

https://dspace.org/

Rates of initial virological suppression in patients with resistance to antiretroviral therapy

Hunt, Gillian

2020
https://hdl.handle.net/10539/29987

Downloaded from a DSpace repository. https://dspace.org/

RATES OF INITIAL VIROLOGICAL SUPPRESSION IN PATIENTS WITH RESISTANCE TO ANTIRETROVIRAL THERAPY

Gillian Hunt

Student No: 9100717H

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree Master of Science in Epidemiology and Biostatistics

Johannesburg, June 2020

DECLARATION

I, Gillian Hunt, declare that this research report is my own, unaided work. It is being submitted for the degree of Master of Science in the Faculty of Health Sciences, School of Public Health at the University of the Witwatersrand, Johannesburg. It has not been submitted for any degree or examination at any other university.



Gillian Mary Hunt

18th day of June, 2020

ABSTRACT

Given increasing levels of pre-treatment HIV drug resistance in South Africa (SA), particularly to the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug class, the efficacy of standardised NNRTI-based first-line regimens used routinely to achieve virological suppression in patients initiating first-line ART in SA remains unclear. As part of the joint HIV/TB prospective cohort surveillance study "Prospective Sentinel Surveillance of Tuberculosis and Human Immunodeficiency Virus in South Africa and Related Drug Resistance", conducted between November 2014 and December 2017, a medical chart review was performed for participants enrolled in the study 6-months post initiation of antiretroviral therapy (ART) to monitor rates of retention-in-care and virological response to ART. Factors associated with having a viral load ≥1,000 copies/mL were explored amongst participants with or without detectable levels of pre-treatment drug resistance (PDR) at treatment initiation.

Patients initiating ART at 9 high burden clinics in 6 South African provinces were consented and enrolled into the primary study. Standardised interviews and medical chart reviews were performed by surveillance officers at each site at time of enrolment.

Of 1330 participants enrolled in the primary study, 6-month follow up data was available for 918 (69%) participants. Inclusion was found not to be at random; participants enrolled into the study 2016-2017 were significantly more likely to be included in to the secondary analysis. In addition, female participants, participants who were unemployed or had regular employment, participants with CD4 count >500 cells/μL at treatment initiation, or participants with prior ART exposure were more likely to be excluded from the secondary analysis. Modified Poisson regression was performed to determine factors associated with retention-in-care and having a 6-month viral load result ≥ 1,000 copies/mL. Sensitivity analyses were performed to assess the robustness of the findings.

Of the 918 participants included in the secondary analysis, 502 (55%) participants were retained in care, whereas 416 (45%) participants had no evidence of a 6-month visit. Of these, 375 (41%) were documented as or assumed to be LTFU, 36 (4%) were transferred to a different facility, and 5 were deceased. At a multivariate level, retention in care was significantly associated with enrolment during 2016 (adjusted incidence rate ratio (aIRR)

1.31, 95% CI 1.07 – 1.61), a relationship that maintained significance throughout the sensitivity analyses.

Of 502 participants retained in care, 358 (71%) had a viral load result available; of these, 305 (85%) had a VL result <1,000 copies/mL, and 53 (15%) had a VL result that was ≥1,000 copies/mL PDR at treatment initiation was significantly associated with 4 fold increased risk of VL≥1,000 copies/mL (IRR = 4.33, 95% CI 2.63 – 7.12). Being of older age (IRR = 0.43 (95% CI 0.24 – 0.78) for 15-24 years' age group and IRR=0.09 (95% CI 0.01 – 0.56) for participants >50 years of age) and CD4 count >200 cells/μL (IRR=0.05, 95% CI 0.36 - 0.98) were associated with significantly reduced risk of VL≥1,000 copies/mL).

Our analysis showed that high proportions of participants enrolled in the parent study were not retained-in-care at 6-month post-initiation of ART. However, as these figures may reflect incomplete record keeping at the facilities, the implementation of a unique patient identifier and electronic record keeping systems that can provide real-time monitoring of patients must remain a priority activity for the national programme. In addition, having a VL ≥ 1,000 copies/mL at 6-months post initiation of ART was significantly associated with having PDR at treatment start. As such, real-time monitoring of patients with viraemia to allow for rapid management response and treatment switch must remain a priority activity for improved patient management.

The study is limited by difficulty of access to paper-based medical charts at facilities and inadequate record keeping in paper-based medical files. In addition, follow-up was not performed in all facilities due to unavailability of staff. As such, rates of retention-in-care and virological outcomes may be compromised by inadequate recording of the 6-month VL result into the patients' files.

ACKNOWLEDGEMENTS

I would like to thank the following people:

The participants involved in these studies, for their willingness to provide samples for analysis.

The HIV drug resistance surveillance laboratory team at NICD, including Johanna Ledwaba, Monalisa Kalimashe, Mary Phoswa, and Asiashu Bongwe.

The GERMS staff, including Linda Erasmus, Vanessa Quan, Mokupi Manaka, Tiisetso Lebaka, Thandeka Kosana, Sibongile Rasmeni, Badikazi Matiwana, Molly Morapeli, Nelisiwe Buthelezi, Nkosinathi Mbhele, Ennica Ntlemo, Sanelisiwe Mtetwa, Neo Legare, Sunnieboy Njikho, Cecilia Miller, Nuraan Paulse, Phumeza Vazi, Riyadh Manesen, and Linsay Blows.

My supervisor, Dr Tendesayi Kufa-Chakezha, for her support, guidance and endless patience.

The AIDS Virology Unit team, including Profs Lynn Morris and Penny Moore for their continued support and encouragement.

My children, family and friends for their support and encouragement.

TABLE OF CONTENTS:

CHAPTER ONE: INTRODUCTION 10

1.1 General Introduction 10

1.2 Literature review 11

1.2.1 Global epidemiology of HIV 11

1.2.2 The life cycle of HIV-1 12

1.2.3 Treatment for infection with HIV-1 12

1.2.4 Epidemiology of HIV Drug Resistance 13

1.2.5 Management and treatment of HIV infection in South Africa 17

1.3 Problem statement 19

1.4 Justification for the study 19

1.5 Research question 19

1.6 Research aims 20

CHAPTER 2: METHODS 21

2.1 Study design 21

2.2 The GERMS-SA HIV/TB surveillance study (parent study) 21

2.3 Study population 22

2.4 Sampling strategy 22

2.5 Inclusion criteria 22

2.6 Definition of terms 22

2.7 Description of outcomes 23

2.8 Data management 24

2.9 Data analysis by objective 24

2.10 Ethical considerations 27

2.10.1 Approvals 27

2.10.2 Assessment of risk and benefits 27

2.10.3 Confidentiality 27

2.10.4 Informed Consent 27

CHAPTER THREE: RESULTS 28

3.1 Study flow and summary 28

3.1.1 Description of participants included in the analysis 29

3.1.2 Assessment of randomness of missing data 30

3.2 Retention in care (Objective 1) 31

3.2.1 Factors associated with retention-in-care 31

3.2.2 Sensitivity analysis rates of retention-in-care 32

3.3 Virological outcome at 6 – 9 months' post initiation of ART (Objective 2) 37

3.3.1 Factors associated with having a VL ≥1,000 copies/mL at 6 months' clinic visit 37

3.3.2 Sensitivity analysis of factors associated with retention-in-care 37

CHAPTER FOUR: DISCUSSION 42

REFERENCES 46

APPENDIX 1: GERMS-SA HIV/TB STUDY ENROLMENT FORM 55

APPENDIX 2: WITS HREC ETHICAL APPROVAL 61

APPENDIX 3: PLAGIARISM DECLARATION 62

LIST OF FIGURES

Figure 1.1 Prevalence of pre-treatment HIV resistance to NNRTI by year of sampling .16

Figure 2.1. Data flow diagram contextualizing the current study objectives within the parent study.....23

Figure 3.1. Study flow and summary 29

LIST OF TABLES

Table 2.1. Description of data analysis used in analysis 25

Table 3.1. Demographic characteristics of the participants enrolled into the primary study and included in the secondary analysis 30

Table 3.2. Factors associated with retention in care 33

Table 3.3. Sensitivity analysis of factors associated with retention-in-care. 35

Table 3.4. Factors associated with not achieving early virological failure (having a VL result of ≥1,000 copies/mL) 38

Table 3.5. Sensitivity analysis of factors associated with VL ≥1,000 copies/mL. 40

LIST OF ABBREVIATIONS

ART	Antiretroviral therapy
cART	Combination ART
GERMS-SA	Group for Enteric Respiratory and Meningococcal Disease Surveillance
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
IN	Integrase
IRR	Incidence Risk Ratio
ITT	Intention to treat
INSTI	Integrase Strand Transfer Inhibitor
LMIC	Low-to-middle income countries
LTFU	Lost to follow up
µL	microlitre
mL	millilitre
NICD	National Institute for Communicable Diseases
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PDR	Pre-treatment HIV Drug Resistance
PEP	Post-exposure prophylaxis
PI	Protease inhibitor
PMTCT	Prevention of Mother to Child Transmission of HIV
PR	Protease
PrEP	Pre-exposure prophylaxis
RIC	Retention-in-care
RT	Reverse Transcriptase
SA	South Africa
TB	Tuberculosis
UTT	Universal Test and Treat
VL	Viral load
WHO	World Health Organization

CHAPTER ONE: INTRODUCTION

1.1 General Introduction

South Africa (SA) has extremely high rates of infection with Human Immunodeficiency Virus (HIV), with an estimated 8.0 million persons living with HIV in the country (1). In addition, rates of tuberculosis (TB) are the third highest globally, with 834 cases per 100,000 population being recorded in 2015 (2). Levels of HIV and TB co-infection are also high, with 60% of TB patients are HIV-infected.

South Africa's programme for ART provision is the largest in the world. By the end of 2019, SA had ~4.8 million persons on antiretroviral therapy (ART) (3), most of which was provided through primary health care facilities across the country. The country first adopted a public health approach to ART provision in 2004, providing standardised antiretroviral drug regimens and using routine viral load (VL) monitoring to detect treatment failure (4).

Whilst ART provision has substantially reduced HIV-related mortality and morbidity (5), concerns remain about the development of HIV drug resistance (HIVDR) (6). Recent global and local reports have indicated an increase in acquired and transmitted HIVDR (6–9), particularly in regions where ART has been provided for many years. In response to these concerns, the World Health Organization (WHO) has developed a global strategy for surveillance and monitoring of HIVDR (10). This strategy includes prioritizing activities to monitor levels of transmitted, acquired and pre-treatment resistance in resource-limited regions. These activities are reflected by the National Department of Health in the National Strategic Plan (11) to monitor rates of HIVDR in the country and inform continuing efficacy of existing standardised first-line and second-line ART regimens.

Recent reports indicate that levels of pre-treatment drug resistance (PDR) to the non-nucleoside reverse transcriptase inhibitor (NNRTI) drug class have increased in a number of low-to-middle income countries, to estimates of greater than 10% (6,8). Given increasing levels of PDR in the country, particularly to the NNRTI drug class, the efficacy of standardised first-line regimens routinely used to achieve virological suppression in patients initiating first-line ART in SA remains unclear.

The GERMS-SA surveillance platform is a nationwide network of clinical laboratories through which active laboratory-based surveillance of pathogens of public health importance is performed, and is co-ordinated through the National Institute for Communicable Diseases (NICD). In 2014, the programme expanded to include surveillance of sexually transmitted infections, HIV and TB through clinic-based surveillance activities. A joint HIV/TB surveillance study entitled “Prospective Sentinel Surveillance of Tuberculosis and Human Immunodeficiency Virus in South Africa and Related Drug Resistance” was initiated in November 2014, and employed surveillance officers to recruit, enrol and interview participants into the study (12). During the period January 2015 to October 2017, a total 1330 patients were enrolled in the primary study. PDR was detected in 232 participants (19.5%, 95% CI 17.3 – 21.8%), of which NNRTI resistance was most commonly detected. For patients enrolled into the study who were initiating ART, a 6-month medical chart review to assess treatment outcomes was included. A secondary analysis of 6-month data for enrolled patients was performed to determine if PDR was associated with virological outcomes.

1.2 Literature review

1.2.1 Global epidemiology of HIV

Infection with HIV has become one of the largest global public health concerns. Recent estimates from UNAIDS indicate that 37.9 million people globally were living with HIV in 2018, with 1.7 million new infections occurring that year (3). The epidemic is principally concentrated in eastern and southern Africa, with 20.6 million people (54% of infections globally) in this region living with HIV in 2018. Since HIV was first described, 32 million people have died from AIDS-related illnesses. During 2018, 770 000 deaths globally and 310 000 in eastern and southern Africa are estimated to have occurred. HIV-1 can be transmitted by sexual contact across mucosal surfaces, through transmission of mother to infant, or through injection with contaminated needles (13).

South Africa is burdened with one of the highest HIV prevalence rates worldwide. The 2018 Mid-year Population Estimates released by Statistics South Africa estimated the total HIV prevalence to be approximately 13.5% of the South African population, and 19.1% in adults aged 15 to 49 years (1). This prevalence translated into approximately 7.97 million persons living with HIV. HIV infection rates are higher in key populations: the

2015 National Antenatal Sentinel HIV Prevalence Survey in SA reported that 30.8% of pregnant women and up to 78% of female sex workers are living with HIV (14,15).

1.2.2 The life cycle of HIV-1

The primary targets for HIV-1 infection *in vivo* are human CD4+ T-lymphocytes and monocytes. The HIV-1 gp120 envelope protein initially binds to the CD4 membrane receptor present on the surface of target cells (16). The gp120-CD4 complex then binds to chemokine receptors, which induces conformational changes in the envelope glycoprotein allowing it to fuse with the cell membrane and the virion to enter the cell (17). Once internalised, the HIV virion is uncoated and the viral core contents enter the cytoplasm, following which the reverse transcriptase (RT) enzyme copies the viral RNA into a double-stranded DNA replica of the original RNA genome. The integrase (IN) enzyme then inserts the DNA transcript into the genome of the host cell (18,19). Proviral proteins are cleaved by the Protease (PR) enzyme, and assembly of new virions occurs at the plasma membrane of the infected cell. The ribonucleoprotein cores containing the RNA, proteins, PR, IN and RT then bud through the plasma membrane taking a portion of the lipid membrane to form a new virion (20).

