A Third-line ART Referral Process in the Western Cape: Estimating Qualification and Predictors of Referral

by

Sadiyya Sheik

December 2019

Thesis presented in partial fulfilment of the requirements for the degree of Master of Medicine (Public Health) in the Faculty of Medicine and Health Sciences at Stellenbosch University.

Supervisor: Dr Bart Willems

Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the sole author thereof (save to the extent explicitly otherwise stated), that reproduction and publication thereof by Stellenbosch University will not infringe any third party rights and that I have not previously in its entirety or in part submitted it for obtaining any qualification.

Signature:

Date: December 2019

Dedication

All praise to the Almighty

I dedicate this work to my parents Tahera and Akthar Sheik who remain my most enthusiastic cheerleaders,

To Zahir Hoosain who is the greatest support I have ever known, and

To my little girls Zayna and Hanaa - you are my reasons.

Abstract

Introduction

HIV/AIDS is a major contributor to burden of disease in South Africa and with more than 3.7 million people receiving ART in the country, the South African ART programme is the largest in the world. Implementation of a universal test-and-treat policy in recent years is expected to significantly increase the number of South Africans on ART. However, increasing exposure to ART may have additional implications for rates of treatment failure and drug resistance, implying a greater need for second and third-line regimens in the future.

South Africa initiated the world's first public sector third-line access programme in 2013. However, there is a paucity of data quantifying the need for third-line therapy in this setting and the programme itself has not been formally evaluated.

Objective

The overall objective of the study was to evaluate the third-line ART referral process in the Western Cape. This was undertaken by identifying patients meeting the criteria for referral to the committee, a comparison with patients who were actually referred in the same time period and identification of factors predicting referral.

Method

We utilised a three-step study design in relation to the main objectives of the study. Routinely collected data from provincial health information systems (TIER.net, JAC, CDU and NHLS) were analysed to derive an estimate of patients meeting the criteria for referral to the third-line ART committee in the study period. This output was then matched with a list of patients who were actually referred in the same time period. The matching process allowed for delineation into the groups "Met Criteria and Referred", "Met Criteria and Not Referred" and "Did Not Meet Criteria and Referred." Predictors of referral were identified by comparison between the patient groups in which referral criteria were met. In the absence of a validation method, we performed sensitivity analyses to evaluate the impact of varying certain parameters on the findings.

Results

In the period 01 October 2014 to 30 September 2016, 947 adult patients met criteria for referral to the third-line ART committee. In the same period, 167 adult patients were actually referred. Comparison between the two groups revealed a poor overlap of only 42 patients. In multivariate analysis, independent predictors of referral included receiving care at a hospital rather than a PHC facility (aOR=2.15, 95% CI 1.1-4.2), a higher number of VLs ≥1000 copies/ml whilst on a PI (aOR=1.2,

95%CI 1.01-1.42) and a greater number of years on a PI (aOR=1.25, 95% CI 1.07-1.46). Patients with a six-month gap in dispensing records were less likely to be referred (aOR=0.37, 95% CI 0.17-0.81).

Conclusion

This study adds to a limited body of knowledge regarding third-line ART programmes and provides an estimate for the need for third-line therapy in the South African setting. The method for estimating patients meeting the referral criteria could not be validated and is subject to a number of limitations. Nevertheless, the findings indicate missed opportunities for referral and inappropriate referral of patients. Predictors of referral were not unexpected, however clinician awareness of and compliance with the referral criteria remains unknown and may be contributory. Future work should focus on refining and validating the method as well as assessing clinician awareness of the programme.

Acknowledgements

I would like to acknowledge the following individuals for their contribution to this work:

My supervisor and friend, Bart Willems for walking this long and unfamiliar road with me;

Professor Andrew Boulle for hearing my idea for this study and helping make it possible;

Jackie Voget for support and guidance; and

The Biostatistics Unit within the Centre for Evidence Based Health Care (CEBHC) at Stellenbosch University for assistance with the development of a data analysis plan.

I am also grateful to the Discovery Foundation for awarding me a Discovery Foundation Academic Fellowship (MMed) award in 2017.

Contents

Tables

Figures

Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
CDU	Chronic Dispensing Unit
DRM	Drug Resistant Mutations
HIV	Human Immunodeficiency Virus
IQR	Interquartile Range
NDoH	National Department of Health
NHLS	National Health Laboratory Service
NIMART	Nurse Initiated Management of Antiretroviral Therapy
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
PHC	Primary Health Care
PHDC	Provincial Health Data Centre
PI	Protease Inhibitor
VL	Viral Load
WCG:H	Western Cape Government: Health

CHAPTER 1: INTRODUCTION

HIV/AIDS is a major contributor to morbidity and mortality in South Africa and has remained a significant part of the country's burden of disease landscape despite gains in life expectancy linked to the country's response to the HIV epidemic.[1] Public sector antiretroviral therapy (ART) has been available in South Africa for more than a decade and recent estimates indicate that there are more than 3.7 million people receiving ART in the country[2], making the South African ART programme the largest in the world.

Following recommendations from the World Health Organisation (WHO), South Africa has recently adopted a universal test-and-treat policy which makes ART accessible to all HIV positive individuals regardless of CD4 count. This development is expected to significantly increase the number of South Africans on ART but may have additional implications for rates of treatment failure and drug resistance as a result of increasing exposure to ART. It is therefore likely that the need for second and third-line ART in the country will be amplified in the future.

Third-line programmes are in their infancy worldwide and there is little evidence quantifying the need for third-line therapy in the South African setting. Additionally, the referral process by which third-line ART is accessed has not been formally evaluated and predictors of referral are not known. Thus, there exists a critical need to evaluate third-line ART programmes in this setting.

This research project evaluated a third-line ART referral process in the Western Cape province of South Africa with the dual aims of estimating qualification for referral to a central third-line ART committee and identifying predictors of referral. We performed a comprehensive review of the existing literature on this topic (Chapter 2). Study aims and objectives were identified (Chapter 3), followed by a detailed overview of the study methodology (Chapter 4). Results from the study are presented in Chapter 5 followed by a sensitivity analysis (Chapter 6). Relevant findings are discussed in Chapter 7. Chapter 8 outlines conclusions from the study in relation to future research and implications for the provincial ART programme.

CHAPTER 2: BACKGROUND AND LITERATURE REVIEW

Background

HIV/AIDS makes a significant contribution to burden of disease worldwide and is a major contributor to morbidity and mortality in South Africa. Antiretroviral therapy has been shown to be highly effective in the management of HIV and limiting progression to AIDS. As a single intervention, large scale roll-out of ART has been highly successful in reducing HIV-associated mortality and increasing life expectancy in the country.[1]

In the South African public sector, clinical governance of the ART programme is maintained by frequently updated national treatment policies and guidelines which indicate criteria for initiation of therapy and detail clinical management. ART is prescribed in a cascade from first to third-line therapy and there are clear indications for change in therapy[3], the primary indication for which is virological failure, defined as an HIV viral load (VL) >1000 copies/ml on at least two occasions two months apart despite good treatment adherence.

The first-line non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen is considered less robust than the protease inhibitor (PI) based second-line. The NNRTIs (efavirenz and nevirapine) are known to have a low genetic barrier to the development of resistance-associated mutations and accumulation of mutations may be rapid.[4] A recent South African national survey monitoring resistance profiles in patients failing first-line ART found that treatment failure occurred after a median of 36 months.[5] In another study conducted in sub-Saharan Africa drug resistant mutations (DRM) were detected in 87% of patients failing first-line therapy and new mutations accumulated at an average rate of 1.45 DRM per year on therapy.[6] Currently almost 1 in 5 patients reaching 5 years on ART is on a second-line regimen.[7]

Second-line failure rates in low and middle income countries are reportedly higher than first-line failure rates[8] and patients on second-line therapy are less likely to be alive and in care than their counterparts on first-line therapy for equal duration.[9] A systematic review of 19 studies indicated second-line failure rates as high as 38% at 3 years.[8] However, a number of South African studies have indicated that the majority of second-line failure is not associated with significant PI mutations[10–13] and may be impacted by strengthening adherence efforts.[14,15] Nevertheless, for a growing cohort of patients, second-line therapy is no longer an option, necessitating the use of costly third-line drugs such as darunavir, etravirine and raltegravir.

In South Africa, third-line antiretroviral therapy was not available in the public sector prior to 2013. The South African National Department of Health (NDoH) initiated the first public sector third-line ART access programme in the world in April 2013. Unlike the first and second-lines, which are pre-

defined regimens following a public health approach, there is no standard third-line regimen. The choice of individual drugs included in a third-line regimen is made on a case by case basis considering the patient history and results of genotype resistance testing.

The public sector third-line ART access programme is managed centrally at the level of the NDoH and allows clinicians to motivate for genotype resistance testing and third-line ART for a defined group of patients who are failing second-line therapy. Both genotype resistance testing and third-line therapy are not routinely available in the public sector outside of this access programme. Each motivation is reviewed by a panel of experts who may approve or decline a request for genotype resistance testing based on the merits of each individual case. The panel then makes recommendations regarding the need for third-line therapy informed by a resistance score derived from genotype testing. In the Western Cape, this process, which was initially managed by the NDoH, has been managed on a provincial level since October 2014.

The Western Cape Government: Health Circular 158/2014[16] details the process of referral to the provincial third-line antiretroviral therapy committee as well as criteria for referral. For adult patients aged 15 years and older, the patient should have been receiving a PI based regimen for ≥ 2years and have virological non-suppression defined as three viral loads ≥ 1000 copies/ml at least 8-12 weeks apart. Good adherence should have been verified objectively by pharmacy refill records. In addition to ensuring that patients meet these criteria, clinicians are required to complete a formal application form (Appendix A) which collates the patient's clinical history and an adherence assessment form (Appendix B) which is completed together with the patient. The referral process is an electronic one. Clinicians are required to submit the necessary documentation via email and a decision is made based on this documentation.

