ASSESSING TREATMENT OUTCOMES OF PEOPLE LIVING WITH HIV ON ANTIRETROVIRAL THERAPY AT KAKAMEGA COUNTY GENERAL HOSPITAL IN KENYA

MAERO ATHANASIUS LUTTA

STUDENT NUMBER: 3520556

A mini-thesis submitted in partial fulfillment of the requirements for the degree of Master in Public Health at the School of Public Health, University of the Western Cape, South Africa

Supervisor:

Dr. Hanani Tabana

March 2019

KEYWORDS

Antiretroviral therapy

Attrition

Clinical progression

HIV

Immunological progression

Kenya

People living with HIV

Program retention

Treatment outcome

Virological progression

DECLARATION

I declare that this study *Assessing Treatment Outcome of People Living with HIV on Antiretroviral Therapy at Kakamega County General Hospital in Kenya* is my own work, that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full Name: Maero Athanasius Lutta Date: 13th March 2019

Signature: …… ……

ACKNOWLEDGMENTS

I give thanks to the Almighty for the opportunity to take my work to this level and engage in an academic discourse that has made a big difference in my scholarship, and perceptions of progress, success, failure and determination.

I am indebted to my supervisor, Dr. Hanani Tabana for her expert guidance and encouragement throughout my research.

Moreover, I am deeply indebted to the administration of UWC for their patience and support during my research.

I would also like to express my deep gratitude to the teaching fraternity at UWC for their guidance and support during my pursuit for excellence.

The members of staff and administration at Kakamega County General Hospital also deserve many thanks for giving me permission to carry out my research in their premises as well as for the accommodation and support they granted me during my study.

Finally, I express my deep gratitude to my wife Millicent and son Adriel for their support, encouragement, and patience during the difficult times of my research. To my parents, I remembered that I must finish, and, do it well.

Thank you for standing by me through it all. May God bless you!

Table of Contents

KEYWORDS ii
DECLARATION iii
ACKNOWLEDGMENTS iv
Table of Contents v
List of Tables vii
Table of Figures vii
Abstract viii
LIST OF ABBREVIATIONS ix
Operational Definition of Terms x
CHAPTER ONE 1
A DESCRIPTION OF THE STUDY 1
1.1. Introduction 1
1.1.1. HIV Infection and ART Status in Kenya 2
1.2. Rationale for ART 3
1.3. Problem Statement 3
1.4. Study Aim and Objectives 4
1.5. Study Setting 5
CHAPTER TWO 6
LITERATURE REVIEW 6
2.1 Introduction 6
2.2 Initiation of ART 6
2.2.1 Choice of ART 7
2.3 Monitoring HIV Specific Response on ART 9
2.3.1 Clinical Monitoring of Clients on ART 9
2.3.2 Laboratory Monitoring of Clients on ART 10
2.4 Response to ART 10
2.4.1 Clinical Response to ART 11
2.4.2 Immunological Response to ART 11
2.4.3 Virological Response to ART 12
2.5 Treatment Failure 13
2.6.1 Criteria for Identifying ART Failure 13
2.6.2 Factors Associated with ART Treatment Failure 14
2.6.2.1 Virus Related Factors 14
2.6.2.2 Drug-Related Factors 15

2.6.2.3 Host-Related Factors 16
2.7 Retention of Clients on ART 19
2.8. Conceptual Framework for the Present Study 20
2.8 Present Study's Conceptual Framework 21
CHAPTER THREE 22
METHODOLOGY 22
3.1 Study Design 22
3.2 Study Population 22
3.3 Inclusion and Exclusion Criteria 22
3.4 Sampling 23
3.5 Data collection 24
3.6 Data Analysis 24
3.7 Validity and Reliability of Chart Abstraction Tool 26
3.8 Ethical Considerations 26
CHAPTER FOUR 28
RESULTS 28
4.1. Social Demographic Characteristics 28
4.2. Antiretroviral Therapy 28
4.3. Study Outcomes 29
4.3.1. Clinical Outcomes 29
2.5.1 4.3.1.1. Weight 29
2.5.2 4.3.1.2. Opportunistic Infections 30
2.5.3 4.3.1.3. WHO Staging 31
2.5.4 4.3.1.4. Sustained ART Options 32
4.3.2. Immunological Response 33
2.5.5 4.3.2.1. Suspected Treatment Failure 34
4.3.3. Virologic Response 36
4.4. Program Retention 41
CHAPTER FIVE 44
DISCUSSION, CONCLUSION, AND RECOMMENDATIONS 44
5.0. Introduction 44
5.2. ART Initiation and Context 44
5.3. Primary Outcomes 45
2.5.6 5.3.1. Clinical Outcomes 45
2.5.7 5.3.2. Immunological Response 48
2.5.8 5.3.3. Virological Response 49

2.5.9 5.3.4. Program Retention 52
5.4. Secondary Outcome 52
5.5. Study Limitations and Bias 53
5.6. Conclusion 54
5.7. Recommendations 54
References 56
Appendix I: Maps for Kenya and Kakamega County 81
Appendix II: Chart Abstraction Tool 82
Appendix III: Permission to Review and Access Patient Records at Kakamega County General Hospital 84
Appendix IV: BMREC Letter 85

List of Tables

Table 1: Baseline Characteristics of Study Participants Starting ART 28
Table 2: ART initiated to Study Participants 29
Table 3: Reasons for Changing ART Drugs 32
Table 4: Table for CD4 Random Effects 34
Table 5: Comparison of Viral Load Results and Findings of Screening Criteria 37
Table 6: Variate Analysis for Viral Load Response 38
Table 7: Hazard for ART Failure by Time Point 40

Table of Figures

Figure 1. Conceptual Framework for Assessing ART Treatment Outcomes 21
Figure 2: Box Plot for Median Weight Trends by Gender 30
Figure 3: Individual Patient CD4 Counts and Trend Line 33
Figure 4: Results for Treatment Failure Based on Screening Criteria 35
Figure 5: Instantaneous Hazards for ART Failure based on Screening Criteria 36
Figure 6: Individual Patient Viral Load Counts and Trend Line 36
Figure 7: Instantaneous Hazards for ART Failure based on Viral Load Monitoring 39
Figure 8: Kaplan-Meier Estimate for Viral Suppression on ART 41
Figure 9: Kaplan Meier Estimate for Retaining Patients in ART Program at KCGH 42
Figure 10: Kaplan-Meier Estimates for Risk of Attrition by Death and Loss to Follow Up 43

Abstract

Background: The goal of ART therapy is sustained viral load suppression with good immunological and clinical response. This optimal response to therapy results in the prevention of emergent ART drug-resistant mutations, decrease morbidity, and AIDS-related mortality and sustained retention on ART. Kenya, like most countries in Sub-Saharan Africa, has scaled-up the use of ART and is currently implementing a "Test and Treat" strategy in which any client identified and confirmed with an HIV diagnosis is initiated ART. Few studies have been carried out to ascertain the response of HIV patients initiating treatment in resource-limited settings. Moreover, it has been demonstrated that a certain proportion of patients fail to adequately respond to therapy and therefore require therapy modification.

Aim: To assess treatment outcomes and calculate retention of HIV infected adult patients' (15 years and above) initiating ART at Kakamega County General Hospital. The primary study outcome was the treatment outcome of patients-initiated ART two to three years prior to the study; while, the role of WHO criteria for screening treatment failure was assessed as a secondary outcome.

Methods: This was a retrospective cohort study in which patients initiating ART between June 2014 and March 2015 were followed up until they were censored or study closed in August 2017. 284 patients were enrolled in the study after accurately matching information in their clinic files and the electronic medical record. Data were collected from patient records using a chart abstraction tool and transferred to an Access database from where the cleaning and validation of entries were done. Data from Access was transferred to STATA 15.1 for analysis. Descriptive statistics and inferential statistics were then performed to answer the research questions.

Results: More female patients (57%) initiated ART. Nearly all patients started ART based on CD4 count, 93%. About 10% of those starting ART had severe (WHO stage 3 or 4) OI. TB was the commonest severe OI, followed by Kaposi Sarcoma, diarrhea and meningitis at 7%, 2.5%, and 2.1% respectively. Overall, only 15% of patients starting ART had an OI. TDF based regimen was the preferred ART regimen initiated to 77% of the patients. The initiation of ART was associated with a 2-fold reduction in the incidence of OIs. The majority of patients had good CD4 count increases on initiating ART, 97.9% over the follow-up period. Patients with recurrent OIs were less likely to have suboptimal CD4 counts. VL was detectable in 17% of patients. Up to 80% of clients failing ART were identified clinically. Retention in the ART clinic was 89% and this was similar across ages and gender. The death of patients accounted for 55% attrition at an incidence rate of 1.9 per 1000 person-months of follow-up.

Conclusion and Recommendation: Initiating patients on ART has phenomenal clinical, immunological and virological outcomes as it has already been demonstrated the world over. However, there is still a number of patients who continue to fail therapy, thus necessitating a change to a more expensive drug regimen. Hence, clinical surveillance for ART failure should be strengthened to promptly recognize patients who require additional clinical and psychosocial care for the betterment of their health and program outcomes.

LIST OF ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immuno-deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Azidothymidine (Zidovudine)
c-ART	Combination ART
CCC	Comprehensive Clinical Care (Center) for HIV
CCR5	Chemokine receptor type 5
CD4	Cluster of Differentiation 4 cells
D4T	Stavudine
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immuno-deficiency Virus
KCGH	Kakamega County General Hospital
LPV	Lopinavir
NASCOP	National AIDS and STI Control Program
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PI	Protease Inhibitor
R4	Also, CXCR4 - Chemokine receptor type 4
TDF	Tenofovir
TF	Treatment Failure
UNAIDS	The Joint United Nations Programme on HIV/AIDS
VL	Viral Load
WHO	World Health Organization

Operational Definition of Terms

Clinical response consists of the observable, reportable and measurable parameters such as height, weight, body mass index, the occurrence of opportunistic infections; improvement, worsening, the emergence or the disappearance of diseases and/or conditions that are related with HIV; including adherence to therapy. Good response implies an improvement in the health of an HIV infected person, while poor response, a deterioration in progress.

First line Antiretroviral Therapy is the first antiretroviral regime given to HIV naïve patients, i.e. patients who have never been given any form of the antiretroviral drug. This is also called Highly Active Antiretroviral Therapy (HAART) first line regime.

Immunological response is used to describe the progression of HIV in the form of CD4 count. A good immunologic response is qualified by the sustained increase in CD4 over a given period, usually at least 100 – 150 per year and more so in the initial years of therapy.

Opportunistic infections are those diseases such as tuberculosis, pneumonia, meningitis, oral thrush that attack HIV immune-compromised persons who have a low immunity more frequently and severely than in a non-HIV infected individual.

Therapy – word therapy is used interchangeably with antiretroviral therapy.

Treatment failure occurs when a patient who has been taking ART for at least 6 months fails to show the good clinical, immunologic or virological response expected. Such a patient may experience the stagnation of the body immune cells or a worsening.

Virological response is a sustained viral load suppression in a patient who has been on ART for at least six months. The opposite would be a virological failure, in which such a patient's viral load is no longer detectable.

CHAPTER ONE

A DESCRIPTION OF THE STUDY

1.1. Introduction

Human Immunodeficiency Virus (HIV) remains a virus of global health focus (1). There are 70 million people who are infected with the virus, and about 35 million people have lost their lives since 1981 (2) because of it. As at December 2015, about 37 million people were living with HIV the world over. According to Global Health Observatory (GHO) data of 2018, nearly one in every 25 adults in Sub-Saharan Africa lives with HIV, which contributes to 70 percent of people living with the disease. An HIV infection is usually diagnosed through blood tests, but the infection has no cure.

Effective treatment with antiretroviral drugs can control the virus so that people with HIV can enjoy healthy and productive lives (3). In 2011, more than eight million people living with HIV were receiving antiretroviral therapy (ART) in low and middle-income countries (4); this number was almost double (15 million) at the end of 2015 (1). Attaining and sustaining viral suppression is the goal of antiretroviral therapy (ART); which is the optimal response to therapy, that results in the avoidance of the emergence of drug resistance mutations (5).

Treatment guidelines in resource- rich settings recommend VL monitoring every 3–6 months (6). However, in settings like Sub-Saharan Africa and India, treatment efficacy has until recently been monitored through immunological markers like CD4+ T cell count, (7), and clinically. Nonetheless, short-term outcomes of ART in resource-constrained settings are comparable to those in resource-rich settings (8,9). Possible setbacks result from the lack of greater than 95% adherence to therapy, drug-drug interactions, drug-food interactions,

immunological factors, possible undiagnosed opportunistic infections, and the nature of patient-physician engagement (10–13).

1.1.1. HIV Infection and ART Status in Kenya

The HIV estimates report of 2014 (14) ranked Kenya among the high burden countries in Africa with a total of 1, 206, 968 adults and 159, 700 children living with HIV. As at the end of 2015, the burden had increased to 1.5 million Kenyans living with HIV (15). Among the People Living with HIV (PLWH) in Kenya, (14) the AIDS survey of 2012 established that around 89% were going to an HIV clinic; but, only 77% of the PLWH were aware of their HIV status. ART coverage among those who already knew their HIV status was about 85% (15). Yet, among clients on ART in Kenya, viral suppression (a function of retention and adherence to ART) was about 60% (16,17). In 2016, Kenya adopted universal ART coverage for PLWH (18). Use of first-line ART has now been scaled-up in Kenya. Nevertheless, there is a paucity of data on the course of disease progression among PLWH for such therapies (19). Yet some patients on ART require therapy modification due to failed therapy manifested as a sub-optimal virologic response, poor CD4 count response and/or re-emergence of opportunistic infections (20).

Kenya has the second largest ART country program after South Africa with about 900,000 people on antiretroviral therapy (21). Large numbers of patients have been put on first-line antiretroviral therapy in the past five years in a bid to fast-track the provision and accessibility of these drugs (21,22). Consequently, many deaths and HIV related infections have been averted (23). In a study on ART resistance conducted in Coastal Kenya (24), less than 5.0% of clients were found to have drug-resistant HIV. However, another study carried out in Western Kenya established a drug resistance of 9.2% (25). Clearly, as more people are

put on ART, there is also an increasing number of patients failing therapy (21). Unfortunately, ART drug resistance has been shown to compromise the effectiveness of standard antiretroviral regimens (24,26–28).

1.2. Rationale for ART

First-line ART is given to HIV infected clients for five main reasons (20): First, *clinically,* where ART has been shown to prolong life and improve the quality of life (29). Secondly, *virologically* to achieve the greatest reduction in viral load (preferably less than 50 c/ml) for as long as possible to halt disease progression or delay progression (30). Thirdly, *immunologically* ART reconstitutes the immunity that is both quantitative (increases CD4 cell count to normal range) and enhances the pathogen-specific immune response (22,31). Fourthly, *therapeutically, to* focus on a rational selection of drugs to meet clinical, virologic and immune goals while maintaining future treatment options, limiting drug toxicity and facilitating adherence (32); and *epidemiologically to attain a* reduction in HIV transmission (33).

1.3. Problem Statement

Although most patients are on first-line ART, it is expected that the demand for second-line regimens will increase over time. This is the case despite the gains made from potent first-line ART (34). Several studies have suggested that some patients on ART fail therapy (19,25). In a retrospective cohort study in Ethiopia, 4.1% of people living with HIV (PLWH) on ART had failed therapy (35); whereas, in a cross-sectional study conducted in Kenya 6.9% failed; which was similar to a European cohort that reported 10.0% failure (25,27). Among those failing first-line, about 46% of them went on to fail second-line ART due to increased side-effects, drug resistance and treatment fatigue (36). Moreover, they had increased morbidity

and mortality (35). Despite the capacity to promptly identify ART treatment failure through clinical and immunological criteria (29,37), "better evidence and more data are required before more specific recommendations can be made, particularly for resource-limited settings where routine viral load monitoring is not routinely available". Early identification and prevention of treatment failure will help sustain the effectiveness of ART and preserve treatment options (35,38,39).

1.4. Study Aim and Objectives

The aim of this study was to assess treatment outcomes and calculate retention on first-line ART among adults (15 years and above) living with HIV initiated on first-line antiretroviral therapy at Kakamega County General Hospital (KCGH) between July 2014 and March 2015. By using and documenting basic criteria for monitoring response on ART treatment, obtained results provide an insight on HIV disease progression amongst patients on ART, and, the retention on therapy. Predictors for disease progression are highlighted and recommendations made on how resource-poor settings may improve the quality of care and follow up of ART patients.

The specific objectives of the present study were:

- To measure the virologic response to therapy among HIV infected patients initiated first-line ART aged 15 years and above (adults) between July 2014 and March 2015 at KCGH;
- To determine the immunologic response to therapy among adults living with HIV initiated first-line ART between July 2014 and March 2015 at KCGH;
- To assess clinical response to antiretroviral therapy among adults living with HIV initiated first-line ART between July 2014 and March 2015 at KCGH, and,

- To calculate the retention of adults living with HIV initiated first-line ART between July 2014 and March 2015 at KCGH.

1.5. Study Setting

The study was conducted at Kakamega County General Hospital (KCGH). KCGH is situated in Western Kenya, Kakamega County, Lurambi Sub-County. It is the referral center of the county. KCGH has a catchment population of 170,515 according to their Annual Work Plan 2 of 2014-15. The hospital provides both curative and preventive services since it became a fully-fledged hospital in 2007, (40,41) offering general outpatient and inpatient care, maternal and child health services, immunization, sexual and reproductive health, minor surgical care, basic laboratory services, and HIV and Tuberculosis (TB) services. On average, the hospital serves about 5000 patients per month. It has an in-patient bed capacity of 449. The HIV Comprehensive Care Centre (CCC) is sandwiched between the female and paediatric wards, and, the continuous medical education hall. At the time of the study, there were about 3000 adolescents and adults on ART.

Monitoring of treatment response at KCGH is done through three prescribed avenues. People living with HIV (PLWH) on ART are assessed clinically, through CD4 and VL monitoring. Despite challenges accessing VL testing, secondary networks have been set up and are used. Through sample networking for VL testing, at least all PLWH initiated ART have a chance to have their VL samples collected and tested within six months. That is why it was possible to assess the clinical, immunological and virological status and progression (treatment response) of the clients on ART in resource-limited settings like KCGH; thus, making it possible to compare findings to those in resource-rich settings (8,9).

CHAPTER TWO

LITERATURE REVIEW

2.1 Introduction

The future of Kenya towards the fight of HIV mainly rests on efforts towards preventing new infections among millions of young people who will become sexually active in the next few years (42). Although fewer young people are becoming infected in Kenya than at earlier stages of the pandemic (34,43), the disease represents a continuing threat to young people in Kenya especially those 20 – 24-year-old people among whom more than1 person in 25 (4.2%) is already infected when they enter young adulthood (44). There is the need to continue providing antiretroviral therapy (ART) as prevention (treatment as prevention) (45–47).

2.2 Initiation of ART

Initiation of ART in Kenya has evolved over time. According to the Kenya Brief on ART, adults were initiated ART if they had CD4 cell counts ≤ 200 cells / mm^3 between years 2002 and 2005; ≤ 200 cells / mm^3 or a World Health Organization (WHO) clinical stage 4, or WHO stage 3 dependent on CD4 ≤ 350 cells / mm^3 following national guidelines of 2005 through 2007 (48–50). From November 2007 to October 2010, ART was initiated for any adult with a WHO stage 3 or 4 and/or CD4 ≤ 250 cells / mm^3, the 250 cells / mm^3 was revised upward to ≤ 350 cells / mm^3 in October 2010 (7,51,52). From June 2014 to June 2016, ART was initiated to all clients with a CD4 ≤ 500 cells / mm^3 or with WHO stage 3 or 4, or to pregnant women, or to those in a serodiscordant relationship (23,47). Since July 2016, every person diagnosed with HIV in Kenya is now being initiated ART (1,22,53).

2.2.1 Choice of ART

A cross-sectional study conducted in Cameroon (54) confirmed that quality pre-qualified antiretroviral drugs (ARVs) that meet international standards, and that are effective are given to patients. Similarly, there is evidence of good practice in packaging and supply of ARVs (49) with a combination of three or more antiretroviral regimens used. By selecting a combination of nucleoside analogue, reverse transcriptase inhibitors (NRTI) and one non-nucleoside analogue reverse transcriptase inhibitor (NNRTI) and/or protease inhibitor (PI) or integrase inhibitor (INI), highly active antiretroviral therapy (HAART) which has been in use since the mid-1990s to manage HIV infections is achieved (54–56). HAART is also referred to as combination antiretroviral therapy (cART) (57–59).