1.2.3 Treatment for infection with HIV-1

Zidovudine was the first anti-viral agent licensed for clinical use in 1987 to treat HIV infection (21). Over the next 25 years, 25 agents were licensed for the treatment of HIV, classed according to mode of action. During this period, standard of care evolved to include a minimum combination of three antiretroviral agents to suppress viral replication and reduce plasma viral load to below limits of detection of clinical assays, allowing for reconstitution of the immune system and decreasing the risk of opportunistic infection. ART is prescribed as combination ART (cART) for management of HIV infection, or can be used to prevent mother-to-child transmission (PMTCT), or as pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP).

1.2.3.1 Nucleos(t)ide reverse transcriptase inhibitors (NRTI)

Nucleoside / nucleotide reverse transcriptase inhibitors (NRTI) are nucleoside or nucleotide analogues that interfere with the enzymatic action of HIV RT by competing with the natural substrate of the virus and incorporating into the growing nucleotide chain (21,22). This drug class includes zidovudine, abacavir, emtricitabine, lamivudine and

tenofovir. Whilst NRTI were initially prescribed as monotherapy in the 1990s, they are now used as a “backbone” in triple drug combination therapy combinations with a member of a different drug class, typically an NNRTI, a boosted protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI) (23).

1.2.3.2 Non-nucleoside reverse transcriptase inhibitors (NNRTI)

NNRTI are non-competitive inhibitors of the RT enzyme which bind to a hydrophobic pocket close to the RT active site and cause conformational changes in the protein, thereby decreasing the enzyme activity (21,22). NNRTI are effective in achieving virological suppression, but are compromised by drug interactions, side effects and have a low threshold for the emergence of resistant mutants. NNRTI include efavirenz and nevirapine, and the second generation NNRTIs etravirine and rilpivirine. NNRTI have been widely used as part of first-line combinations to treat HIV infection (23).

1.2.3.3 Protease Inhibitors (PI)

Protease inhibitors (PI) function late in the HIV replication cycle by binding to the HIV protease enzyme and blocking the proteolytic activity of the enzyme (21,22). This prevents the formation of mature, infectious virions. PI + NRTI combinations are effective in treating patients who have experienced prior NNRTI-based treatment failure. PI include lopinavir, atazanavir, and darunavir (23).

1.2.3.4 Integrase Inhibitors (INI) / Integrase strand transfer inhibitors (INSTI)

Integrase inhibitors function by preventing the integrase enzyme from incorporating the viral DNA into the host chromosome (21,22). The three agents currently in use include raltegravir, elvitegravir, and dolutegravir, all of which have high potency and are well tolerated. An ART regimen consisting of an INSTI plus two NRTI has recently been recommended by the WHO as a preferred first-line regimen for treatment of naïve patients (24).

1.2.4 Epidemiology of HIV Drug Resistance

Resistance to antiretroviral agents, first reported in 1997 (25), develops as a result of genetic modifications (also known as drug resistance mutations) at the drug target site in the virus genome. These modifications impair the ability of the antiretroviral agent to achieve full binding capacity at the protein level and consequently this ability to block

replication of the virus. The high mutation rate of HIV, reported as nearly one mutation per replication cycle (26,27), as well as the high level of virus production (10^{10} virions per day) (28) results in selection of resistant variants as rapidly as within one week of starting treatment (25). Drug resistance can be selected through drug selection pressure (acquired resistance) or be transmitted from person to person (transmitted resistance) (29).

Increasing levels of HIVDR in LMIC are a growing public health threat, and have the potential to threaten progress towards the UNAIDS global 90-90-90 targets for prevention and management of HIV infection. Population-based treatment programmes in LMIC are at risk of higher rates of selection and transmission of HIVDR, which can, over time, compromise the population-level efficacy of standard first- and second-line ART regimens (30). These risks include lower genetic barrier of some drugs, drug-drug interactions, inappropriate prescribing practices, stock-outs, poor rates of retention in care and lower frequency or even absence of routine viral load monitoring. The WHO has recommended strategies to monitor programme factors associated with the emergence and transmission of HIVDR (31,32). This includes implementing routine standardised surveillance activities, and prescribes targets and levels of HIVDR following which public health interventions must be taken to minimise further emergence and transmission of HIVDR.

1.2.4.1 Levels of acquired drug resistance (ADR)

Levels and patterns of ADR (resistance amongst patients with virological failure, or VL ≥1,000 copies/mL) are reported through clinical trials, facility-based cohort studies or nationally representative surveillance activities. A systematic review and meta-analysis of published global data between January 2006 and May 2013 reported virological suppression rates of 85% for up to 60 months of ART, however when analysed using an intention to treat (ITT) approach (i.e. by including patients who had died, stopped ART or were LTFU), VS rates were 74.7% at 6 months' post initiation of therapy and 61.8% at 48 months (33). ADR rates were further reported as between 70 and 90% to NRTI, NNRTI or both drug classes. More recently, the 2017 and 2019 WHO HIV Drug Resistance Reports (34) documented findings from ADR surveys in 13 LMIC countries, where VL suppression rates ranged from 72 – 95% amongst all patients on treatment surveyed; NNRTI ADR rates ranged from 50 – 95%, and NRTI ADR rates between 15 – 80% of patients with VL ≥1,000 copies/ml. Virological suppression amongst patients receiving PI based regimens are 69.3% and 61.5% at 1 and 2 years post initiation of therapy, using an

ITT analysis approach. Levels of resistance to PI remain low, with global estimates indicating PI resistance prevalence at 17% (35–37). Data from South Africa show rates of resistance amongst first-line failures from a national survey from 2013 at 74.4% NRTI and 82.1% NNRTI resistance (38), with PI resistance amongst second-line failures at 16.4% (39), whilst data collected at a provincial level report resistance rates at >80% amongst first-line failing patients in KZN and Western Cape (40–43).

1.2.4.2 Levels of transmitted resistance (TDR)

An analysis of all Genbank submissions from recently infected individuals reported TDR prevalence in sub-Saharan Africa (SSA) at 2.8% in 2013, whilst south/southeast Asia was 2.9%, Latin America/Caribbean was 7.6%, 9.4%, and 11.5% (44,45). Whilst higher rates were reported in high income countries (upper-income Asian countries: 5.6%, Europe: 9.4%, North America;11.5%), the yearly fold increase on odds of TDR in sub-Saharan Africa was 1.09-fold (95%CI: 1.05–1.14), driven primarily by increases in NNRTI resistance. Data from South Africa has shown that national NNRTI levels were 5.4% in 2012 (46), and 7% in KwaZulu-Natal (8).

Many drug resistance mutations impair HIV fitness and revert back to wild-type in the absence of drug pressure, at rates which depend on relative fitness cost of the mutation, the number of back mutations required to revert to wild-type, the rate of viral turnover, and the presence of compensatory mutations that can minimise the impact of the fitness cost (47). This reversion has diagnostic implications when assessing resistance patterns during treatment failure, but also complicates assessment of patterns of transmitted resistance (48). Therefore, TDR surveys frequently provide an under-estimation of TDR levels.

1.2.4.3 Levels of pre-treatment resistance

Pre-treatment HIV drug resistance (PDR) is a term coined to refer to any drug resistance, whether acquired or transmitted, detected in persons initiating or reinitiating first-line ART. PDR can therefore be either transmitted or acquired drug resistance, or both (34). Reasons for presence of acquired resistance include exposure to prior ART regimens, whether administered as part of prevention of mother to child transmission (PMTCT), pre-exposure prophylaxis (PrEP), post-exposure prophylaxis (PEP), or re-initiation of first-line ART after a period of treatment interruption or disengagement from care. Measuring

patterns and prevalence of PDR is critical for informing first-line regimens in public health treatment programmes, and decisions to change components of a first line regimen are based on a pre-treatment threshold prevalence level of greater than 10%.

Findings show that PDR is increasing at a significant rate in LMIC. A systematic review and meta-regression analysis of 56,044 adults in 63 countries pre-treatment NNRTI resistance levels were 11.0% (95% CI 7.5%–15.9%) in 2016 in southern Africa, 10.1% (5.1–19.4) in eastern Africa, 7.2% (2.9–16.5) in western and central Africa, and 9.4% (6.6–13.2) in Latin America and the Caribbean (Figure 1.2 ((49)). In addition, the analysis showed the yearly increases in the odds of PDR was 23% (95% CI 16–29) per annum in southern Africa (Figure 1.1).

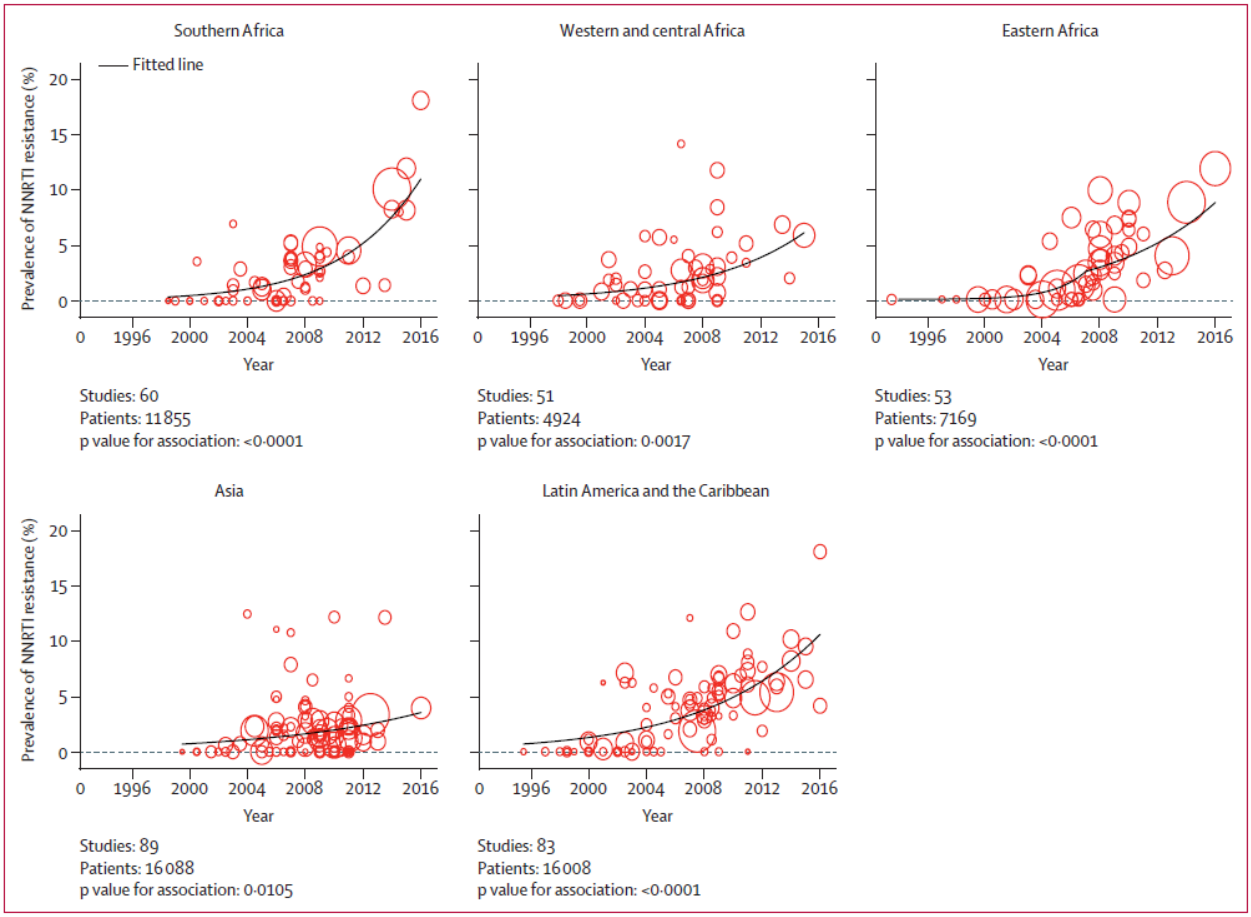


Figure 1.1 Prevalence of pre-treatment HIV resistance to NNRTI by year of sampling (49). *Each bubble represents a study, of which the bubble size is proportional to the study size.*

The 2019 WHO HIVDR report highlights PDR levels of >10% in 12 of 18 countries who had performed a nationally representative PDR surveys conducted between 2014 and

2016. Notably, their findings further reported that NNRTI resistance was significantly higher amongst persons with prior exposure to ART (34). Within the continent, PDR levels to NNRTI are reported at 6.3% in Botswana in 2010 (50), 9.0% in South Africa in 2014 (9), and 10.4% in Cameroon in 2014 (51). A pooled data analysis of sequence data collected between 2010 and 2015 in South Africa showed a peak PDR estimate of 11.9% in 2015, and 1.18 fold annual increase in NNRTI PDR levels during this period (52), whereas PDR levels were 9.5% in the ANRS12249 Treatment-as-Prevention Trial conducted in KwaZulu-Natal between 2012 and 2016 (53).

However, the impact of PDR at treatment initiation on NNRTI-based first line regimens remains unclear. The systematic review and meta-regression analysis performed by Gupta *et al* reported a significant increase in risk of virological failure at 12 months' post initiation of therapy amongst patients initiating ART with PDR (odds ratio 2.91, 95% CI 1.48 – 5.72), after adjustment for age, viral load, CD4 T-cell count, ART, adherence, WHO clinical stage, year of initiation and sex (49). In the PASER-M study, PDR was associated with an increased risk of virological failure (OR 2.13 (95% CI 1.44 – 2.13)) (54). Patients with PDR were more likely to have been previously exposed to ART or PMTCT and to be of younger age. Alternatively, patients enrolled in the ANRS 12249 Treatment-As-Prevention Trial with detectable levels of NNRTI pre-treatment resistance were no less likely to achieve virological suppression than those without resistance (adjusted hazard ratio 1.05, 95% CI 0.82 – 1.34) (53).