Literature Review

A literature review was conducted to explore available evidence on aspects relating to third-line ART. Evidence pertaining to the need for third-line ART, the implications of a delayed switch in therapy and factors associated with delays in switching between ART regimens are presented here.

Estimating the Need for Third-line ART

There is a paucity of data estimating the need for third-line therapy in South Africa. One study from Latin America, indicated that at least 6% of patients accessing ART will require third-line therapy within 5 years of starting treatment.[17] This however is a crude estimate and the authors concede that there are a number of limitations to the study which may have underestimated the need for third-line ART. Firstly, the need for third-line therapy was described as a function of the frequency of viral load measurements and adherence data were not utilised in the estimate. Secondly, the study excluded patient groups accessing ART prior to the year 2000 and others whose initiation of ART began as participants in clinical trials. Additionally, due to programmatic differences between the regions, it is unclear if the results of this study can be easily extrapolated to the South African context. The need for third-line therapy in the South African context is therefore difficult to quantify with resultant implications on planning for and evaluating third-line ART access in the country.

Implications of Delayed Switch in ART Regimens

Prior to the introduction of the third-line ART access programme in South Africa, patients experiencing virological failure on second-line regimens had little choice but to remain on a failing regimen. In a context where third-line therapy is available and should be accessible to those who require it, a description of the impact of delays in accessing the appropriate treatment is relevant.

A Nigerian study[18] which looked at the impact of the duration of second-line failure on the accumulation of drug resistant mutations found that patients who had been failing on a second-line regimen for >24 months had a median of 5 (IQR 0-6) PI mutations compared with 1 (IQR 0-4) for patients failing for 13-24 months and 2 (IQR 0-5) for those failing for a year or less. The authors estimated that patients accumulated PI mutations at a rate of 0.6 mutations for every 6 months on a failing second-line regimen. In this study, susceptibility to darunavir, the PI often included in third-line regimens, was maintained, however in 28% of patients high or intermediate-level resistance was demonstrated to another third-line drug, etravirine. This study highlights the importance of access to third-line therapy for patients in whom second-line ART is no longer effective due to drug resistance. Furthermore, the study indicates that prolonged exposure to a failing ART regimen may restrict third-line treatment options due to the accumulation of resistant mutations and cross-resistance.

Little is known about the impact of delays in switching from second to third-line regimens on patient outcomes. Given that PI based second-line regimens are considered more robust than first-line regimens and accumulate drug resistant mutations at a slower rate it is unclear whether the impact of delays in switching from first to second-line regimens can be extrapolated to delays in switching from second to third-line. Nevertheless, numerous studies have shown adverse outcomes due to delays in switching from first to second-line ART. In patients failing first-line therapy in sub-Saharan Africa, new drug resistant mutations (DRMs) accumulated at an average rate of 1.45 DRM per year and predicted drug susceptibility declined significantly with continued exposure.[6] Other studies have demonstrated that delays in change from first to second-line ART were associated with an increased risk of lack of virological suppression[19], elevated mortality[20–23] and poorer clinical outcomes.[24]

Factors Associated with Delayed Switching from First to Second-line ART regimens: Lessons Learned

Delays in switching from first to second-line therapy have been well described and studies identifying predictors of delayed switching have indicated both individual patient and health system factors associated with delayed switch. Further description of these predictors is relevant as it is likely that these factors may also predict delays in referral to third-line programmes.

Individual Patient Factors

Studies attempting to identify reasons for delays in switching therapy have considered patient non-adherence[22,25] to be a relevant factor. However, adherence to therapy is challenging to quantify and proxy measures are often utilised. A study assessing predictors of switching to second-line therapy in 9 South African HIV clinics found that missed visits were more common amongst patients with a longer time to treatment switch.[21] Similarly, another study found that patients with no clinic contact in the four months preceding a visit were less likely to switch regimens.[26] These studies indicate that clinicians may delay changes in ART regimens due to concerns that virological failure is a result of patient non-adherence rather than drug resistance. This knowledge is particularly relevant because as described earlier, it is well established that in the South African setting most virological failure is in fact related to poor adherence. [10,12,13]

Viral load magnitude, immune status and rate of immune decline are patient-level clinical factors that have been identified as predictors of switching from first to second-line. One study found that a viral load of $\log_{10} \geq 4$ at the most recent result was independently associated with a switch in therapy.[26] This finding is supported by other studies in similar patient populations.[20,21] A CD4 count <100 cells/mm^3 was also associated with a greater chance of switching therapy[26].Again this finding was supported by a number of studies[20,21,27] including one which found that higher rates of CD4 count decline also predicted a switch in therapy.[28]

Health Systems Factors

An important factor limiting access to third-line ART where it is available is clinician compliance with clinical guidelines and referral procedures. Compliance with the Western Cape Government: Health (WCG: H) circular detailing the third-line ART referral procedure has not been evaluated. Additionally, few studies have objectively analysed and reported on clinician compliance relating to the management of HIV positive patients. In one such study which audited clinician compliance with the 2010 South African ART guidelines over a three-year period at a hospital-based ART Clinic in Cape Town,[29] clinician compliance was favourable in terms of choice of ART. This was demonstrated by an expected decline in stavudine and increase in tenofovir prescriptions over the three-year period which reflected a change in the preferred first-line NRTI recommended by the guideline. Compliance with the blood testing schedule was however less favourable. Excessive ordering of blood tests was demonstrated and monitoring tests recommended by the 2010 guideline were not requested at the recommended intervals. This study did not assess factors contributing to clinician non-compliance in this setting.

Compliance with ART guidelines has been less formally evaluated by studies of delays in switching from first to second-line therapy. A number of studies have found that despite access to virological monitoring and clear guidelines describing the management of patients failing first-line ART, a significant proportion of patients remained on failing regimens.[20,30]

Other health system factors associated with delays in switching from first to second-line ART relate to access to and implementation of viral load monitoring and health service variation between urban and rural settings. In sub-Saharan Africa, limited access to viral load monitoring may contribute to delays in treatment switch. However even in South Africa where viral load monitoring is routinely available, there is evidence of underutilisation. In a study which compared patient outcomes in public and private sector clinics, less than half of the patients studied in either setting had evidence of a viral load test at 12 months on treatment.[31] This finding suggests that inadequate viral load monitoring may limit the identification of patients requiring a change in therapy. Differences in viral load monitoring have also been demonstrated in a study comparing HIV care between urban and rural treatment settings. In this study, patients receiving treatment in an urban setting had a significantly higher number of viral load measurements per year than their rural counterparts.[32] This same study found that patients accessing care in the rural setting were also more likely to have failed first-line therapy for longer and had more resistant mutations. This study demonstrates differences in patient care by geographic area and suggests that these may be attributable to health system factors such as differing management approaches, access to information and human resources.

CHAPTER 3: AIMS AND OBJECTIVES

Research Problem and Study Rationale

There is little data available to guide the implementation of third-line ART programmes in South Africa. Estimates of the need for third-line therapy have not been enumerated in this setting and there have been no formal evaluations of third-line ART programmes to date. Additionally, due to the novelty of third-line ART programmes, little is known about individual patient and health system factors impacting on referral of patients to such programmes.

Access to third-line therapy is an important part of South Africa's ART programme for three reasons. Firstly, third-line therapy is the only treatment option for patients who, due to the accumulation of resistant mutations, are no longer able to achieve viral suppression on a second-line regimen despite good treatment adherence. Secondly, studies looking at outcomes from the implementation of the national third-line ART access programme have demonstrated that these regimens are effective in achieving viral suppression.[33] Thirdly, South Africa's implementation of a universal test and treat policy is likely to accelerate the need for second and third-line regimens in the future.

An evaluation of the Western Cape third-line ART access programme is therefore both warranted and timely. In particular, it is necessary to quantify the need for referral to the third-line ART committee and identify discrepancies between patients meeting the criteria for referral to the committee and those who were actually referred. Additionally, it is important to identify factors predicting referral.

Research Questions

In the Western Cape, how many adult patients met the criteria for referral to the third-line ART committee between 01 October 2014 and 30 September 2016; how does this compare with the patients who were actually referred and what factors predict referral?

Study Objectives

1. To estimate the need for third-line ART in the Western Cape.
2. To evaluate the third-line ART referral process in the Western Cape.

Study Aims

1. To identify adult patients meeting the criteria for referral to the third-line ART committee in the period 01 October 2014 to 30 September 2016.

2. To compare patients meeting the criteria for referral with those who were actually referred in the same time period.

3. To identify factors associated with referral to the third-line ART committee in the case of patients who meet criteria for referral.

CHAPTER 4: METHODS

Study Area

The study area is the Western Cape province of South Africa. There is one metropolitan district and five rural districts in the Western Cape. Approximately two-thirds of the Western Cape population resides in the Cape Town Metro district. In 2015, the antenatal HIV prevalence was 17.6% in the province and district prevalence varied from 11.6% in the Central Karoo to 18.9% in the Cape Town Metro.[34] In 2014/2015, approximately 60% (180 769) of the estimated HIV-infected population were on antiretroviral therapy.[35]

Antiretroviral therapy is offered at a range of facilities including PHC and hospital-based clinics. In many PHC facilities, patients are attended to primarily by NIMART-trained (Nurse Initiated Management of Antiretroviral Therapy) nurses and doctors might only visit the facility on specified days of the week. In facilities where the patient load is high, doctors are generally available on a daily basis. NIMART-trained nurses are not authorised to change patient regimens and referral to third-line ART committee is primarily a function of the doctors.

Study Design

This quantitative study was approved by the Health Research Ethics Committee of the University of Stellenbosch (S16/09/162). The study was designed in three-steps in relation to the primary objectives of the research.