The use of ART in Kenya has continually changed in line with the World Health Organization (WHO) recommendations, and the country readiness to adopt and implement new findings and interventions for HIV prevention, care, and treatment has been good (52). For instance, in 2009, in Kenya "55% of adults (15-year old and above) were on stavudine (D4T), lamivudine (3TC) and nevirapine (NVP) combination i.e. D4T/3TC/NVP. 17.1% were on zidovudine (AZT), 3TC and NVP. 12% on D4T/3TC and efavirenz (EFV) i.e. D4T/3TC/EFV. 9.2% on AZT/3TC/EFV, 3.6% on tenofovir (TDF) and 3TC/NVP i.e. TDF/3TC/NVP, 2.5% were on TDF/3TC/EFV while the rest of adults, mainly prevention of mother to child transmission of HIV patients were on non-standard dual therapy 3TC/AZT" (34).

Over the years, the proportion of PLWH initiated on various ART regimes in resource-limited settings has changed remarkably because of changing evidence and HIV financing (1,52,59). Nevertheless, Kenya has kept pace with WHO recommendations for changes in ART guidelines (14). The preferred ARV regime in Kenya as at 2011 was TDF/3TC/EFV with NVP substituting EFV in alternative regimes and/or AZT for TDF since the fourth Kenyan ART guideline was rolled out (60,61). However, the choice of ART drug at initiation sometimes does not change as

fast despite new evidence. For instance (48,52), D4T based regimen was phased out due to adverse drug events in 2006, but six years later, the median percentage of patients initiated on D4T-based regimen in two facilities in Kenya and Uganda was 7% (IQR: 3%-17%) and 0% (IQR: 0%-2%) respectively, and 4% (IQR: 2%-9%) for Zambia in 2010-2011. D4T was phased-out due to its toxicities such as lactic acidosis, lipodystrophy and peripheral neuropathy negatively affecting the quality of life (52,62).

Also, factors such as the cost of therapy have been shown to influence the availability and hence the choice of ART. In 2010, the Clinton Health Access Initiative expressed that AZT based and TDF based regimes were about 80% and 250% more costly than D4T based regimen annually (63). The cost of AZT and TDF based regimes progressively went down to four and five-fold for AZT and TDF based regimes in 2014 (64). ART optimization is on the rise and private facilities were found to be more likely to prescribe TDF-based regimes in Uganda, unlike AZT-based regimes which were preferred in public facilities citing lack of explicit national guidelines and policy statements on TDF (65), especially, where clients required drug substitution.

In a study in Uganda, the odds of a client with a baseline WHO stage IV was more than twice the odds of a client not being initiated a TDF-based therapy as opposed to those classified as stage I at initiation (52). Nearly 11% of patients in a cohort study conducted in Abidjan experienced ART stock outs (66) necessitating ART discontinuation or substitution. The discontinuation of ART regimen increases the risk of interrupting care or death for nearly three-fold compared to those retained on ART (AHR 2.83; 95% CI, 1.25 – 6.44) (66–68). High ART workloads, staffing levels, and competencies have also been shown to influence the choice of ART initiated to PLWH (69). Facilities with doctors were more likely to initiate a TDF-based therapy in Uganda (OR: 2.86; 95% CI: 1.48-5.51) (52). Moreover, clients with co-infections such as tuberculosis are more likely to be initiated EFV-based therapy compared to those with hepatitis TDF-based regimes. On the other hand, pregnant women were more likely to be

initiated on NVP based regimes (60).

2.3 Monitoring HIV Specific Response on ART

Clinical assessment and laboratory markers are used to monitor the progress of HIV infection (70). Clinical monitoring involves using the WHO staging system in which HIV infection is classified based on the presence of related signs and symptoms *ibid*. Initiation and monitoring of progress on ART have principally relied on clinical (WHO staging) and immunological (i.e. CD4 county) evaluations (48). In 2010, the WHO recommended the use of viral load (VL) monitoring every 6 months to assess viraemia and to confirm suspected ART treatment failure (virological failure) (7). Since 2013, VL has been considered the preferred monitoring and diagnosis approach (22,61) globally (WHO, 2013).

2.3.1 Clinical Monitoring of Clients on ART

Clinical response to first-line ART is evidenced by the absence of WHO stage three or four opportunistic infections (OIs) together with a reduction of papular pruritic eruptions at least six months after starting ART (20). The WHO HIV Clinical staging has been phenomenal in monitoring HIV infections in resource-limited settings since it does not carry any additional cost implications but has been shown to have low sensitivity in identifying treatment failure (71,72). WHO stage 3 represents advanced HIV while stage 4 represents acquired immunodeficiency syndrome (AIDS) (72).

WHO stage 3 conditions include unexplained weight loss (over 10% of presumed or measured body weight), unexplained chronic gastrointestinal, respiratory, oral, and urogenital infections as well as atypical central nervous system infections among others (60). WHO stage 4 conditions include HIV wasting syndrome, extensive and non-common infections, malignancies and disorders of the central nervous system following HIV infection *ibid*. WHO stage 2 comprises none of the severe bacterial infections of the skin and upper

respiratory infections (7,48,53); WHO stage 1 PLWH will typically have no symptom except for lymphadenopathy. WHO staging is done each time a client visits an ART clinic (18).

2.3.2 Laboratory Monitoring of Clients on ART

In resource-constrained settings like Sub- Saharan Africa and India, treatment efficacy was typically monitored through CD4+ T cell count, (7) conducted every 3-6 months to track HIV disease progression (73,74). Not until 2016, treatment guidelines for resource-rich settings principally recommended VL monitoring every 3–6 months (1,6,47). In Kenya, CD4 monitoring was recommended at the start of ART and every six months thereafter (60). Targeted VL monitoring was recommended in case of suspected clinical or immunological treatment failure; otherwise, PLWH would have a VL test done prior to initiating ART, six months later and thereafter yearly *ibid*. Targeted VL monitoring was pegged on the scarcity of funding particularly of international origin as in Kenya, over 50% of funds used to fight HIV are international (75).

However, with changes in ART guidelines in Kenya in 2016, HIV specific laboratory monitoring calls for CD4 cell counts at the start of ART and subsequently only in instances of suspected treatment failure (15,18,43). Similarly, PLWH recording CD4 cell counts less than or equal to 100 cells / mm^3 should do a serum cryptococcal antigen test (sCRAG) to diagnose or exclude Cryptococcus meningitis (CM) prior to starting ART (15,47). Clients on CM prophylaxis should have CD4 testing semiannually until they achieve greater than 100 cells/mm^3 on two consecutive occasions six months apart *ibid*. VL monitoring, an HIV type 1 ribonucleic acid (HIV-1 RNA) test recommendation continues to be at the initiation of ART, then six months later and yearly should the client report less than 1000 copies/ml (47,60).

2.4 Response to ART

The efficacy of ART is paramount to the effective management of HIV infection (13,57).

While the combination of ART regimes have been proven effective in developed countries, the effectiveness of prolonged ART is not homogeneous in developing countries, probably due to rampant suboptimal adherence, different HIV strains and drug-resistant strains (10,24,25,59,76).

2.4.1 Clinical Response to ART

Substantial reduction in the risk of new opportunistic infections and in mortality has been documented following ART (13,39,58,77). However, without ART, HIV infection attacks the immunity increasing vulnerability to OIs (31,78). Many studies have documented a marked reduction in mortality and morbidity among PLWH initiated on ART, especially, in the first year of therapy (13,31,35,79,80). A meta-regression analysis on these studies by Low and team revealed the greatest reduction of OIs in oral candidiasis, cerebral toxoplasmosis and pneumocystis pneumonia (PCP); and, equivocal response with cryptococcal meningitis, herpes zoster, Kaposi sarcoma, esophageal candidiasis, and genital ulcer disease (13).

The risk of unspecified tuberculosis (TB) decreased by over 55%, by 38% for pulmonary TB, and by 43% for extra-pulmonary TB on initiating ART (13,81,82). However, in a prospective cohort study, oral fungal infections were observed to quickly resolve with cART unlike oral hairy leukoplakia; enlarged parotid glands, melanotic hyperpigmentation, and oral Kaposi sarcoma were more persistent and slowly responded to ART (83); no improvement was reported in the five months of follow up for linear gingival erythema. Emergence or persistence of WHO stages 3 or 4 clinical conditions, and/or papular pruritic eruptions at least six months after initiating ART suggests treatment failure (20,37,84,85).

2.4.2 Immunological Response to ART

Without censoring the progression of HIV infection, depending on the viral load, CD4 cell count will usually decline at a rate ranging between 30 and 100 cells / µl per year, increasing the person's susceptibility to OIs, and mortality (70,86–88). According to several clinical

trials and cohort studies, CD4 count is used for assessing immunologic response to ART and in deciding if OI prophylaxis can be discontinued (89). In a prospective study conducted in Nigeria (90), out of 113 PLWH, 105 clients had substantially higher CD4 counts than pretreatment level ($p < 0.001$); the remaining 8 clients had their CD4 counts reducing or remaining the same post ART initiation.

CD4 response in the first 3 – 4 months of initiating combined ART is expected to increase with viral load suppression of 30 – 70/mm^3 in the first 4 months, then 100 – 150/mm^3 per year (91,92). The total increase in CD4 count is often limited to 300 – 400/mm^3 above nadir (20). Similar findings were observed in a Swiss cohort study in which a rise in CD4 counts of between 50 and 150 cells / mm^3 was recorded in the first year of therapy and beyond until a steady level was reached; the highest rise in CD4 cell counts was noted in the first three months of therapy (73).

2.4.3 Virological Response to ART

Initial infection with HIV results in a rapid rise in the levels of the viral load usually greater than 100, 000 copies/ml; which declines after 3 to 6 months after the primary infection and maintains a steady state thereafter (93,94). In a cohort initiated ART, HIV viraemia reduced to 1.8 log copies/ml (10,58) within 3 months of therapy. Complete viral suppression in patients on ART results in immunological response evidenced by an increase in CD4+ T-cell count. Furthermore, early and good immunological response to antiretroviral therapy portends good clinical outcomes (19,20,26,85,95).

Viral load monitoring is a critical test for ART treatment response (96). Meta-analyses of clinical trials revealed that the least significant rise in VL was three-fold although the optimal response to ART is persistent once a patient reaches undetectable VL levels (97).

However, it is not uncommon to find successfully treated patients with viral blips (transient detectable viral loads) (97–99) which have an unsettled role in predicting virologic failure. Individuals without resistance strains of HIV who have been adherent to their ART regime should achieve viral suppression within 8 to 24 weeks of initiating therapy (20,22,30,100). In contrast (101), clients with baseline viral loads greater than 100, 000 copies/ml may have a slower rate of viral suppression.

2.5 Treatment Failure

Treatment failure is the progression of HIV disease despite using ART for at least six months. Therapy failure is demonstrated clinically as emergence or recurrence of WHO stage 3 or 4 and/or papular pruritic eruptions; or immunologic with CD4 cell count dropping or not responding appropriately; or virologic rebound with detectable viral load (6,31,35). The concern with ART failure is that it leads to switching to more costly regimes (102). Hence, the decision on when to switch from first to second-line therapy continues to be a critical step in ART management; however, as programs evolve, evidence change and more patients continue on ART (15,29,103). These failures (clinical, immunological or virological) may occur in isolation or in combination due to poor ART adherence, or sub-optimal ART dosing over a duration of time resulting in a cascade of viral failure followed by an immunological lack of response to therapy and finally, clinical manifestations of AIDS-related illnesses (6,20,28,54,104).

2.6.1 Criteria for Identifying ART Failure

WHO recommends clinical and immunological criteria for monitoring ART failure (37,60,102). Criteria for screening ART failure includes clinical, immunological and virological markers administered to patients who have been on therapy for at least 6 months (105). Clinical failure is defined by the emergence of new or recurrent WHO stage 3

or 4 conditions or pruritic papular eruptions; while immunological failure is characterized by a drop in CD4 cell count or percentage in baseline levels or a decline of more than 30% in CD4 count or percentage (29,60). In patients who have received more than 12 months of ART, immunological failure may be CD4 count increase < 51 CD4 cells/µl or CD4 cell counts that persistently remain below 100 cells/µl on the other hand, VL above 1000 at least six months after initiating ART is considered virological failure (102,105).

However, monitoring failure immunologically and clinically has been shown not to provide accurate results. For this reason, VL monitoring is recommended as the preferred approach (6,61,84,85,102). VL monitoring differentiates treatment failure from non-adherence to therapy hence its use as a determinant for assessing the risk of HIV transmission in the populations (32,61,106). In contrast, a trial comparing the utilization of VL monitoring with the criteria for ART failure did not show any difference in mortality, the incidence of clinical failures, switching to second-line or presence of drug resistance (107).

2.6.2 Factors Associated with ART Treatment Failure

There are determinants that influence how long viral suppression could be sustained.

2.6.2.1 Virus Related Factors

Variations in the HIV genome have been associated with varied rates of HIV progression (89). HIV variants with a deleted *nef* gene show a slow progression while HIV strains (the X4 virus also called the syncytia-inducing virus) that use CXCR4 proteins as entry co-receptors progress rapidly *ibid*. Drug-resistant mutations affect the efficiency of virus replication (viral fitness) with those with decreased viral fitness having slower immunodeficiency than the wild-type (20,89). Similarly, clients with HIV type 1 infections progress faster than those with type 2 (74,91). Clients with a high baseline viral load greater

than 1 million copies/ml have increased chances of failure (108). On the other hand, patients starting therapy with a low detectable viral load below 1000 copies/ml may have notable 'return to mean' episodes also referred to as virologic blips nonrelated to adherence problems or resistance to therapy (98,99) which is of limited clinical significance.

2.6.2.2 Drug-Related Factors

In a Canadian cohort study, drug resistance was detected in 25% of clients on cART (93). In the Canadian study, like several other studies, drug resistance (DR) mutations were common in clients who started therapy with high baseline plasma viral loads; or, had prior exposure to NNRTIs (multivariate HR 1.84, p=.001) (26,93,106,109). Similarly, in a case-control study conducted in South Africa, treatment interruption due to non-adherence increased the odds of failure 8 times and increased 9 times in those who used NVP based PMTCT regimen (110).

Certain ART regimes are associated with high side-effects and toxicities and have recorded high rates of discontinuation or regimen switching these include NVP-based therapy at 60.7% and D4T based regimes at 39.3%. However, 3TC has been found to be well tolerated with no toxicities (111). Buck established that the average time for switching to first-line was 2 months and 16 months for second-line regimes. Furthermore, patients on didanosine-based therapy failed more than those on 3TC-based regimes (112). Among ART-experienced patients with treatment failure, NNRTI resistance mutations 184V were seen in 62.3% of patients; 103N in 48.1%; 190 A/S in 11.7%; and, L90M in 11.7% (9,113). A sizeable 12% of those who failed therapy had thymidine analogue mutations (TAMs) but only 1% had more than 1 TAM; conferring a 95% chance of treatment success among naïve clients on ART compared to 84% in experienced patients (113).

Regimen potency has been identified as an important factor for treatment success

(20,114,115). Boosted protease inhibitor and non-nucleoside reverse transcriptase inhibitor (NNRTI) containing ART were shown to have the highest potency of 64% compared to nucleoside reverse transcriptase inhibitors (NRTIs) and non-boosted protease inhibitors at 54% and 43% respectively with viral load < 50 copies /ml (20). CD4 increase was highest with protease inhibitors followed by NNRTIs and eventually NRTIs (20,115). The highest risk of resistance to a PI-based regimen is with virologic failure in the face of good adherence (20).

Bartlett and Gallant conducted a systematic review of literature and conference presentations of clinical trials on treatment-naive patients from 1994 to July 2006. The two researchers covered 53 trials and sampled 14,264 participants. The percentage of patients who achieved a viral load < 50 copies/ml at 48 weeks increased with time and by ARV drug and class. In 1998, viral load increased to 41%; to 50% in the year 1999–2000, to 56% in 2001-2002 and, to 64% in 2003-2004. Increases in viral load and CD4 count NNRTI containing regimes was 64% and 173 copies/µl respectively. Boosted PIs with ritonavir (PI/r) was 64% and 200 copies/µl; while those who were on triple NRTIs reported 54% and 161 copies/µl; and, those on unboosted PIs had 43% increase in viral load and 179 copies/µl of CD4 cells. Those on boosted PIs i.e. PI/r combination had statistically significant (P<0.05) better immunological response.

Finally, particular drug-drug and drug-food interaction have been shown to negate the effect of ART by inhibiting the optimal response of some ART components. The use of antifungals like ketoconazole together with nevirapine inhibit liver action, thus increasing adverse reactions and reducing the active components of the drugs (12,20,116).

2.6.2.3 Host-Related Factors

Adherence to ART of greater than 95% to the prescribed doses contributes to at least 80%

probability of viral suppression at 24 weeks on ART (18,91,117); poor adherence predicts virologic failure but not necessarily resistance to ART (118). However, imperfect adherence as has been seen in drug holidays are a threat to treatment success leading to treatment failure and consequently drug resistance because drug concentrations fall within a mutation-selection window or sub-optimal levels allowing the replication of the virus in the wake of therapy (119).

A retrospective cohort study conducted in Ethiopia found that treatment failure was more likely to occur in PLWH with poor adherence and those who delayed starting ART until their CD4 count was lower than 100 cells / mm^3 (35). Young age and the presence of an active WHO stage 3 or 4 OI such as tuberculosis increased the likelihood of failure (28). A cross-sectional study in Colombia established that advanced HIV disease and CD4 cell count below 200 cells/mm^3 were associated with primary resistance to ART, p=0.0040 respectively (113). Patients beginning ART with very low CD4 counts (≤200 cell/mm^3) or elderly patients tend to have a poor increase in their CD4 counts despite achieving viral suppression (91,120).

Substance abuse such as excessive alcohol intake among PLWH on ART is a contributor to non-adherence (12,121). Patients hazardously abusing a substance, are at risk of scaffolded or 'triply' conditions of HIV and psychiatric comorbidities (122). Community peer support, a good physician-client relationship, and similar social support such as from family members, has a positive effect on viral suppression (11,76). Conversely, some cultural predispositions and family circumstances have been found to affect the attitudes of clients towards ART and their adherence (45). Choosing not to disclose was found to be a coping mechanism and was not necessarily linked to adverse psychological effects or treatment success (17). Children and adolescents undergoing enhanced adherence counseling (EAC)

were seen to achieve better viral suppression (10).

In a retrospective cohort conducted in Thailand, adherence below 95% and clients below the age of 40 years were independent predictors for virologic failure among clients on ART (85). However, in a cohort study conducted in Kenya, HIV infected patients older than 64 years of age were more likely to die and had faster disease progression due to a less robust CD4 cell response to ART and higher non-AIDS related morbidities (123) compared to the youth aged between 15 and 24 years. The survival time for the elderly patients in the Kenya study was 5.0, [95% CI (4.0 – 6.2)] and for the youth 11.0, [95% CI (10.7 – 11.7)] respectively; no difference was reported between males and females. In an exploratory descriptive study done in Peru (116), virologic failure was recorded at a median age of 35 years.

PLWH with high interleukin 6 (IL-6) and D-dimer have been shown to progress faster and even die earlier due to end-organ damage that does not seem to return to normal even with ART (89). Various human leukocyte antigen alleles appear to determine rates of viral progression with individuals with CCR5 variants having a slower progression of HIV (60). Malnutrition, especially among children, reduces the bioavailability of certain drugs like EFV and LPV and increases NVP (124). Reduced bioavailability of drugs decreases their efficacy, while toxicity and side effects are associated with an increased bioavailability *ibid*.

Finally, viral blips, severe immunological status (such as very low CD4 counts at baseline) and immunological discordancy (in which the client's CD4 are non-responsive in the presence of good virological and clinical picture) are also critical precursors of poor treatment response (22,104,125). In a Swiss cohort study, 71% change of ART regimen was in clients with low CD4 counts (baseline median of 105 cells/ml) and in those with follow-up CD4 counts below 201 cells/ml; a significant 8% change in ART regimen was noted to

occur within the first 12 weeks of starting therapy (30). Globally, between 20% and 40% of clients initiating ART have a discordant response to therapy (126). Unlike clients with concordant response to therapy, discordant responses 3 to 9 months after initiation of ART was associated with a short time to an OI or death (104,126).

2.7 Retention of Clients on ART

In a systematic review and meta-analysis conducted in low and middle-income countries, 78%, 71%, and 69% of patients were retained on therapy at 12, 24, and 36 months following initiation of ART (127). A large number of studies in Sub-Saharan Africa have identified high attrition on ART (128–130). PLWH not retained on ART will often be among those who die, stop follow up or discontinue ART or self-transfer to other programs (131). Attrition is happening notwithstanding knowledge that the greatest impacts of ART accrue with lifelong uninterrupted adherence to therapy, without which treatment failure ensues, drug resistance emerges, and there is an increase in morbidity and mortality (132).

Attrition of clients on ART is the loss of these patients from the ART program; whereas retention on ART regards patients staying alive on therapy and active on follow up at the ART clinic (84). ART attrition is a function of patients on ART dying, becoming lost to follow up or discontinuing ART, including transfer outs in attrition and giving a crude status *ibid*; lost to follow up is defined as a client not honouring their ARV pick up for more than 90 days (84,133). High attrition rates are associated with high rates of ART failure (134,135). Possible predictors of attrition on ART include high costs incurred by patients to get care, unacceptable models for ART provision, extremes CD4 counts, male patients, and adverse drug events (18,71,85,129,136).