1.2.5 Management and treatment of HIV infection in South Africa

By end of 2017, ART was provided through ~4500 public health facilities across the country. Standardised first-line and second-line drug regimens are provided to all patients at all facilities, coupled with routine VL monitoring to detect viral suppression. Treatment regimens include two NRTI plus one NNRTI for first-line, with the NNRTI being substituted for a PI in second-line treatment regimens. At time of this research, first-line regimens used were tenofovir + emtricitabine + efavirenz in fixed-dose formulation, replacing tenofovir with zidovudine and efavirenz with ritonavir-boosted lopinavir (or atazanavir) for second-line ART (55). First-line treatment guidelines will be updated in 2020 to replace efavirenz with dolutegravir, in line with WHO recommendations (56,57). Access to third line ART is managed centrally by the National Department of Health, and can contain

darunavir, raltegravir and etravirine. The provision of tenofovir + lamivudine for pre-exposure prophylaxis was implemented through sex-worker programmes in 2016 (58).

Estimates from mid-2016 showed that of 3.4 million persons on ART, ~145 000 (~4%) were receiving second line treatment and >700 (0.02%) on third-line treatment (59). VL monitoring is performed at 6 months' post-initiation of treatment, at 12 months and annually thereafter; patients with detectable viremia are counselled to intensify and improve treatment adherence, and the VL repeated after 2 months (or 6 months on PI-based regimens). If the repeat VL is >1000 copies/ml, patients are switched to the next line regimen. In the South African public sector programme, HIVDR testing is only routinely performed at second-line failure to assess levels of PI resistance and guide 3rd-line regimen selection.

1.2.5.1 Retention in care in patients receiving ART

Retaining patients in care remains one of the biggest challenges of an effective HIV treatment programme. Whilst definitions of lost-to-follow-up (LTFU) are not standardised, cohort studies from South Africa indicate rates of LTFU between 23 – 42% over a period of ~3 years (60,61), using a definition of no clinic visit for ≥3 months (62). Data from the national programme indicate that rates of patients defaulting from care are high (~ 15% of patients are LTFU by 6 months, ~25% by 12 months and >30% after ≥24 months) (63), and are increasing as the treatment programme expands. These high rates of LTFU are documented in other LMIC settings: a systematic review of >7300 patients who started ART in 9 different studies showed that 32% of patients were LTFU, 23% had defaulted therapy, 15% had transferred to a different facility, and 22% were no longer alive (64). A similar systematic review of levels of retention in care after antiretroviral therapy initiation among adult populations in sub-Saharan Africa showed 65 – 70% retention at 36 months. As HIV-related mortality rates are declining, reduced retention in care is likely to be as a result of patients not returning for clinical assessment and prescription refills, possibly due to long patient waiting times at facilities and increased patient discomfort. Understanding rates and reasons of treatment defaulting is necessary to improve programmatic function and minimise selection of HIVDR variants.

1.2.5.2 Rates of virological suppression

Information on outcomes of the public sector treatment programme is lacking at national, district and health facility levels, due to fragmented health information systems and a lack of patient unique identifiers (65). The District Health Information System (DHIS) reports numbers of patients on ART, the proportion of patients with viral load tests performed and captured, and the proportion of VL results that show viral suppression. A recent cross-referencing between the DHIS and the National Health Laboratory System data warehouse showed that at the national level between 2014 and 2015, 75% of patients in the public sector had received a VL test in the previous 12 months and 78% of those tested had a suppressed VL (66). A programmatic analysis of progression towards 90-90-90 targets reported viral suppression rates of 76% (67); however given gaps in access to care, this figure translates into 26% of people living with HIV.

1.3 Problem statement

Recent reports indicate that levels of PDR to the NNRTI drug class are increasing in a number of LMIC, to estimates of greater than 10%. The WHO recommends that when PDR levels exceed 10% in a country or region, then new first-line regimens should be considered. Given increasing levels of PDR in the country, particularly to the NNRTI drug class, the efficacy of standardised first-line regimens used routinely to achieve virological suppression in patients initiating first-line ART in SA remains unclear.

1.4 Justification for the study

Recent data from South Africa and internationally show that HIVDR rates amongst persons initiating ART are increasing, possibly compromising the efficacy of standardised first-line ART regimens. The impact of PDR on achieving early virological suppression post initiation of ART remains unclear as do the factors associated with lack of early viral suppression among those with or without detectable PDR. This aim of this analysis was to assess levels of retention-in-care and 6-month virological outcomes in patients enrolled in to the GERMS-SA HIV/TB study, including those with resistance to first-line regimens. Factors associated with having a VL ≥1,000 copies/mL 6-months post-initiation of ART among those with or without detectable PDR will be explored.

1.5 Research question

What is the likelihood of achieving early virological suppression amongst patients receiving standardised first-line ART with detectable levels of resistance at initiation of therapy?

1.6 Research aims

The aim of this sub-study was to assess levels of retention-in-care and 6-month virological outcomes in patients enrolled in to the GERMS-SA HIV/TB study, including those with resistance to first-line regimens and those who were predicted to be fully susceptible. The objectives of the study are:

- Objective 1: To measure the proportion of participants retained in care in the GERMS-SA HIV/TB surveillance study at 6 months' post enrolment.
- Objective 2: To estimate rates of and assess predictors for achieving early virological suppression at 6 months' post-initiation of ART among those with and without PDR.

CHAPTER 2: METHODS

This chapter describes the methods used in this analysis, including study design, sampling strategy, inclusion criteria and data management. This chapter further describes the use of modified Poisson regression with robust error estimation to assess factors associated with patient retention-in-care and virological outcomes at 6-months post-initiation of ART.

2.1 Study design

Secondary analysis of data from a prospective cohort study of patients initiating ART at 9 sentinel surveillance sites

2.2 The GERMS-SA HIV/TB surveillance study (parent study)

An integrated TB-HIV surveillance study was established in 2014/15 using the GERMS-SA hospital-based surveillance platform. In this study, persons initiating ART in 9 sentinel high-burden clinics were consented and enrolled into a study which set out to determine presence of HIVDR in persons initiating ART. In addition, standardised medical chart reviews at start of ART and during the following 6 months follow up visit were performed and completed by surveillance officers (Appendix 2). HIVDR genotyping on HIV isolates extracted from viraemic patients (VL ≥ 1,000 copies/mL) using a validated in-house assay and the Stanford University Genotypic Resistance Interpretation Algorithm (https://hivdb.stanford.edu/hivdb).

Convenience sampling was used to select participating sentinel sites, principally based on HIV burden and numbers of patients initiating ART. Participant enrolment and specimen collection took place in the following clinics:

- Mpumalanga Province: Hluvukani Clinic, Hoedspruit (n=122) and Kabokweni Clinic, Nelspruit (n=97)
- KwaZulu-Natal Province: Eastboom Clinic, Pietermaritzburg (n=249) and Phoenix Clinic, Durban (n=89)
- Gauteng Province: Chiawelo Clinic, Johannesburg (n=246)
- North-West Province: Jouberton Clinic, Klerksdorp (n=199)
- Eastern Cape Province: Gqebera Clinic (n=82) and Zwide Clinic (n=150), Port Elizabeth.

- Free State Province: Heidedal Clinic (n=96), Bloemfontein.

At all participating sites, enrolment questionnaires as well as standardised 6-month post-enrolment medical chart medical record reviews were performed and completed by surveillance officers (Appendix 2). All data forms, questionnaires and whole blood specimens were assigned the same unique specimen ID used at study enrolment. The same unique ID was captured on the 6-month medical chart review to facilitate linkage to the participant and primary data collection form. Patient names, clinic file numbers and unique specimen IDs were recorded by the surveillance officers at time of enrolment and kept in a secure location at the facility. The 6-month medical chart review was performed by accessing clinical medical files, electronic files or laboratory records. At all facilities, medical chart review was attempted at least 9 months' post enrolment to provide opportunity for the 6-month clinic visit to have occurred. Data entry into Excel was be performed by a data capturing team. The database was located on servers managed by the NHLS information technology department.

2.3 Study population

The study population for the secondary analysis comprised adult patients initiating first-line ART, enrolled in to the parent study at participating facilities (n=1330) between November 2014 and December 2017.

2.4 Sampling strategy

All enrolled adult patients who had a 6-month medical chart review performed and who had a HIVDR result at primary study enrolment were included in the secondary study analysis.

2.5 Inclusion criteria

The inclusion criteria for enrolment into the secondary analysis are:

- Enrolled into GERMS HIV/TB survey between November 2014 and December 2017
- Six-month medical chart review was performed
- Medical chart was located
- Participant had HIVDR genotyping result at time of enrolment.

2.6 Definition of terms

Key study terms are defined as follows:

- Pre-treatment resistance: having had major mutations (n≥1) associated with resistance to first-line ART at enrolment
- Prior ART exposure: having documented or self-reported exposure to ART at least 3 months prior to (re)initiation of current ART regimen.
- Retention in care is defined as participants with evidence of a 6-month clinic visit in the medical files post-6 months of initiation of ART. This evidence is determined as a recorded clinic visit date or a laboratory test result associated with HIV treatment management (CD4 or VL test result) at 6 (±3) months post treatment initiation.
- Virological failure is defined as having a viral load test result of ≥1,000 copies/ml whilst receiving ART.

2.7 Description of outcomes

Two main outcomes were measured in the secondary analysis. These are illustrated in Figure 2.1 below:

- Proportion of participants with evidence of a clinic visit 6 months' post initiation of ART (participants retained in care; objective 1).
- Proportion of participants who had evidence of virological failure at 6 months' post-initiation of therapy (participants with virological failure; objective 2).

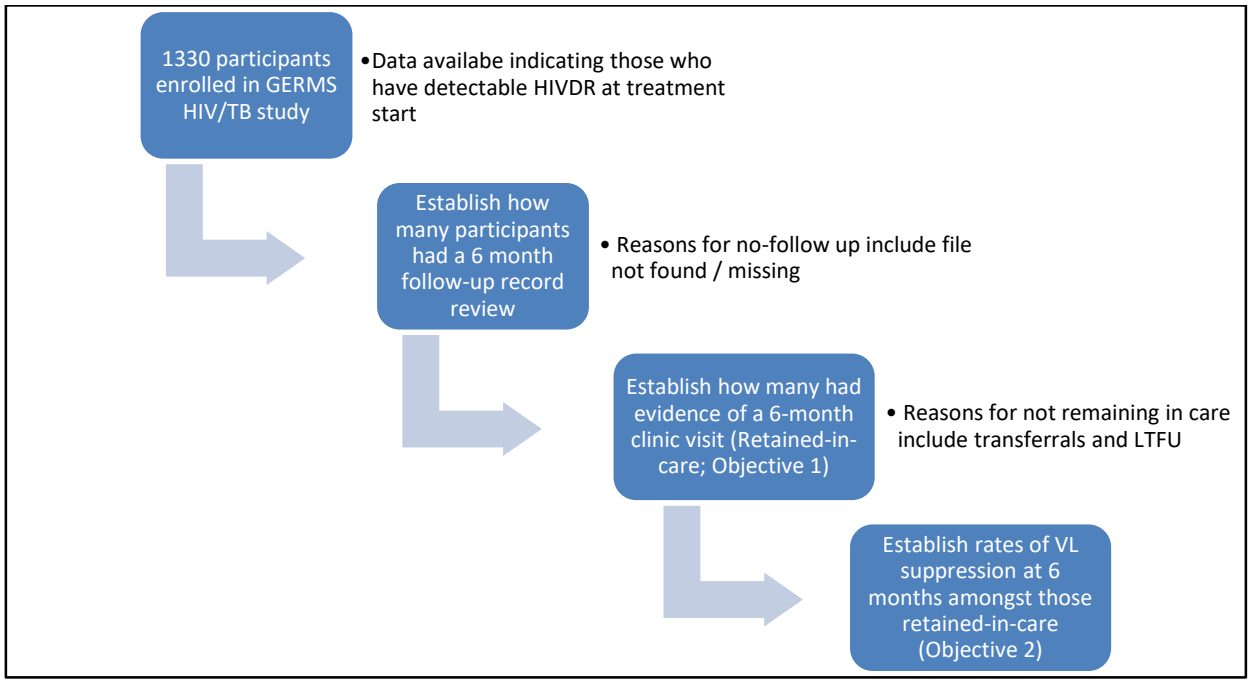


Figure 2.1. Data flow diagram contextualizing the current study objectives within the parent study.

2.8 Data management

The 6-month MS-Excel database was located on servers managed by the NHLS information technology department. Data cleaning was performed manually, including investigation of incorrect dates, correct date formatting, investigation of outliers and incorrect values, and removal of duplicate entries. Where possible, missing data was verified by cross-reference with enrolment forms.

2.9 Data analysis by objective

Data analyses performed per objective are described in Table 2.1, including activity, method of analysis, and required data variables. Modified Poisson regression with robust error estimation was used to identify independent factors associated with retention-in-care, and having viral load ≥1,000 copies/mL, based on the commonality of the expected outcome (68–70). Sensitivity analyses were performed by redistributing missing data counts to either outcome (retained-in-care (yes/no) and virological suppression (yes/no), thereby providing adjusted hypothetical proportion estimates. Modified Poisson regressing was similarly performed on hypothetical data counts. Data variables that had a p-value of ≤0.2 at the univariate level were selected for multivariable model building; however, PDR status, age and gender were included *a priori*. Significance was set at p-value of less than 0.05. All analyses were conducted using STATA version 14 (STATA Corp., College Station, TX, USA).