The study integrated data from provincial health information systems to derive an estimate of patients meeting the criteria for referral to the third-line ART committee. The patient list from the derived estimate of patients meeting the criteria for referral was then matched with a list of patients who were actually referred to the committee. This process allowed for delineation of patients into three groups i.e. “Met Criteria and Referred”, “Met Criteria and Not Referred” and “Did Not Meet Criteria and Referred.” Thereafter, comparisons were made between the patient groups “Met Criteria and Referred” and “Met Criteria and Not Referred” and statistical analysis was undertaken to identify predictors of referral.

Figure 1 is a graphic representation of the three-step study design and each of the steps is discussed in further detail below.

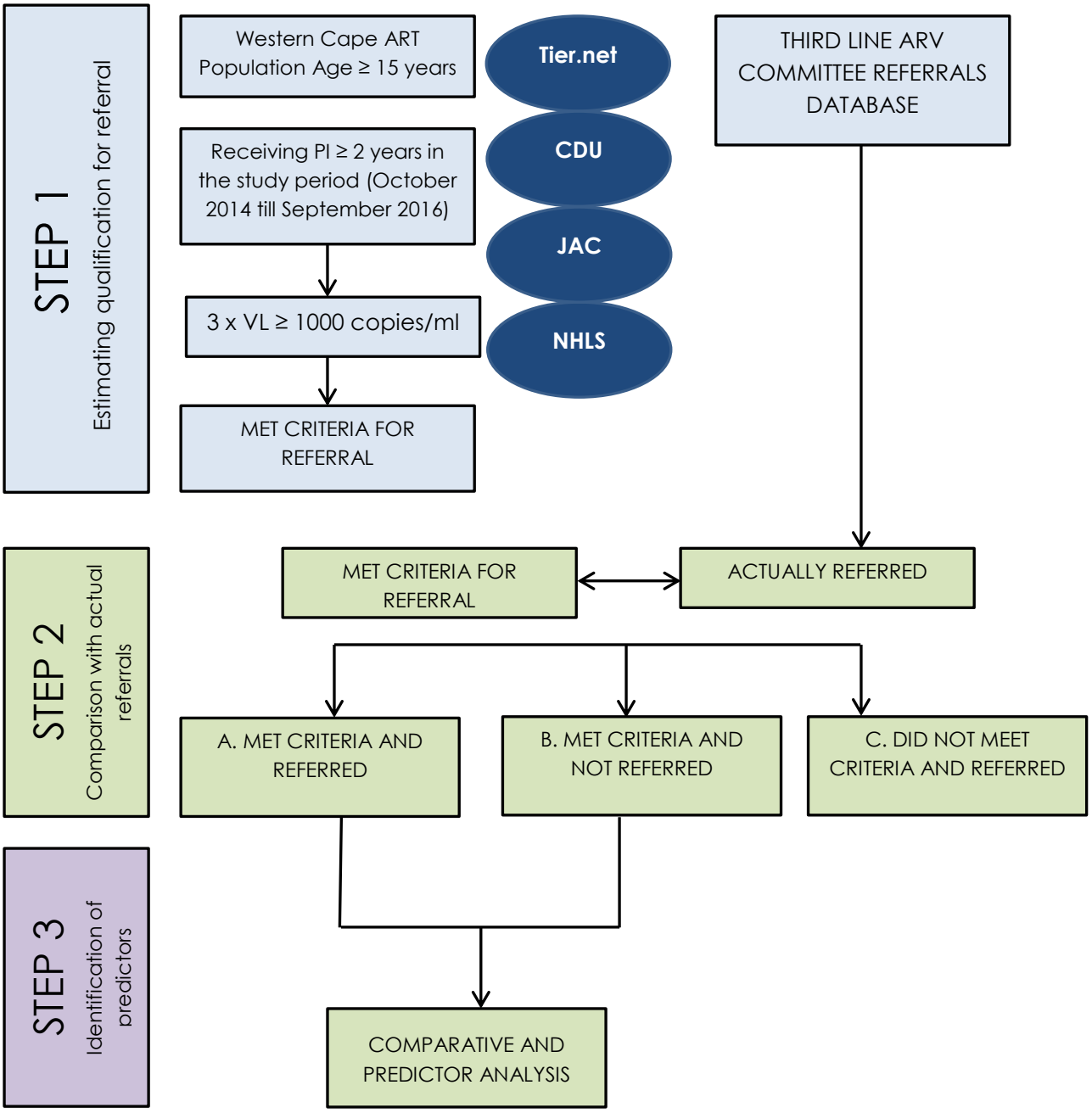

Figure 1. Graphic representation of study design

Data Collection and Management

Step 1: Estimating qualification for referral

The aim of the first step of the study was to identify adult patients who met the criteria for referral to the third-line ART committee in the study period (01 October 2014 – 30 September 2016). Criteria for referral to the committee included age ≥15 years, receiving a PI based regimen for at least 2 years and virological non-suppression defined as at least three viral load measurements of ≥ 1000 copies/ml (≥ log 3).

Routinely collected data for patients aged 15 years and older receiving PI-based antiretroviral therapy during the study period was requested from the newly established Provincial Health Data Centre (PHDC). The centre curates data from a number of stand-alone primary information systems and incorporates an inter-operability component which allows for the linkage of patient level data from each individual system using the Patient Master Index (PMI) which uniquely identifies individuals.

Based on the criteria specified, the PHDC provided two research datasets. The first contained all pharmacy records for patients aged 15 years and older receiving PI based therapy during the study period. For this dataset, data was derived from three sources i.e. TIER.net (Three Interlinked Electronic Registers.net), the JAC pharmacy management system and the CDU (Chronic Dispensing Unit). TIER.net is an electronic patient management system which progresses from paper registers (tier1) to stand-alone electronic registers (tier 2) to networked electronic medical records (tier 3). The system is utilised for monitoring and evaluation of the HIV programme. Currently, 77% of ART sites in the Western Cape use the TIER.net system. The remainder make use of alternate systems (e.g. eKapa and PREHMIS) which then feed data into the TIER.net database. JAC is a pharmacy management system created by the company JAC Computer Services. The system captures routine pharmaceutical dispensing data and is currently in use at 109 facilities in the Western Cape. The CDU database houses dispensing data for stable patients who receive their medication via this mechanism. Where available JAC and CDU are preferred sources of dispensing data because the recording of data is automated and less prone to error than the TIER.net data (which requires manual capturing by information clerks).

The second dataset was derived from the National Health Laboratory Service (NHLS) and contained all HIV viral load records for the group of patients identified. The two databases were cleaned and analysed to identify patients meeting the criteria for referral to the third-line ART committee in the study period.

Step 2: Comparison with actual referrals

In the second step of the study, a database of actual referrals to the third-line ART committee was obtained and analysed. This database is an Excel spreadsheet which is maintained by the third-line ART committee and is used for tracking the referrals to the committee. Salient information pertaining to each case is manually entered into the spreadsheet on a case-by-case basis. The database was cleaned and records occurring outside the study period were excluded. This database was then matched with the estimate of patients meeting the criteria for referral (i.e. the output of Step1) and based on the matching process, patients were classified into three categories i.e. "Met Criteria and Referred", "Met Criteria and Not Referred" and "Did Not Meet Criteria and Referred."

Step 3: Identification of predictors

In the third step of the study, a comparative analysis of the groups "Met Criteria and Referred" and "Met Criteria and Not Referred" was undertaken with the aim of identifying predictors of referral. Comparator variables were obtained from routinely collected data and two categories of variables were collected i.e. demographic (e.g. age, sex, facility type) and clinical (e.g. time on PI) data.

The initial study design included collection of patient-level data obtained from folder review and facility-level data obtained from facility visits. However, these two data sources were excluded after piloting the folder review. The pilot exercise identified a number of challenges impacting on the ability to obtain complete and accurate data. Firstly, folders were often misplaced and could not be retrieved. Secondly, due to patient transfers between facilities, data pertaining to the time-frame of interest were sometimes housed in a different facility and thirdly, even when folders could be retrieved and contained data relevant to the time-frame of interest, records were sparse and poorly maintained. Attempts were made to collect facility-level data telephonically however this exercise was eventually abandoned due to poor progress and a lack of available time to complete the data collection.

Data Analysis

Data was analysed using Stata version 13.1 (Statacorp Texas 2013) and p value of <0.05 was considered statistically significant. Continuous variables were described using relevant summary statistics depending on the distribution of the data i.e. mean and standard deviation for normally distributed data and median and interquartile range for non-normally distributed data. Categorical data were described according to proportion distribution.

Further analysis involved the testing of hypotheses to determine if each variable was independently associated with the outcome i.e. referral. Associations between dependent variables and the outcome variable were identified using chi-squared or Fischer's exact tests for categorical data and the

Wilcoxon rank sum test for non-normally distributed numerical data. Following univariate analysis, variables were entered into a logistic regression model and a backward selection procedure was used to eliminate non-significant variables. Findings are presented as crude and adjusted odds ratios with 95% confidence intervals.

CHAPTER 5: RESULTS

Study results are presented separately for each of the study steps.

Step1: Estimating qualification for referral

947 adult patients met the criteria for referral to the third-line ART committee in the period 01 October 2014 to 30 September 2016. Figure 2 illustrates the data cleaning and analysis process undertaken to derive the estimate of patients meeting the criteria for referral. The mean age of patients meeting the referral criteria was 38.6 years and most (59.4%) were female. The majority of patients (73.4%) had visited a primary health care (PHC) facility at their last visit in the study period and 71.5% were seeking care in the Cape Town Metro district. The remainder (28.5%) accessed care in one of 5 rural districts in the Western Cape. This geographic distribution of patients reflects the population distribution in the Western Cape. Patients were on a PI for a median of 3.2 years by the end of the study period and had a median of 5 HIV VLs ≥1000 copies/ml by the end of the study period. Table 1 provides descriptive characteristics for this cohort of patients.