The ability to retain patients for treatment remains limited (84). For instance, African ART programs reported, on average, higher failure and attrition rates than Latin American and

Asian programs in 2014 despite the need for these programs to ensure that at least 90% of "all people diagnosed with HIV infection receive sustained ART" and are retained in the program by the year 2020 (23). Pressing evidence points to the need to optimize ART goals by relooking and fostering aspects that identify HIV positive clients and get them referred and enrolled in an HIV clinic (linkage), engaging and consistently following them up (retention), as well as providing comprehensive and integrated services (137,138). However, HIV is recognized as a single but complex infection with a multitude of potential socio-economic factors that should be sought after and addressed to minimize disparities in retention occasioned by limited health insurance; stigma, violence and gender disparities, difficulties and challenges due to geographic location, steep gradients in health literacy, unemployment, poverty and loss of income (130,133).

2.8. Conceptual Framework for the Present Study

Initiating ART among HIV infected patients coupled with optimal adherence to therapy results in a decrease in viral load and a concurrent increase in CD4 counts, a reduction in OIs and improved quality of life. Good response to ART is thus associated with prolonged life and maintained therapy options (Figure 1); such a patient is said to have ART treatment success. On the contrary, the patients who continue to experience an increase in VL, a drop in CD4 counts, have recurrent and/or emergent OIs after at least six months of ART are said to fail therapy. Patients failing ART will experience deteriorating health, will often require a change of their regime and are more likely to die. Hence, poor ART treatment outcomes are as a result of therapy failure.

2.8 Present Study's Conceptual Framework

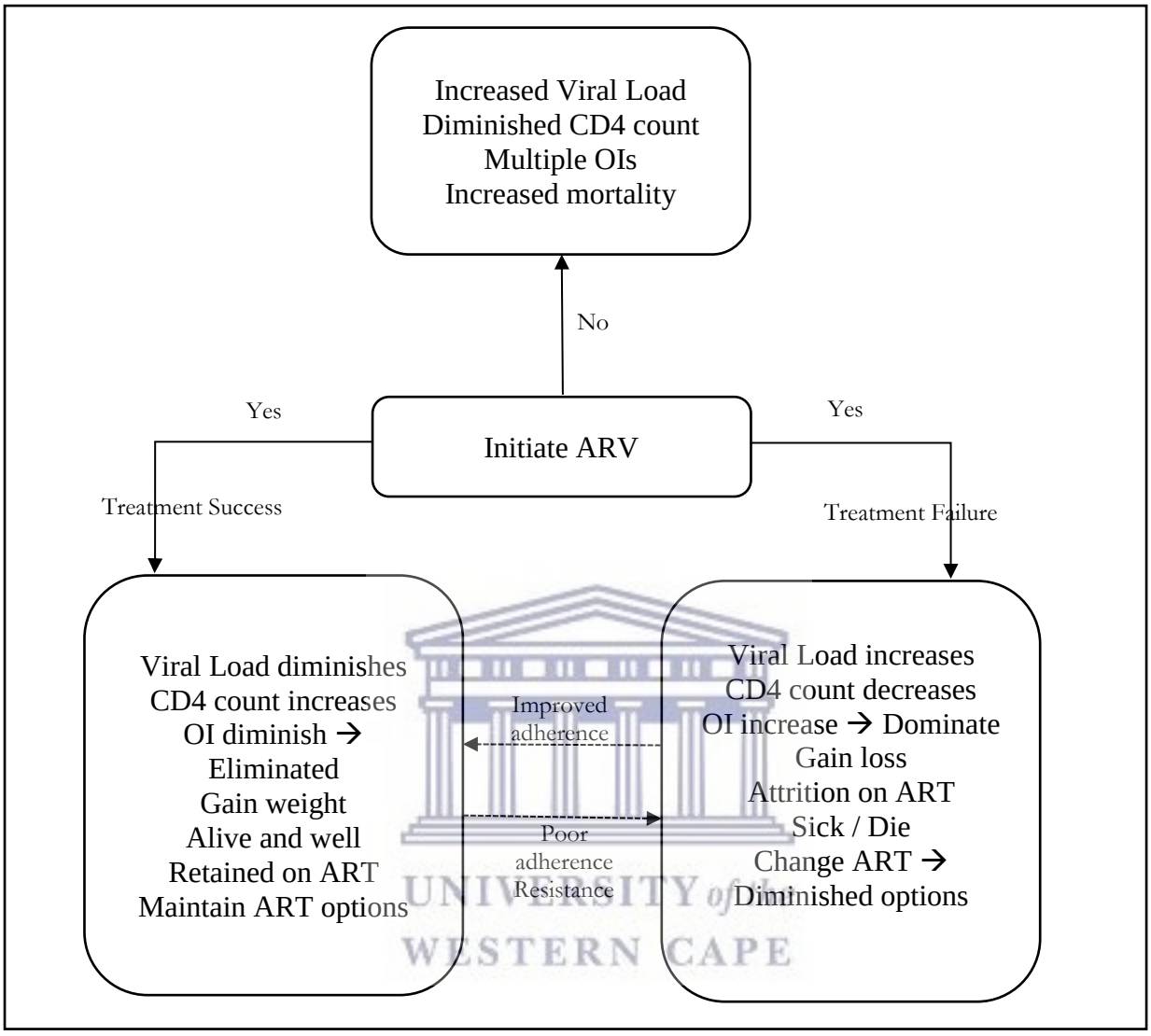


Figure 1. Conceptual Framework for Assessing ART Treatment Outcomes

CHAPTER THREE

METHODOLOGY

3.1 Study Design

This was a retrospective cohort study based on a retrospective review of patient clinical care and treatment data at Kakamega County General Hospital (KCGH) from July 2014 to June 2015. The researcher was able to follow up a group of clients back in time from the time they initiated ART until they became lost to follow-up, died or the observation period concluded in August 2017, whichever occurred first, to determine the causes of poor treatment outcome – clinical, immunologic and virologic failure, estimate incidence and the risk of attrition – a loss to follow-up and mortality for an accurate measurement of exposure variables.

3.2 Study Population

A retrospective clinical record review was conducted for clients aged 15 years and above initiated on first-line ART between July 2014 and June 2015 and on follow up at Kakamega County General Hospital (KCGH) Comprehensive Care Clinic (CCC). KCGH being a county referral hospital based in Kakamega Central (Appendix I), the study population were adults drawn from both its primary and secondary catchment populations.

3.3 Inclusion and Exclusion Criteria

Inclusion criteria - To be included in this study, clients must have been initiated on ART between July 2014 and June 2015 in the CCC at KCGH, aged 15 years and above; whose clinic information was available; and, had been on ART two to three years at the commencement of the study. These clients started on a standard first-line ART regimen according to the national ART guidelines of 2011.

Exclusion criteria – All clients at KCGH CCC started ART more than three years or less than two years before the commencement of the study; those initiated on ART elsewhere other than at KCGH and those initiated on nonstandard first-line ART regimen according to national ART guidelines; those not on ART and clients aged below 15 years.

3.4 Sampling

This study used data from the enrollment and follow up databases at KCGH CCC. The electronic medical record was matched with client files and clinic registers. Of 548 adult client records accessed, 37 records had wrongfully indicated their age and so were excluded; 82 records had the wrong ART start date; 7 records were found to be duplicates and 174 records were incomplete, missing key study variables such as ART regimen, WHO clinical stages, CD4 counts, viral load results and follow up information. All the remaining 284 records were therefore selected for the study as shown in figure 3.1 below.

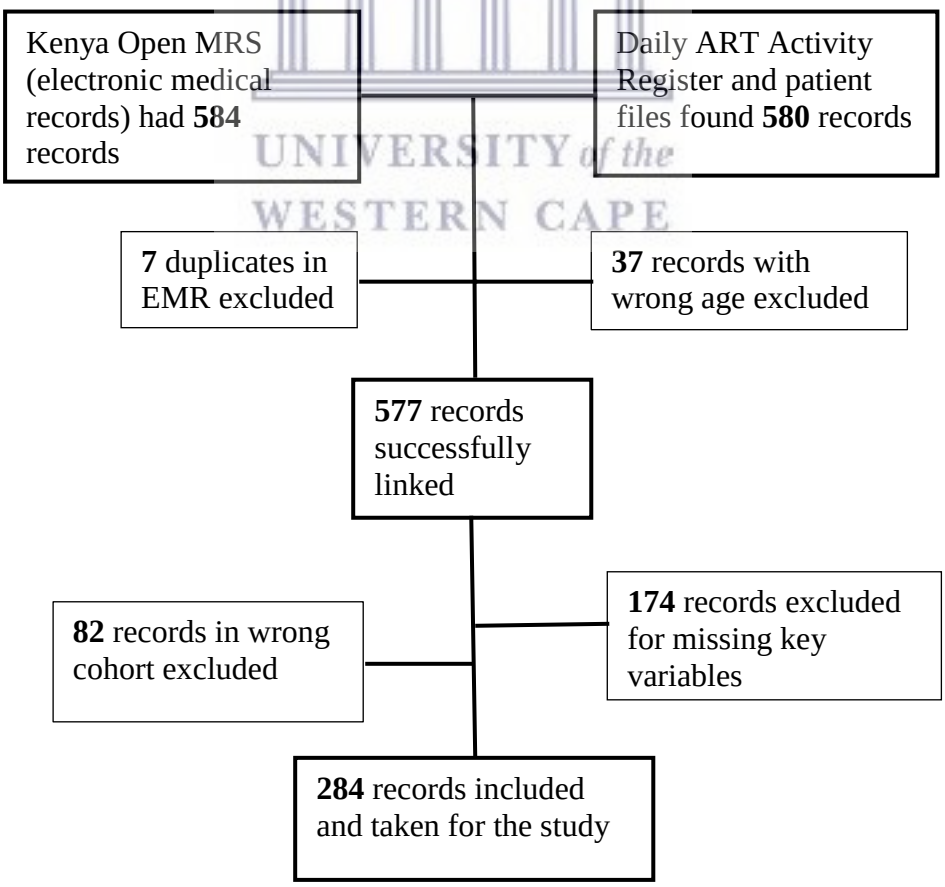


Figure 3.1 Flow chart of the records that were accessed and included in the study

3.5 Data collection

A quantitative method relying on secondary data was used. Data were obtained from routine patient records in the ART clinic at KCGH. Patients enrolling and starting ART had their details first captured in patient files on the medical and follow up cards, and the Daily ART Register which is a cohort register capturing client information based on year and month of starting ART. Patient information was recorded in the clinic files then routinely updated in the electronic medical records (EMR) called Kenya Open MRS by data officers employed by the clinic. A list of unique identifier numbers was generated by the data officers based at the clinic. The research compared the details of the unique identifier number list and those in the ART cohort register. Clients whose ART start dates occurred between July 2014 and June 2015 were identified and their clinic records retrieved. Key variables on client demographics, age, gender, and medical information such as the presence of opportunistic infections, CD4 level, WHO staging, viral load results, ART regimen and follow-up status in the clinic were collected from the files by the researcher through a chart abstraction tool (Appendix II). The researcher then transferred the details of each patient's information from the chart abstraction tool to an Access database from where data was then cleaned and final records and variables picked for analysis.

3.6 Data Analysis

Outcome measures for this study were: opportunistic infections (OIs), WHO staging, CD4 counts, virological suppression and loss to follow up (LTFU). The information entered in the EMR was obtained and exported to an excel spreadsheet. It was cleaned by cross-checking it with information in patient files and the daily ART activity register and then imported into Access database, from where it was imported into STATA 15.1 for analysis. The analysis for descriptive statistics was done using frequency and relative frequencies to

determine trends in categorical data (such as age group, ART regimen) while measures of central tendency and dispersion i.e. mean, standard deviation, median and interquartile range were determined for continuous data such as age, CD4 and VL counts were compared by gender. Immunological and virological outcomes were assessed by calculating and plotting median CD4, viral load and months on ART. Clinical outcomes were assessed by comparing the proportions of those who had OIs and WHO stages III and IV at 0, 6, 12, 18 and 24 months of initiating ART. ART follow up status was analyzed based on follow up status at the time of conducting the study. Bivariate data analysis was done to assess the relationships between the variables for each study outcome using T-tests for continuous variables and chi-square for categorical variables.

Three models were fitted with CD4 and VL as response variables. Multivariate modeling for random effects that could account for intra- and inter-subject variations and demonstrate factors associated with the outcomes of interest at least after six months of ART were conducted were considered. Mixed models allow a flexible approach to modeling longitudinal and hierarchical data; and, they handle non-homogeneous data points for subjects observed at different time points (139). Variables in this study were defined at the 5% significance level but a continuous scale of effect size estimation was utilized. Different from the traditional approach in which significance is strictly considered at 5% significance, this study considered value between 5% and 10% to be marginal.

Survival time (time from start of ART to death) and the hazard of getting lost were evaluated by Kaplan-Meier survival analysis and multivariate Cox proportional hazards modeling. Variables that were significantly associated with events occurring in univariate analysis at a $p=0.02$ level were those included for evaluation in multivariate modeling. Only those that retained significance $p<0.05$ in the multivariate model were further included in the final model. Potential independent predictor variables were evaluated for

collinearity by examining non-parametric rank correlation coefficients (such as Spearman correlation coefficient) and a variety of models tested and compared using the -2log likelihood measures for the goodness of fit. Clients who were LTFU were censored as of the last date of the clinic visit, 90 days after their last clinic date.

3.7 Validity and Reliability of Chart Abstraction Tool

The variables in the chart abstraction tool (Appendix II) were national standards of care similar to WHO recommendations (1,15). Clinical, immunological, virological and retention were treated as time-varying covariates. Virological failure was set at 1000 copies/ml while treatment failure was aligned to WHO criteria for screening therapy failure using clinical and immunological elements (29,60). The chart abstraction instrument was adopted from a current ART program.

Reliability was ensured by collecting data from both patient files and cross-examining with the existing electronic medical records available in the hospital. The chart abstraction tool was checked for chronology and construct by the study supervisor. Data obtained was cleaned and validated. Out of range data was confirmed on site during the study period. The hierarchical model used was adjusted for missing values in the analysis panels. Confounders such as age and sex were considered a priori and examined.

3.8 Ethical Considerations

Study participants: This study's proposal was submitted and received ethical clearance from the University of the Western Cape (BM17/1/11), and in Kenya through the guidance of National Commission of Science Technology and Innovations obtained ethical clearance at Maseno University (TT17200R) and the hospital – Appendix III.

Patient-level information: such as names, phone number, clinic identification numbers, physical locator information were removed and a database unique identification number

assigned.

Benefits: Future clients at the clinic are bound to receive improved ART care and treatment services following the results of this study.

Informed consent: Secondary data was used, and some patients included in the study had already left the clinic or died; however, the hospital granted permission to use the ART clinic data in this study.

Confidentiality: Only staff at the health records office in the ART clinic could access the database for this study which was password protected and saved on a password-protected computer in their office. Furthermore, no patient will be identified when the results of this study are presented.

CHAPTER FOUR

RESULTS

4.1. Social Demographic Characteristics

The study enrolled 284 HIV infected adult patients comprising 96 males and 188 females starting ART at Kakamega CGH between July 2014 and March 2015. Follow up was done from the start of ART to the end of August 2017 through retrospective review of patient records captured in the electronic medical records. Except for age, baseline WHO stage and baseline OIs, both males and females had similar baseline characteristics (Table 1). The difference in age categories was marginal, p=0.0060.

Table 1: Baseline Characteristics of Study Participants Starting ART

Characteristics	**Male** (n=96)	**Female** (n=188)	**p-value**
Age mean (SD)	39.9 (10.2)	35.7 (10.7)	0.0019
Youths (15 – 35 years old), %	37.5%	56.9%	0.0060
Married, %	40.6%	51.1%	0.5460
Days to ART from enrollment, mean (SD)	611.5 (893.4)	616.0 (756.0)	0.9644
Weight mean (SD)	60.5 (9.5)	61.0 (9.5)	0.6614
Advanced disease WHO stage (3&4), %	47.9%	28.2%	0.0100
CD4, mean (SD)	226.5 (121.1)	245.6 (125.9)	0.2369
Not disclosed, %	13.5%	15.4%	0.6720

There were 50.4% (143) youths (aged 15 to 35 years) in the study, compared to 42.6% (121) middle-aged patients (aged 36 to 54 years). Those older than 54 years were considered elderly. Among the youths, 56.9% were females.

4.2. Antiretroviral Therapy

The median time to initiating ART upon enrolment into care was 4.3 months. Female patients took thrice the median time to initiate therapy compared to males, 5.7 and 1.9 respectively;

however, the average time to ART by sex was similar, p=0.9646. There was an association between the type of regimen initiated and age group, p=0.0090 but none between regimen initiated and the sex of the participants, p=0.7350.

Table 2: ART initiated to Study Participants

Age Group	Youth (n, %)	Mid Age (n, %)	Elderly (n, %)	Total (N, %)
3TC+ABC+EFV	0 (0.0%)	0 (0.0%)	1 (5%)	1 (0.4%)
3TC+EFV+AZT	2 (1.4%)	0 (0.0%)	0 (0.0%)	2 (0.7%)
3TC+D4T+NVP	5 (3.5%)	5 (4.1%)	0 (0.0%)	10 (3.5%)
3TC+AZT+EFV	8 (5.6%)	8 (6.6%)	1 (5.0%)	17 (6.0%)
3TC+AZT+NVP	11 (7.7%)	22 (18.2%)	2 (10.0%)	35 (12.3%)
3TC+NVP+TDF	41 (28.7%)	24 (19.8%)	8 (40.0%)	73 (25.7%)
3TC+EFV+TDF	76 (53.2%)	62 (51.2%)	8 (40.0%)	146 (51.4%)
Total (N)	**143**	**121**	**20**	**284**

The proportion of patients initiated on a TDF based regimen was 77.5% (this includes the patient initiated on an ABC based regimen), while 19.0% were on an AZT based regimen, and the rest were started on a D4T based regimen (Table 2). A higher proportion of the youths (81.8%) was initiated on a TDF based regimen compared to the rest of the age categories 72.3%. Among 93.3% of patients, ART was initiated based on a CD4 count less than 501 cells/mm^3, the rest were due to advanced HIV disease qualified as either WHO stage 3 or 4.

4.3. Study Outcomes

4.3.1. Clinical Outcomes

2.5.1 4.3.1.1. Weight

Baseline mean and median weights for study participants were similar, 60.8 ±9.5 and 60.7 (IQR 54.0 to 66.2) respectively, and did not differ by sex, p=0.6614. The baseline median

weight for male patients was 60.5 kg (IQR: 52.9 to 65.9) and 61.0 kg (IQR: 54.3 to 67.0) for female patients. Weight gain peaked at one year of ART with a median of 62.0 kg (IQR: 55.0 to 67.0), where male patients recorded 62.0 kg (IQR: 55.0 to 65.5) and females 61.1 kg (IQR: 55.4 to 67.3) (Figure 2).

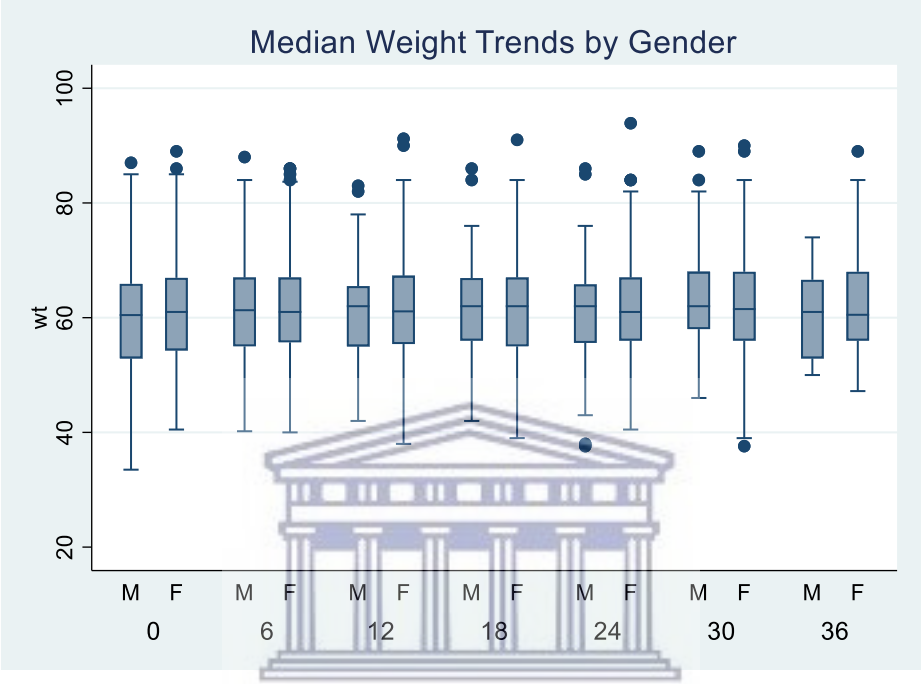


Figure 2: Box Plot for Median Weight Trends by Gender

Among those patients who lost weight, 60.0% (9) were female patients, 66.7% (10) were middle-aged patients followed by 26.7% (4) the youths; while only 6.7% of those who lost weight were required to change therapy, and 13.3% of those who lost weight died.