Table 2.1. Description of data analysis used in analysis

	Activity	Methods for analysis	Data variables
Descriptive statistics	Describing those eligible for inclusion i.e. those for whom a completed 6 month chart review was investigated and for those for whom a HIVDR result is available at time of enrolment	Descriptive statistics (proportions for categorical variable, median plus IQR for continuous variables)	Specimen ID Year of enrolment Gender Age CD4 count Education level Employment status Smoking status Alcohol consumption status Prior/current diagnosis with TB PDR status at treatment start Prior exposure status at treatment start
	Assessment of randomness of inclusion;	Chi squared test	
Objective 1: To measure the proportion of participants for whom a 6-month VL test result is available at 6 months post enrolment.	Establish proportions who have evidence of a 6-month VL test result	Proportions	Specimen ID # participants LTFU (comment) # participants transferred-out (comment) # participants with evidence of retention in care Year of enrolment Gender Age CD4 count Education level Employment status Smoking status Alcohol consumption status Prior/current diagnosis with TB PDR status at treatment start Prior exposure status at treatment start
	Assess predictors of retention-in-care	Poisson regression	

Objective 2: To estimate rates of and assess predictors for having virological failure at 6 months post-initiation of ART among those with and without PDR.	Establish proportions who have evidence of a 6-month VL test result	Proportions	Specimen ID Year of enrolment Gender Age CD4 count Education level Employment status Smoking status Alcohol consumption status Prior/current diagnosis with TB PDR status at treatment start Prior exposure status at treatment start
	Establish predictors of having a VL result ≥1,000 copies/mL	Poisson regression with robust error variance	

2.10 Ethical considerations

2.10.1 Approvals

Ethical approval for the GERMS-SA Joint HIV/TB surveillance study – the primary study was obtained in 2013 (M131021). Participant enrolment did not commence until permission had been obtained from participating site administration. Ethical approval for this secondary analysis was obtained from the Wits Human Research Ethics committee (M180629) and permission to conduct this analysis from the Centre for HIV and Sexually Transmitted infections and the Centre for Tuberculosis at the National Institute for Communicable Diseases.

2.10.2 Assessment of risk and benefits

There are no major risks and/or benefits to participants.

2.10.3 Confidentiality

Patient confidentiality is strictly maintained at all stages of data management, with access given to study personnel only. Completed study forms are stored in secure facilities (e.g. locked cupboards or offices) at participating sites. Copies of the data collection forms were mailed to the NICD in sealed envelopes. Database access is restricted to study personnel only.

2.10.4 Informed Consent

At time of enrolment, study content, purpose, risks and benefits were discussed with the participant. Enrolment into the study was voluntary, and written consent obtained.

CHAPTER THREE: RESULTS

This chapter describes the outcomes of the analysis performed, including rates of retention-in-care, and virological outcomes in patients who had a 6-month VL test recorded. The analysis explores factors associated with either outcome, and the strength of the associations are explored with sensitivity analyses.

3.1 Study flow and summary

The secondary study flow is indicated in Figure 3.1. At study closure, no medical chart reviews were performed for 145 participants due to administrative reasons. In addition, the medical chart was not found by surveillance officers for 154 participants at all facilities. A further subset of 138 participants did not have a HIVDR genotype at time of enrolment (25 of which did not have a 6-month review performed, or their medical file was not found). As such, these 412 participants were excluded from the secondary analysis.

Of the 918 participants included in the secondary analysis, 502 (55%) participants had evidence of a 6-month visit and therefore considered as retained in care, whereas 416 (45%) participants had no evidence of a 6-month visit. Of these, 375 (41%) were documented as or assumed to be LTFU, 36 (4%) were transferred to a different facility, and 5 were deceased.

Of 502 participants retained in care, 358 (71%) had a viral load result available, whereas 144 participants did not have a VL result evident. Amongst the 358 participants with a VL result, 305 (85%) had a VL result < 1,000 copies/mL, and 53 (15%) had a VL result than was ≥1,000 copies/mL.

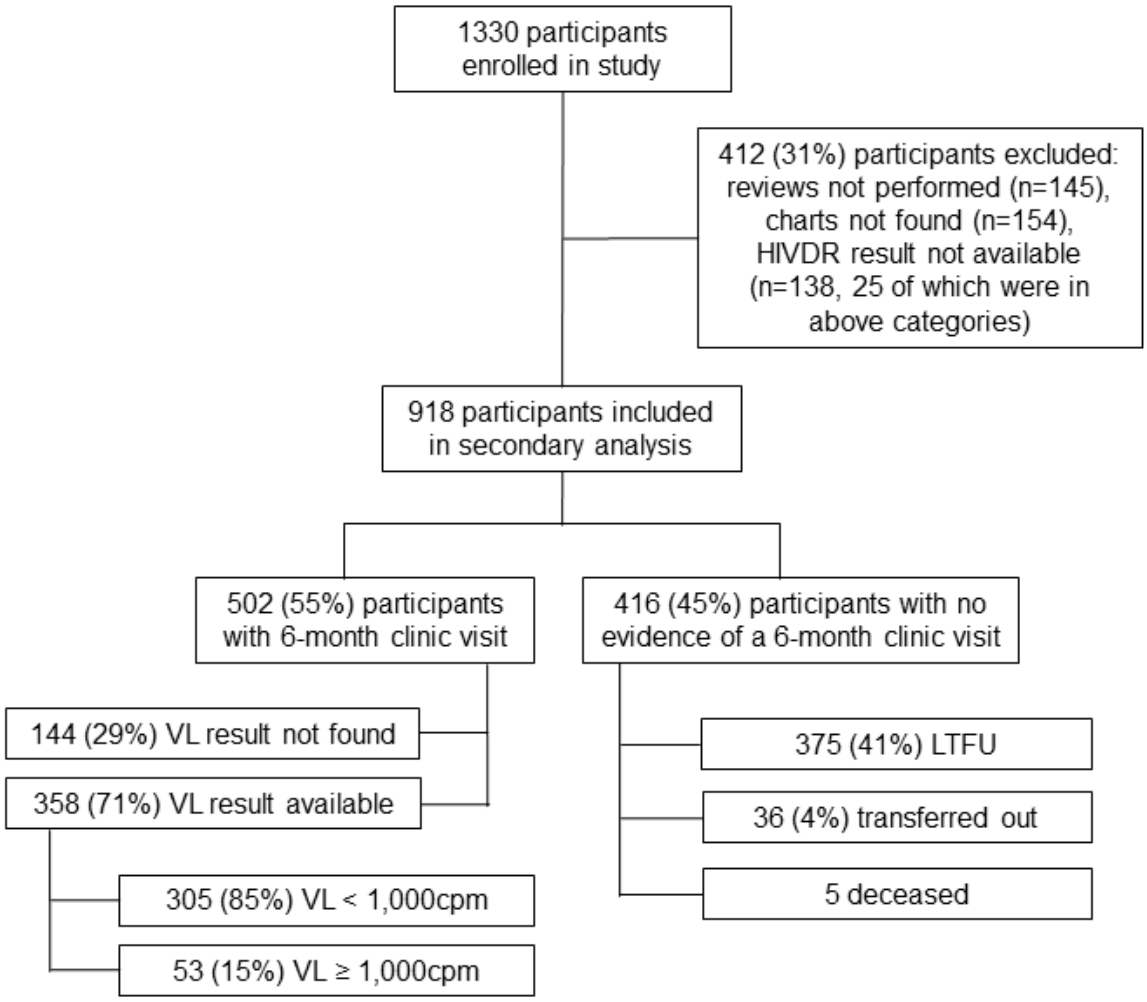


Figure 3.1. Study flow and summary

3.1.1 Description of participants included in the analysis

During the period January 2015 to October 2017, a total 1330 patients were enrolled in the primary study. Sixty-eight percent of enrolled participants were female; the median age at enrolment was 33 years (IQR 27 – 41). The median CD4 count at time of enrolment (ART initiation) was 300 cells/µL (IQR 154 - 450), and 14% had ever been diagnosed with tuberculosis. One hundred and eighty-three participants (14%) reported prior exposure to ART;124 had received combination ART (cART), 56 had received PMTCT, and 3 had received PEP. PDR was detected in 232 participants (19.5%, 95% CI 17.3 – 21.8%), of which NNRTI resistance was most commonly detected.

A total of 918 participants were included in the analysis, as indicated above. Of these, 158 (17.2%) were enrolled in 2015, 292 (31.8%) in 2016 and 468 (51.0%) in 2017 (Table 3.1). Two thirds were female, and median age at time of enrolment was 34 years (IQR 28 – 42). Median CD4 count at time of enrolment was 276 cells/µL (IQR 141 – 431). Fifty-seven percent of enrolees were unemployed, and three quarters had received secondary schooling. One fifth were smokers; one third consumed alcohol regularly. Thirteen percent had a prior or current diagnosis of infection with *Mycobacterium tuberculosis*. One hundred and twelve participants reported prior ART exposure; 182 (19.8%) had evidence of PDR at time of ART initiation.

3.1.2 Assessment of randomness of missing data

An assessment of randomness of study data was performed to assess factors associated with inclusion into the secondary analysis (Table 3.1). Inclusion was found not to be at random; participants enrolled into the study 2016-2017 were significantly more likely to be included in to the secondary analysis. In addition, female participants, participants who were unemployed or had regular employment, participants with CD4 count >500 cells/µL at treatment initiation, or participants with prior ART exposure were more likely to be excluded from the secondary analysis.

Table 3.1. Demographic characteristics of the participants enrolled into the primary study and included in the secondary analysis

	Participants included in secondary analysis (n=918)		*Participants excluded from secondary analysis (n=412)*		*p-value*
	Number	*%*	*Number*	*%*	
Year of Enrolment					0.000
2015	158	17.2	186	45.2	
2016	292	31.8	89	21.6	
2017	468	51.0	137	33.3	
Age					0.432
15-24 years	144	15.9	75	18.6	
25-49 years	673	74.1	293	72.5	
>50 years	91	10.0	36	8.9	
Gender					0.009
Male	312	34.3	111	27.0	
Female	598	65.7	300	73.0	
Employment Status					0.032
Unemployed	524	57.3	254	61.7	

Student/scholar	29	3.2	6	1.5	
Irregular employment	73	8.0	19	4.6	
Regular employment	288	31.5	133	32.3	
Education					0.721
None	32	3.5	14	3.4	
Primary	133	14.6	62	15.1	
Secondary	690	75.5	316	76.7	
Tertiary	59	6.5	20	4.9	
Current smoker					0.436
No	727	79.7	336	81.6	
Yes	185	20.3	76	18.4	
Regular alcohol use					0.870
No	612	67.8	276	67.3	
Yes	291	32.2	134	32.7	
TB diagnosis					0.129
No	763	87.0	337	83.8	
Yes	114	13.0	65	16.2	
CD4 count at ART initiation					0.000
<200 cells/μL	306	37.2	73	25.4	
200-499 cells/μL	384	46.7	135	46.9	
500 cells/μL or higher	132	16.1	80	27.8	
Prior ART exposure					0.017
No	795	87.7	341	82.8	
Yes	112	12.4	71	17.2	
PDR detected					0.563
No	736	80.2	224	81.8	
Yes	182	19.8	50	18.2	

3.2 Retention in care (Objective 1)

3.2.1 Factors associated with retention-in-care

For the purposes of this analysis, retention-in-care was defined as having evidence of a 6-month (±3 months) clinic visit at the same facility. Of the 918 participants included in the secondary analysis, 502 (55%) participants had evidence of a 6-month visit and therefore considered as retained in care, whereas 416 (45%) participants had no evidence of a 6-month visit. Of these, 375 (41%) were documented as or assumed to be LTFU, 36 (4%) were transferred to a different facility, and 5 were deceased.

Table 3.2 indicates factors associated with retention-in-care. At a univariate level, retention-in-care was significantly associated with enrolment during 2016 and having regular employment. However, at a multivariate level, participants enrolled into the study

during 2016 were more likely to be retained in care than those enrolled in 2015 (IRR = 1.31 (95% CI 1.06 – 1.62); however, at multivariable level there was no association between year of enrolment and retention in care. CD4 category was excluded from multivariate analysis due to lower number of observations.

3.2.2 Sensitivity analysis rates of retention-in-care

A sensitivity analysis was performed to explore the robustness of these findings (Table 3.3). Proportions of participants retained in care was determined to be 55% and ranged between 38% and 69%. The association of retention-in-care and study enrolment during the latter part of the survey (2016 and 2017) maintained levels of significance throughout the sensitivity analysis.

Table 3.2. Factors associated with retention in care

	n/N (%)	*crude IRR (n=918)*	*95% CI*	*p-value*	*adjusted IRR (n=861)*	*95% CI*	*p-value*
Year of Enrolment							
2015	72/158 (45.6)	(ref)			(ref)		
2016	176/292 (60.3)	**1.32**	**1.09 - 1.61**	**0.005**	1.31	1.07 - 1.61	0.010
2017	254/468 (54.3)	1.19	0.99 - 1.44	0.071	1.21	0.99 - 1.49	0.060
Age							
15-24 years	72/144 (50.0)	(ref)			(ref)		
25-49 years	375/673 (55.7)	1.11	0.93 - 1.33	0.230	1.18	0.95 - 1.45	0.126
>50 years	51/91 (56.0)	1.12	0.88 - 1.43	0.361	1.20	0.91 - 1.58	0.203
Gender							
Male	163/312 (52.2)	(ref)					
Female	334/598 (55.9)	1.07	0.94 - 1.21	0.306	1.10	0.96 - 1.26	0.163
Employment Status							
Unemployed	272/524 (51.9)	(ref)			(ref)		
Student/scholar	17/29 (58.6)	1.13	0.82 - 1.55	0.452	1.22	0.84 - 1.77	0.291
Irregular employment	40/73 (54.8)	1.06	0.84 - 1.32	0.636	1.05	0.83 - 1.32	0.697
Regular employment	170/288 (59.0)	**1.14**	**1.00 - 1.29**	**0.047**	1.13	0.99 - 1.30	0.068
Education							
None	16/32 (50.0)	(ref)					
Primary	78/133 (58.7)	1.17	0.81 - 1.71	0.404			
Secondary	374/690 (54.2)	1.08	0.76 - 1.54	0.654			
Tertiary	31/59 (52.5)	1.05	0.69 - 1.61	0.818			
Current smoker							
No	405/727 (55.7)	(ref)					
Yes	93/185 (50.3)	0.90	0.77 - 1.06	0.201			
Regular alcohol use							
No	335/612 (54.7)	(ref)					
Yes	156/291 (53.6)	0.98	0.86 - 1.11	0.751			

TB diagnosis (previous or current)											
No	421/763 (55.2)	(ref)					(ref)				
Yes	54/114 (47.4)	0.86	0.70	-	1.05	0.142	0.89	0.72	-	1.10	0.283
CD4 count at ART initiation											
<200 cells/μL	167/306 (54.6)	(ref)					(excluded)				
200-499 cells/μL	208/384 (54.2)	0.99	0.86	-	1.14	0.915					
500 cells/μL or higher	83/132 (62.9)	1.15	0.98	-	1.36	0.095					
Prior ART											
No	434/795 (54.6)	(ref)									
Yes	60/112 (53.6)	0.98	0.82	-	1.18	0.841					
PDR detected											
No	400/736 (54.3)	(ref)					(ref)				
Yes	102/182 (56.0)	1.03	0.89	-	1.19	0.677	1.05	0.90	-	1.21	0.551

IRR = incidence rate ratio. PDR = pre-treatment drug resistance. ART = antiretroviral therapy

Table 3.3. Sensitivity analysis of factors associated with retention-in-care (n=1330).