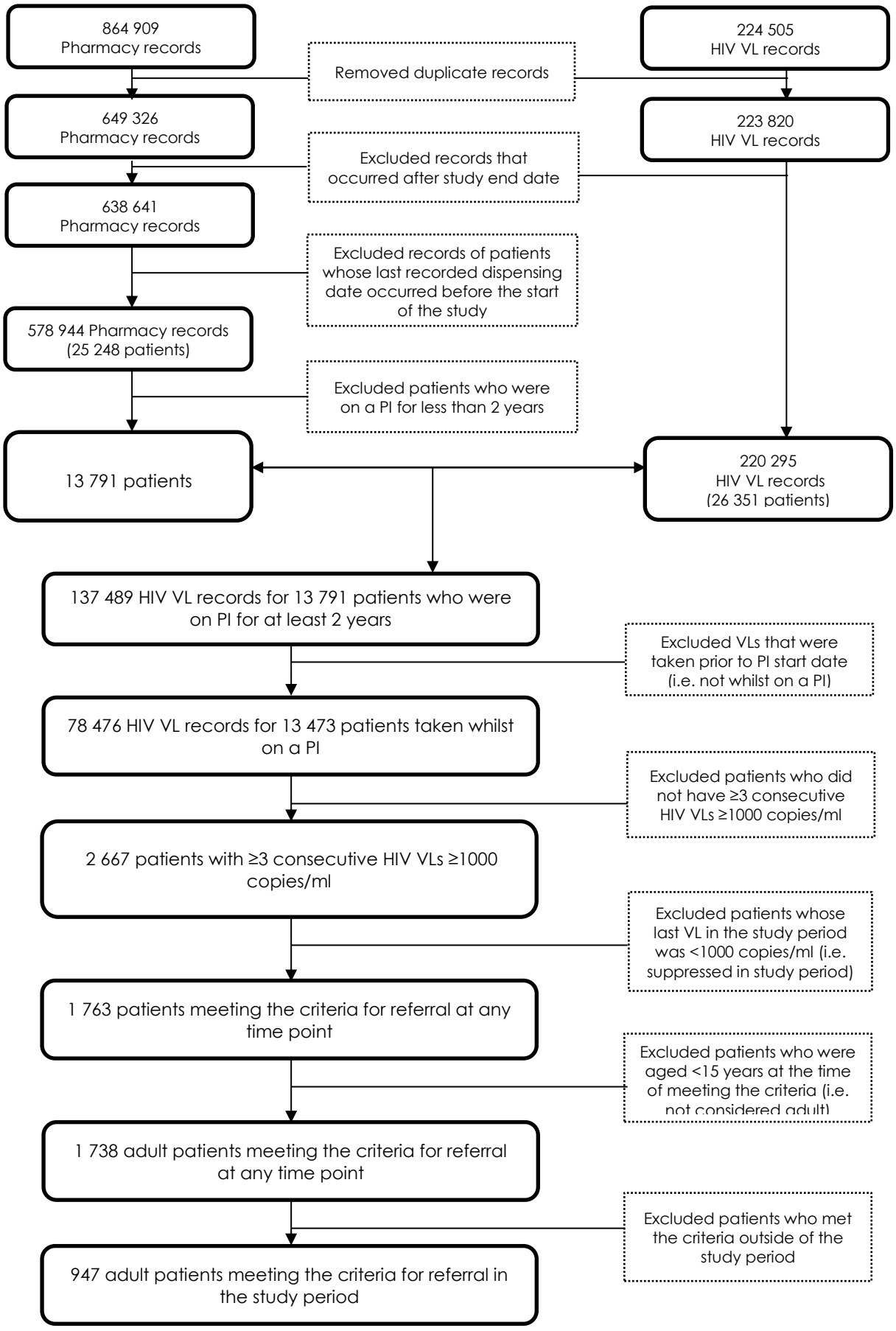

Figure 2. Estimating qualification for referral: Data Cleaning and Analysis Process

Table 1. Descriptive characteristics: Patients who met the criteria for referral

Variable	**N=947**
Age, mean (SD)	38.6 (9.9)
Female sex, n (%)	562 (59.4)
Facility Type, n (%)	
Hospital	252 (26.6)
PHC	695 (73.4)
District, n *(%)*	
Cape Town Metro	677 (71.5)
Cape Winelands	133 (14)
Eden	77 (8.1)
Overberg	32 (3.4)
West Coast	18 (1.9)
Central Karoo	10 (1.1)
Rural, n (%)	270 (28.5)
Time on PI in years, median (IQR)	3.2 (2.6-4.2)
Total number of high VLs in study period whilst on a PI*, median (IQR)	5 (4-6)

*High VL defined as ≥1000 copies/ml.

Step 2: Comparison with actual referrals

In the second step of the study the output from the first step was matched with a database of actual referrals to the third-line ART committee. A descriptive analysis of all the patients who were actually referred in the study period is presented in Table 2 prior to the results of the matching process.

Descriptive Analysis: Patients actually referred to the third-line ART committee in the study period

167 adult patients were referred to the third-line ART committee in the period 01 0ctober 2014 to 30 September 2016. Patients were a mean age of 38.4 years and most were female. The majority (46.4%) were referred from a hospital and more than 80% were seeking care in the Cape Town Metro district. Of the 167 patients referred, 129 (77.3%) had their request for genotype testing approved, 14 (8.4%) of patients had accessed genotype testing via an alternate procedure and for another 14, the request for a genotype test was rejected.

Table 2. Descriptive characteristics: Patients who were actually referred to the committee

Variable	N=167
Age, mean (SD)	38.4 (9.1)
Female Sex, n (%)	115 (68.9)
Facility Type, n (%)	
Hospital	77 (46.1)
PHC	90 (53.9)
District, n (%)	
Cape Town	136 (81.4)
Cape Winelands	22 (13.2)
Eden	7 (4.2)
Overberg	1(0.6)
West Coast	1 (0.6)

Rural, n (%)	31 (18.6)
Outcome of Request for Genotype test, n (%)	
Approved	129 (77.3)
Rejected	14 (8.4)
Provided	14 (8.4)
Not recorded	10 (6)

Matching Process

The cohort of patients meeting the criteria for referral (N=947) was then matched with the patients who were actually referred (N=167). This matching process allowed for the delineation of patients into three groups i.e. "Met Criteria and Referred", "Met Criteria and Not Referred" and "Did Not Meet Criteria and Referred". Figure 3 indicates the results of the matching process.

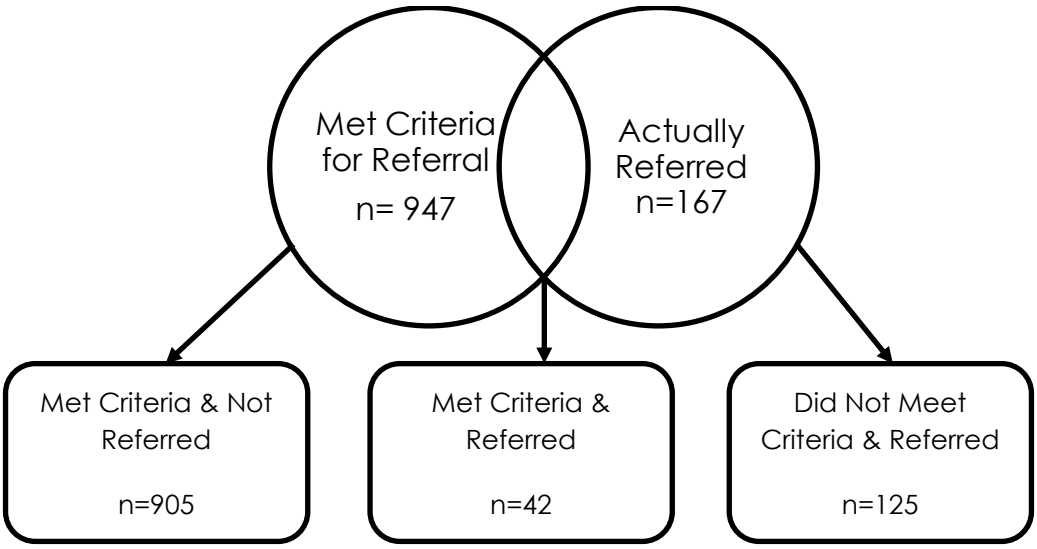

Figure 3. Results of Matching Process

The groups "Met Criteria and Referred" and "Met Criteria and Not Referred" are described further in the third step of the study. Further analysis of the group "Did Not Meet Criteria and Referred" is presented thereafter.

Step 3: Identification of predictors

The third step of the study took the form of a comparative analysis between the groups "Met Criteria and Referred" and "Met Criteria and Not Referred" with the aim of identifying predictors of referral. Further analysis of the group "Did Not Meet Criteria and Referred" was also undertaken in order to better understand the third-line ART referral process. Table 3 below summarises demographic and clinical characteristics of the two groups.