2.5.2 4.3.1.2. Opportunistic Infections

Among patients starting ART, 69.0% did not have an OI. Overall among the 31% patients that had an OI, 23.2% had advanced disease opportunistic infections at baseline. 7.0% patients had TB/HIV co-infection, 3.2% had papular pruritic eruptions, 2.8% (8) had Kaposi's sarcoma, 2.5% (7) had PCP and a similar proportion chronic diarrhea, while 2.1% (6) had Cryptococci meningitis. The frequency of these diseases went down at least two-fold

below baseline frequencies in subsequent months as patients continued ART. There was a statistically significant reduction in the recurrence of advanced OIs among those who had advanced OIs at baseline to as low as 15.1% compared to 84.9% among those who neither had OIs nor had advanced disease at the start of therapy, p<0.0001. Nonetheless, the incidence of pulmonary TB (PTB) did not go down over the study period, with at least 30.8% of patients on ART being diagnosed with PTB over the follow-up period.

There was a statistically significant difference between the presence of baseline severe OIs and sex, p=0.0490 but this became marginally significant with therapy, p=0.0650. However, male patients had more episodes of recurrent advanced disease OIs at 19.8% (133 episodes) compared to 12.8% (168 episodes) among female patients, p<0.0001. Likewise, there was a statistically significant association between age group and recurrent advanced disease OIs. The proportion of youths with severe disease was 12.9% compared to 16.5% middle-aged patients, and 25.0% among elderly patients, p<0.0001.

2.5.3 4.3.1.3. WHO Staging

The proportion of patients with advanced WHO staging i.e. WHO 3 or 4 at baseline was 34.9% (99) and decreased to 6.5% (18) at month six and thereafter to less than 5.1% (13). Males had 1.6 times more cases of advanced WHO staging at baseline, 47.9% (46), compared to female patients, p=0.0430; however, there was a marked reduction in the frequency of advanced WHO staging among the male patients at six months of ART, p=0.0280. After six months of follow up, the frequency of advanced WHO stage remained below 10.0% with no statistical difference between the sexes. Advanced WHO staging and age group were not associated, p=0.6230; but, 45.0% (9) of elderly patients had advanced WHO staging at baseline, compared to 33.9% (41) of middle-and 34.3% of youths.

2.5.4 4.3.1.4. Sustained ART Options

Among patients initiating ART, 91.2% were retained on their initial ART regimen. Single-drug substitutions were the commonest reason for changing a patient's therapy, accounting for 56.0% of drug changes followed by the switch to second-line therapy at 24% due to patients failing ART. Some patients switched regimen because they had adverse drug reactions or were sharing their doses, at 8% respectively; one patient discontinued therapy because they did not have the financial means for their treatment. D4T phase-out was the main reason for single drug substitution, accounting for 85.7%; otherwise, a single ARV drug substitution was done to accommodate TB treatment (Table 3).

Table 3: Reasons for Changing ART Drugs

Therapy Change Reason	**Counts**	**Percentage**
Therapy not changed	259	91.2%
Substitution (including D4T)	12	4.2%
Treatment failure	6	2.1%
Adverse Reaction	3	1.1%
Share with others	2	0.7%
TB treatment	2	0.7%
Total	284	100%

Half of the patients who switched regimen to second-line therapy were male. Youths contributed 66.7% (4) of switches to second-line therapy and the rest, 33.3% (2), were middle-aged patients. Optimal adherence to ART (assessed as greater than 94.0% of adherence) as at the last patient's ART visit was 77.1% (219), 20.8% (59) had fair adherence (between 90.0 and 94.0% adherence) to ART and the rest had poor adherence. Despite there being no association between ART regimen and age group, 82.0% of mid-aged patients had better adherence to ART, followed by the youths at 74.1% and the elderly at 70.0%.

4.3.2. Immunological Response

Over 95% of patients who were enrolled and initiated ART at KCGH had access to CD4 testing every six months from baseline. Males had a 97.9% insignificantly different CD4 response compared to 96.8% of females, p=0.5934. Similarly, 97.2% of the youths initiated on ART, 97.5% of the middle-aged and 95.0% of elderly patients had optimal CD4 response, p=0.8190 There was a progressive rise in CD4 counts over time upon initiating ART (Figure 3). Mean baseline CD4 count was 239.2 ±124.4 which rose to 301.7 ±130.5 at six months, 375.7 ±140.0 at one year, 495.9 ±163.9 at two years and 556.8 ±179.5 at 3 years of follow up.

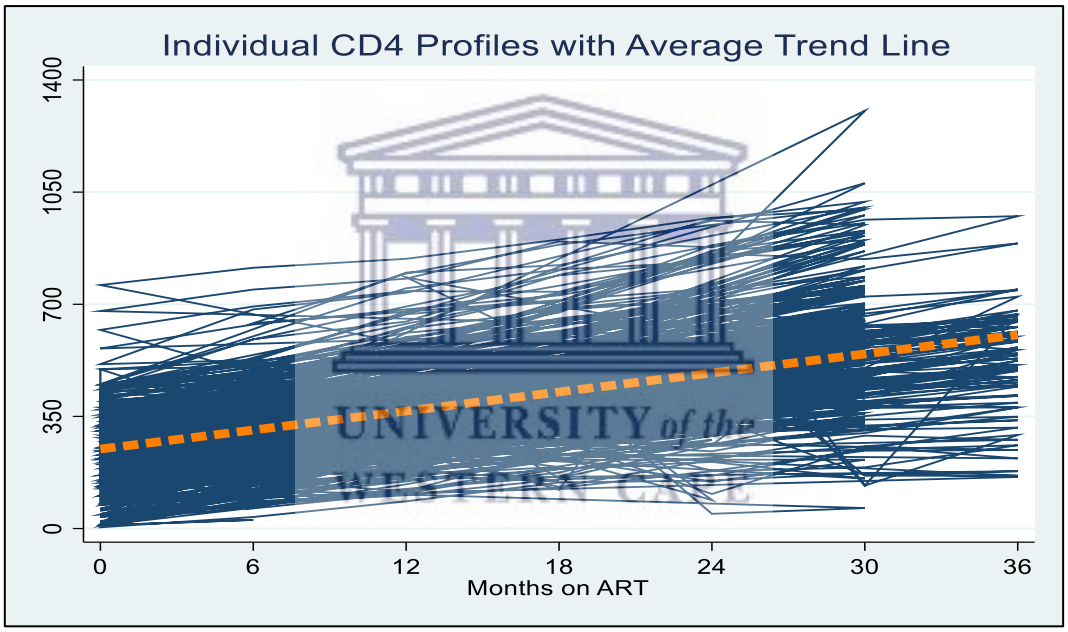


Figure 3: Individual Patient CD4 Counts and Trend Line

CD4 failure is time-varying; for each unit increase in time among patients on ART, cases of CD4 failure increased by 2.10, p=0.0010. Recurrent WHO stage 3 or 4 conditions, and pruritic papular eruptions at least six months on initiating ART was associated with 14.4 times the likelihood of CD4 failure compared to those who had good CD4 response (p<0.0001). Elderly patients and those who had detectable viral load results had an

insignificantly increased likelihood of failing CD4, of 4.9 times compared to youths, and 0.62 times, p=0.2550 and p=0.8240, respectively, (Table 4). Patients with a recurring advanced OI disease were .01 times less likely to have sub-optimal CD4 progression compared to those who did not have recurrent advanced OIs, p=0.9730, an insignificant finding. Middle-aged patients had 1.4 times fewer chances of reporting poor CD4 progression compared to youths, p=0.5240. Female patients were 81.3% less likely to have poor CD4 counts over time, but this was not statistically different from male patients, p=0.7300.

Table 4: Table for CD4 Random Effects

CD4 Failure	Coef.	Std. Err.	Z	P>z	95% CI	
Female	-0.8131	2.3523	-0.35	0.7300	-5.4236	3.7974
Age Group						
Middle Age	-1.4139	2.2212	-0.64	0.5240	-5.7674	2.9396
Elderly	4.9042	4.3054	1.14	0.2550	-3.5343	13.3427
Recurrent OI	-0.1011	2.9686	-0.03	0.9730	-5.9195	5.7174
Advanced WHO	14.4128	2.4618	5.85	0.0000	9.5877	19.2379
Detectable VL	0.6217	2.7918	0.22	0.8240	-4.8501	6.0935
Months on ART	2.0968	0.6087	3.44	0.0010	0.9037	3.2899
_cons	-101.8613	22.021	-4.63	0.0000	-145.0216	-58.701
/lnsig2u	5.1298	0.2133			4.7117	5.5479
sigma_u	12.9992	1.3865			10.5469	16.0216
Rho	0.9809	0.004			0.9713	0.9873

2.5.5 4.3.2.1. Suspected Treatment Failure

The proportion of patients with recurring advanced disease (WHO stage 3 or 4) was 23.6% (67), or those with papular pruritic rash, or drop of CD4 count below baseline level, or a drop of CD4 count of greater than 30% of peak at least six months on initiating ART or those who had a drop in their weight for greater than 10% (Figure 2). Recurrent advanced disease OI

was the commonest cause of suspecting therapy failure with 68.7% (46). The frequency of patients identified to have recurrent advanced OIs did not correlate with the frequency of patients suspected to fail therapy based on CD4 count 11.9% (8), (r=0.0407, p=0.4947) (Figure 3). None of the patients was suspected for therapy failure entirely based on weight trend, 47.8% (32).

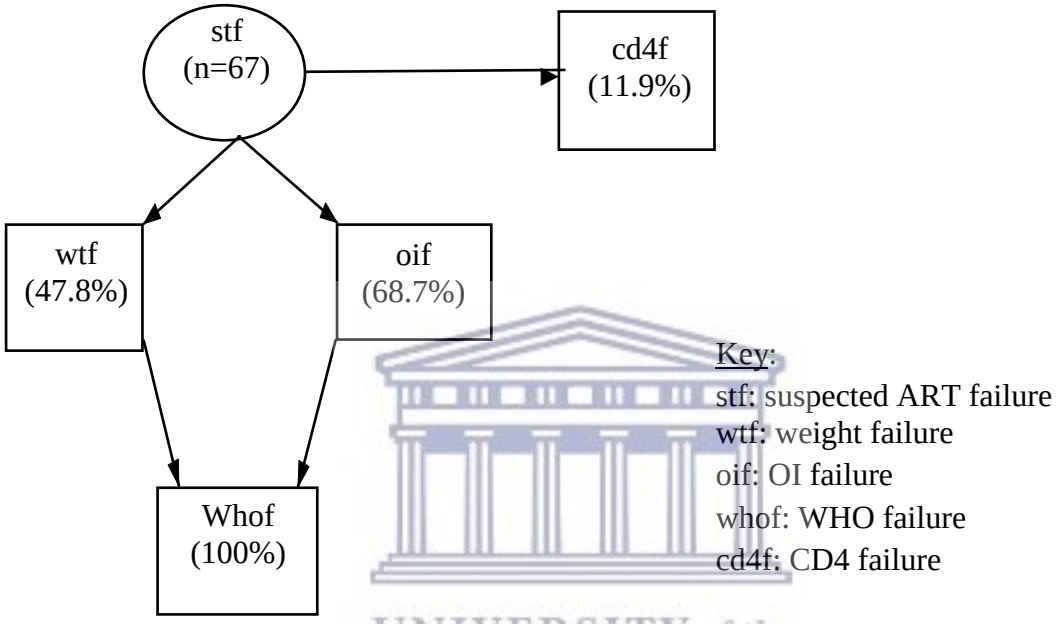


Figure 4: Results for Treatment Failure Based on Screening Criteria

There was a marginal association between patients suspected for therapy failure and sex, but not by age group, p=0.0990, and p=0.1450 respectively. Among those who failed, 29.4% of male patients were suspected of ART therapy compared to 20.1% females. Elderly patients contributed 43.8% of those suspected of ART failure. Relative to male patients being suspected for therapy failure, female patients suspected for treatment failure had an all-time decreased hazard of failure (HR = 0.6613) though this was not a statistically significant benefit, p=0.1170 (Figure 4).

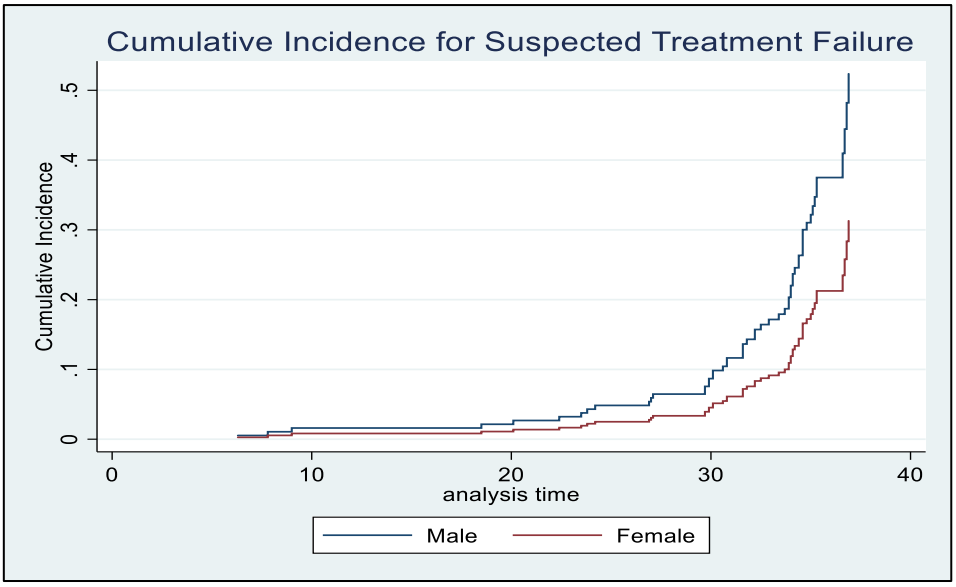


Figure 5: Instantaneous Hazards for ART Failure based on Screening Criteria

4.3.3. Virologic Response

More than 98.5% of patients eligible for viral load monitoring received the test and the results were available during the study period at six months, one year, and each subsequent year of follow up on initiating ART. 83.0% (229) of patients on ART had undetectable viral loads in the study period (Figure 5). Among those who failed, the incidence rate ART 15.8% (43) was highest at six months of initiating and sharply diminished in the months that followed, 1.1% (3) at 12 months and less than 1% thereafter. Female patients with detectable viral load were 14.8% (27), and compared with 21.5% (20) of males, p=0.5476. There was no association

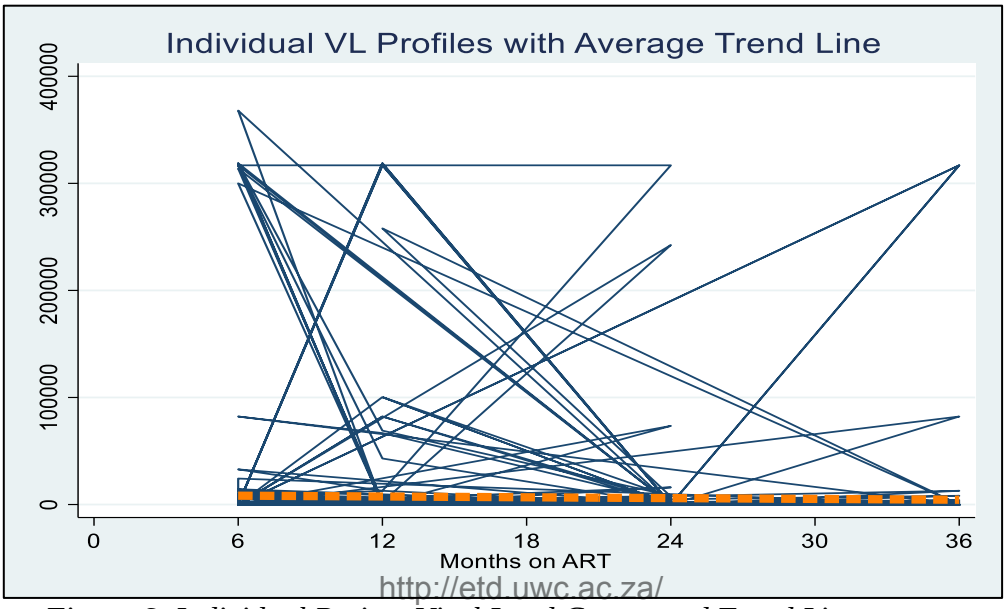


Figure 6: Individual Patient Viral Load Counts and Trend Line

between having a detectable viral load and age group, among those who failed therapy.

Youths who had not disclosed their HIV status, 58.3% (7), were more likely to have detectable viral load at least 6 months on initiating ART compared to 33.3% (4), middle-aged patients, and only 8.3% (1) elderly patients on ART, p=0.8900. There was a positive correlation with the results of suspected treatment failure and viral load failure, detectable viral load counts (r=0.6047, p<0.0001). The 60.3% (35) patients on ART suspected for therapy failure were correctly classified as having failed therapy as confirmed by viral load testing (Table 5).

Table 5: Comparison of Viral Load Results and Findings of Screening Criteria

Status	**Undetectable VL**	**Detectable VL**	**Total**
Unsuspected TF, count (%)	172 (20.45%)	9 (75.73%)	181
Suspected TF, count (%)	23 (79.55%)	35 (24.27%)	58
Total	**195**	**44**	**239**

Following bivariate analysis, the probability of patients on ART for at least six months having detectable viral loads with a baseline history of not having disclosed their HIV status was 69.7% higher for each patient that failed therapy compared to their counterparts who had disclosed, p=0.0410, while those who had a WHO stage 3 or 4 disease, were seen to be 1.66 times more likely to have detectable viral loads compared to those with WHO stage 1 or 2 disease, p<0.0001 (table 6). The probability that a patient would have detectable viral load decreased as one's CD4 counts increased. Patients with CD4 counts of between 351 – 500 cells/mm^3 and those with greater than 500 cells/mm^3 had less than 1.87 and 2.45 times, respectively; those who had less than 200 cells/mm^3 were likely to have detectable viral loads, p<0.0001.

The time a patient takes on ART was related to a reduction in the probability that such a

patient would have detectable viral by 3.9%, p=0.0030. Females and middle-aged patients were associated with a statistically insignificant reduction in the likelihood of failing therapy of 38.16% and 13.42, compared to males and youths respectively. Patients with suboptimal adherence, rated at 90 – 94%, experienced less than 14.53% likelihood of having undetectable viral loads compared to those with optimal adherence of > 95%, p=0.6990.

Table 6: Variate Analysis for Viral Load Response

Variable	**Bivariate Analysis**		**Multivariate Analysis**	
	Coefficient	p-value	Coefficient	p-value
Gender				
Female	- 0. 3867	0.1960	- 0. 3155	0. 3110
Age group				
Middle aged (36 – 54 years	- 0. 1342	0.6700	- 0. 2864	0. 3870
Elderly (55+ years old)	0. 3741	0.4540	0. 6623	0.2140
PHDP*				
Undisclosed	0. 6968	0.0410	0. 5520	0.1390
Adherence				
Fair (94 – 90%)	- 0. 1453	0.6990	- 0. 3044	0.4420
Poor (< 90%)	0.5800	0.5760	1. 7976	0.1170
WHO Stage				
Severe disease (WHO 3 / 4)	1. 6632	0.0000	1. 2746	0.0010
CD4 count				
201 – 350 cells/mm^3	- 0. 4646	0. 1710	- 0. 2365	0.5320
351 – 500 cells/mm^3	- 1. 8730	0.0000	- 1. 9156	0.0010
≥501 cells/mm^3	- 2. 4524	0.0000	- 2. 7073	0.0000
Time	- 0.0389	0.0030	0.0401	0.0160

- PHDP – Positive health, dignity, and prevention

Adjusting for random effects and fitting a model illustrating determinants associated with viral load failure established that CD4 count levels, WHO stage, and time taken on ART were critical predictors of treatment failure. For each month a patient was on ART, there was a significant likelihood of having a detectable viral load of 4.0%, p=0.0160; those with

advanced WHO stage on the other hand were 1.66 more likely to have viral load failure, p=0.0010, compared to those with mild disease (WHO stage 1 or 2). Patients with CD4 counts greater than 200 cells/mm^3 had reduced likelihood of having detectable viral loads; those with counts between 351 and 500 cells / mm^3 and greater had less than 1.92 times and 2.71 times with p=0010 and p<0.0001 respectively. Relative to males, female patients on ART for at least six months had an insignificantly lower (aHR= 15.52%, p=0.5760) risk of failing therapy for the same (Figure 6).