	All missing visits: retained in care			*All missing visits: not retained in care*		
Characteristic	*crude IRR*	*95% CI*	*p-value*	*crude IRR*	*95% CI*	*p-value*
Year of Enrolment						
2015	(ref)			(ref)		
2016	0.93	0.85 - 1.01	0.102	**2.21**	**1.75 - 2.78**	**0.000**
2017	**0.86**	**0.79 - 0.94**	**0.001**	**2.01**	**1.60 - 2.51**	**0.000**
Age						
15-24 years	(ref)			(ref)		
25-49 years	1.03	0.93 - 1.14	0.567	1.18	0.96 - 1.45	0.113
>50 years	1.02	0.88 - 1.19	0.790	1.22	0.92 - 1.62	0.168
Gender						
Male	(ref)			(ref)		
Female	**1.09**	**1.00 - 1.18**	**0.040**	0.97	0.83 - 1.11	0.638
Employment Status						
Unemployed	(ref)			(ref)		
Student/scholar	0.97	0.76 - 1.24	0.820	1.39	0.97 - 1.98	0.069
Irregular employment	0.95	0.81 - 1.11	0.519	1.24	0.97 - 1.60	0.090
Regular employment	1.06	0.99 - 1.15	0.111	1.15	0.99 - 1.34	0.061
Education						
None	(ref)			(ref)		
Primary	1.10	0.88 - 1.38	0.410	1.15	0.75 - 1.77	0.526
Secondary	1.05	0.85 - 1.30	0.646	1.07	0.71 - 1.60	0.747
Tertiary	0.99	0.76 - 1.29	0.940	1.13	0.70 - 1.83	0.624
Current smoker						
No	(ref)			(ref)		
Yes	0.93	0.84 - 1.02	0.140	0.94	0.78 - 1.12	0.467
Regular alcohol use						
No	(ref)			(ref)		

	All missing visits: retained in care			*All missing visits: not retained in care*		
Characteristic	*crude IRR*	*95% CI*	*p-value*	*crude IRR*	*95% CI*	*p-value*
Yes	0.99	0.92 - 1.07	0.835	0.97	0.84 - 1.13	0.722
TB diagnosis (previous or current)						
No	(ref)			(ref)		
Yes	0.96	0.86 - 1.08	0.528	**0.79**	**0.62 - 1.00**	**0.047**
CD4 count at ART initiation						
<200 cells/μL	(ref)			(ref)		
200-499 cells/μL	1.04	0.95 - 1.15	0.395	0.91	0.78 - 1.06	0.230
500 cells/μL or higher	**1.21**	**1.09 - 1.35**	**0.000**	0.89	0.73 - 1.09	0.253
Prior ART						
No	(ref)			(ref)		
Yes	1.05	0.95 - 1.16	0.344	0.86	0.69 - 1.07	0.174
PDR detected						
No	(ref)			(ref)	-	
Yes	1.01	0.91 - 1.12	0.882	1.06	0.90 - 1.24	0.520

3.3 Virological outcome at 6 – 9 months' post initiation of ART (Objective 2)

3.3.1 Factors associated with having a VL ≥1,000 copies/mL at 6 months' clinic visit

Of 502 participants retained in care, 358 (71%) had a viral load result available. Amongst the 358 participants, 305 (85%) had a VL result <1,000 copies/mL, and 53 (15%) had a VL result than was ≥1,000 copies/mL (Figure 3.1).

Table 3.4 indicates factors associated with having a VL ≥1,000 copies/mL. In univariate analysis, older age, having regular employment, and having a CD4 count >200 cells/µL at start of ART were significantly associated with reduced risk of having a VL ≥ 1,000 copies/mL, whereas prior ART exposure and having PDR at treatment initiation were associated with increased risk of VL ≥1,000 copies/mL. In multivariate analysis, older age (IRR = 0.43 (95% CI 0.24 – 0.78) for 15-24 years' age group and IRR=0.09 (95% CI 0.01 – 0.56) for >50 years) and CD4 count >200 cells/µL (IRR=0.59 (95% CI 0.36 – 0.98)) were associated with significantly reduced risk of VL≥1,000 copies/mL), and having PDR at treatment initiation (IRR=4.33 (95% CI 2.63 – 7.12)) was significantly associated with increased risk of VL≥1,000 copies/mL.

3.3.2 Sensitivity analysis of factors associated with retention-in-care

A sensitivity analysis was performed to explore the robustness of these findings (Table 3.5). Proportions of participants with VL≥1,000 copies/mL was determined to be 15%, but ranged between 6% and 67%. The association of older age (>50 years) and having regular employment maintained levels of significance throughout the sensitivity analysis. In addition, prior ART exposure and having PDR at start of ART maintained levels of association with VL ≥ 1,000 copies/mL throughout the sensitivity analysis.

Table 3.4. Factors associated with not achieving early virological failure (having a VL result of ≥1,000 copies/mL; n=358).

Characteristic	*n/N (%)*	*crude IRR (n=358)*	*95% CI*	*p-value*	*adjusted IRR (n=315)*	*95% CI*	*p-value*
Year of Enrolment							
2015	9/41 (22.0)	(ref)			(ref)		
2016	21/107 (19.6)	0.89	0.45 - 1.79	0.752	0.94	0.52 - 1.70	0.838
2017	23/210 (11.0)	0.50	0.25 - 1.00	0.050	0.55	0.29 - 1.03	0.060
Age							
15-24 years	14/55 (25.5)	(ref)			(ref)		
25-49 years	38/260 (14.6)	**0.57**	**0.33 - 0.99**	**0.044**	**0.43**	**0.24 - 0.78**	**0.005**
>50 years	1/40 (2.5)	**0.10**	**0.01 - 0.72**	**0.022**	**0.09**	**0.01 - 0.56**	**0.010**
Gender							
Male	14/109 (12.8)	(ref)			(ref)		
Female	39/247 (15.6)	1.23	0.70 - 2.17	0.476	0.85	0.51 - 0.41	0.523
Employment Status							
Unemployed	41/189 (21.7)	(ref)			(ref)		
Student/scholar	2/15 (13.3)	0.61	0.16 - 2.30	0.470	0.55	0.15 - 1.95	0.351
Irregular employment	1/33 (3.0)	0.14	0.02 - 0.99	0.048	0.32	0.06 - 1.79	0.196
Regular employment	9/118 (7.6)	**0.35**	**0.18 - 0.70**	**0.003**	0.55	0.29 - 1.04	0.066
Current smoker							
No	45/296 (15.2)	(ref)					
Yes	8/58 (13.8)	0.91	0.45 - 1.82	0.785			
Regular alcohol use							
No	39/249 (15.7)	(ref)					
Yes	13/103 (12.6)	0.80	0.45 - 1.43	0.453			
TB diagnosis (previous or current)							
No	43/302 (14.2)	(ref)					
Yes	6/32 (18.8)	1.32	0.61 - 2.85	0.486			
CD4 count at ART initiation							
<200 cells/μL	25/115 (21.7)	(ref)			(ref)		

200-499 cells/µL	18/149 (12.1)	**0.56**	**0.32**	**-**	**0.97**	**0.038**	**0.59**	**0.36**	**-**	**0.98**	**0.040**
500 cells/µL or higher	4/61 (6.6)	**0.30**	**0.11**	**-**	**0.83**	**0.020**	0.43	0.16	-	1.14	0.090
Prior ART											
No	39/315 (12.4)	(ref)					(ref)				
Yes	14/40 (35.0)	**2.83**	**1.69**	**-**	**4.73**	**0.000**	1.37	0.79	-	2.37	0.258
PDR detected											
No	24/288 (8.3)	(ref)					(ref)				
Yes	29/70 (41.4)	**4.97**	**3.09**	**-**	**8.00**	**0.000**	**4.33**	**2.63**	**-**	**7.12**	**0.000**

Table 3.5. Sensitivity analysis of factors associated with VL ≥1,000 copies/mL (n=918).

	All missing VL = ≥1,000 copies/mL			*All missing VL = <1,000 copies/mL*		
Characteristic	crude IRR	95% CI	p-value	crude IRR	95% CI	p-value
Year of Enrolment						
2015	(ref)			(ref)		
2016	**0.89**	**0.79 - 0.99**	**0.026**	1.26	0.59 - 2.69	0.546
2017	**0.75**	**0.68 - 0.84**	**0.000**	0.86	0.41 - 1.82	0.700
Age						
15-24 years	(ref)			(ref)		
25-49 years	0.94	0.83 - 1.05	0.270	0.58	0.32 - 1.04	0.069
>50 years	**0.80**	**0.65 - 0.98**	**0.032**	**0.11**	**0.02 - 0.85**	**0.034**
Gender						
Male	(ref)			(ref)		
Female	0.94	0.85 - 1.03	0.180	1.45	0.80 - 2.63	0.218
Employment Status						
Unemployed	(ref)			(ref)		
Student/scholar	0.77	0.55 - 1.07	0.121	0.88	0.22 - 3.46	0.857
Irregular employment	**0.78**	**0.63 - 0.97**	**0.022**	0.18	0.02 - 1.25	0.083
Regular employment	**0.86**	**0.78 - 0.96**	**0.007**	**0.40**	**0.20 - 0.81**	**0.011**
Current smoker						
No	(ref)			(ref)		
Yes	**1.11**	**1.00 - 1.23**	**0.038**	0.70	0.34 - 1.45	0.339
Regular alcohol use						
No	(ref)			(ref)		
Yes	1.05	0.95 - 1.15	0.353	0.70	0.38 - 1.29	0.256
TB diagnosis (previous or current)						
No	(ref)			(ref)		
Yes	**1.17**	**1.04 - 0.31**	**0.006**	0.93	0.41 - 2.14	0.872
CD4 count at ART initiation						

<200 cells/µL	(ref)					(ref)				
200-499 cells/µL	0.93	0.84	-	1.03	0.186	0.57	0.32	-	1.03	0.064
500 cells/µL or higher	**0.80**	**0.68**	**-**	**0.95**	**0.010**	0.37	0.13	-	1.04	0.061
Prior ART										
No	(ref)					(ref)				
Yes	**0.18**	**1.05**	**-**	**1.32**	**0.005**	**2.54**	**1.43**	**-**	**4.54**	**0.002**
PDR detected										
No	(ref)					(ref)		-		
Yes	**1.20**	**1.10**	**-**	**1.33**	**0.000**	**4.88**	**2.91**	**-**	**8.18**	**0.000**

CHAPTER FOUR: DISCUSSION

This chapter discusses the findings of this analysis in the context of previously reported literature, and presents some recommendations to improve retention-in-care and virological outcomes in patients receiving first-line ART in South Africa.

This secondary analysis set out to assess levels of retention-in-care and 6-month virological outcomes in patients enrolled in the GERMS-SA HIV/TB study, including assessment of virological outcomes in patients with resistance to first-line regimens that were initiating ART as per standardised national treatment guidelines. The primary study showed reported that PDR was detected in 19.5% of 1330 participants enrolled between January 2015 and October 2017, across 9 high-burden sentinel clinics. The study was successful in recruiting high proportions of participants, and showed rates of PDR that were higher than those previously reported in South Africa (9,52). Of the 918 (918/1330, 69%) participants included in this analysis, 502 (55%) participants had evidence of a 6-month visit and therefore considered as retained in care, and 361 (71%) had evidence of a 6-month VL result. Amongst these, 308 (85%) of 361 participants with a VL test done at 6 months had a VL result <1,000 copies/mL.

Participants were not included in the secondary analysis because of unavailability of staff to perform the follow-up, not finding the medical chart, or not having a successful drug resistance test at time of enrolment. Participant inclusion into the secondary analysis was not at random, but was not associated with the primary variable of interest, being PDR status at enrolment.

The analysis showed that 55% of participants included in the secondary analysis had evidence of retention-in-care at ~ 6-months post-initiation of therapy. These figures are lower than those reported from national South Africa programme estimates (~15% of patients are LTFU by 6 months (63)), but not considerably different form other South African and African studies, wherein rates of up to 42% have been reported over extended periods of time (60,61). It remains possible that these high rates of LTFU are reflection of poor record keeping in the medical files. However, either option remains an area of

concern, and shows significant weaknesses in providing optimal care for patients receiving care.