Table 3. Demographic and clinical characteristics: "Met Criteria and Referred" and "Met Criteria and not Referred" groups

Variable	Met Criteria and Referred (N=42)	Met Criteria and Not Referred (N=905)	p value
Age, median (IQR)	38.5 (31-46.5)	38 (32-45)	0.9505
Female sex, n (%)	27 (64.2)	537 (59.3)	0.477
Year of Meeting Referral Criteria, n (%)			
2014	3 (7.1)	114 (12.6)	0.348
2015	27 (64.3)	486 (53.7)	
2016	12 (28.6)	305 (33.7)	
Year Referred, n (%)			
2014	2 (4.8)		
2015	14 (33.3)		
2016	26 (62)		
Facility type, n (%)			
Hospital	18 (42.9)	234 (25.9)	**0.015**
PHC	24 (57.1)	671 (74.1)	
District, n (%)			0.298
Cape Town Metro	36 (85.7)	641 (70.8)	
Cape Winelands	5 (11.9)	128 (14.1)	
Eden	1 (2.4)	77 (8.5)	
Overberg	0	31 (3.4)	
West Coast	0	18 (2)	
Central Karoo	0	10 (1.1)	
Rural, n (%)	6 (14.3)	264 (29.2)	**0.037**
Time on PI in years, median (IQR)	3.6 (2.9-4.9)	3.2 (2.6-4.2)	**0.0281**
Total number of VLs whilst on a PI, median (IQR)	7 (6-10)	6 (4-7)	**0.0001**
Total number of high VLs whilst on a PI, median (IQR)	6 (5-7)	5 (3-6)	**0.0001**
Presence of 6-month dispensing gap, n (%)	13 (31)	464 (51.3)	**0.010**
Presence of 12-month dispensing gap, n (%)	7 (16.7)	255 (71.8)	0.103
Magnitude of third high VL, n (%)			0.816
<10 000 copies/ml	13 (31)	265 (29.3)	
≥10 000 copies/ml	29 (69)	640 (70.7)	
Magnitude of last high VL, n (%)			0.363
<10 000 copies/ml	9 (21.4)	252 (27.9)	
≥10 000 copies/ml	33 (78.6)	653 (72.2)	

Comparison of the groups "Met Criteria and Referred" and "Met Criteria and Not Referred" indicated a statistically significant association between the outcome variable i.e. referral and the type of facility attended by the patient, the geographic location of the facility and the presence of a six-month gap in dispensing. Additionally, there was a statistically significant difference in the median time on a PI, number of viral loads on the PI and number of high viral loads on the PI between the two groups.

Predictor Analysis

Univariate logistic regression was undertaken as an initial step in identifying predictors of referral. In univariate analysis, several factors were associated with referral: receiving ART at a hospital rather than a PHC facility (OR =2.15, 95% CI 1.1-4.0), number of years on a PI (OR=1.22, 95% CI 1.07-1.39), number of viral loads taken whilst on the PI (OR=1.23, 95% CI 1.13-1.34) and number of high viral loads (i.e. ≥ 1000 copies/ml) whilst on the PI (OR=1.37, 95% CI 1.18-1.59). Factors associated with non-referral were receiving ART care in a rural district (OR=0.4, 95% CI 0.35-0.46) and the presence of a six-month gap in dispensing (OR=0.43, 95% CI 0.22-0.83). Detailed results of the univariate analysis are presented in Table 4 below.

Table 4. Predictors of Referral: Univariate Analysis

Variable	Odds Ratio	95% CI	p value
Age	0.99	0.97-1.03	0.870
Female Sex	0.79	0.41-1.52	0.478
Year of Meeting Referral Criteria			
2014	1		
2015	2.11	0.63-7.08	0.226
2016	1.5	0.41-5.4	0.539
Facility Type (Hospital)	**2.15**	**1.1-4.0**	**0.017**
Rural	**0.4**	**0.35-0.46**	**0.000**
Time on PI in years	**1.22**	**1.07-1.39**	**0.002**
Total number of VLs whilst on a PI	**1.23**	**1.13-1.34**	**0.000**
Total number of high VLs whilst on a PI	**1.37**	**1.18-1.59**	**0.000**
Presence of 6-month dispensing gap	**0.43**	**0.22-0.83**	**0.012**
Presence of 12-month dispensing gap	0.51	0.22-1.16	0.109
Third VL 1000-10 000 copies/ml	1.08	0.55-2.12	0.816
Last VL 1000-10 000 copies/ml	0.71	0.33-1.5	0.365

Variables were then entered into a multiple logistic regression model and a backward stepwise selection procedure was used to identify predictors of referral. Variables were removed from the model at p values >0.05. Multivariate analysis (Table 5) showed that independent determinants of referral included receiving care at a hospital rather than a PHC facility (aOR=2.15, 95% CI 1.1-4.2), a higher number of VLs ≥1000 copies/ml whilst on a PI (aOR=1.2, 95%CI 1.01-1.42) and a greater number of years on a PI (aOR=1.25, 95% CI 1.07-1.46). Patients with a six-month gap in dispensing were less likely to be referred (aOR=0.37, 95% CI 0.17-0.81). The final model in the multivariate logistic regression analysis was highly statistically significant (p=0.0000).

Table 5. Predictors of Referral. Multivariate Analysis

Variable	**Adjusted Odds Ratio (aOR)**	**95% CI**	**p value**
Presence of 6-month dispensing gap	0.37	0.17-0.81	0.013
Total number of high VLs (≥1000 copies/ml) whilst on a PI	1.2	1.01-1.42	0.040
Time on PI in years	1.25	1.07-1.46	0.004
Facility Type (Hospital)	2.15	1.1-4.2	0.025

Did Not Meet Criteria and Referred

Table 6 below provides descriptive characteristics for the group "Did Not Meet Criteria and Referred". While this group is not the focus of the study, further analysis of the patients in this group is relevant to a comprehensive evaluation of the third-line ART referral process.

Table 6. Descriptive Characteristics: "Did Not Meet Criteria and Referred" group

Variable	**Did Not Meet Criteria & Referred (N=125)**
Age, mean (SD)	38.3 (9.3)
Female sex, n (%)	88 (70.4)
Year Referred, n (%)	
2014	7 (5.6)
2015	48 (38.4)
2016	70 (56)
Facility type, n (%)	
Hospital	58 (46.4)
PHC	67 (53.6)
District, n (%)	
Cape Town	98 (78.4)
Cape Winelands	19 (15.2)
Eden	7 (5.6)
Overberg	0
West Coast	1 (0.8)
Central Karoo	0
Rural, n (%)	27 (21.6)
Time on PI in years, median (IQR)	4 (1.7 -6.2)
Total number of VLs whilst on a PI, median (IQR)	7 (4-11)
Total number of high VLs whilst on a PI, median (IQR)	6 (2-9)
Presence of 6-month dispensing gap, n (%)	44 (41.1)
Presence of 12-month dispensing gap, n (%)	28 (26.2)
Outcome of Request for Genotype test, n (%)	
Approved	92 (73.6)
Rejected	13 (10.4)
Provided	14 (11.2)
Not recorded	6 (4.8)

Of the 125 patients who were referred despite not meeting the criteria for referral in the study period, 107 patient records were identified for further analysis using the folder number provided in the referral documentation. Where present, the folder number allowed for the identification of the PMI (Patient Master Index) which facilitated linkage with records in the study dataset. Figure 4 below demonstrates the reasons why these patients were not included in the estimate of patients meeting the criteria for referral to the committee. An important finding is that 36 of the 125 patients in this group did actually meet the criteria for referral and that they were eventually excluded from the estimate

because they had met the referral criteria prior to and not in the study period. The implication of this finding is explored further in the sensitivity analysis which is reported on in the following chapter.

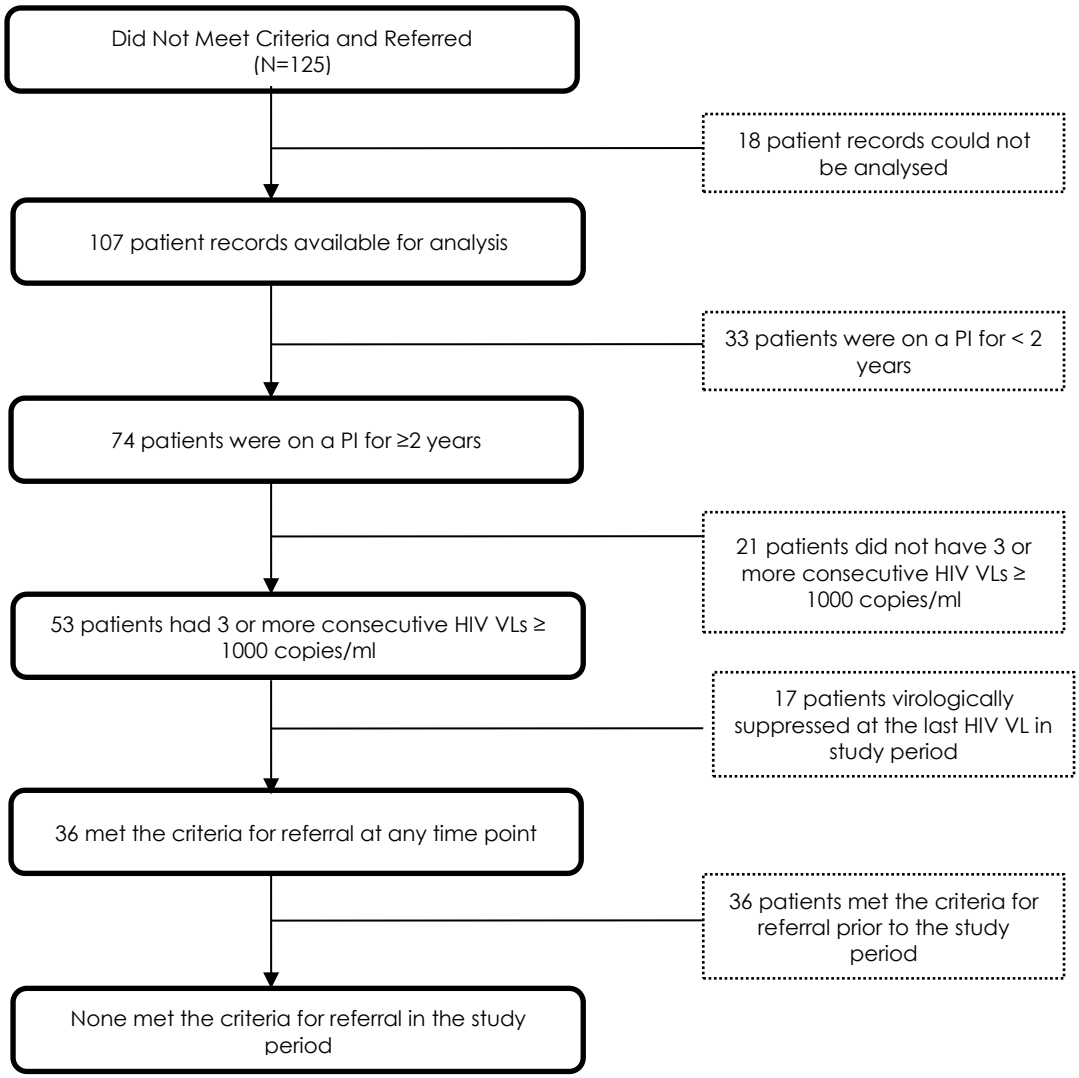

Figure 4. Further Analysis: "Did Not Meet Criteria and Referred" group

CHAPTER 6: SENSITIVITY ANALYSIS

A sensitivity analysis was undertaken due to two main concerns relating to the procedure used in Step 1 to derive an estimate of patients meeting the criteria for referral to the third-line ART committee in the study period.