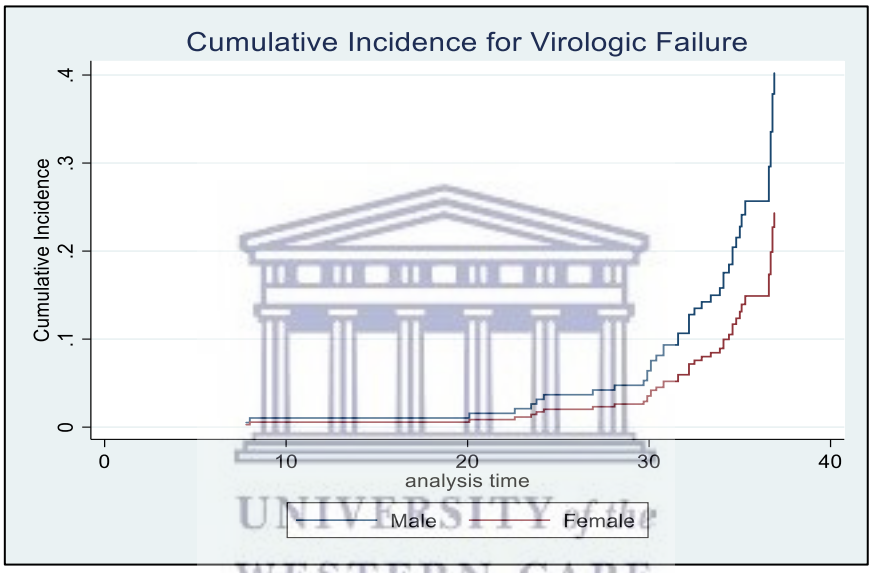


Figure 7: Instantaneous Hazards for ART Failure based on Viral Load Monitoring

On the other hand, not having disclosed HIV status at the start of ART was associated with an all-time marginal increase in the risk of having detectable viral loads (aHR=17.7%), p=0.0930. All-time risk of patients with CD4 counts greater than 200 cells / mm^3 reduced from 30.96% (201 – 350 cells / mm^3) to 80.32% (351 – 500 cells / mm^3) and 89.69% (>500 cells / mm^3) compared to those who record CD4 counts below 201 cells / mm^3, p = 0.3250, p=0.0030, and p=0.0020 respectively. The incidence for detectable viral load was highest at six and 12 months of initiating therapy, rapidly declining in subsequent years of testing (Table 7).

Table 7: Hazard for ART Failure by Time Point

Cohort	Person-time	Failures	Rate *PMFU (1000)	95% CI	
6 months	1704	20	11.74	7.57	18.19
1 year	1584	18	11.36	7.16	18.04
2 years	2952	5	1.69	0.7	4.07
> 2 years	2892	4	1.38	0.52	3.69
Overall	9132	47	5.15	3.87	6.85

*PMFU – Patients Months of Follow Up

After at least six months of taking ARVs, among the 93 male patients who accessed viral load, 20.4% had viral load counts greater than 1000 copies/ml compared to 14.8% of the 183 female patients, but the difference was not significantly different with p = 0.6144. The Hazard Ratio (HR) for patients failing ART at Kakamega CGH by sex suggested that female adult patients on ART were 45.4% less likely to develop virologic failure compared to male adult patients-initiated ART in the same period, p=0.0470 (95% CI: 30.00% to 99.3%) (Figure7); however, there was not enough evidence suggesting that hazards varied by sex, on adjusting for other variables (aHR 0.55; p=0.083), nor by age (aHR1.01; p=0.3770). Hazard rates were significantly dissimilar for baseline CD4 counts (aHR 1.0; p=0.026), and baseline WHO stage (aHR 1.64; p=0.007).

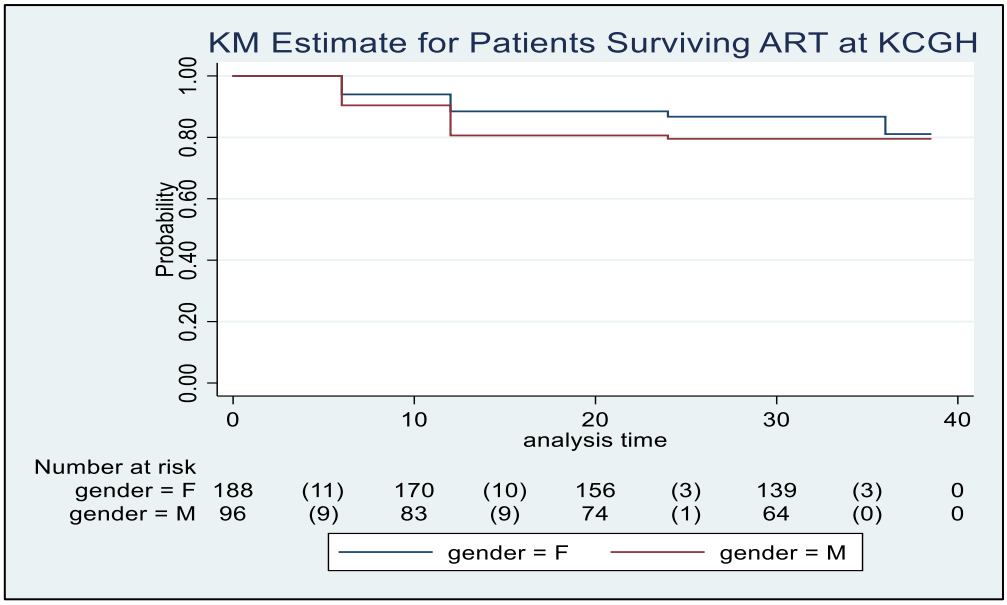


Figure 8: Kaplan-Meier Estimate for Viral Suppression on ART

The incidence rate for virologic failure was 5.6 cases per 1000 patients-initiated ART per month of follow up (95% CI: 4.20 to 7.49); differing significantly between females (4.9 cases per 1000 female patients-initiated ART per month of follow up) and males (7.2 cases per 1000 male patients-initiated ART per month of follow up), p= 0.0437).

4.4. Program Retention

The proportion of active patients on ART at the end of the study was 89.1 % (253), (p < 0.0001). Among those who were not retained, 54.8% died while the rest were lost to follow up. The attrition rate was 3.4 cases per 1000 patients-initiated ART per month of follow up, 95% CI: 2.4 to 4.9. The mortality rate on ART was 1.9 deaths per 1000 patients-initiated ART per month of follow up (95% CI: 1.2 to 3.0); while that of patients being lost to follow up was 1.5 cases per 1000 patients-initiated ART per month of follow up (95% CI: 0.9 to 2.6). Among those that got lost, 8.3% were males compared to 12.2% who were females on ART follow up, but the difference was not statistically significant, p=0.5450. While there was no association between the patient being retained in the ART program and patient age group, p=0.9050, age group was found to confound the risk of attrition (aRR = 1.38; p=0.0375).

The mortality rates for males and females did not differ, p=0.6523, 1.6 male deaths per 1000 patients on ART per month of follow up compared with 2.0 female deaths per 1000 patients on ART per month of follow up. There was no difference in the rates of lost to follow up between the sexes.; There were 1.0 cases of males being lost to follow-up per 1000 male patients initiated ART per month of follow up compared to 1.8 cases of female patients being lost to follow-up per 1000 female patients initiated ART per month of follow up in the clinic, p=0.3278 (figure 8).

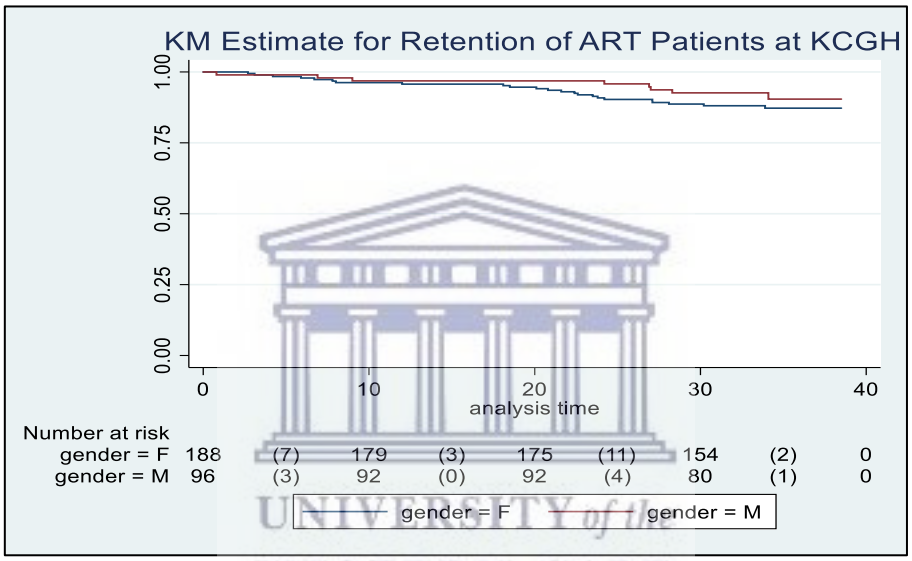


Figure 9: Kaplan Meier Estimate for Retaining Patients in ART Program at KCGH

Relative to male patients on ART, female patients had an insignificantly higher hazard of not being retained into the ART program throughout the follow-up period (HR = 1.27; p=0.6530). The proportion of youths not being retained was 12.6% (12), whereas 9.9% (10) middle-aged patients either died or were lost to follow up, and, only 5.0% (1) of the elderly patients died (Figure 9).

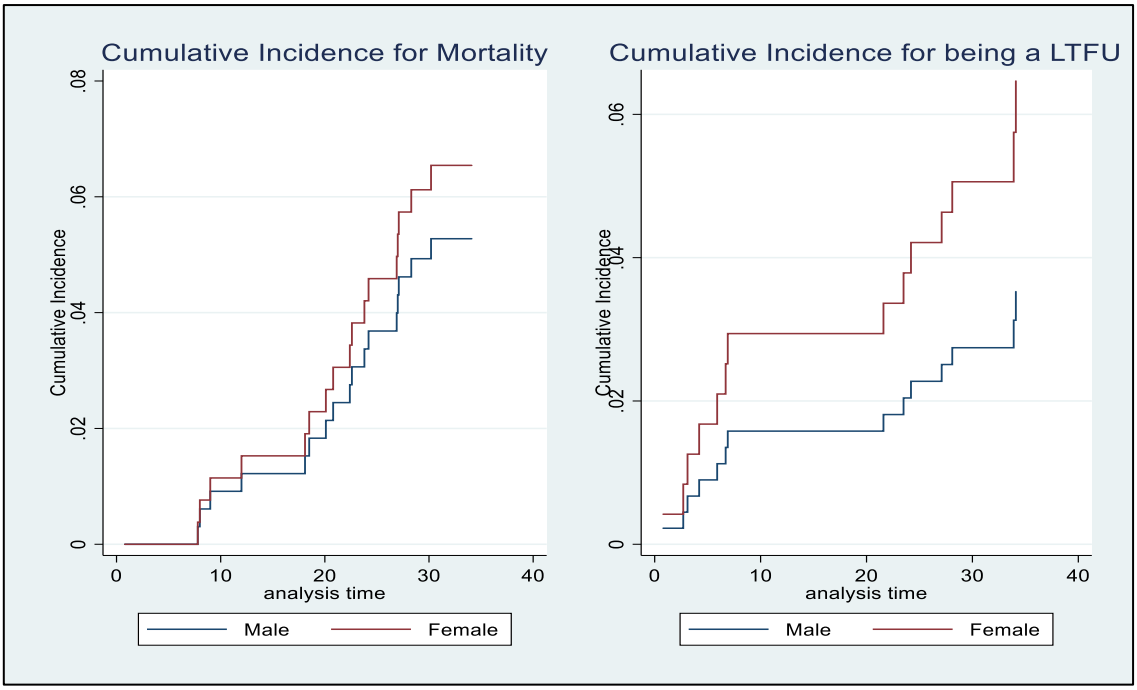


Figure 10: Kaplan-Meier Estimates for Risk of Attrition by Death and Loss to Follow Up

For every patient that had disclosed their HIV status at the start of the study that was not retained in the ART clinic, there was nearly a threefold increase in the risk of being lost among those who had not disclosed (aHR=2.9; p=0.0390). On the other hand, for each patient that was not retained in the clinic and was not suspected for treatment failure by WHO staging, had a significantly lower, three times, the risk of not being retained had they been suspected to have failed therapy by WHO staging (aHR=3.0; p=0.0410). Failing therapy identified by CD4 trend analysis was not associated with patient retention. There was a marginal significance in the risk of not being retained in the clinic if a patient was confirmed to have failed treatment by viral load count (aHR=2.43; p=0.0990).

CHAPTER FIVE

DISCUSSION, CONCLUSION, AND RECOMMENDATIONS

5.0. Introduction

This chapter discusses the key findings of the study and compares these findings with other studies. The peculiarity of the study is highlighted and its limitations are presented. Recommendations that are aligned with the study findings are also given.

5.1. Socio-demographics

The study enrolled significantly fewer male adult patients than female adult patients initiating ART. It also had more youths amongst whom were more females than males. About half the proportion of youths were married. More than three-quarters of the patients in the study had disclosed their HIV status at the time they were being initiated ART. However, similar differences in gender were seen in a retrospective review done in Zimbabwe (129) where 64.0% female participants were enrolled, and in an early cohort study among patients initiating ART in Ghana (136), 67.9% were female patients. (140) During the Kenya AIDS Indicators Survey of 2012, youths testing HIV positive accounted for 43.8% (284) while female participants who tested positive accounted for 70.2% (455). The Kenyan survey also found that HIV prevalence was high among females, 6.9% (95% CI: 6.0 to 7.7) compared to males 4.4% (95% CI: 3.6 to 5.2). These findings from the literature suggest that the sociodemographic profile for this study did not depart from previous studies conducted on HIV infection in Kenya and other near similar settings in Africa.

5.2. ART Initiation and Context

The World Health Organization published new guidelines on the use of antiretroviral drugs for treating and preventing HIV infection in June 2013, this was followed by the release of a

Rapid Advice on ART by the National AIDS and STI Control Program (NASCOP) in Kenya in May 2014, transitioning the country into new cut-offs and guidelines for initiating ART among HIV infected patients. Training of trainers was done by NASCOP in May 2014, and guidelines on the use of antiretroviral drugs for treating and preventing HIV infection in Kenya was released in June 2014. This study began in July 2014, at the wake of new treatment guidelines in which all adult and adolescent non-pregnant HIV infected patients with a CD4 count of 500 cells / mm^3 were supposed to be initiated ART, or those with WHO staging 3 or 4 irrespective of CD4 counts; and, TDF based regimen is the preferred antiretroviral regime.

A very high proportion of patients initiated ART based on CD4 counts most of whom were on a TDF based regimen. Merits and demerits of starting ART with high CD4 counts having been documented in multiple studies ((O'Connor et al., 2017) (141) (142)) point out that starting patients with high pretreatment CD4 counts has the benefits of reducing the risk of severe OIs accrued by improved immunological reconstitution, decreasing transmission of HIV infection, decreasing the risk of HIV related comorbidities such as cardiovascular disease (143). Few patients die due to HIV related deaths; however, due to better immunity (31) i.e. high CD4 counts, there are increased chances of suboptimal adherence to ART, especially among young patients which is a precursor for therapy failure, and transmission of resistant HIV strains (26).

5.3. Primary Outcomes

2.5.6 5.3.1. Clinical Outcomes

Before ARVs were easily accessible, HIV infections and AIDS was commonly referred to as the "sliming disease" characterized by severe body weight and emaciation (144). Concerns have been raised over the rapid increases in weight and obesity among patients starting ART

(80), and, Yuh suggests that the rapid increase in weight in the initial months of therapy include a reduction in the metabolic demand from viral replication which suggests better clinical outcome (5). At KCGH, weight gain among study participants was not statistically significant to warrant investigating for unintentional causes of weight gain associated with dietary disorders, extraneous factors such as kidney disease, endocrine malfunctions or largely metabolic misnomers such as may arise with interactions with ARVs or other treatment substances used by patients (80). An insignificant proportion of those who lost weight either died or required a change in therapy, this implies that the study participants were not at additional risk of poor immunological risks or of death in view of documented evidence (144).

A significant reduction in the frequency of opportunistic infections was witnessed among patients upon initiating ART, and this benefit increased with time. Less than 20% of OIs should occur in patients on ART (59). Similarly, systematic reviews conducted to explore the prevalence and incidence of OIs with ART (13,145) have shown a marked reduction in WHO stage 3 or 4 OIs, but less so for PTB (146,147) possibly because of TB replaces and varied timing in initiating ART for patients with very low CD4 counts. In this study at least 30.8% of patients who were clinically staged WHO 3 or 4 had PTB; however, the overall rates of infection remained lower than 4.0% which was at least half the baseline rate. Nevertheless, recurrence of PTB is associated with patients failing therapy possibly because of poor adherence (122) since ART has been shown to significantly reduce the rates of TB infections (148).

Response rates on ART for TB co-infected patients and those uninfected with TB have been shown to be similar (149). In the present study, there was no correlation between recurrent PTB infections and treatment failure, a finding reported by Khan et al. However, in the

systematic review by Khan, most PTB relapses were due to sub-optimal treatment with rifampicin suggesting at least 7 months of TB chemotherapy (148). There were no statistically significant differences between male and female patients with recurrent TB as was the case in a cross-sectional in South Africa (146), in which most of the patients were male, and had sputum negative results in their previous TB infection or had EPTB; or in an Indian cohort study whose participants had an history of higher than 19 mm Mantoux reading or used TB chemotherapy for less than 9 months (82).

The dramatic decline in new OIs is associated with a reduction in the frequency of WHO stage 3 or 4. By suppressing the viral load, ARVs enable the multiplication of CD4 cells counts, and hence reducing the risk of OIs and HIV related malignancies (150) with the use of potent ART. 91.2% of the patients stayed on their initial regimen throughout the study period; as high as possible levels of retention on ART regimen is required (59). Yet, prolonged use of ART in the face of incomplete viral suppression is associated with extensive viral mutations favouring the development of drug-resistant viruses (151) which necessitate a change of regimen and switching to a higher level treatment options which become limited in the presence of drug-resistant strains (31). The importance of preserving treatment options longer, therefore, cannot be over-emphasized. The proportion of patients who switched to second-line ART was 2.1%, and this group as suggested by an Ethiopian cohort, and a modeling study is, again, due to poor adherence which leads to poor immune response (35,119). Poor adherence on ART is the commonest cause of unsuppressed viral load (76). While this study did not explore the factors associated with poor adherence, at least 30% of the patients on follow up had sub-optimal adherence i.e. less than 95% adherence to treatment. Mid-aged patients had better adherence compared to elderly patients who had the worst levels of optimal adherence to ART, and the study did not find a statistical difference in the adherence of male and female patients.

2.5.7 5.3.2. Immunological Response

The study rhymes existing evidence that CD4 counts increase remarkably with the use of ART (19). Over 95% of the patients had optimal CD4 response with ART. But this contrasts with evidence that state that younger patients, those with advanced clinical stage, females, as well as those who with lower CD4 counts pre-treatment have better improvements in CD4 counts (120,149) since elderly patients had a median increase of CD4 counts of 390 cells / mm^3 compared to youths who had an increase of 320 cells / mm^3 over the three years of follow up. However, more elderly patients (5%) were suspected to mount suboptimal improvements in CD4 counts which were nearly as twice the proportion for youths, a finding that partly agrees with that of a Swaziland survey (10). Similarly, despite female patients having better median CD4 count (315 cells/mm^3) improvements over the three-year period compared to male patients (263 cells/mm^3), this improvement was not statistically better than that of male patients. Male patients had better CD4 improvements by baseline CD4 category greater than 200 cells / mm^3 over the three year period in contrast to a systematic review that pooled findings from Sub-Saharan Africa, Latin America and Asia (152).

Discordant CD4 counts were suspected in two patients, whose counts remained below 100 cells / mm^3 at 6 months of therapy, and only increased by less than 50 cells / mm^3 after a year of therapy. This paradoxical phenomenon in which CD4 count response to ART is poor is considered CD4 discordancy (104) and is related to suboptimal immune reconstitution. Kelly admits that discordant immune response (DIR) is largely looked at in two ways, by considering failure to achieve pre-specified absolute CD4 count values at predefined time points or, failure to achieve a pre-specified rise in CD4 count from baseline at predefined time points as was the case in this study. Of the two patients who had DIR, the male patient died at 27 months of follow-up while the female patient was censored at the end of the study period. There was no data to support the actual cause of death in this patient that had DIR,.

There are possibilities that deaths in such patients, especially those that occur early in therapy are related to immune reconstitution inflammatory syndrome (IRIS), which is characterized by the exacerbation of an underlying OI that has not been sufficiently treated at the start of ART due to severe immunosuppression (31).