Of the 502 participants retained in care, viral load results were documented in 361 (71%) participant medical files. Either the 6-month viral load test was not performed, or had not been recorded in the patient file. Of these, 53 (15%) had a VL result than was ≥1,000 copies/mL. This result is consistent with reported levels of viraemia in patients receiving ART both locally (38,43) and internationally (33,34). Following South African treatment guidelines, patients with a VL ≥1,000 copies/mL should receive intensified adherence counselling from the facility nurse or counsellor to identify and manage issues with treatment adherence, and a repeat VL test be performed after a further 3 months of first-line ART (71). If the repeat VL test remains ≥1,000 copies/mL, the patient is switched to second-line regimens. However, many health programmes have poor rates of prompt regimen switch, increasing the risk of additional drug resistance and transmission of drug-resistant virus, as well as morbidity and mortality (72–74). Our results show that having PDR at treatment initiation was significantly associated with increased risk of VL≥1,000 copies/mL (IRR=4.33, 95% CI 2.63 – 7.12) at 6-months post-initiation of ART; therefore, it can be presumed that viraemia in these patients is due to infection with a resistant virus and not necessarily due to non-adherence, and that these patients are unlikely to ever achieve virological suppression whilst taking NNRTI-based regimens. It is therefore recommended that patients with viraemia as early as 6-months post-initiation of therapy should be prioritized as candidates for prompt regimen switch to second-line ART. Significant efforts should be made to track treatment responses in patients over time, including regular VL monitoring, and to rapidly switch to second-line regimens at time of virological failure or other adverse treatment responses.

Of note, participants who were of younger age and lower CD4 count at treatment initiation were significantly less likely to achieve virological control, findings which are consistent with other reports (72,75–78). Interestingly, a systematic review of peer-reviewed literature exploring interventions to improve ART adherence in adults and adolescents in LMIC showed that no single intervention is successful enough to warrant wide-scale implementation, and that the needs continues to develop interventions for this high-priority population group (79). Interventions such as community-based adherence interventions,

adherence reminders and group adherence counselling approaches remain promising approaches.

The study is limited by access to medical charts at facilities, and rates of retention-in-care may be under-estimated by inadequate recording of the 6-month VL result into the patient files. Of concern is the number of participants who have evidence of a 6-month visit, but there is no evidence of a VL test being performed. According to national guidelines, VL testing should be performed at 6 months to assess early virological response to ART. Given that patients with PDR are at 4 times greater risk of viremia at 6-months, it can be assumed that this viremia is due to resistance to first-line ART regimens and that these patients are likely to not achieve virological suppression. It is recommended that health-care provider training explore reasons for regular virological testing, and rapid response to adverse events. Providing rapid and effective monitoring of patients an ART is critical to achieving the 90% virological suppression UNAIDS target, and to reduce morbidity and mortality in these patients, as well as selection and transmission of resistant HIV variants.

Effective health services and improved clinic operations play a critical role in influencing ART initiation and retention-in-care (80). All health services, whether clinic-based, point-of-care, dispensaries or laboratory-based, depend heavily on effective health information services that allow patients to be tracked between service delivery points (81). Many systems still rely on manual records in the paper-based patient file, and centralised data systems necessary for monitoring and evaluation purposes is hand written in registers and aggregated results captured into electronic health information systems. The South African eHealth Strategy acknowledges that health information systems should be used to strengthen the public health care system, yet implementation remains limited (82). In addition, as many patients have extensive migratory patterns within and between South African provinces, the implementation of a unique patient identifier and electronic record keeping systems that can provide real-time monitoring of patients must remain a priority activity for the national programme (65), thereby allowing a more rapid and informative response to adverse events and effective treatment monitoring.

HIVDR remains a relevant threat to the success of ART programmes worldwide. A recent modelling exercise predicted that PDR, if present at >10%, will contribute to 16% of AIDS deaths, 9% of new infections, and 8% or ART program costs in sub-Saharan Africa (83). Increased levels of HIVDR are likely to compromise viral suppression rates, and can lead

to increased rates of new infections, thereby compromising successes made to reach the UNAIDS 90-90-90 targets. Ideally, HIVDR testing should be provided to all patients. However, as the test remains expensive and complicated, this is extremely difficult to achieve in LMIC with limited laboratory capacity and high infection numbers. LMIC that have high rates of NNRTI-based PDR should prioritise moving to more potent ART regimens to promote patient health and public health targets (84).

Of note, 68% of the participants enrolled into the study were female, and the mean age at time of enrolment was 33 years. This finding is consistent with the epidemiology of HIV in South Africa, where HIV point prevalence estimates were highest amongst women aged 35-39 years but also high amongst women aged 20 to 49 years (85). High rates of HIVDR and specifically PDR remain concerning amongst this population group, and will compromise efforts to reduce vertical transmission if not managed. Pregnant women should be prioritised for more frequent VL monitoring and HIVDR testing in the event of documented virological failure, irrespective of current regimen.

South Africa will be implementing DTG-based first-line ART in 2020 in public health facilities. The advantages of this new regimen include superior efficacy, tolerability and durability, faster rates of viral suppression, fewer side effects, higher genetic barrier to resistance, and smaller tablet size (86). However, it is imperative for the programme in South Africa to address issues of quality-of-care, in order to maximise the benefits of this new regimen.

In conclusion, our study showed that 45% of participants enrolled into a surveillance study at 9 facilities across SA were LTFU at 6-months, and amongst those retained in care, having NNRTI-based PDR at time of treatment initiation was associated with a 4-fold risk of virological failure 6-month post initiation of treatment. These findings support the urgent need to improve centralised electronic record systems to monitor patients on ART, couple with the implementation of a unique patient identifier. In addition, these finding strongly support the implementation of dolutegravir-based first-line ART regimens in South Africa, to improve patient health, reduce the onward transmission of HIVDR, and facilitate achievement of 90% virological suppression in South Africa.

REFERENCES

1. Statistics South Africa. Mid-year population estimates 2019 [Internet]. 2019 [cited 2019 Dec 17]. Available from: www.statssa.gov.za

2. Massyn N, Peer N, English R, Padarath A, Barron P, Day C. District Health Barometer 2015/16 [Internet]. Health Systems Trust. 2016 [cited 2019 Nov 10]. Available from: https://www.hst.org.za/publications/District Health Barometers/District Health Barometer 2015_16.pdf

3. UNAIDS. UNAIDS Data [Internet]. Joint United Nations Programme on HIV/AIDS (UNAIDS). 2019 [cited 2020 Jan 9]. Available from: https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdf

4. Gilks CF, Crowley S, Ekpini R, Gove S, Perriens J, Souteyrand Y, et al. The WHO public-health approach to antiretroviral treatment against HIV in resource-limited settings. Lancet [Internet]. 2006;368(9534):505–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16890837

5. UNAIDS. AIDS by the numbers 2015 [Internet]. UNAIDS, editor. 2015. Available from: http://www.unaids.org/sites/default/files/media_asset/AIDS_by_the_numbers_2015_en.pdf

6. Gupta RK, Jordan MR, Sultan BJ, Hill A, Davis DH, Gregson J, et al. Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis. Lancet [Internet]. 2012;380(9849):1250–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22828485

7. Sigaloff KC, Ramatsebe T, Viana R, al. et. Accumulation of HIV drug resistance mutations in patients failing first-line antiretroviral treatment in South Africa. AIDS Res Hum Retroviruses. 2012;28:171–5.

8. Manasa J, Danaviah S, Lessells R, Elshareef M, Tanser F, Wilkinson E, et al. Increasing HIV-1 Drug Resistance Between 2010 and 2012 in Adults Participating in Population-Based HIV Surveillance in Rural KwaZulu-Natal, South Africa. AIDS Res Hum Retroviruses [Internet]. 2016;32(8):763–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27002368

9. Steegen K, Carmona S, Bronze M, Papathanasopoulos MA, van Zyl G, Goedhals D, et al. Moderate Levels of Pre-Treatment HIV-1 Antiretroviral Drug Resistance Detected in the First South African National Survey. PLoS One [Internet]. 2016;11(12):e0166305. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27907009

10. World Health Organization. World Health Organization Global Strategy for the Surveillance and Monitoring of HIV Drug Resistance [Internet]. Programme H, editor. Geneva: World Health Organization; 2012. Available from: http://apps.who.int/iris/bitstream/10665/77349/1/9789241504768_eng.pdf

11. South African National AIDS Council. National Strategic Plan on HIV, STIs and TB

[Internet]. http://www. National Department of Health,: National Department of Health,; 2011. Available from: http://www.thepresidency.gov.za/MediaLib/Downloads/Home/Publications/SANACCallforNominations/A5summary12-12.pdf

12. GERMS-SA. GERMS South Africa Annual Report 2017 [Internet]. Johannesburg, South Africa; 2016. Available from: http://www.nicd.ac.za/wp-content/uploads/2017/03/GERMS-SA-AR-2016-FINAL.pdf

13. Shaw GM, Hunter E. HIV transmission. Cold Spring Harb Perspect Med. 2012;2(11).

14. National Department of Health of the Republic of South Africa, National Department of Health. The 2015 National Antenatal Sentinel HIV and Syphilis Survey Report [Internet]. Pretoria: Department of Health; 2017. Available from: www.doh.gov.za

15. South African National AIDS Council. South African National Sex Worker HIV Plan 2016-2019 [Internet]. Pretoria: National Department of Health,; 2016. Available from: http://sanac.org.za/wp-content/uploads/2016/03/South-African-National-Sex-Worker-HIV-Plan-2016-2019-FINAL-Launch-Copy....pdf

16. Sattentau QJ, Moore JP. The role of CD4 in HIV binding and entry. Philos Trans R Soc Lond B Biol Sci [Internet]. 1993 Oct 29 [cited 2019 Oct 26];342(1299):59–66. Available from: http://www.ncbi.nlm.nih.gov/pubmed/7904348

17. Alkhatib G, Combadiere C, Broder CC, Feng Y, Kennedy PE, Murphy PM, et al. CC CKR5: A RANTES, MIP-1α, MIP-1β receptor as a fusion cofactor for macrophage-tropic HIV-1. Science (80-). 1996 Jun 28;272(5270):1955–8.

18. Fauci A, Desrosiers R. Pathogenesis of HIV and SIV. Retroviruses. 1997.

19. Levy JA. Chapter 1 Discovery and nature of the HIV virion. In: Discovery and nature of the HIV virion. Washington DC: ASM Press; 1994. p. 1–10.

20. Luciw PA. Chapter 60 - Human immunodeficiency viruses and their replication. In: Fields BN, Knipe DM, Howley PM, editors. Fields Virology. Third. Philadelphia: Lippincott-Raven; 1996. p. 1881–952.

21. De Clercq E. Anti-HIV drugs: 25 compounds approved within 25 years after the discovery of HIV. International Journal of Antimicrobial Agents. 2009.

22. Pau AK, George JM. Antiretroviral therapy: Current drugs. Infectious Disease Clinics of North America. 2014.

23. Vella S, Schwartländer B, Sow SP, Eholie SP, Murphy RL. The history of antiretroviral therapy and of its implementation in resource-limited areas of the world. AIDS [Internet]. 2012 Jun [cited 2020 Jan 10];26(10):1231–41. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00002030-201206190-00012

24. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health

approach. 2nd ed. World Health Organization, editor. Geneva, Switzerland: World Health Organization.; 2016.

25. Richman DD, Havlir D, Corbeil J, Looney D, Ignacio C, Spector SA, et al. Nevirapine resistance mutations of human immunodeficiency virus type 1 selected during therapy. J Virol [Internet]. 1994;68(3):1660–6. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=7509000

26. Osmanov S, Heyward WiL, Esparza J. UNAIDS: HIV-1 Genetic Variability [Internet]. 1995 [cited 2019 Oct 26]. Available from: http://data.unaids.org/publications/irc-pub05/hiv-genetic-variability_en.htm

27. Cuevas JM, Geller R, Garijo R, López-Aldeguer J, Sanjuán R. Extremely High Mutation Rate of HIV-1 In Vivo. PLoS Biol. 2015 Sep 16;13(9).

28. Coffin JM. HIV population dynamics in vivo: implications for genetic variation, pathogenesis, and therapy. Science (80-). 1995;267:483–9.

29. Tang MW, Shafer RW. HIV-1 Antiretroviral Resistance. Drugs. 2012 Sep;72(9):e1--e25.

30. Bertagnolio S, Sutherland D. WHO approach to track HIV drug resistance emergence and transmission in countries scaling up HIV treatment. Aids [Internet]. 2005;19(12):1329–30. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=16052091

31. Bennett DE, Myatt M, Bertagnolio S, Sutherland D, Gilks CF. Recommendations for surveillance of transmitted HIV drug resistance in countries scaling up antiretroviral treatment. Antivir Ther [Internet]. 2008;13 Suppl 2:25–36. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=18575189

32. Hong SY, Nachega JB, Kelley K, Bertagnolio S, Marconi VC, Jordan MR. The global status of HIV drug resistance: clinical and public-health approaches for detection, treatment and prevention. Infect Disord Drug Targets [Internet]. 2011;11(2):124–33. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=21406052

33. Boender TS, Sigaloff KC, McMahon JH, Kiertiburanakul S, Jordan MR, Barcarolo J, et al. Long-term Virological Outcomes of First-Line Antiretroviral Therapy for HIV-1 in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. Clin Infect Dis [Internet]. 2015;61(9):1453–61. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26157050

34. World Health Organization. WHO | HIV drug resistance report 2019. WHO [Internet]. 2019 [cited 2019 Sep 13]; Available from: https://www.who.int/hiv/pub/drugresistance/hivdr-report-2019/en/

35. Hamers RL, Rinke de Wit TF, Holmes CB. HIV drug resistance in low-income and middle-income countries. Vol. 5, The Lancet HIV. Elsevier Ltd; 2018. p. e588–96.

36. Stockdale AJ, Saunders MJ, Boyd MA, Bonnett LJ, Johnston V, Wandeler G, et al. Effectiveness of Protease Inhibitor/Nucleos(t)ide Reverse Transcriptase Inhibitor-Based Second-line Antiretroviral Therapy for the Treatment of Human Immunodeficiency Virus Type 1 Infection in Sub-Saharan Africa: A Systematic Review and Meta-analysis. Clin Infect Dis [Internet]. 2018 [cited 2019 Nov 2];66(12):1846–57. Available from: https://academic.oup.com/cid/article-abstract/66/12/1846/4767830

37. Edessa D, Sisay M, Asefa F. Second-line HIV treatment failure in sub-Saharan Africa: A systematic review and meta-analysis. PLoS One. 2019 Jul 29;14(7):e0220159.