The first of these concerns relates to the impact of patient adherence to therapy on the outcome i.e. referral. As described earlier, referral to the third-line ART committee requires verification of adherence by pharmacy refill records and the completion of an adherence assessment form. Adherence data is not captured by routine information systems and therefore could not be incorporated into the estimate. Since clinician knowledge of adherence may impact on the referral decision, it is likely that the number of patients meeting criteria for referral is overestimated. In the sensitivity analysis, the presence of gaps between dispensing events was utilised as a proxy measure for non-adherence. Twelve and six month gaps in dispensing were considered.

The second concern pertains to the time period in which the criteria for referral were met. The study undertook to identify only those patients who had met the criteria in the period 01 October 2014 to 30 September 2016. The start of this time period marks the handover of the referral process from the NDoH to the WCG: H. An important consideration here is that prior to April 2013 no third-line ART referral system was available to patients failing second-line regimens. It is therefore plausible that patients who met the criteria for referral prior to the start of this period would be referred once the referral process and committee was established. This hypothesis is supported by the analysis of the "Did Not Meet Criteria and Referred" group which indicates that a sizeable number of this group did in fact meet the criteria for referral prior to the study period. For this reason, variation in the time period of meeting the criteria for referral was analysed. Patients meeting the referral criteria from 2012, 2013 and 2014 were considered.

Step 1: Estimating qualification for referral

Adherence data

Of the 947 patients who met the criteria for referral, 262 (27.7%) and 477 (50.4%) had twelve and six-month dispensing gaps respectively. Table 7 below summarises the impact of incorporating the dispensing gaps into the estimate.

Table 7. Sensitivity Analysis: Adherence Data

Variation in adherence data	Result
Initial estimate (No dispensing gaps considered)	947
Excluding patients with a twelve-month dispensing gap	685

Excluding patients with a six-month dispensing gap	470

Time period for meeting referral criteria

Table 8 below demonstrates the impact of variation in the time period for meeting referral criteria on the estimate.

Table 8. Sensitivity Analysis: Time period

Variation in time period	Result
Initial estimate (Met criteria 01 October 2014-30 September 2016)	947
Included patients meeting criteria from 01 January 2014-30 September 2016	1 237
Included patients meeting criteria from 01 January 2013-30 September 2016	1 470
Included patients meeting criteria from 01 January 2012-30 September 2016	1 590

Combination of two factors

In order to further the analysis, a combination of the two factors was considered. This variation allowed for inclusion of patients meeting criteria for referral from 2012 until the end of the study period and excluded patients with a dispensing gap of twelve months. The resultant estimate was 1 079 patients meeting the criteria for referral to the third-line ART committee.

Step 2: Comparison with actual referrals

The revised estimate (n=1079) was matched with the database of actual referrals in the study period. Ideally the revised estimate should have been matched with a database of actual referrals including patients referred to the committee during the tenure of the NDoH i.e. from initiation of the third-line programme in 2013. However, this was not possible due to incomplete data capture and lack of a common patient identifier to facilitate the matching process. This limitation of the matching procedure must be borne in mind and is likely to underestimate the numbers of patients in the "Met Criteria and Referred" group.

The results of the revised matching process are summarised in the diagram (Figure 5) below.

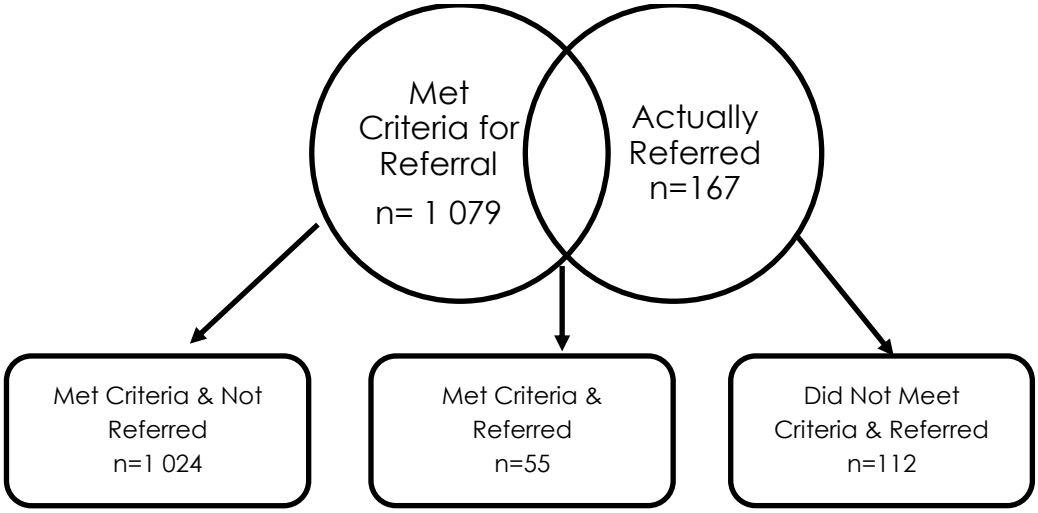

Figure 5. Sensitivity Analysis: Results of Matching Process

Revision of the estimate improved the match of patients who met the criteria and were actually referred from 42 to 55 however the number of patients meeting criteria and not referred was also substantially higher having increased from 947 to 1 024. It is likely that the match may have been higher had actual referrals prior to 2013 been included.

Step 3: Identification of predictors

The results of predictor analysis are summarised in Table 9 below. In univariate analysis, factors that were associated with referral included: receiving care at a hospital rather than a PHC facility (OR=1.9, 95% CI 1.06-3.3), the number of years on a PI (OR=1.2, 95% CI 1.05-1.43), the total number of VLs taken whilst on a PI (OR=1.15, 95% CI 1.07-1.24) and the number of VLs ≥ 1000 copies/ml whilst on the PI (OR=1.23, 95% CI 1.12-1.36). Patients receiving care at a rural facility were less likely to be referred (OR=0.46, 95% CI 0.40-0.52).

Table 9. Sensitivity Analysis: Predictors of Referral

Variable	Odds Ratio	95% CI	p value
Age	0.98	0.95-1.01	0.232
Female Sex	0.93	0.51-1.7	0.819
Year of Meeting Referral Criteria			
2012	1		
2013	0.81	0.23-2.89	0.756
2014	0.79	0.25-2.52	0.686
2015	1.1	0.37-3.27	0.870
2016	0.63	0.2-2.1	0.459
Facility Type (Hospital)	**1.9**	**1.06-3.3**	**0.031**

Rural	**0.46**	**0.40-0.52**	**0.000**
Time on PI in years	**1.2**	**1.05-1.43**	**0.008**
Total number of VLs whilst on a PI	**1.15**	**1.07-1.24**	**0.000**
Total number of high VLs whilst on a PI	**1.23**	**1.12-1.36**	**0.000**
Presence of 6-month dispensing gap	0.53	0.28-1.02	0.057
Third VL 1000-10 000 copies/ml	0.67	0.35-1.3	0.236
Last VL 1000-10 000 copies/ml	0.68	0.34-1.3	0.258

In multivariate analysis, following a backward stepwise selection procedure with variables removed from the model at $p>0.05$, only the number of VLs $\geq$ 1000 copies/ml whilst on a PI remained independently associated with the outcome i.e. referral. For each additional high VL, patients had 1.2 times the odds of being referred (95% CI 1.09-1.34, p=0.000).

CHAPTER 7: DISCUSSION

The study found that in the period 01 October 2014 to 30 September 2016, 947 patients met criteria for referral to the Western Cape third-line ART committee - to be evaluated for genotype resistance testing as a precursor for consideration for third-line ART. This estimate, obtained from analysis of routinely collected data, was far larger than the number of patients actually referred to the committee in the same period (n=167). A comparison of the group of patients meeting the criteria for referral with the group actually referred identified only a small overlap in patients (n=42) indicating both a large proportion of missed opportunities for referral and a considerable proportion of inappropriate referrals.

The study identified patients who should have been evaluated for third-line ART in a two-year time period. As far as the author is aware, this is the first study to enumerate the need for third-line therapy in this setting. This information is particularly useful for public health planning and may be considered a proxy for evaluation of second-line programmes.

The estimate is however subject to a number of limitations. Firstly, the estimate of patients meeting the criteria for referral was derived from primary data sources which may have been prone to data error. The TIER.net information system in particular is less robust than other sources of pharmaceutical dispensing data because of its reliance on manual data capture by information clerks whose limited medical knowledge may have resulted in incorrect data entry. Unfortunately, TIER.net was a vital data source to the estimate enabling calculation of the duration of time an individual had been receiving a PI. Other sources of pharmaceutical dispensing data (JAC, CDU) have only been established in recent years and did not have wide facility and patient coverage.