Additional predictors based on multilevel modeling for factors associated with CD4 outcomes confirmed that there was no statistical difference between CD4 response in male compared to female patients, detectable viral load was associated with increased CD4 failure, being an elderly patient, and pre-treatment advanced diseases and WHO stage 3 or 4 were associated with poor CD4 outcomes; similar findings were obtained in a retrospective cohort study done in Ethiopia on predictors of CD4 response. In the Ethiopian study, CD4 count increased by about 1.5 cells/mm^3 per month of follow up, baseline age was negatively associated with CD4 count, sex was not found to be an independent predictor of CD4 response, but time on ART was found to be an independent variate, and with lower CD4 count pre-treatment, the higher the likelihood that the comparative increase in CD4 count will be relatively lower (92). On the other hand, following a prospective study at Johns Hopkins, Moore and Keruly suggest that most patients with baseline CD4 counts of at least 350 cells/mm^3 tend to achieve normal immune ranges while on ART (91).

2.5.8 5.3.3. Virological Response

HIV RNA viral load (VL) is an important measure of the efficiency of ART. Evidence suggests that VL is the single most reliable predictor of HIV disease progression (106). In Kenya, VL monitoring is not widely accessible except through secondary networking of patient samples. Over 98% of patients enrolled in this study accessed VL which was entirely through sample networking to reference laboratory in Western Kenya. At least 97% of patients whose samples were collected at six months, then at 12 months and thereafter yearly

had optimal VL response which is undetectable VL. The capacity to keep a patient's VL undetectable for a long time has the promise of ensuring that the patient's immune system is robust and it reduces the risk of morbidity and mortality among these patients to equal or better than those of the general population (152) and preserves potent ART treatment alternatives for them.

The incidence rate for patients failing ART was highest in the first year of follow up and tremendously diminished in subsequent months (100). VL failure was 5.6 per 1000 patients after 36 ART months of follow up. 3% patients on first-line ART failed therapy; a finding that differs with a retrospective study done in Myanmar between 2005 and 2015 in which 33% of the patients on ART failed therapy (100) in Myanmar which had an incidence rate of 3.2 per 100 person-years of follow-up. In the Myanmar study, routine VL monitoring was not readily available and 58% of the patients were male. A prospective cohort study in China established a virologic failure of 11% which was more common among patients initiated NNRTIs, male patients and had resistant HIV strains at 5%, commonly K103N and M184V (106), and yet in a Kenyan study, 23% of patients were confirmed to have failed therapy (102). In the present study, female patients were less likely to have detectable viral loads aHR 17.7 though this was not statistically significant as adherence on ART did not vary by sex contrasting with the Chinese study Abdissa in which fewer women missed their ART.

Middle-aged female patients in this study had better VL outcomes compared to their male counterparts. Nonetheless, female patients who experienced adverse drug effects were more likely to end up with VL failure compared to male patients (106); suggesting that women had better adherence behavior until life-threatening events related to the medication happened to them. Disclosure status at the start of ART in this study was found to be a predictor of VL failure. Youths who had not disclosed their status were at a higher risk of VL failure

compared to the others (100); emphasizing the need to address disclosure at the start of ART especially among young people, and by extension suggesting the importance of treatment buddies for ART. Suboptimal response to therapy is associated with poor adherence (153) which is also related to a lack of disclosure of HIV status.

Among patients confirmed to have failed therapy, 80% (38) who had detectable viral load counts, were patients with pre-treatment CD4 counts less than 351 cells / mm^3 which matches findings from the literature that higher pretreatment CD4 counts are protective of VL failure (26). But, for every month a patient was on ART, the probability of such a patient failing VL were as high as 4% especially so among elderly patients, finding which differs with a study conducted in Cameroon that disputed any relationship between failing viral load among adolescent patients and time (22) and partly with a study conducted in Ethiopia which found that youths with low CD4 counts, poor adherence to treatment and experienced on ART, were positively and significantly associated with VL failure (154).

Considering that no viral load was done at baseline, patients were also monitored for viral blips. A transient rise in viral load levels above undetectable levels to counts below thresholds considered virologic failure (99). Importantly so because literature confirms that viral blips are as frequent as 22.7% among patients with suppressed viral loads on ART and such incidences occurring in about three consecutive occasions are highly associated with virologic failure (125). (99) highlights that viral blips are common among patients on NNRTIs compared to the other drug regimen, however, all patients in the study were initiated therapy on NNRTI based regimen. However, a breakdown of the six patients who had episodes of viral blips indicates that 66.67% of these patients were on EFV containing regimes, in which three-quarters of those patients on EFV containing regimes were on TDF. Fortunately, none of the documented cases failed virologically.

2.5.9 5.3.4. Program Retention

A high retention of 89% was found in this study similar to that done in Myanmar of 84% (130); but this level of retention is considerably higher than that in literature as documented by a systematic review conducted on Sub-Saharan Africa of 78% (128) and much lower at 65% at 36 months of follow up (155). Yet, program retention is such an important marker for ART programs because it tells how well the ARVs have averted mortalities and morbidities (Fox & Rosen, 2015). The incidence of deaths (55%) was higher than patients getting lost to follow up (45%), unlike evidence in literature in which deaths accounted for 43% and the rest of the majority were lost to follow up (Fox & Rosen, 2015).

74% of female patients were less likely to be retained in the program and still accounted for a higher proportion of those who died or got lost compared to male patients on ART, and at the same time, those who had CD4 counts less than 200 cells / mm^3 were more likely to die (73%) compared with the rest, whereas those who had CD4 counts between 201 and 350 were more likely (64%) to be lost to follow up. This is similar with (Fox & Rosen, 2015) findings that those who had AIDS-defining CD4 counts were less likely to be retained compared with the other patients, but also pointed out that female patients were better retained than male patients. 13% of youths were equally less likely to be retained although this was not seen to be associated with adherence in the study nor disclosure status. (156) highlight that poor retention in HIV programs in resource-limited settings like KCGH is related to multiple factors relating to health systems, the community from which the patient comes and, individual patient factors.

5.4. Secondary Outcome

Suitability of Clinical Based Monitoring of Treatment Failure

Using the clinical criteria to screen for patients suspected of dealing with failure, the study

established that the WHO criteria for the detection of treatment failure had a sensitivity of 80% but a slightly higher specificity of 87%. The chance that someone would be identified as a treatment failure given they have failed therapy was 57%. However, studies elsewhere reported much lower performance for these screening criteria which was lower than 14% sensitivity, as high as 98% specificity and, as low as 20% positive predictive value (37), elsewhere, these criteria were found to inaccurately identify virological failure among children on ART (108).

5.5. Study Limitations and Bias

This was a retrospective study that relied on information generated for clinical care and follow up of patients. The data used therefore was not complete. Medical records in the clinic were also undergoing reconstruction and validation, and only data for patients started on ART between July 2014 and March 2015 could be accessed and used in the study. Hence, the study could not control for information and measurement biases arising due to documentation errors.

Measurement bias could not be overcome considering this study was retrospective and relied on secondary data, but the stratification and regression analysis was done to address this. However, a sensitivity analysis was not done since it had not been considered at the design phase.

Selection bias was a possible source of errors; however, all eligible subjects in the study population and for the study period whose records were available were included in the study. There still exists potential bias considering generalizability. and the way the study population and its target population are compared. This study could not ascertain the accuracy of all the clinical and laboratory information such as WHO staging, CD4 count and viral load results that were collected for every single client in the study, and so, bias

and confounding could only be reduced during data analysis. For example, CD4 results were matched and compared by gender and months on follow up, and this applied in each treatment outcome. Nonetheless, unmeasured confounding could potentially affect the results of this study.

Finally, the study period and scope were limited to explore additional predictors and various methods of generating rich information were used to explain some of the study findings. An exploratory qualitative study would help understand what happens with female patients who experience adverse drug events that lead them to fail therapy; could they be feigning compliance?

5.6. Conclusion

This study established that a high proportion of patients had a remarkable improvement in their clinical condition, CD4 counts and viral load upon initiating on their first line regimen. However, a critical proportion of patients failed therapy and require to be transitioned to second line ART regimen. The clinical criteria for identifying treatment failure had better performance in this study compared with that in literature, but viral load monitoring remains gold standard. Whereas retention in ART program was high, more needs to be done to achieve at least 90% of the UNAIDS goal for patient retention particularly to address underlying system level, community, and individual patient treatment support and adherence.

5.7. Recommendations

1. With a high proportion of patients with recurrent WHO stage 3 or 4 diseases being confirmed to fail therapy or being lost in the ART program, there is a need to continuously screen and manage those at risk and with the disease to prevent negative

outcomes. Such management may include psychosocial care that may address non-overt challenges with therapy adherence and treatment support.

2. CD4 monitoring at least every six months should be encouraged to ensure closer monitoring of immunological progression as well as the screening of patients who may be at risk of death due to conditions or OIs arising from non-responsive or failing immunity. Such patients are also at high risk of failing ART.
3. Viral load monitoring should be enforced as the gold standard to monitoring treatment response and those with viral blips as well as those suspected to be failing virologically should be screened for poor adherence, immunological failure, and presence of resistant HIV strains.
4. For enhanced retention in ART programs, there is a need to explore and address health systems, clinics, community, and individual level barriers and facilitators to retention.
5. The use of clinical criteria for identifying ART failure should be promoted in the routine clinical care of patients on ART especially where viral load monitoring is not timeously available. Further investigation should be conducted into the efficiency of these criteria in the current context of test and treat and in varied contexts and.

References

1. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. World Health Organization; 2016.
2. Spector JM, Agrawal P, Kodkany B, Lipsitz S, Lashoher A, Dziekan G, et al. Improving quality of care for maternal and newborn health: prospective pilot study of the WHO safe childbirth checklist program. PLoS One [Internet]. 2012;7(5):e35151. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22615733
3. Hiremath R, Kulkarni A, Kunte R, Sinha S, Bhalla S, Ghodke S. Human immunodeficiency virus infection/acquired immunodeficiency syndrome Vaccine: Biggest challenge in medical sciences - Some see a hopeless end, while others see an endless hope. Indian J Allergy, Asthma Immunol [Internet]. 2014 [cited 2018 Sep 22];28(1):3. Available from: www.ijaai.in
4. WHO U, UNICEF. Progress report 2011: {Global} {HIV}/{AIDS} response. Geneva World Heal Organ. 2011;
5. Staszewski S, Miller V, Sabin C, Schlecht C, Gute P, Stamm S, et al. Determinants of sustainable CD4 lymphocyte count increases in response to antiretroviral therapy. Aids [Internet]. 1999 May;13(8):951–6. Available from: https://doi.org/10.1097%2F00002030-199905280-00011
6. Aldous JL, Haubrich RH. Defining treatment failure in resource-rich settings. Curr Opin HIV AIDS [Internet]. 2009 Nov;4(6):459–66. Available from: https://doi.org/10.1097%2Fcoh.0b013e328331dea5
7. World Health Organization. Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach-2010 revision. 2010;
8. Ivers LC, Kendrick D, Doucette K. Efficacy of Antiretroviral Therapy Programs in

Resource-Poor Settings: A Meta-analysis of the Published Literature. Clin Infect Dis [Internet]. 2005 Jul;41(2):217–24. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/431199

9. Barth RE, van der Loeff MFS, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. Lancet Infect Dis [Internet]. 2010 Mar;10(3):155–66. Available from: https://doi.org/10.1016%2Fs1473-3099%2809%2970328-7

10. Jobanputra K, Parker LA, Azih C, Okello V, Maphalala G, Kershberger B, et al. Factors associated with virological failure and suppression after enhanced adherence counselling, in children, adolescents and adults on antiretroviral therapy for HIV in Swaziland. Paraskevis D, editor. PLoS One [Internet]. 2015 Feb;10(2):e0116144. Available from: https://doi.org/10.1371%2Fjournal.pone.0116144

11. Schneider J, Kaplan SH, Greenfield S, Li W, Wilson IB. Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. J Gen Intern Med [Internet]. 2004 Nov;19(11):1096–103. Available from: https://doi.org/10.1111%2Fj.1525-1497.2004.30418.x

12. Lucas GM. Substance abuse, adherence with antiretroviral therapy, and clinical outcomes among HIV-infected individuals [Internet]. Vol. 88, Life Sciences. NIH Public Access; 2011 [cited 2018 Sep 5]. p. 948–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20888839

13. Low A, Gavriilidis G, Larke N, B-Lajoie M-R, Drouin O, Stover J, et al. Incidence of Opportunistic Infections and the Impact of Antiretroviral Therapy Among HIV-Infected Adults in Low- and Middle-Income Countries: A Systematic Review and Meta-analysis. Clin Infect Dis [Internet]. 2016 Mar;62(12):1595–603. Available from:

https://academic.oup.com/cid/article-lookup/doi/10.1093/cid/ciw125

14. NASCOP. Kenya AIDS Indicator Survey 2012: Final Report. J Acquir Immune Defic Syndr. 2014;

15. Ministry of Health, National AIDS and STI Control Program. Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya 2016. [Internet]. Nairobi, Kenya: NASCOP; 2016. Available from: https://www.prepwatch.org/wp-content/uploads/2016/08/Guidelines-on-ARV-for-Treating-Preventing-HIV-Infections-in-Kenya.pdf

16. Ministry of Health, CDC. Evaluation of HIV-1 Viral Load Measure Using DBS in Nyanza and Nairobi Regions [Internet]. 2013. Available from: www.nascop.or.ke

17. Daskalopoulou M, Lampe FC, Sherr L, Phillips AN, Johnson MA, Gilson R, et al. Non-Disclosure of HIV Status and Associations with Psychological Factors, ART Non-Adherence, and Viral Load Non-Suppression Among People Living with HIV in the UK. AIDS Behav [Internet]. 2017 Sep;21(1):184–95. Available from: https://doi.org/10.1007%2Fs10461-016-1541-4

18. National AIDS and STI Control Programme. Improving the quality and efficiency of health services in Kenya A Practical Handbook for HIV Managers and Service Providers on Differentiated Care [Internet]. Nairobi, Kenya; 2016 [cited 2018 Sep 4]. Available from: http://www.differentiatedcare.org/Portals/0/adam/Content/6ExZQGTZikegfDfhw5FSwg/File/Kenya-A-Practical-Handbook-for-HIV-Managers-and-Service-Providers-on-Differentiated-Care.pdf

19. Achieng MO. Evaluation of early immunological response among patients on first line highly active anti-retroviral therapy (HAART) at Kenyatta National Hospital [Internet]. University of Nairobi, Kenya; 2008. Available from:

http://datad.aau.org:8080/jspui/handle/123456789/36055

20. Bartlett J, Gallant J. Medical management of HIV infection. 1 edition. Hopkins Fulfillment Services; 2007. 61 p.

21. UNAIDS. Global AIDS Update: UNAIDS report [Internet]. WHO. World Health Organization; 2016. Available from: http://www.who.int/hiv/pub/arv/global-aids-update-2016-pub/en/

22. Fokam J, Billong SC, Jogue F, Ndiang SMT, Motaze ACN, Paul KN, et al. Immuno-virological response and associated factors amongst HIV-1 vertically infected adolescents in Yaoundé-Cameroon. PLoS One. 2017 Nov;12(11):e0187566.

23. UNAIDS. 90-90-90: an ambitious treatment target to help end the AIDS epidemic. Geneva: UNAIDS. 2014;

24. Hassan AS, Mwaringa SM, Obonyo CA, Nabwera HM, Sanders EJ, Rinke de Wit TF, et al. Low Prevalence of Transmitted HIV Type 1 Drug Resistance Among Antiretroviral-Naive Adults in a Rural HIV Clinic in Kenya. AIDS Res Hum Retroviruses [Internet]. 2013 Jan;29(1):129–35. Available from: http://online.liebertpub.com/doi/abs/10.1089/aid.2012.0167

25. Onywera H, Maman D, Inzaule S, Auma E, Were K, Fredrick H, et al. Surveillance of HIV-1 pol transmitted drug resistance in acutely and recently infected antiretroviral drug-naï¿½ve persons in rural western Kenya. Menéndez-Arias L, editor. PLoS One [Internet]. 2017 Feb;12(2):e0171124. Available from: https://doi.org/10.1371%2Fjournal.pone.0171124

26. Kan W, Teng T, Liang S, Ma Y, Tang H, Zuohela T, et al. Predictors of HIV virological failure and drug resistance in Chinese patients after 48 months of antiretroviral treatment, 2008-2012: A prospective cohort study. BMJ Open [Internet]. 2017 Sep 7 [cited 2018 Sep 24];7(9):e016012. Available from:

http://www.ncbi.nlm.nih.gov/pubmed/28882911

27. Wittkop L, Günthard HF, de Wolf F, Dunn D, Cozzi-Lepri A, de Luca A, et al. Effect of transmitted drug resistance on virological and immunological response to initial combination antiretroviral therapy for HIV (EuroCoord-CHAIN joint project): A European multicohort study. Lancet Infect Dis [Internet]. 2011 May;11(5):363–71. Available from: https://doi.org/10.1016%2Fs1473-3099%2811%2970032-9

28. Bulage L, Ssewanyana I, Nankabirwa V, Nsubuga F, Kihembo C, Pande G, et al. Factors Associated with Virological Non-suppression among HIV-Positive Patients on Antiretroviral Therapy in Uganda, August 2014-July 2015. BMC Infect Dis [Internet]. 2017 May;17(1). Available from: https://doi.org/10.1186%2Fs12879-017-2428-3

29. World Health Organization. WHO Consultation on ART Failure in the Context of Public Health Approach [Internet]. Switzerland; 2008. Available from: http://www.who.int/hiv/pub/arv/art_meeting_art_fail.pdf

30. Ledergerber B, Egger M, Opravil M, Telenti A, Hirschel B, Battegay M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: A prospective cohort study. Lancet [Internet]. 1999 Mar;353(9156):863–8. Available from: https://doi.org/10.1016%2Fs0140-6736%2899%2901122-8

31. Wilson EMP, Sereti I. Immune Restoration After Antiretroviral Therapy: The Pitfalls Of Hasty Or Incomplete Repairs. Immunol Rev. 2013;254(1):343–54.