38. Steegen K, Bronze M, Papathanasopoulos MA, van Zyl G, Goedhals D, Variava E, et al. HIV-1 antiretroviral drug resistance patterns in patients failing NNRTI-based treatment: results from a national survey in South Africa. J Antimicrob Chemother [Internet]. 2017;72(1):210–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27659733

39. Steegen K, Bronze M, Papathanasopoulos MA, van Zyl G, Goedhals D, Van Vuuren C, et al. Prevalence of Antiretroviral Drug Resistance in Patients Who Are Not Responding to Protease Inhibitor-Based Treatment: Results From the First National Survey in South Africa. J Infect Dis [Internet]. 2016;214(12):1826–30. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27923946

40. Van Zyl GU, Liu TF, Claassen M, Engelbrecht S, De Oliveira T, Preiser W, et al. Trends in Genotypic HIV-1 Antiretroviral Resistance between 2006 and 2012 in South African Patients Receiving First- and Second-Line Antiretroviral Treatment Regimens. PLoS One [Internet]. 2013 [cited 2019 Nov 2];8(6):e67188. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23840622

41. Manasa J, Lessells RJ, Skingsley A, Naidu KK, Newell ML, McGrath N, et al. High-levels of acquired drug resistance in adult patients failing first-line antiretroviral therapy in a rural HIV treatment programme in KwaZulu-Natal, South Africa. PLoS One [Internet]. 2013;8(8):e72152. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23991055

42. Kiepiela P, Manasa J, Moosa M-Y, Moodley P, Gordon M, Parikh UM, et al. HIV Drug Resistance Patterns at the Epicentre of the HIV-1 Epidemic in Kwazulu-Natal, South Africa 2003-2013. J AIDS Clin Res. 2014;5(5):299.

43. Hunt GM, Dokubo EK, Takuva S, de Oliveira T, Ledwaba J, Dube N, et al. Rates of virological suppression and drug resistance in adult HIV-1-positive patients attending primary healthcare facilities in KwaZulu-Natal, South Africa. J Antimicrob Chemother. 2017;72(11):3141–8.

44. Tang MW, Rhee SY, Bertagnolio S, Ford N, Holmes S, Sigaloff KC, et al. Nucleoside reverse transcriptase inhibitor resistance mutations associated with first-line stavudine-containing antiretroviral therapy: programmatic implications for countries phasing out stavudine. J Infect Dis [Internet]. 2013;207 Suppl:S70-7. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23687292

45. Rhee SY, Blanco JL, Jordan MR, Taylor J, Lemey P, Varghese V, et al. Geographic and Temporal Trends in the Molecular Epidemiology and Genetic Mechanisms of Transmitted HIV-1 Drug Resistance: An Individual-Patient- and Sequence-Level Meta-Analysis. PLoS Med [Internet]. 2015 Apr 1 [cited 2020 Feb 9];12(4):e1001810. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25849352

46. Hunt GM, Ledwaba J, Kalimashe M, Salimo A, Cibane S, Singh B, et al. Provincial and national prevalence estimates of transmitted HIV-1 drug resistance in South Africa measured using two WHO-recommended methods. Antivir Ther [Internet]. 2019 [cited 2019 Nov 2];24(3):203–10. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30741163

47. Boettiger DC, Kiertiburanakul S, Sungkanuparph S, Law MG. The impact of wild-type reversion on transmitted resistance surveillance. Vol. 19, Antiviral Therapy. International Medical Press Ltd; 2014. p. 719–22.

48. Bennett DE, Camacho RJ, Otelea D, Kuritzkes DR, Fleury H, Kiuchi M, et al. Drug resistance mutations for surveillance of transmitted HIV-1 drug-resistance: 2009 update. PLoS One [Internet]. 2009;4(3):e4724. Available from: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=19266092

49. Gupta RKRK, Gregson J, Parkin N, Haile-Selassie H, Tanuri A, Andrade Forero L, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. Lancet Infect Dis [Internet]. 2018;18(3):346–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/29198909

50. Mungati M, Mhangara M, Gonese E, Mugurungi O, Dzangare J, Ngwende S, et al. Pre-treatment drug resistance among patients initiating antiretroviral therapy (ART) in Zimbabwe: 2008-2010. BMC Res Notes. 2016 Jun 10;9(1).

51. Tchouwa GF, Eymard-Duvernay S, Cournil A, Lamare N, Serrano L, Butel C, et al. Prevalence of pretreatment HIV drug resistance in Cameroon following a nationally representative WHO survey. J Antimicrob Chemother [Internet]. 2018 Sep 1 [cited 2019 Nov 2];73(9):2468–74. Available from: https://academic.oup.com/jac/article/73/9/2468/5040491

52. Chimukangara B, Lessells RJ, Rhee SY, Giandhari J, Kharsany ABM, Naidoo K, et al. Trends in Pretreatment HIV-1 Drug Resistance in Antiretroviral Therapy-naive Adults in South Africa, 2000–2016: A Pooled Sequence Analysis. EClinicalMedicine. 2019 Mar 1;9:26–34.

53. Derache A, Iwuji CC, Baisley K, Danaviah S, Marcelin A-G, Calvez V, et al. Impact of Next-generation Sequencing Defined Human Immunodeficiency Virus Pretreatment Drug Resistance on Virological Outcomes in the ANRS 12249 Treatment-as-Prevention Trial. Clin Infect Dis. 2019;69(2):207–14.

54. Hamers RL, Schuurman R, Sigaloff KC, Wallis CL, Kityo C, Siwale M, et al. Effect of pretreatment HIV-1 drug resistance on immunological, virological, and drug-resistance outcomes of first-line antiretroviral treatment in sub-Saharan Africa: a

multicentre cohort study. Lancet Infect Dis [Internet]. 2012;12(4):307–17. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22036233

55. Meintjes G, Moorhouse MA, Carmona S, Davies N, Dlamini S, Van Vuuren C, et al. Adult antiretroviral therapy guidelines 2017. South Afr J HIV Med. 2017;18(1).

56. World Health Organization. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV: interim guidelines. Supplement to the 2016 consolidated guidelines on the use of antiretrovir. World Heal Organ [Internet]. 2018 [cited 2019 Dec 8];(December):1–79. Available from: https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf?ua=1

57. Bhengu L. KZN leading the fight against HIV as health minister launches new ARV. Times Live [Internet]. 2019 [cited 2019 Dec 8]; Available from: https://www.timeslive.co.za/news/south-africa/2019-11-27-kzn-leading-the-fight-against-hiv-as-health-minister-launches-new-arv/

58. National Department of Health. INTRODUCTION TIMELINE: PrEP IMPLEMENTATION SA POLICY & GUIDELINES WHO guidelines [EXECUTIVE SUMMARY] NDoH PrEP policy [FULL] NDoH PrEP guidelines [FULL] FACILITY AUDIT TOOL IEC MATERIALS MONITORING & EVALUATION M&E guidelines/job aid [FULL] JOB AIDS ACKNO. 2016.

59. Venter WDF, Kaiser B, Pillay Y, Conradie F, Gomez GB, Clayden P, et al. Cutting the cost of South African antiretroviral therapy using newer, safer drugs. South African Med Journal,. 2017;107(1):28–30.

60. Mberi MN, Kuonza LR, Dube NM, Nattey C, Manda S, Summers R. Determinants of loss to follow-up in patients on antiretroviral treatment, South Africa, 2004-2012: a cohort study. BMC Heal Serv Res [Internet]. 2015;15:259. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26141729

61. Lippman SA, Shade SB, El Ayadi AM, Gilvydis JM, Grignon JS, Liegler T, et al. Attrition and Opportunities Along the HIV Care Continuum: Findings from a Population-Based Sample, North West Province, South Africa. J Acquir Immune Defic Syndr. 2016;

62. Chi BH, Yiannoutsos CT, Westfall AO, Newman JE, Zhou J, Cesar C, et al. Universal definition of loss to follow-up in HIV treatment programs: a statistical analysis of 111 facilities in Africa, Asia, and Latin America. PLoS Med [Internet]. 2011;8(10):e1001111. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22039357

63. National Department of Health. Joint Review of HIV, TB and PMTCT Programmes in South Africa - April 2014 [Internet]. 2014. Available from: http://www.hst.org.za/publications/joint-review-hiv-tb-and-pmtct-programmes-south-africa-april-2014

64. Chammartin F, Zürcher K, Keiser O, Weigel R, Chu K, Kiragga AN, et al. Outcomes

of Patients Lost to Follow-up in African Antiretroviral Therapy Programs: Individual Patient Data Meta-analysis. Clin Infect Dis. 2018;

65. Masilela TC, Foster R, Chetty M. The eHealth Strategy for South Africa 2012-2016: how far are we? [Internet]. South African Health Review Review. 2013 [cited 2020 Feb 9]. Available from: https://www.eldis.org/document/A71323

66. MacLeod W, Bor J, Crawford K, Carmona4 S. Analysis of Big Data for better targeting of ART Adherence Strategies: Spatial clustering analysis of viral load suppression by South African province, district, sub-district and facility (April 2 [Internet]. 2015. Available from: https://openknowledge.worldbank.org/handle/10986/25399

67. HE2RO. Towards 90-90-90: how close is South Africa to reaching the UNAIDS HIV treatment targets? [Internet]. 2016. Available from: https://sahivsoc.org/Files/NHLS AIDS 2016 HE2RO Policy Brief.pdf

68. Zou G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am J Epidemiol [Internet]. 2004 [cited 2020 Feb 3];159(7):702–6. Available from: https://academic.oup.com/aje/article-abstract/159/7/702/71883

69. Chen W, Qian L, Shi J, Franklin M. Comparing performance between log-binomial and robust Poisson regression models for estimating risk ratios under model misspecification. BMC Med Res Methodol [Internet]. 2018 Dec 22 [cited 2020 Feb 9];18(1):63. Available from: https://bmcmedresmethodol.biomedcentral.com/articles/10.1186/s12874-018-0519-5

70. Barros AJ, Hirakata VN. Alternatives for logistic regression in cross-sectional studies: An empirical comparison of models that directly estimate the prevalence ratio. BMC Med Res Methodol [Internet]. 2003 Dec 20 [cited 2020 Feb 9];3(1):1–13. Available from: http://bmcmedresmethodol.biomedcentral.com/articles/10.1186/1471-2288-3-21

71. National Department of Health. National Consolidated Guidelines for the prevention of mother to child transmission of HIV and the management of HIV in children, adolescents and adults. 2015.

72. Shroufi A, Van Cutsem G, Cambiano V, Bansi-Matharu L, Duncan K, Murphy RA, et al. Simplifying switch to second-line antiretroviral therapy in sub Saharan Africa: Predicted effect of using a single viral load to define efavirenz-based first-line failure. AIDS [Internet]. 2019 Aug 1 [cited 2020 Feb 23];33(10):1635–44. Available from: http://insights.ovid.com/crossref?an=00002030-201908010-00011

73. Petersen ML, Tran L, Geng EH, Reynolds SJ, Kambugu A, Wood R, et al. Delayed switch of antiretroviral therapy after virologic failure associated with elevated mortality among HIV-infected adults in Africa. AIDS [Internet]. 2014 Sep 10 [cited 2020 Feb 23];28(14):2097–107. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24977440

74. Fox MP, Van Cutsem G, Giddy J, Maskew M, Keiser O, Prozesky H, et al. Rates and Predictors of Failure of First-line Antiretroviral Therapy and Switch to Second-

line ART in South Africa. J Acquir Immune Defic Syndr [Internet]. 2012 [cited 2020 Feb 23];60(4):428–37. Available from: http://www.iedea-sa.org/

75. Mutevedzi PC, Lessells RJ, Rodger AJ, Newell ML. Association of age with mortality and virological and immunological response to antiretroviral therapy in rural south african adults. Myer L, editor. PLoS One [Internet]. 2011 Jul 1 [cited 2020 Feb 23];6(7):e21795. Available from: https://dx.plos.org/10.1371/journal.pone.0021795

76. Ingole N, Mehta P, Pazare A, Paranjpe S, Sarkate P. Performance of immunological response in predicting virological failure. AIDS Res Hum Retroviruses. 2013 Mar 1;29(3):541–6.

77. Meireles M V., Pascom ARP, Duarte EC. Factors Associated With Early Virological Response in HIV-Infected Individuals Starting Antiretroviral Therapy in Brazil (2014-2015): Results From a Large HIV Surveillance Cohort. J Acquir Immune Defic Syndr [Internet]. 2018 Aug 1 [cited 2020 Feb 23];78(4):e19–27. Available from: http://journals.lww.com/00126334-201808010-00004

78. Mujugira A, Celum C, Tappero JW, Ronald A, Mugo N, Baeten JM. Younger Age Predicts Failure to Achieve Viral Suppression and Virologic Rebound among HIV-1-Infected Persons in Serodiscordant Partnerships. AIDS Res Hum Retroviruses. 2016 Feb 1;32(2):148–54.

79. Ridgeway K, Dulli LS, Murray KR, Silverstein H, Santo LD, Olsen P, et al. Interventions to improve antiretroviral therapy adherence among adolescents in low- and middle-income countries: A systematic review of the literature. Vol. 13, PLoS ONE. Public Library of Science; 2018.

80. Fox MP, Rosen S, Geldsetzer P, Bärnighausen T, Negussie E, Beanland R. Interventions to improve the rate or timing of initiation of antiretroviral therapy for HIV in sub-Saharan Africa: Meta-analyses of effectiveness: Meta-analyses. Vol. 19, Journal of the International AIDS Society. Wiley Blackwell; 2016.

81. Rosen S, Fox MP, Larson BA, Sow PS, Ehrenkranz PD, Venter F, et al. Accelerating the Uptake and Timing of Antiretroviral Therapy Initiation in Sub-Saharan Africa: An Operations Research Agenda. PLoS Med [Internet]. 2016;13(8):e1002106. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27505444

82. Wright G, O'Mahony D, Cilliers L. Electronic health information systems for public health care in South Africa: a review of current operational systems. J Heal Informatics Africa [Internet]. 2017 [cited 2020 Jun 16]; Available from: https://www.researchgate.net/publication/320859337_Electronic_health_information_systems_for_public_health_care_in_South_Africa_a_review_of_current_operational_systems

83. Phillips AN, Stover J, Cambiano V, Nakagawa F, Jordan MR, Pillay D, et al. Impact of HIV Drug Resistance on HIV/AIDS-Associated Mortality, New Infections, and Antiretroviral Therapy Program Costs in Sub-Saharan Africa. Br Rep J Infect Dis J Infect Dis ®. 2017;215:1362–7.