While every attempt was made to model the estimate around the criteria for referral to the third-line ART committee, some parameters could not be established. For example, the referral criteria specified three consecutive high viral loads (≥1000 copies/ml) 8-12 weeks apart. The estimate was able to identify patients who had three consecutive high viral loads but did not determine the duration of time between each result. Furthermore, in order to identify patients meeting the referral criteria at any point in the two-year study period, the three consecutive high viral load results may have occurred at any point in the patient's history of receiving a PI and not necessarily at the end of the study period. This means that patients identified as meeting the criteria for referral may have achieved virologic re-suppression following the three high viral load results and therefore would not have been referred. In an attempt to mitigate this, the estimate excluded patients who achieved virologic suppression at the last recorded viral load in the study period.

The referral criteria also specified objective verification of adherence by pharmacy refill records and the completion of an adherence assessment. This could not be incorporated reliably into the estimate

and was therefore excluded. This may have resulted in an overestimate of patients meeting the criteria for referral. An attempt was made to address this limitation by undertaking sensitivity analyses which looked at the impact of dispensing gaps (as a proxy for poor adherence) on the estimate. However, further analysis of patients who were actually referred revealed a high proportion of patients with dispensing gaps twelve months or longer. Based on the information at hand and because of the inability to validate the estimate (discussed further below), it is unclear whether this finding relates to poor quality of the pharmaceutical dispensing data which was utilised to determine gaps in dispensing.

The inability to validate the estimate is also an important limitation of the study. No single data source could be used as a gold standard to verify the key clinical criteria utilised to derive the estimate. Folder review formed part of the initial study design for the purposes of validation and collection of additional data. However, as described earlier, following a pilot exercise, this aspect of the study was abandoned due to reasons of non-feasibility. This impacted both on the ability to verify the estimate and on the collection of data pertaining to potential predictors.

Despite these limitations, this exercise demonstrated the use of routine data on a population level to identify patients requiring further intervention. In the future, widespread permeation of pharmaceutical information systems and improved data usage and quality may allow this exercise to prompt clinicians to refer patients appropriately. Similarly, this exercise may allow programme managers to evaluate the effectiveness of the second-line ART programme on provincial, district and sub-district levels.

The study found a poor match between individuals meeting the criteria for referral and those who were referred in the study period. This indicates both a large number of missed opportunities and inappropriate application of the referral criteria. The match is subject to the same limitations plaguing the estimate and it is possible that these limitations present an altered view of the reality. One consideration which is supported by both the sensitivity analyses and further analysis of the group of patients who were referred despite not meeting the criteria for referral is that of a delay between meeting the criteria and actual referral. In the sensitivity analyses, inclusion of patients meeting the criteria from 2012 onwards increased the match between the groups from 42 to 55 patients and analysis of the “Did Not Meet Criteria and Referred” group showed that 36 of the 125 (29%) patients in this group did actually meet the criteria for referral but were excluded from the estimate because the criteria were met prior to the study period. It is also important to acknowledge that referral of patients who did not meet the referral criteria may have been appropriate under certain special circumstances such as virological failure in pregnancy or virological failure due to incorrect PI dosing in the setting of concomitant tuberculosis.

Predictor analysis identified that factors independently associated with the outcome (referral) included receiving care at a hospital rather than a PHC facility, the number of years a patient was receiving a PI for and the total number of high viral load tests whilst on the PI. Patients who had at least a six-month gap between dispensing records were less likely to be referred than those without. These findings are challenging to contextualise due to a lack of similar studies assessing predictors of third-line referral. However, as described earlier, in the absence of data pertaining to third-line referral, these findings may be compared to factors predicting switch in therapy from first to second–line ART.

The study found that patient non-adherence (evaluated by the presence of a six-month gap in dispensing as a proxy measure) resulted in patients being less likely to be referred. Patients with a six-month gap in dispensing were 63% less likely to be referred than those without. This finding is supported by studies which found that patients who missed visits[21] and those who had no clinic contact for four months[26] were less likely to switch from first to second-line ART.

The study also found that patients who were receiving care in a hospital were more than twice as likely to be referred than those who were receiving care at a PHC facility. This finding is not supported by a study analysing predictors of switching from first to second-line regimens which did not find a significant difference in rates of switching between treatment providers, including providers in both hospital and PHC settings.[28] However, variation in rates of treatment switch between clinics has been described previously.[26] It is possible that the higher rate of referral from hospitals compared to PHC facilities in our study reflects differences in the ART programme and patient profile in these settings. Patients in hospital-based ART centres may have more complicated treatment histories and may be more likely to be seen by doctors than by NIMART-trained nurses. Additionally, the higher proportion of referrals from hospitals may be masking prior up-referral from PHC to hospital-based ART centres due to treatment failure. Clinician awareness and compliance with the referral procedure has not been investigated, however, differences in clinician awareness between these settings may also explain some of the findings.

In this study, for every additional year on a PI after the two-year referral criterion, patients had 1.25 times the odds of being referred. This finding is not dissimilar to another study which found a decreased likelihood of switching from first to second-line therapy in patients who started ART in a more recent calendar year.[27] Since clinicians are likely to first attempt adherence interventions prior to referral, this finding may reflect the referral of patients for whom adherence interventions were unsuccessful.

The study also found that for every additional high viral load result on the PI, patients were 1.2 times more likely to be referred. This factor was independently associated with the referral outcome, indicating that even with the length of time receiving a PI held constant, patients who had more viral load tests done were more likely to be referred. Frequent viral load testing suggests clinician

awareness of treatment failure and most likely reflects frequent review of adherence intervention efforts.

Other studies looking at predictors of treatment switch have indicated magnitude of the viral load result as a significant factor, with values greater than log 4 more likely to result in switch[20,21,26]. In our study, however, viral load magnitude at the third of the three high viral loads and at the last recorded viral load was not significantly associated with the referral outcome. Selection of these time points may explain why the study did not find an association between viral load magnitude and referral. It is possible that the findings may have differed if more sophisticated analysis were possible by selecting the viral load result closest to the date of meeting referral criteria instead.

Parameters not evaluated in this study include CD4 count magnitude and rate of decline which were found to be predictors of switching from a first to second-line regimen.[20,21,26–28] Additionally the study did not investigate the impact of clinician knowledge of the referral criteria and process.

CHAPTER 8: CONCLUSION

This study evaluated a third-line ART referral process in the Western Cape province of South Africa – the country with the largest ART programme in the world and the first public sector third-line access programme. This work adds to a limited body of knowledge pertaining to the need for third-line ART in South Africa, providing information that is valuable for public health planning and health programme evaluation.

Using routinely collected pharmaceutical and laboratory data, it was determined that in the two-year study period, 947 patients met criteria for referral to the third-line ART committee to be evaluated for genotype testing. The number of patients actually referred to the committee in this period was far less and comparison between these two patient groups revealed a poor overlap indicating both missed opportunities for referral and inappropriate referral. In multivariate analysis, facility type, length of time on a PI and the number of viral load tests predicted referral while the presence of a six-month gap in dispensing resulted in patients being less likely to be referred.

The estimate of patients meeting the referral criteria was subject to a number of limitations and could not be reliably validated. However, with ongoing data usage, improved data quality and more sophisticated analysis, this method of identifying patients meeting the referral criteria could be used to prompt referral. Overall, factors predicting referral were not unexpected. However, a number of these factors may be linked to clinician awareness of and compliance with the referral criteria and procedure which was not evaluated in this study.

Future work should focus on refining the methods used to identify patients meeting the criteria for referral and determining the validity of the method. Additionally, clinician awareness of the referral criteria and procedure should be evaluated to give a comprehensive view of the referral process and guide future intervention.

REFERENCES

1. Reniers G, Blom S, Calvert C, Martin-Onraet A, Herbst AJ, Eaton JW, et al. Trends in the burden of HIV mortality after roll-out of antiretroviral therapy in KwaZulu-Natal, South Africa: an observational community cohort study. Lancet HIV. 2017;4(3):e113–21.

2. South Africa's National Strategic Plan for HIV, TB and STIs 2017-2022. 2017.

3. National Consolidated Guidelines for the Prevention of Mother-To-Child Transmission of HIV (PMTCT) and the Management of HIV in children, adolescents and adults. 2015.

4. Luber AD. Genetic barriers to resistance and impact on clinical response. J Int AIDS Soc [Internet]. 2005;7(3). Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2804709&tool=pmcentrez&rendertype=abstract

5. 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. 2017;72(1):210–9.

6. Boender TS, Kityo CM, Boerma RS, Hamers RL, Ondoa P, Wellington M, et al. Accumulation of HIV-1 drug resistance after continued virological failure on first-line ART in adults and children in sub-Saharan Africa. J Antimicrob Chemother. 2016;71(10):2918–27.

7. Boulle A, Cutsem G Van, Hilderbrand K, Cragg C, Abrahams M, Mathee S, et al. Seven-year experience of a primary care antiretroviral treatment programme in Khayelitsha, South Africa. AIDS. 2010;24:563–72.

8. Ajose O, Mookerjee S, Mills EJ, Boulle A, Ford N. Treatment outcomes of patients on second-line antiretroviral therapy in resource-limited settings : a systematic review and meta-analysis. AIDS. 2012;26(November 2011):929–38.

9. Fox MP, Ive P, Long L, Maskew M, Sanne I. High Rates of Survival, Immune Reconstitution, and Virologic Suppression on Second-Line Antiretroviral Therapy in South Africa. J Acquir Immune Defic Syndr. 2010;53(4):500–6.

10. Kuritzkes DR, Fu N, Levison JH, Orrell C, Freedberg KA, Wood R. Virologic Failure of Protease Inhibitor-Based Second-Line Antiretroviral Therapy without Resistance in a Large HIV Treatment Program in South Africa. 2012;7(3):3–7.