32. Orrell C, Harling G, Lawn SD, Kaplan R, McNally M, Bekker LG, et al. Conservation of first-line antiretroviral treatment regimen where therapeutic options are limited. Antivir Ther [Internet]. 2007;12(1):83–8. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L46340429

http://novacat.nova.edu:4550/resserv?sid=EMBASE&issn=13596535&id=doi:&atitle=

Conservation+of+first-line+antiretroviral+treatment+regimen+where+therapeutic+options+are+limit

33. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [Internet]. 2016. Available from: http://www.aidsinfo.nih.gov/ContentFiles/Adul-

34. UNAIDS. Outlook Breaking News: Young People Are Leading the HIV Prevention Revolution [Internet]. Geneva; 2010. Available from: http://files.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2010/20100713_outlook_youngpeople_en.pdf

35. Biset Ayalew M, Kumilachew D, Belay A, Getu S, Teju D, Endale D, et al. First-line antiretroviral treatment failure and associated factors in HIV patients at University of Gondar Teaching Hospital, Gondar, Northwest Ethiopia. HIV/AIDS - Res Palliat Care [Internet]. 2016 Sep;Volume 8:141–6. Available from: https://www.dovepress.com/first-line-antiretroviral-treatment-failure-and-associated-factors-in--peer-reviewed-article-HIV

36. Todd J, Grosskurth H, Changalucha J, Obasi A, Mosha F, Balira R, et al. Risk Factors Influencing HIV Infection Incidence in a Rural African Population: A Nested Case-Control Study. J Infect Dis [Internet]. 2006 Feb;193(3):458–66. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1086/499313

37. Le NK, Riggi E, Marrone G, Vu T Van, Izurieta RO, Nguyen CKT, et al. Assessment of WHO criteria for identifying ART treatment failure in Vietnam from 2007 to 2011. De Socio GV, editor. PLoS One [Internet]. 2017 Sep 6;12(9):e0182688. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28877173

38. El-Khatib Z, Katzenstein D, Marrone G, Laher F, Mohapi L, Petzold M, et al. Adherence to drug-refill is a useful early warning indicator of virologic and

immunologic failure among HIV patients on first-line art in South Africa. Maartens G, editor. PLoS One [Internet]. 2011 Mar;6(3):e17518. Available from: https://doi.org/10.1371%2Fjournal.pone.0017518

39. Mutevedzi PC, Lessells RJ, Rodger AJ, Newell M-LL. 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 2018 Sep 5];6(7):e21795. Available from: http://dx.plos.org/10.1371/journal.pone.0021795

40. Kenya Gazette. Kenya Gazette 11 May 2007 [Internet]. Government Printers, Nairobi; 2007. Available from: http://kenyalaw.org/kenya_gazette/gazette/volume/Mzk5/Vol.CIX-No.34

41. Division of Health Services. eHealth-Kenya Master Facility List [Internet]. 2007. Available from: http://www.ehealth.or.ke

42. Sup Lee, Soong. World development indicators 2010 (English) [Internet]. Washington, DC: World Bank; 2010 [cited 2018 Sep 5]. Available from: http://documents.worldbank.org/curated/en/988271468149678303/World-development-indicators-2010

43. UNAIDS. GLOBAL AIDS UPDATE 2016 [Internet]. 2016 [cited 2018 Sep 23]. Available from: http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf

44. Statistics KNB of. 2009 Kenya Population and Housing Census: Volume 1A [Internet]. Nairobi, Kenya; 2010. Available from: http://54.213.151.253/nada/index.php/catalog/55

45. Heffron R, Ngure K, Mugo N, Celum C, Kurth A, Curran K, et al. Willingness of Kenyan HIV-1 serodiscordant couples to use antiretroviral-based HIV-1 prevention strategies. J Acquir Immune Defic Syndr [Internet]. 2012 Sep;61(1):116–9. Available

from: https://doi.org/10.1097%2Fqai.0b013e31825da73f

46. Brown JL, Sales JM, DiClemente RJ. Combination HIV Prevention Interventions: The Potential of Integrated Behavioral and Biomedical Approaches [Internet]. Vol. 11, Current HIV/AIDS Reports. NIH Public Access; 2014 [cited 2018 Sep 5]. p. 363–75. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25216985

47. Ministry of Health, National AIDS and STI Control Programme. Guidelines on Use of Antiretroviral Drugs for Treating and Preventing HIV Infection in Kenya - 2016 Edition [Internet]. 2016. Available from: https://aidsfree.usaid.gov/sites/default/files/kenya_art_2016.pdf

48. World Health Organization. Antiretroviral Therapy for Adults and Adolescents: Recommendations for a public health approach. World Heal Organ [Internet]. 2006;1–134. Available from: http://www.who.int/hiv/pub/guidelines/artadultguidelines.pdf

49. World Health Organization. Guidelines on Packaging for Pharmaceutical Products. WHO Technical Report Series, No. 902, 2002, Annex 9 [Internet]. 2002. Available from: http://apps.who.int/medicinedocs/en/d/Js19638en/

50. Kenya Brief on ART. Kenya Gazette 11 May 2007 [Internet]. Nairobi, Kenya; 2007. Available from: http://mygov.go.ke/wp-content/uploads/2015/05/Brief-on-ART-in-Kenya

51. Hope R, Israel E. The Essentials of Antiretroviral Therapy for Health Care and Program Managers, Technical Guidance Series Number 5. 2007; Available from: https://books.google.co.za/books?id=AYN60n_sc1YC&pg=PA62&lpg=PA62&dq=Hope,+R+and+Israel,+E.,+(2007),+The+Essentials+of+Antiretroviral+Therapy+for+Health+Care+and+Program+Managers,+Technical+Guidance+Series+Number+5,+Pathfinder+International&source=bl&ots=

52. Duber HC, Dansereau E, Masters SH, Achan J, Burstein R, DeCenso B, et al. Uptake

of WHO recommendations for first-line antiretroviral therapy in Kenya, Uganda, and Zambia. Paraskevis D, editor. PLoS One [Internet]. 2015 Mar 25 [cited 2018 Sep 5];10(3):e0120350. Available from: http://dx.plos.org/10.1371/journal.pone.0120350

53. Ministry of Health MCP. National Guidelines for the diagnosis, treatment and prevention of malaria in Kenya [Internet]. 5th ed. Nairobi, Kenya: Ministry of Health National Malaria Control Program, Kenya; 2016. 62 p. Available from: http://www.thehealthcompass.org/sites/default/files/project_examples/Kenya_Malaria_Tx_Guideline_2010.pdf

54. Djobet MPN, Singhe D, Lohoue J, Kuaban C, Ngogang J, Tambo E. Antiretroviral therapy supply chain quality control and assurance in improving people living with HIV therapeutic outcomes in Cameroon. AIDS Res Ther [Internet]. 2017 Apr;14(1). Available from: https://doi.org/10.1186%2Fs12981-017-0147-x

55. Ram'irez-Amador V, Esquivel-Pedraza L, Sierra-Madero J, Anaya-Saavedra G, González-Ram'irez I, Ponce-de-León S. The changing clinical spectrum of human immunodeficiency virus (HIV)-related oral lesions in 1,000 consecutive patients: a 12-year study in a referral center in Mexico. Medicine (Baltimore). 2003;82(1):39–50.

56. Schmidt-Westhausen AM, Priepke F, Bergmann FJ, Reichart PA. Decline in the rate of oral opportunistic infections following introduction of highly active antiretroviral therapy. J Oral Pathol Med [Internet]. 2000 Aug;29(7):336–41. Available from: https://doi.org/10.1034%2Fj.1600-0714.2000.290708.x

57. Agu KA, Ochei UM, Oparah AC, Onoh OU. Treatment outcomes in patients receiving combination antiretroviral therapy in Central Hospital, Benin City, Nigeria. Trop J Pharm Res [Internet]. 2010 Mar;9(1):1–10. Available from: https://doi.org/10.4314%2Ftjpr.v9i1.52028

58. Erb P, Battegay M, Zimmerli W, Rickenbach M, Egger M. Effect of antiretroviral

therapy on viral load, CD4 cell count, and progression to acquired immunodeficiency syndrome in a community human immunodeficiency virus-infected cohort. Arch Intern Med [Internet]. 2000 Apr;160(8):1134–40. Available from: https://doi.org/10.1001%2Farchinte.160.8.1134

59. Corey DM, Kim HW, Salazar R, Illescas R, Villena J, Gutierrez L, et al. Brief Report: Effectiveness of Combination Antiretroviral Therapy on Survival and Opportunistic Infections in a Developing World Setting. JAIDS J Acquir Immune Defic Syndr [Internet]. 2007 Apr;44(4):451–5. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00126334-200704010-00012

60. National AIDS/STI Control Program. Guidelines for Antiretroviral Therapy in Kenya. 4th Edition: 2011. Print [Internet]. 4th ed. Nairobi, Kenya: Print; 2011. Available from: http://guidelines.health.go.ke:8000/media/Final_guidelines_re_print_11-09-2012.pdf

61. World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection [Internet]. WHO. World Health Organization; 2013. Available from: http://www.who.int/hiv/pub/guidelines/arv2013/en/

62. Menezes CN, Maskew M, Sanne I, Crowther NJ, Raal FJ. A longitudinal study of stavudine-associated toxicities in a large cohort of South African HIV infected subjects. BMC Infect Dis [Internet]. 2011 Dec 17 [cited 2018 Sep 5];11(1):244. Available from: http://www.ncbi.nlm.nih.gov/pubmed/21923929

63. Waning B, Diedrichsen E, Jambert E, Bärnighausen T, Li Y, Pouw M, et al. The global pediatric antiretroviral market: analyses of product availability and utilization reveal challenges for development of pediatric formulations and HIV/AIDS treatment in

children. BMC Pediatr [Internet]. 2010;10(1):74. Available from: https://doi.org/10.1186/1471-2431-10-74

64. World Health Organization. Access to anti-retroviral drugs in low and middle income countries. World Heal Organ [Internet]. 2014 [cited 2018 Sep 23];(July):1–37. Available from: www.who.int

65. Labhardt ND, Sello M, Lejone T, Ehmer J, Mokhantso M, Lynen L, et al. Adoption of new HIV treatment guidelines and drug substitutions within first-line as a measure of quality of care in rural Lesotho: Health centers and hospitals compared. Trop Med Int Heal [Internet]. 2012 Jul;17(10):1245–54. Available from: https://doi.org/10.1111%2Fj.1365-3156.2012.03051.x

66. Pasquet A, Messou E, Gabillard D, Minga A, Depoulosky A, Deuffic-Burban S, et al. Impact of drug stock-outs on death and retention to care among HIV-infected patients on combination antiretroviral therapy in Abidjan, Côte d'ivoire. Myer L, editor. PLoS One [Internet]. 2010 Oct;5(10):e13414. Available from: https://doi.org/10.1371%2Fjournal.pone.0013414

67. Sarna A, Luchters S, Musenge E, Okal J, Chersich M, Tun W, et al. Effectiveness of a community-based positive prevention intervention for people living with HIV who are not receiving antiretroviral treatment: a prospective cohort study. Glob Heal Sci Pract. 2013;

68. Nosyk B, Lourenço L, Min JE, Shopin D, Lima VD, Montaner JSG. Characterizing retention in HAART as a recurrent event process: Insights into "cascade churn." Aids [Internet]. 2015 Aug;29(13):1681–9. Available from: https://doi.org/10.1097%2Fqad.0000000000000746

69. Callaghan M, Ford N, Schneider H. A systematic review of task- shifting for HIV treatment and care in Africa. Hum Resour Health [Internet]. 2010 Mar;8(1). Available

from: https://doi.org/10.1186%2F1478-4491-8-8

70. Vajpayee M, Mohan T. Current practices in laboratory monitoring of HIV infection. Indian J Med Res [Internet]. 2011;134(December):801–22. Available from: https://doi.org/10.4103%2F0971-5916.92627

71. Kumarasamy N, Venkatesh KK, Mayer KH, Freedberg K. Financial burden of health services for people with HIV/AIDS in India. Indian J Med Res [Internet]. 2007 Dec;126(6):509–17. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2365908/

72. Munthali C, Taegtmeyer M, Garner PG, Lalloo DG, Squire SB, Corbett EL, et al. Diagnostic accuracy of the WHO clinical staging system for defining eligibility for ART in sub-Saharan Africa: a systematic review and meta-analysis. J Int AIDS Soc [Internet]. 2014 Jun 12;17(1):18932. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4057784/

73. Kaufmann GR, Perrin L, Pantaleo G, Opravil M, Furrer H, Telenti A, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: The Swiss HIV cohort study. Arch Intern Med [Internet]. 2003 Oct;163(18):2187–95. Available from: https://doi.org/10.1001%2Farchinte.163.18.2187

74. Mellors JW, Muñoz A, Giorgi J V, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. Ann Intern Med [Internet]. 1997 Jun 15 [cited 2018 Sep 5];126(12):946–54. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9182471

75. NACC. Kenya National Aids Spending Assessment Report for the Financial Years. 2014 [cited 2018 Sep 24];(August). Available from: http://files.unaids.org/en/media/unaids/contentassets/documents/data-and-

analysis/tools/nasa/20141017/kenya_2011_en.pdf

76. Schaecher KL. The importance of treatment adherence in HIV. Am J Manag Care. 2013 Sep;19(12 Suppl):s231-237.

77. Marston M, Zaba B, Salomon JA, Brahmbhatt H, Bagenda D. Estimating the net effect of HIV on child mortality in African populations affected by generalized HIV epidemics. J Acquir Immune Defic Syndr [Internet]. 2005 Feb 1 [cited 2018 Sep 5];38(2):219–27. Available from: http://www.ncbi.nlm.nih.gov/pubmed/15671809

78. SM H, MS S, M S, et al. Treatment for adult hiv infection: 2006 recommendations of the international aids society–usa panel. JAMA [Internet]. 2006;296(7):827–43. Available from: +

79. World Health Organization. Quality of care: A process for making strategic choices in health systems. J Am Med Assoc [Internet]. 2006;267:1–50. Available from: http://www.who.int/management/quality/assurance/QualityCare_B.Def.pdf

80. Yuh B, Tate J, Butt AA, Crothers K, Freiberg M, Leaf D, et al. Weight change after antiretroviral therapy and mortality. Clin Infect Dis. 2015 Jun;60(12):1852–9.

81. Chaisson LH, Katamba A, Haguma P, Ochom E, Ayakaka I, Mugabe F, et al. Theory-informed interventions to improve the quality of tuberculosis evaluation at Ugandan health centers: A quasi-experimental study. PLoS One. 2015;

82. Thakur R, Vk S. A Study of Clinical Profile of Recurrent Tuberculosis in People Living with HIV/AIDS. J AIDS Clin Res. 2018 Apr;9(4):1–5.

83. Taiwo OO, Hassan Z. The impact of Highly Active Antiretroviral Therapy (HAART) on the clinical features of HIV - related oral lesions in Nigeria. AIDS Res Ther [Internet]. 2010;7(1):19. Available from: https://doi.org/10.1186%2F1742-6405-7-19

84. Renaud-Théry F, Duncombe C, Kerr S, Thierry S. Title : Adult antiretroviral therapy in resource limited settings : a systematic review of first-line failure and attrition rates

[Internet]. Who. 2008 [cited 2018 Sep 4]. Available from: http://www.who.int/hiv/topics/treatment/First_Line_ART_failure_RLS_metanalysis.pdf

85. Khienprasit N, Chaiwarith R, Sirisanthana T, Supparatpinyo K. Incidence and risk factors of antiretroviral treatment failure in treatment-naïve HIV-infected patients at Chiang Mai University Hospital, Thailand. AIDS Res Ther [Internet]. 2011;8(1):42. Available from: https://doi.org/10.1186%2F1742-6405-8-42

86. Kannangai R, Kandathil AJ, Ebenezer DL, Nithyanandam G, Samuel P, Abraham OC, et al. Evidence for lower CD4+ T cell and higher viral load in asymptomatic HIV-1 infected individuals of India: implications for therapy initiation. Indian J Med Microbiol [Internet]. 2008 [cited 2018 Sep 6];26(3):217–21. Available from: http://www.ncbi.nlm.nih.gov/pubmed/18695317

87. Hammer S, Saag M, Schechter M, Montaner J, Schooley R, Jacobsen D, et al. Treatment for Adult HIV infection: 2006 recommendations of the International AIDS Society-USA Panel. Jama. 2006;296(7):827–43.

88. O'Connor J, Vjecha MJ, Phillips AN, Angus B, Cooper D, Grinsztejn B, et al. Effect of immediate initiation of antiretroviral therapy on risk of severe bacterial infections in HIV-positive people with CD4 cell counts of more than 500 cells per μL: secondary outcome results from a randomised controlled trial. Lancet HIV. 2017 Mar;4(3):e105–12.

89. Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents [Internet]. 2016. Available from: http://aidsinfo.nih.gov/guidelines

90. Olawumi HO, Olatunji PO, Salami AK, Odeigah L, Iseniyi JO. Effect of highly active

antiretroviral therapy on CD4 count and weight in AIDS patients seen at the UITH, Ilorin. Niger J Clin Pr. 2008;11(4):312–5.

91. Moore RD, Keruly JC. CD4+ Cell Count 6 Years after Commencement of Highly Active Antiretroviral Therapy in Persons with Sustained Virologic Suppression. Clin Infect Dis [Internet]. 2007 Feb 1 [cited 2018 Sep 5];44(3):441–6. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/510746

92. Gezie LD. Predictors of CD4 count over time among HIV patients initiated ART in Felege Hiwot Referral Hospital, northwest Ethiopia: Multilevel analysis. BMC Res Notes [Internet]. 2016 May 25;9(1). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4967525/

93. Harrigan PR, Hogg RS, Dong WWY, Yip B, Wynhoven B, Woodward J, et al. Predictors of HIV Drug-Resistance Mutations in a Large Antiretroviral-Naive Cohort Initiating Triple Antiretroviral Therapy. J Infect Dis [Internet]. 2005 Feb;191(3):339–47. Available from: https://academic.oup.com/jid/article-lookup/doi/10.1086/427192

94. Schacker TW, Hughes JP, Shea T, Coombs RW, Corey L. Biological and virologic characteristics of primary HIV infection. Ann Intern Med [Internet]. 1998 Apr 15 [cited 2018 Sep 5];128(8):613–20. Available from: http://www.ncbi.nlm.nih.gov/pubmed/9537934

95. Kinyanjui SM, Mwangi T, Bull PC, Newbold CI, Marsh K. Protection against clinical malaria by heterologous immunoglobulin G antibodies against malaria-infected erythrocyte variant surface antigens requires interaction with asymptomatic infections. J Infect Dis. 2004;

96. Babiker A, Bartlett J, Breckenridge A, Collins G, Coombs R, Cooper D, et al. Human immunodeficiency virus type 1 RNA level and CD4 count as prognostic markers and surrogate end points: A meta-analysis. AIDS Res Hum Retroviruses.

2000;16(12):1123–33.

97. Havlir D V., Bassett R, Levitan D, Gilbert P, Tebas P, Collier AC, et al. Prevalence and predictive value of intermittent viremia with combination HIV therapy. J Am Med Assoc [Internet]. 2001 Jul;286(2):171–9. Available from: https://doi.org/10.1001%2Fjama.286.2.171

98. Lee PK, Kieffer TL, Siliciano RF, Nettles RE. HIV-1 viral load blips are of limited clinical significance. J Antimicrob Chemother [Internet]. 2006 May 1 [cited 2018 Sep 4];57(5):803–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/16533823

99. Sörstedt E, Nilsson S, Blaxhult A, Gisslén M, Flamholc L, Sönnerborg A, et al. Viral blips during suppressive antiretroviral treatment are associated with high baseline HIV-1 RNA levels. BMC Infect Dis. 2016 Jun;16.

100. Kyaw NTT, Harries AD, Kumar AMV, Oo MM, Kyaw KWY, Win T, et al. High rate of virological failure and low rate of switching to second-line treatment among adolescents and adults living with HIV on firstline ART in Myanmar, 2005-2015. Vol. 12, PLoS ONE. 2017.

101. Phillips AN, Staszewski S, Weber R, Kirk O, Francioli P, Miller V, et al. HIV Viral Load Response to Antiretroviral Therapy According to the Baseline CD4 Cell Count and Viral Load. Jama [Internet]. 2001 Nov;286(20):2560. Available from: http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.286.20.2560

102. Waruru A, Muttai H, Ng'ang'a L, Ackers M, Kim A, Miruka F, et al. Positive predictive value of the WHO clinical and immunologic criteria to predict viral load failure among adults on first, or second-line antiretroviral therapy in Kenya. Fox MP, editor. PLoS One [Internet]. 2016 Jul;11(7):e0158881. Available from: https://doi.org/10.1371%2Fjournal.pone.0158881

103. Davies MA, Moultrie H, Eley B, Rabie H, Van Cutsem G, Giddy J, et al. Virologic

failure and second-line antiretroviral therapy in children in South Africa-the IeDEA Southern Africa collaboration. J Acquir Immune Defic Syndr [Internet]. 2011 Mar;56(3):270–8. Available from: https://doi.org/10.1097%2Fqai.0b013e3182060610

104. Kelly C, Gaskell KM, Richardson M, Klein N, Garner P, MacPherson P. Discordant immune response with antiretroviral therapy in HIV-1: A systematic review of clinical outcomes. PLoS One [Internet]. 2016 May 25;11(6):e0156099. Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0156099

105. Charles M, Leger PD, Severe P, Guiteau C, Apollon A, Gulick RM, et al. Virologic, clinical and immunologic responses following failure of first-line antiretroviral therapy in Haiti. J Int AIDS Soc [Internet]. 2012 Jun;15(2). Available from: https://doi.org/10.7448%2Fias.15.2.17375

106. Abdissa A, Yilma D, Fonager J, Audelin AM, Christensen LH, Olsen MF, et al. Drug resistance in HIV patients with virological failure or slow virological response to antiretroviral therapy in Ethiopia. BMC Infect Dis. 2014 Dec;14(1):181.

107. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, Traisaithit P, Barbier B, Techapornroong M, et al. PHPT-3: A Randomized Clinical Trial Comparing CD4 vs Viral Load ART Monitoring/Switching Strategies in Thailand. In: 18th Conference on Retrovirology and Opportunistic Infections Paper # 44. Boston, MA; 2011. p. CROI 2011.

