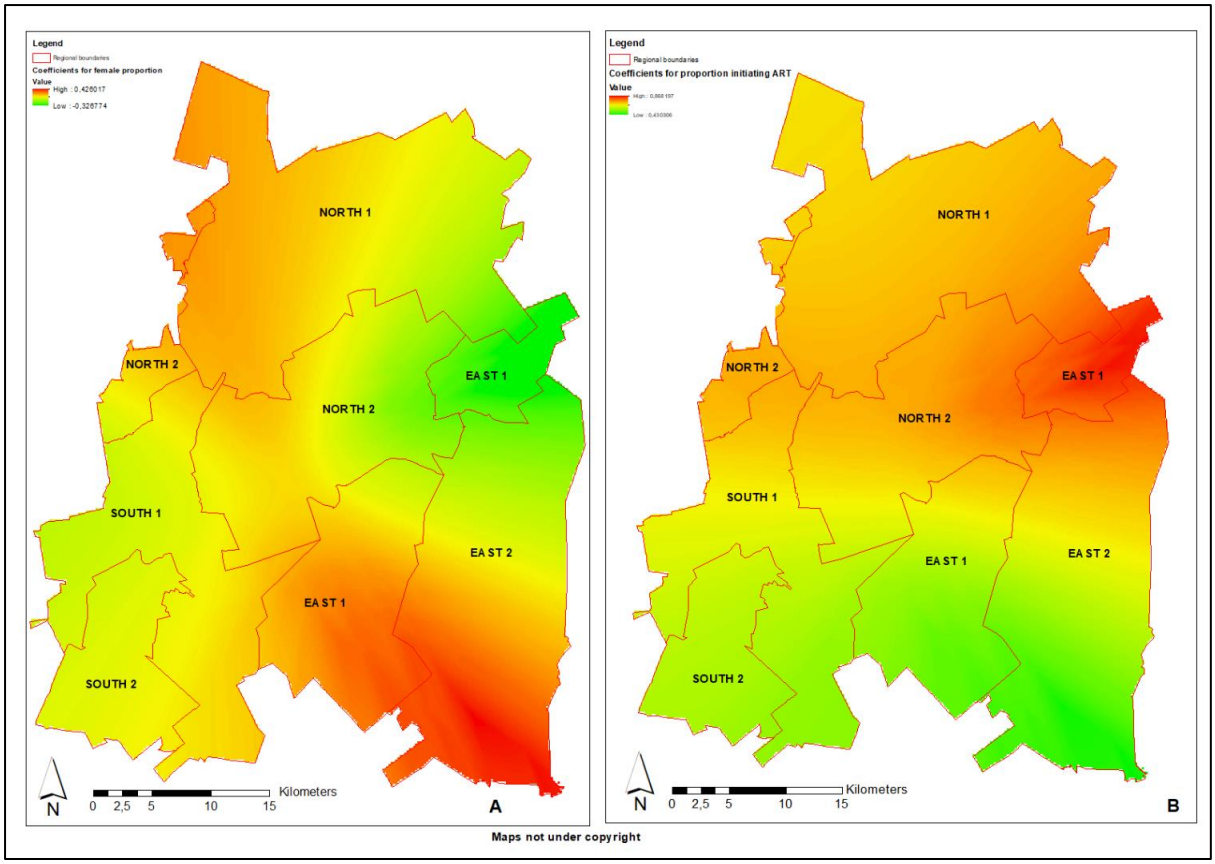


Figure 2: The relationship between proportion of females and ART initiation per ward and high viral load suppression (<400 copies/ml)

The areas in red/orange colour (East 1, East 2 and North 1) show where an increasing proportion of women is a strong predictor of increased VLS for <400 copies/mL threshold (Figure 2A). The wards in green colour show where an increasing female proportion is not a strong predictor (Figure 2A). The areas in red colour show where an increasing proportion of PLHIV on ART is a strong predictor of increased VLS rates in Ekurhuleni (East 1 and North 2). The green areas show where ART initiation is not a strong predictor (Figure 2B).

Discussion

The study shows the heterogenous distribution of HIV viral suppression at a local level in Ekurhuleni district, South Africa. The findings from this analysis showed the increasing ART initiation and female population as important predictors of high viral load suppression rates in Ekurhuleni.

In South Africa, studies have shown that at an individual level, being female is a predictor of viral load suppression. A multi-centre study in KwaZulu Natal, Johannesburg and Cape Town showed that adult women were 26% more likely to report greater viral load suppression rates than men (17). Our findings, confirm that an increasing female population in Ekurhuleni was likely to reduce viral load suppression rate at a ward level. In such areas, focusing on reaching women and strengthening retention are important strategies. To the best of our knowledge, no study has assessed viral load suppression and visually highlighting the existing variations at a localized level study. Previous studies on pregnant women, highlighted the failure to achieve viral load suppression by the third trimester (18, 19). Delayed entry into antenatal care, delayed initiation, poor adherence, and infrequent clinic visits during the 3rd trimester were the main reasons cited for a viral load >50 copies/mL (19,

20). Although this study was not specific to Ekurhuleni, it underscores the importance of improving early antenatal care and ART initiation among pregnant women and improving HIV care to women living with HIV. In those areas where the relationship between an increasing female population is not as strong, finding missing men, conducting HIV testing campaigns, linking, and retaining men in care is necessary.

Our findings confirmed the increasing proportion of ART initiation as a strong predictor of viral load suppression (11, 13, 17). In areas where this was the case, strategies that increase uptake of HIV testing such as self-testing are needed. Thereafter, strengthening linkage to care programmes is required. Same-day initiations and differentiated delivery of care are necessary approaches to ensure proper linkage to care. Where increasing ART initiation was not a strong predictor, improved retention strategies are recommended. Proper follow-up of PLHIV, monitoring and evaluation data is needed to identify patients defaulting from care. Tracing, referral, and tracking programmes are therefore required to maintain retention in HIV care.

These findings are aligned with the need by policy makers for more localized analysis to inform strategies for resource allocation. The findings support the use of spatial prediction modelling as a useful method to leverage decision-making to improve viral load suppression across Ekurhuleni Metropolitan Municipality.

Limitations

Interpretation of these findings should be done with caution in consideration of study limitations. Firstly, there were few variables available for selection, a limitation of secondary data analysis . This affected the predictive value of the model which would greatly improve by adding other factors including related information from the health system level. Secondly, our models may not be generalizable to other settings but may be representative of other high priority districts. Lastly, routine data may be incomplete with missing laboratory results of viral load counts and lacked sufficient data time points obtained after implementation of universal test and treat. Nevertheless, using GWR, we predicted the local predictors associated with high viral load suppression in Ekurhuleni.

List of abbreviations

ART: antiretroviral treatment
GIS: geographical information systems
GWR: geographically weighted regression
OLS: ordinary least squares
SD: standard deviation
VIF: variance inflation factor
VLS: viral load suppression

Declarations

Ethics approval and consent to participate

Ethical clearance was sought from the Wits Human Research Ethics committee (HREC; M181088). Additional permission was sought and approved from the National and Gauteng Department of Health (to access DHIS data), National Health Laboratory Services ethics committee and the Ekurhuleni Metropolitan Municipality Research Committee. Patient consent was waived due to the use of retrospective data.

Consent for publication

The authors declare consent for publication.

Availability of data and materials

The dataset used and analysed is submitted as a supplementary file.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

LC was a major contributor to designing the study, methods used. LC collected the data; LC compiled the data and interpreted the results. LC, TK-C, SC, and EM contributed to writing the manuscript. All authors read and approved the final manuscript.

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Supplementary files
Supplementary 1: Dataset