84. Ndashimye E, Arts EJ. The urgent need for more potent antiretroviral therapy in low-

income countries to achieve UNAIDS 90-90-90 and complete eradication of AIDS by 2030 [Internet]. Vol. 8, Infectious Diseases of Poverty. BioMed Central Ltd.; 2019 [cited 2020 Jun 16]. p. 63. Available from: https://idpjournal.biomedcentral.com/articles/10.1186/s40249-019-0573-1

85. Human Sciences Research Council (HSRC). The Fifth South African National HIV Prevalence, Incidence, Behaviour and Communication Survey, 2017: HIV Impact Assessment Summary Report [Internet]. 2018. Available from: http://www.hsrc.ac.za/uploads/pageContent/9234/SABSSMV_Impact_Assessment_Summary_ZA_ADS_cleared_PDFA4.pdf

86. Dorward J, Lessells R, Drain PK, Naidoo K, de Oliveira T, Pillay Y, et al. Dolutegravir for first-line antiretroviral therapy in low-income and middle-income countries: uncertainties and opportunities for implementation and research. Vol. 5, The Lancet HIV. Elsevier Ltd; 2018. p. e400–4.

Appendix 1: GERMS-SA HIV/TB STUDY ENROLMENT FORM

SECTION 1: (fill in for new TB cases AND HIV positive patients initiating ART)				
Section 1: PATIENT DETAILS – PATIENT INTERVIEW				
CRF start date: ☐☐/☐☐/☐☐☐☐(dd/mm/yyyy)		CRF finalised date: (dd/mm/yyyy) ☐☐/☐☐/☐☐☐☐		
CRF completed by Surveillance Officer name:	Signature:		Informed Consent Obtained: Yes☐ No☐	
Hospital / Clinic name:		Hospital / Clinic number:		
Gender: Male ☐ Female ☐				
Race: Asian ☐ Black ☐ Coloured ☐ White ☐ Unknown ☐				
Date of Birth:	☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)	DOB Unknown ☐	Age:	
Identity No:	☐☐☐☐☐☐☐☐☐☐☐☐☐	Identity No: Unknown ☐		
Weight : _____ kg				
Height: _____ m				
Patient surname:	Patient first names:		Other name:	
Current Address:				
	Town/ City:		Province:	
Different address in the last 6 months:				
	Town/City		Province:	
	Ward:			
Telephone No: (H)	(Work)		(Cell)	
Occupation:				
Have you stayed in another province for >1 month in the last 6 months?	Yes ☐	No ☐	Unk☐	If yes, which province
Have you spent more than one month outside of South Africain the last year?	Yes ☐	No ☐	Unk☐	If yes, in which country?
How many rooms in your dwelling place are used for sleeping?☐☐				
How many children do you have?				
How many people in the dwelling place are under 5 years of age?☐☐		How many people in the dwelling place are 5-16 years of age?☐☐		
How many people sleep in the dwelling place?☐☐		How many people (including yourself) sleep in the same room as you?☐☐		
Do you receive an income (other than welfare grants)? Yes ☐No☐Unk☐		If yes, is it regular ☐ or irregular☐		
If yes, where do you work? In the formal sector ☐ in the Informal sector ☐				

Do you receive a welfare grant? Yes☐No☐Unk ☐	If you receive an income/grant , mark range per month <R1000☐ R1000–R5000☐R5000–R10,000☐>R10,000☐
What is the highest level of education that you have completed? No formal ☐Primary☐ Secondary ☐ Tertiary☐	
How many years of school have you completed? ☐☐	

Do you smoke currently? Yes ☐ No ☐	Have you smoked in the last 5 years? Yes ☐ No ☐	Have you EVER smoked? Yes ☐ No ☐
If Yes how many cigarettes do/did you smoke per day? ≤5 ☐6-20 ☐ >20 ☐	For how many years have you smoked? ☐☐	
Do you currently use recreationaldrugs or have you regularly used drugs in the last 5 years? Yes ☐ No☐ Unk☐		
Do you currently drink alcohol? Yes ☐No☐Unk ☐	How many days a week do you drink alcohol?	
In the last month how often did you have at least any one of the following? 5 quarts of beer OR 10 glasses of wine OR 10 shots spirit **in a single day?**☐☐		

In the last 10 years, have you been imprisoned?	Yes☐No ☐Unk☐	If Yes, for how long? _____ years. Where?
Did you work in the mines?	Yes ☐No ☐Unk☐	When did you work in the mines? Year to year
Did you work underground in the mines? Yes ☐No ☐		Did you work on a gold mine? Yes☐No☐
Have you worked in a clinic/hospital/medical lab?	Yes ☐No ☐Unk☐	If Yes, for how long? _____ years
How long does it take you to get to your local clinic (one direction)?<15 mins ☐15-30 mins ☐ 30-60 mins☐> 1 hour ☐		

Do you own a car? Yes ☐No ☐	Does a family member own a car and give you transport? Yes ☐ No☐Unknown☐
Do you use public transport? Yes ☐ No☐	How many hours a week do you spend in public transport?
What does it cost you to travel from your home to the local clinic (one direction)?<R10☐ R10-20☐ R20-40 ☐>R40☐	

Have you ever been previously diagnosed with TB (non-MDR)? Yes☐No ☐Unk☐	If Yes, how many times? ☐☐
What was the date of the most recent TB (non-MDR) episode? ☐☐/☐☐/☐☐☐☐(dd/mm/yyyy)	
Have you ever been previously diagnosed with MDR-TB ? Yes☐No ☐Unk☐	If Yes, how many times? ☐☐
What was the date of the most recent MDR-TB episode? ☐☐/☐☐/☐☐☐☐(dd/mm/yyyy)	

Have you ever been previously treated for TB (non-MDR)? Yes ☐No☐Unk☐N/A☐	If Yes, how many treatment episodes? ☐☐ Unk☐
Did the last treatment last for > 1 month? Yes☐No☐Unk☐N/A☐	Did you complete the last TB treatment? Yes ☐No☐Unk☐N/A☐
Have you ever been previously treated for MDR-TB? Yes ☐No☐Unk☐N/A☐	If Yes, how many treatment episodes? ☐☐ Unk☐
Did the last MDR-TB treatment last for > 1 year? Yes☐No☐Unk☐N/A☐	
Has this patient been included in GERMS before? Yes ☐ No ☐Unknown☐	If yes, for TB start of treatment ☐ or ART initiation☐
Was this a case that defaulted for > 2 months (TB)? Yes ☐ No ☐	Was this a case that defaulted for > 3 months (ART)? Yes ☐ No ☐
Notes:	

SECTION 3 (continued): HIV – MEDICAL CHART REVIEW

Date of HIV diagnosis: ☐ Unknown			Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
Date of most recent clinic visit: ☐ Unknown			Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
Has the patient transferred-in from another clinic? Yes☐ No☐ Unknown ☐			
CD4 count at HIV diagnosis: Unknown ☐	Absolute:	Percentage:	Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
Most recent CD4 count (if different from above: Unknown ☐	Absolute:	Percentage:	Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
Most recent Viral Load: Not available ☐	Absolute		Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

Are any of the following lab results recorded in the patient file: Yes☐ No☐		If Yes, please indicate most recent result; if no please state N/A:	
Creatinine Clearance:	Result:	Date: ☐☐/☐☐/☐☐☐ ☐	N/A ☐
ALT:	Result:	Date: ☐☐/☐☐/☐☐☐ ☐	N/A ☐
Hb:	Result:	Date: ☐☐/☐☐/☐☐☐ ☐	N/A ☐

WHO Staging 1☐ 2☐ 3☐ 4☐			
Any current or recent clinical markers for HIV: Yes☐ No ☐		If Yes, tick all that apply:	
Diarrhoea > 10 days ☐	HIV wasting ☐	Oral candidiasis ☐	Cryptomeningitis☐
Suspected PCP ☐	Kaposi's sarcoma ☐	Other (specify):	

Has the patient previously been exposed to Antiretroviral Therapy (ART)? Yes☐ No ☐ Unknown ☐

If Yes, tick **ALL** previous ART exposures that apply:

(If received any option more than once, please complete the same details below for any prior exposure in the comments section)

PMTCT: Yes☐ No ☐	How many times?
Date of Initiation of PMTCT: ☐☐/☐☐/☐☐☐☐	Date PMTCT was stopped: ☐☐/☐☐/☐☐☐☐

What drugs did the patient receive? (please tick all that apply): Unknown ☐

	AZT Zidovudine		3TC Lamivudine		EFV Efavirenz
	D4T Stavudine		FTC Emtricitabine		NVP Nevirapine
	TDF Tenofovir				LPV/r Lopinavir
	FDC Fixed dose combination				
	Other:				

Post Exposure Prophylaxis: Yes☐ No ☐	How many times?
Date of Initiation of PEP: ☐☐/☐☐/☐☐☐☐	Date PEP was stopped: ☐☐/☐☐/☐☐☐☐

What drugs did the patient receive? (please tick all that apply): Unknown ☐

	AZT Zidovudine		3TC Lamivudine		EFV Efavirenz
	D4T Stavudine		FTC Emtricitabine		NVP Nevirapine
	TDF Tenofovir				LPV/r Lopinavir
	FDC Fixed dose combination				
	Other:				

Pre-Exposure Prophylaxis: Yes☐ No ☐	How many times?
Date of Initiation of PrEP: ☐☐/☐☐/☐☐☐☐	Date PrEP was stopped: ☐☐/☐☐/☐☐☐☐

What drugs did the patient receive? (please tick all that apply): Unknown ☐

	AZT Zidovudine		3TC Lamivudine		EFV Efavirenz
	D4T Stavudine		FTC Emtricitabine		NVP Nevirapine
	TDF Tenofovir				LPV/r Lopinavir
	FDC Fixed dose combination				
	Other:				

Has the patient previously received cART for treatment of HIV but interrupted therapy/defaulted: Yes☐ No ☐

If Yes to previous exposure to cART, fill in the following:

Number of times cART re-initiated?	(If received ART more than once, please complete the details below for each time in the comments section)
Date of Initiation of cART: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)	Date cART was stopped: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

What cART drugs did the patient receive? (please tick all that apply):

Unknown ☐

	AZT Zidovudine		3TC Lamivudine		EFV Efavirenz
	D4T Stavudine		FTC Emtricitabine		NVP Nevirapine
	TDF Tenofovir				LPV/r Lopinavir
	FDC Fixed dose combination				
	Other:				

What ART regimen is the patient currently receiving / currently being initiated on? (please tick all that apply):

Unknown ☐

	AZT Zidovudine		3TC Lamivudine		EFV Efavirenz
	D4T Stavudine		FTC Emtricitabine		NVP Nevirapine
	TDF Tenofovir				LPV/r Lopinavir
	FDC Fixed dose combination				
	Other:				

Notes / Comments:

SECTION 3 (continued): HIV – MEDICAL CHART REVIEW (6-9 MONTH)

Hospital / Clinic name:			Hospital / Clinic number:
DOB: ☐☐/☐☐/☐☐☐☐(dd/mm/yyyy)			Gender: Male ☐ Female ☐
Date of most recent clinic visit: Yes☐ No☐ Unknown ☐			Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
Patient name:			Germs Study ID:
Date of most recent clinic visit: Unknown ☐			Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
CD4 count at ART initiation: Unknown ☐	Absolute:	Percentage:	Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
Most recent CD4 count: Unknown ☐	Absolute:	Percentage:	Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)
Most recent Viral Load: Not available ☐	Absolute		Date: ☐☐/☐☐/☐☐☐☐ (dd/mm/yyyy)

Are any of the following lab results recorded in the patient file: Yes☐ No☐		If Yes, please indicate most recent result	
Creatinine Clearance:	Date: ☐☐/☐☐/☐☐☐☐ ☐	ALT:	Date: ☐☐/☐☐/☐☐☐☐ ☐

Other (please specify):

Any current or recent clinical markers for HIV: Yes☐ No☐		If Yes, tick all that apply:	
Diarrhoea > 10 days ☐	HIV wasting ☐	Oral candidiasis ☐	Cryptomeningitis☐
Suspected PCP ☐	Kaposi's sarcoma ☐	Other (specify):	

Has the patient interrupted therapy/defaulted: Yes☐ No ☐If Yes, fill in the following:	
Date cART was stopped: ☐☐/☐☐/☐☐☐☐	Date of re-initiation of current cART: ☐☐/☐☐/☐☐☐☐ ☐

What ART regimen is the patient currently receiving? (please tick all that apply): Unknown ☐

	AZT Zidovudine		3TC Lamivudine		EFV Efavirenz
	D4T Stavudine		FTC Emtricitabine		NVP Nevirapine
	TDF Tenofovir				LPV/r Lopinavir
	FDC Fixed dose combination				
	Other:				

Notes / Comments:

Appendix 2: Wits HREC ethical approval

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr Gillian Hunt

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M180629

NAME: (Principal Investigator)	Dr Gillian Hunt
DEPARTMENT:	School of Public Health National Institute for Communicable Diseases Centre for HIV and STIs
PROJECT TITLE:	Rates of initial virological suppression in patients with resistance to antiretroviral therapy
DATE CONSIDERED:	29/06/2018
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr Tendesayi Kufa-Chakezha
APPROVED BY:	Professor CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	29/06/2018

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 Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **June** and will therefore be due in the month of **June** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix 3: Plagiarism Declaration

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I, Gillian Hunt (Student number: 9100717H), am a student registered for the degree of Masters of Science in Epidemiology and Biostatistics in the academic year 2019.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- 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 that 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 that I have failed to acknowledge the source of the ideas or words in my writing.

Signature:  Date: 18 June 2020