11. Van Zyl GU, Van Mens TE, McIlleron H, Zeier M, Nachega JB, Decloedt E, et al. Low lopinavir plasma or hair concentrations explain second-line protease inhibitor failures in a

resource-limited setting. J Acquir Immune Defic Syndr. 2011;56(4):333–9.

12. El-Khatib Z, Ekstrom AM, Ledwaba J, Mohapi L, Laher F, Karstaedt A, et al. Viremia and drug resistance among HIV-1 patients on antiretroviral treatment: A cross-sectional study in Soweto, South Africa. AIDS. 2010;24(11):1679–87.

13. Wallis CL, Mellors JW, Venter WDF, Sanne I, Stevens W. Protease Inhibitor Resistance Is Uncommon in HIV-1 Subtype C Infected Patients on Failing Second-Line Lopinavir / r-Containing Antiretroviral Therapy in South Africa. 2011;2011:1–5.

14. Garone DB, Conradie K, Patten G, Cornell M, Goemaere E, Kunene J, et al. High rate of virological re-suppression among patients failing second-line antiretroviral therapy following enhanced adherence support : A model of care in Khayelitsha , South Africa. South Afr J HIV Med. 2013;14(4):166–9.

15. Fox MP, Berhanu R, Steegen K, Firnhaber C, Ive P, Spencer D, et al. Intensive adherence counselling for HIV-infected individuals failing second-line antiretroviral therapy in Johannesburg, South Africa. Trop Med Int Heal. 2016;21(9):1131–7.

16. Western Cape Government: Health Circular 158/2014. Third Line regimens in Western Cape Province (Adults and Children). 2014.

17. Cesar C, Shepherd BE, Jenkins CA, Ghidinelli M, Castro JL, Veloso VG, et al. Use of third line antiretroviral therapy in Latin America. PLoS One. 2014;9(9):1–8.

18. Rawizza HE, Chaplin B, Meloni ST, Darin KM, Olaitan O, Scarsi KK, et al. Accumulation of Protease Mutations among Patients Failing Second-Line Antiretroviral Therapy and Response to Salvage Therapy in Nigeria. PLoS One. 2013;8(9):1–8.

19. Levison JH, Orrell C, Losina E, Lu Z, Freedberg KA, Wood R. Early outcomes and the virologic impact of delayed treatment switching on second-line therapy in an antiretroviral roll-out program in South Africa. Antivir Ther. 2011;16(6):853–61.

20. Ssempijja V, Nakigozi G, Chang L, Gray R, Wawer M, Ndyanabo A, et al. Rates of switching to second-line antiretroviral therapy and impact of delayed switching on immunologic, virologic, and mortality outcomes among HIV-infected adults with virologic failure in Rakai, Uganda. BMC Infect Dis. 2017;17(1):582.

21. Rohr JK, Ive P, Robert Horsburgh C, Berhanu R, Shearer K, Maskew M, et al. Marginal structural models to assess delays in second-line HIV treatment initiation in South Africa. PLoS One [Internet]. 2016;11(8):1–11. Available from:

http://dx.doi.org/10.1371/journal.pone.0161469

22. 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. 2014;28(14):2097–107.

23. Estill J, Ford N, Salazar-Vizcaya L, Haas AD, Blaser N, Habiyambere V, et al. The need for second-line antiretroviral therapy in adults in sub-Saharan Africa up to 2030: A mathematical modelling study. Lancet HIV [Internet]. 2016;3(3):e132–9. Available from: http://dx.doi.org/10.1016/S2352-3018(16)00016-3

24. Li L, Eron JJ, Ribaudo H, Gulick RM, Johnson BA. Evaluating the Effect of Early Versus Late ARV Regimen Change if Failure on an Initial Regimen: Results From the AIDS Clinical Trials Group Study A5095. J Am Stat Assoc. 2012;107(498):542–54.

25. Murphy RA, Court R, Maartens G, Sunpath H. Second-line antiretroviral therapy in sub-Saharan Africa: It's time to mind the gaps. AIDS Res Hum Retroviruses [Internet]. 2017;33(12). Available from: http://online.liebertpub.com/doi/10.1089/AID.2017.0134

26. Johnston V, Fielding KL, Charalambous S, Churchyard G, Phillips A, Grant AD. Outcomes Following Virological Failure and Predictors of Switching to Second-line Antiretroviral Therapy in a South African Treatment Programme. J Acquir Immune Defic Syndr. 2012;61(3):1–19.

27. Palombi L, Marazzi MC, Guidotti G, Germano P, Buonomo E, Scarcella P, et al. Incidence and Predictors of Death, Retention, and Switch to Second-Line Regimens in Antiretroviral-Treated Patients in Sub-Saharan African Sites with Comprehensive Monitoring Availability. Clin Infect Dis [Internet]. 2009;48(1):115–22. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/593312

28. 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. 2012;60(4):428–37.

29. Khwitshana AK, Greef OBW, Hurrell T. Assessing adherence to the 2010 antiretroviral guidelines in the antiretroviral roll-out clinic at 1 Military Hospital, South Africa: A retrospective, cross-sectional study. South African Med J. 2014;104(7):495–500.

30. Keiser O, Tweya H, Braitstein P, Dabis F, Mac Phail P, Boulle A, et al. Mortality after failure of antietroviral therapy in sub-Saharan Africa. Trop Med Int Heal. 2011;15(2):251–8.

31. Moyo F, Chasela C, Brennan AT, Ebrahim O, Sanne IM, Long L, et al. Treatment outcomes of HIV-positive patients on first-line antiretroviral therapy in private versus public HIV clinics in Johannesburg, South Africa. Clin Epidemiol. 2016;8:37–47.

32. Rossouw TM, Nieuwoudt M, Manasa J, Malherbe G, Lessells RJ, Pillay S, et al. HIV drug resistance levels in adults failing first-line antiretroviral therapy in an urban and a rural setting in South Africa. HIV Med. 2017;18(2):104–14.

33. Meintjes G, Dunn L, Coetsee M, Hislop M, Leisegang R, Regensberg L, et al. Third‐line antiretroviral therapy in Africa: effectiveness in a Southern African retrospective cohort study. AIDS Res Ther [Internet]. 2015;12:1–7. Available from: "http://dx.doi.org/10.1186/s12981-015-0081-8

34. Western Cape Antenatal Survey Report 2015.

35. Western Cape Government Health Annual Performance Plan 2016/2017.

APPENDICES

APPENDIX A: Application Form

REQUEST FOR THIRD LINE ANTIRETROVIRAL THERAPY															
PATIENT DETAILS															
Patient First Name															
Patient Surname															
Date of Birth Day/month/year									Patient number						
Identity number													**Age**		**Gender** M/F
Weight (kg)				**BMI** (kg/m^2)									**Height (child)**		
FACILITY DETAILS															
Facility Name															
Authorised Prescriber															
Contact Number															
Email Address															
Date															
Signature of Authorised Prescriber															

Past medication history:			
Date started / Date stopped	Regimen	Reason for discontinuation	Concurrent TB therapy
Reason for discontinuation codes: SE = Side effect, AL = Allergy, FC = Formulary change, NC = Non adherent			
Current regimen			
Has adherence been assessed? y/n			

What is the adherence level
Children: PMTCT history
Was the mother on therapy during pregnancy or breastfeeding?
What treatment did the mother take and for how long?
Was child breastfed?
Did child receive any ARV at birth/after birth/ and during breastfeeding? State ARV and duration.

CD 4 count			**Viral load**	
Last 3 CD 4 counts results:		Children CD4%	*Last 3 VL results:*	
Date:			Date:	
Date:			Date:	
Date:			Date:	

Laboratory Resistance test attached: y/n		**Results of Viral Resistance Test** Date:
Most recent available tests:		
Hb (g/dL)		
ALT (U/L)		
Creatinine (µmol/L)		
Creatinine Clearance (mL/min/1.73 m^2)		
White cell count (x 10^9/L)		
Neutrophil count (x 10^9/L)		
Hepatitis B status?		

Concomitant medication and indication
Children: Is child able to swallow a tablet? y/n
For office use only:
Date received:
Recommendation: Date:

Appendix B: Adherence Assessment Form

ADHERENCE TO TREATMENT ASSESSMENT FORM

Patient name: _____ Date: _____
Clinician's name: _____
Ask the client the following set of questions and make comments below each question. If the client is a child or adolescent, these questions need to be asked to the caregiver:

No.	Question
1.	Explain how you take your ART – what time and how many tablets each time
2.	Have you forgotten to take your ART? If yes, how many doses have you missed since your last appointment?
3.	What were the reasons for you not remembering to take your ART? What do you do to remember to take your medication and not forget?
4.	What do you do when you miss a dose of your ART? Do you take the dose when you remember or wait until it's time for the next dose?
5.	Tell me 3 reasons why you want to adhere to your ART (why you take your tablets)?
6.	Have you disclosed your HIV status to someone? If so, do you have a treatment supporter?
7.	Do you have extra tablets stored in case you run out before you can go back to your clinic? What do you do if you plan to travel?
8.	How do you get to the clinic each month? Do you have a backup plan to get to the clinic if needed?

9.	**Are you having any side effects from your tablets? Are you worried about taking your tablets?**
10.	**Are you taking any other medication? If yes, what are you taking and how many pills?**
11.	**Have you had problems swallowing your tablets, or do you vomit after taking the tablets? If yes, how often do you struggle to swallow the medication?**
12.	**How do you plan to make sure you take your ART if you use alcohol or drugs?**
13.	**Do you know what an undetectable viral load is? Do you know what a high viral load is? Why do you think your viral load is high?**

This adherence assessment tool must accompany the "Request for third line antiretroviral therapy" application form. If poor adherence is detected from the questions above, clinicians should increase tailored adherence support that assists the client in addressing the reasons for poor adherence.