108. Davies MA, Boulle A, Eley B, Moultrie H, Technau K, Rabie H, et al. Accuracy of immunological criteria for identifying virological failure in children on antiretroviral therapy - The IeDEA Southern Africa Collaboration. Trop Med Int Heal [Internet]. 2011;16(11):1367–71. Available from: https://onlinelibrary.wiley.com/doi/pdf/10.1111/j.1365-3156.2011.02854.x

109. Kiertiburanakul S, Sungkanuparph S. Emerging of HIV drug resistance: epidemiology,

diagnosis, treatment and prevention. Curr HIV Res [Internet]. 2009 May;7(3):273–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19442122

110. Datay MI, Boulle A, Mant D, Yudkin P. Associations With Virologic Treatment Failure in Adults on Antiretroviral Therapy in South Africa. JAIDS J Acquir Immune Defic Syndr [Internet]. 2010 Aug;54(5):489–95. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00126334-201008150-00007

111. Buck WC, Kabue MM, Kazembe PN, Kline MW. Discontinuation of standard first-line antiretroviral therapy in a cohort of 1434 Malawian children. J Int AIDS Soc [Internet]. 2010;13(1):31. Available from: https://doi.org/10.1186%2F1758-2652-13-31

112. Ma Y, Zhao D, Yu L, Bulterys M, Robinson ML, Zhao Y, et al. Predictors of Virologic Failure in HIV-1–Infected Adults Receiving First-Line Antiretroviral Therapy in 8 Provinces in China. Clin Infect Dis [Internet]. 2010 Jan 15 [cited 2018 Sep 5];50(2):264–71. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20017637

113. DiazGranados CA, Mantilla M, Lenis W. Antiretroviral drug resistance in HIV-infected patients in Colombia. Int J Infect Dis [Internet]. 2010 Apr;14(4):e298--e303. Available from: https://doi.org/10.1016%2Fj.ijid.2009.05.006

114. Amin E, Ngu R, Abanda M, Kika B, Mvilongo T, Fon P. Modification of antiretroviral therapy regimen: Incidence and predictors in two major HIV/AIDS treatment centers in the Southwest Region of Cameroon. Int J Adv Med Heal Res [Internet]. 2018 [cited 2018 Sep 25];5(1):7. Available from: http://www.ijamhrjournal.org/text.asp?2018/5/1/7/235612

115. Cohen CJ. Successful HIV treatment: lessons learned. J Manag Care Pharm [Internet]. 2006 [cited 2018 Sep 25];12(7 Suppl B):S6-11. Available from: www.amcp.org

116. Alave J, Paz J, González E, Campos M, Rodríguez M, Willig J, et al. [Risk factors associated with virologic failure in HIV- infected patients receiving antiretroviral therapy at a public hospital in Peru]. Rev Chilena Infectol [Internet]. 2013 Feb [cited 2018 Sep 5];30(1):42–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23450408

117. Duber HC, Dansereau E, Masters SH, Achan J, Burstein R, DeCenso B, et al. Uptake of WHO recommendations for first-line antiretroviral therapy in Kenya, Uganda, and Zambia. Paraskevis D, editor. PLoS One [Internet]. 2015 Mar;10(3):e0120350. Available from: https://doi.org/10.1371%2Fjournal.pone.0120350

118. Bezabhe WM, Chalmers L, Bereznicki LR, Peterson GM. Adherence to Antiretroviral Therapy and Virologic Failure: A Meta-Analysis. Shang. L, editor. Medicine (Baltimore) [Internet]. 2016 Apr 18;95(15):e3361. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4839839/

119. Cadosch D, Bonhoeffer S, Kouyos R. Assessing the impact of adherence to anti-retroviral therapy on treatment failure and resistance evolution in HIV. J R Soc Interface [Internet]. 2012 Mar;9(74):2309–20. Available from: https://doi.org/10.1098%2Frsif.2012.0127

120. Althoff KN, Justice AC, Gange SJ, Deeks SG, Saag MS, Silverberg MJ, et al. Virologic and immunologic response to HAART, by age and regimen class. Aids [Internet]. 2010 Oct;24(16):2469–79. Available from: https://doi.org/10.1097%2Fqad.0b013e32833e6d14

121. Durvasula R, Miller TR. Substance abuse treatment in persons with HIV/AIDS: Challenges in managing triple diagnosis. Behav Med [Internet]. 2014 Apr 3 [cited 2018 Sep 25];40(2):43–52. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24274175

122. Altice FL, Kamarulzaman A, Soriano V V., Schechter M, Friedland GH. Treatment of medical, psychiatric, and substance-use comorbidities in people infected with HIV who use drugs. Lancet [Internet]. 2010 Jul;376(9738):367–87. Available from: https://doi.org/10.1016%2Fs0140-6736%2810%2960829-x

123. Sang RKA, Miruka FO. Factors Associated with Virologic Failure Amongst Adults on Antiretroviral Therapy in Nyanza Region, Kenya. {IOSR} J Dent Med Sci [Internet]. 2016 Jul;15(07):108–21. Available from: https://doi.org/10.9790%2F0853-15076108121

124. Bartelink IH, Savic RM, Dorsey G, Ruel T, Gingrich D, Scherpbier HJ, et al. The effect of malnutrition on the pharmacokinetics and virologic outcomes of lopinavir, efavirenz and nevirapine in food insecure HIV-infected children in Tororo, Uganda. Pediatr Infect Dis J [Internet]. 2015 Mar;34(3):e63–70. Available from: https://doi.org/10.1097%2Finf.0000000000000603

125. Pernas B, Grandal M, Pertega S, Cañizares A, Castro-Iglesias Á, Mena Á, et al. Any impact of blips and low-level viraemia episodes among HIV-infected patients with sustained virological suppression on ART? J Antimicrob Chemother. 2016 Apr;71(4):1051–5.

126. Tan R, Westfall AO, Willig JH, Mugavero MJ, Saag MS, Kaslow RA, et al. Clinical outcome of HIV-infected antiretroviral-naive patients with discordant immunologic and virologic responses to highly active antiretroviral therapy. J Acquir Immune Defic Syndr [Internet]. 2008 Apr;47(5):553–8. Available from: https://doi.org/10.1097%2Fqai.0b013e31816856c5

127. Fox MP, Rosen S. Retention of adult patients on antiretroviral therapy in low- and middle-income countries: Systematic review and meta-analysis 2008-2013. J Acquir Immune Defic Syndr [Internet]. 2015 May 1 [cited 2018 Sep 5];69(1):98–108.

Available from: http://www.ncbi.nlm.nih.gov/pubmed/25942461

128. Rosen S, Fox MP, Gill CJ. Patient Retention in Antiretroviral Therapy Programs in Sub-Saharan Africa: A Systematic Review. PLOS Med. 2007 Oct;4(10):e298.

129. Mutasa-Apollo T, Shiraishi RW, Takarinda KC, Dzangare J, Mugurungi O, Murungu J, et al. Patient retention, clinical outcomes and attrition-associated factors of HIV-infected patients enrolled in Zimbabwe's National Antiretroviral Therapy Programme, 2007-2010. PLoS One. 2014 Jan;9(1):e86305.

130. Thida A, Tun STT, Zaw SKK, Lover AA, Cavailler P, Chunn J, et al. Retention and risk factors for attrition in a large public health ART program in myanmar: A retrospective cohort analysis. Beck EJ, editor. PLoS One [Internet]. 2014 Sep;9(9):e108615. Available from: https://doi.org/10.1371%2Fjournal.pone.0108615

131. Wilkinson LS, Skordis-Worrall J, Ajose O, Ford N. Self-transfer and mortality amongst adults lost to follow-up in ART programmes in low- and middle-income countries: Systematic review and meta-analysis. Trop Med Int Heal [Internet]. 2015 Jan;20(3):365–79. Available from: https://doi.org/10.1111%2Ftmi.12434

132. Nosyk B, Lourenço L, Min JE, Shopin D, Lima VD, Montaner JSG. Characterizing retention in HAART as a recurrent event process: Insights into "cascade churn." Aids. 2015;29(13):1681–9.

133. Fox MP, Shearer K, Maskew M, Meyer-Rath G, Clouse K, Sanne I. Attrition through multiple stages of pre-treatment and ART HIV care in South Africa. Graham SM, editor. PLoS One [Internet]. 2014 Oct 20 [cited 2018 Sep 5];9(10):e110252. Available from: http://dx.plos.org/10.1371/journal.pone.0110252

134. Geng EH, Nash D, Kambugu A, Zhang Y, Braitstein P, Christopoulos KA, et al. Retention in Care among HIV-Infected Patients in Resource-Limited Settings: Emerging Insights and New Directions. Curr HIV/AIDS Rep [Internet]. 2010 Nov 7

[cited 2018 Sep 25];7(4):234–44. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20820972

135. Geng EH, Bangsberg DR, Musinguzi N, Emenyonu N, Bwana MB, Yiannoutsos CT, et al. Understanding Reasons for and Outcomes of Patients Lost to Follow-Up in Antiretroviral Therapy Programs in Africa Through a Sampling-Based Approach. JAIDS J Acquir Immune Defic Syndr [Internet]. 2010 Mar [cited 2018 Sep 25];53(3):405–11. Available from: http://www.ncbi.nlm.nih.gov/pubmed/19745753

136. Ohene SA, Addo NA, Zigah F, Newman M, Lartey M, Romero MA, et al. Evaluation of antiretroviral therapy (ART) provision in an early cohort of patients initiating ART in Ghana. Pan Afr Med J. 2013 Nov;16:117.

137. Maina G, Mill J, Chaw-Kant J, Caine V. A systematic review of best practices in HIV care. J HIV AIDS Soc Serv [Internet]. 2016 Mar 22 [cited 2018 Sep 25];15(1):114–26. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27152102

138. Koirala S, Deuba K, Nampaisan O, Marrone G, Ekström AM, group for the C-S. Facilitators and barriers for retention in HIV care between testing and treatment in Asia—A study in Bangladesh, Indonesia, Lao, Nepal, Pakistan, Philippines and Vietnam. Stoddart CA, editor. PLoS One [Internet]. 2017 May 1;12(5):e0176914. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5411091/

139. Gallop RJ, Dimidjian S, Atkins DC, Muggeo V. Quantifying Treatment Effects When Flexibly Modeling Individual Change in a Nonlinear Mixed Effects Model [Internet]. Vol. 9, Journal of Data Science. 2011 [cited 2018 Sep 27]. Available from: http://www.jds-online.com/files/JDS-683.pdf

140. Kimanga DO, Ogola S, Umuro M, Ng'ang'a A, Kimondo L, Murithi P, et al. Prevalence and Incidence of HIV Infection, Trends, and Risk Factors Among Persons Aged 15–64 Years in Kenya. JAIDS J Acquir Immune Defic Syndr [Internet]. 2014

May;66(Suppl 1):S13–26. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00126334-201405011-00003

141. Longenecker CT, Triant VA. Initiation of Antiretroviral Therapy at High CD4 Counts: Does it Reduce the Risk of Cardiovascular Disease? Curr Opin HIV AIDS. 2014 Jan;9(1):54–62.

142. Tang Z, Pan SW, Ruan Y, Liu X, Su J, Zhu Q, et al. Effects of high CD4 cell counts on death and attrition among HIV patients receiving antiretroviral treatment: An observational cohort study. Sci Rep. 2017 Jun;7(1):3129.

143. Longenecker CT, Triant VA. Initiation of antiretroviral therapy at high CD4 cell counts: Does it reduce the risk of cardiovascular disease? [Internet]. Vol. 9, Current Opinion in HIV and AIDS. NIH Public Access; 2014 [cited 2018 Sep 5]. p. 54–62. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24275676

144. Mangili A, Murman DH, Zampini AM, Wanke CA. Nutrition and HIV infection: review of weight loss and wasting in the era of highly active antiretroviral therapy from the nutrition for healthy living cohort. Clin Infect Dis. 2006 Mar;42(6):836–42.

145. B-Lajoie M-R, Drouin O, Bartlett G, Nguyen Q, Low A, Gavriilidis G, et al. Incidence and Prevalence of Opportunistic and Other Infections and the Impact of Antiretroviral Therapy Among HIV-infected Children in Low- and Middle-income Countries: A Systematic Review and Meta-analysis. Clin Infect Dis An Off Publ Infect Dis Soc Am. 2016 Jun;62(12):1586–94.

146. Akpabio US, De Villiers PJT. A description of patients with recurrence of pulmonary tuberculosis in a tuberculosis hospital, Ermelo. African J Prim Heal Care Fam Med. 2011 Nov;3(1):8.

147. Stockdale AJ, Nkuranga J, Török ME, Faragher B, Lalloo DG. Initiation of

antiretroviral therapy in HIV-infected tuberculosis patients in rural Kenya: an observational study. Trop Med Int Heal [Internet]. 2013;18(7):907–14. Available from: http://doi.wiley.com/10.1111/tmi.12110

148. Khan FA, Minion J, Pai M, Royce S, Burman W, Harries AD, et al. Treatment of Active Tuberculosis in HIV-Coinfected Patients: A Systematic Review and Meta-Analysis. Clin Infect Dis. 2010 May;50(9):1288–99.

149. Schomaker M, Egger M, Maskew M, Garone D, Prozesky H, Hoffmann CJ, et al. Immune recovery after starting ART in HIV-infected patients presenting and not presenting with tuberculosis in South Africa. J Acquir Immune Defic Syndr. 2013 May;63(1):142–5.

150. Mocroft A, Bannister WP, Kirk O, Kowalska JD, Reiss P, D'Arminio-Monforte A, et al. The clinical benefits of antiretroviral therapy in severely immunocompromised HIV-1-infected patients with and without complete viral suppression. Antivir Ther [Internet]. 2012 [cited 2018 Sep 5];17(7):1291–300. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23013779

151. Sungkanuparph S, Manosuth W, Kiertiburanakul S, Piyavong B, Chumpathat N, Chantratita W. Options for a Second-Line Antiretroviral Regimen for HIV Type 1-Infected Patients Whose Initial Regimen of a Fixed-Dose Combination of Stavudine, Lamivudine, and Nevirapine Fails. Clin Infect Dis [Internet]. 2007 Feb;44(3):447–52. Available from: https://academic.oup.com/cid/article-lookup/doi/10.1086/510745

152. Nash D, Katyal M, Brinkhof MWG, Keiser O, May M, Hughes R, et al. Long-term immunologic response to antiretroviral therapy in low-income countries: A collaborative analysis of prospective studies. AIDS. 2008 Nov;22(17):2291–302.

153. Prabhakar B, Banu A, Pavithra HB, Chandrashekhara P, Sasthri S. Immunological failure despite virological suppression in HIV seropositive individuals on antiretroviral

therapy. Indian J Sex Transm Dis. 2011;32(2):94–8.

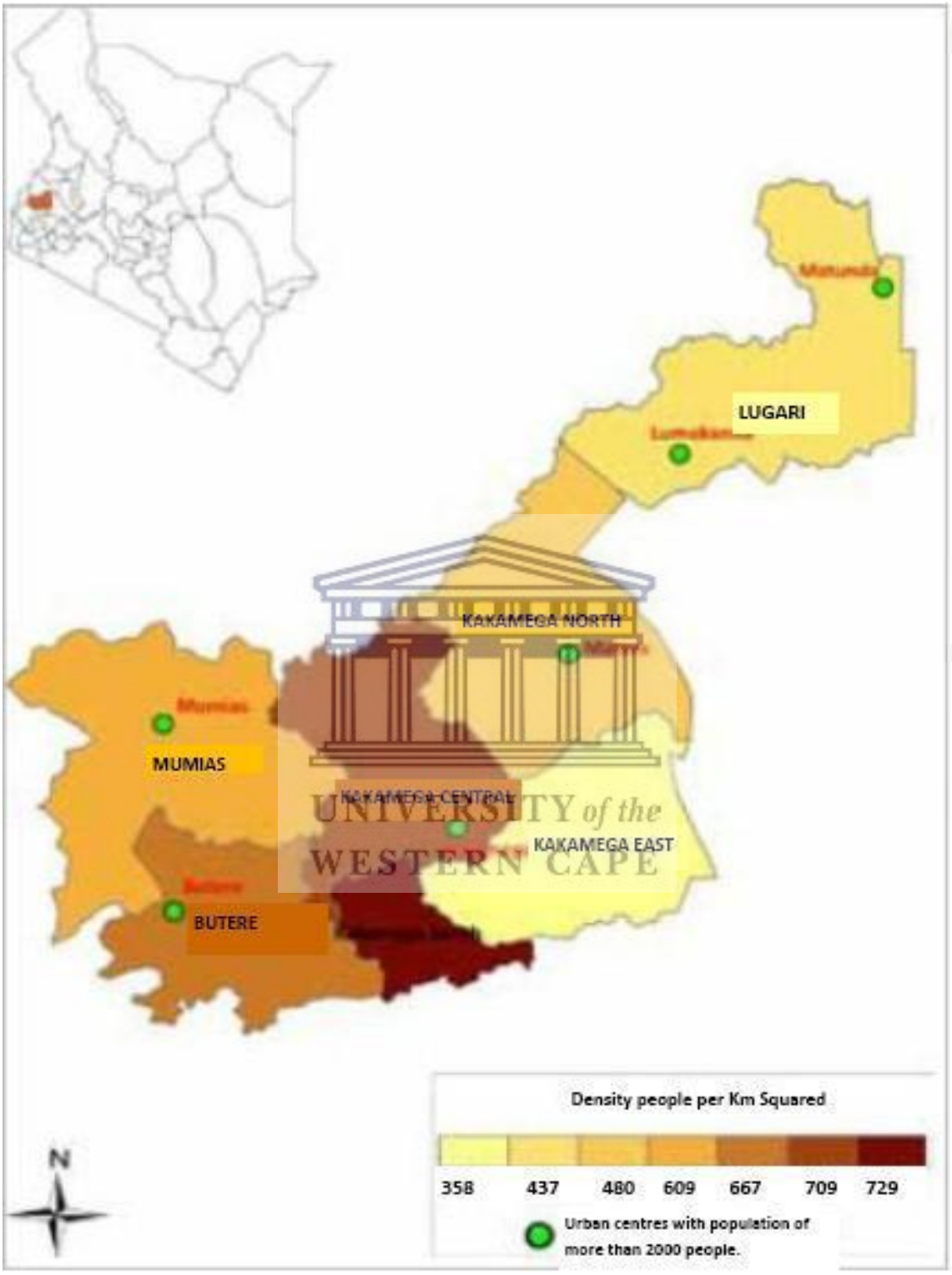
154. Bayu B, Tariku A, Bulti A, Habitu Y, Derso T, Teshome D. Determinants of virological failure among patients on highly active antiretroviral therapy in University of Gondar Referral Hospital, Northwest Ethiopia: a case–control study. HIV/AIDS - Res Palliat Care [Internet]. 2017 Aug;Volume 9:153–9. Available from: https://www.dovepress.com/determinants-of-virological-failure-among-patients-on-highly-active-an-peer-reviewed-article-HIV

155. Fox MP, Rosen S. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: Systematic review. Trop Med Int Heal. 2010 Jun;15(SUPPL. 1):1–15.

156. Assefa Y, Lynen L, Wouters E, Rasschaert F, Peeters K, Van Damme W. How to improve patient retention in an antiretroviral treatment program in Ethiopia: a mixed-methods study. BMC Health Serv Res. 2014 Jan;14:45.

Global Health Observatory (GHO) data, 2018 http://www.who.int/gho/hiv/en/ accessed on 16th September, 2018.

Appendix I: Maps for Kenya and Kakamega County



Source: http://www.kenyampya.com/index.php?county=Kakamega

Appendix II: Chart Abstraction Tool

ART Chart Abstraction Tool

General Details Section

Unique ID …… Date Born …/…/… Age ……

Patient's Location Available: Yes … No … Patient Has Treatment Supporter: (Check) Yes … No …

Date HIV diagnosis …/…/… Date Enrolled …/…/… Date Started ART …/…/…

Follow up Ended: Yes … No … Date Follow up Ended …/…/…

Reason for Termination: Transferred Out … Died … LTFU* … Discontinued ART … Unknown …

Treatment History Section

Laboratory Test:	Date:	ARV Regimen:	Date:	Duration on Rx:
CD4 at enrolment ……	…./…./….	Current Regimen ……	…/…/…	……Months
CD4 at ART start ……	…./…/….	Past Regimen ……	…/…/…	……Months
Baseline Viral load ……	…./…/….	Past Regimen ……	…/…/…	……Months
Follow up Viral load …..	…/…/…	Past Regimen ……	…/…/…	……Months
Follow up Viral load …..	…/…/…	CD4 at suspected Failure ……	…/…/…	

Opportunistic Infections History

Name		MM / YY	MM / YY	Name	MM / YY	MM / YY
PTB:		/	/	Cryptococcal Meningitis	/	/
Smear +	Smear -	/	/	Encephalopathy / Dementia	/	/
Extra Pulmonary TB		/	/	Neuro (Toxo, PML, lymphoma)	/	/
PCP		/	/	Chronic diarrhoea / Wasting	/	/
Pneumonia		/	/	Salmonellosis	/	/
Mycobacteria other		/	/	Septicemia	/	/
Oral Thrush		/	/	KS – Cutaneous	/	/

Oesophageal Candidiasis	/	/	KS – Visceral	/	/
CMV retinitis	/	/	Genital ulcerative disease	/	/
Herpes zoster	/	/	Urethritis / cervicitis	/	/
Herpes simplex	/	/	PID	/	/
Lymphoma	/	/	Other	/	/
Other	/	/	Other	/	/

Section on Routine Visit Tallies

Date	Weight	Height	Missed Drug	Neck Stiff	Photo-phobia	Mental State	Opportunistic Infection	WHO stage	CD4 Count	Viral Load	ART change

Appendix III: Permission to Review and Access Patient Records at Kakamega County General Hospital

REPUBLIC OF KENYA

COUNTY GOVERNMENT OF KAKAMEGA

MINISTRY OF HEALTH

Telegram: "COUNMED", Kakamega.
Telephone: Kakamega 056-30050/1/2

REF: CGH/KAK/HRI/155

COUNTY GENERAL HOSPITAL
P.O. BOX 15, G.P.O. 50100
KAKAMEGA
9th September, 2016

Dear Sir / Madam,

RE: MAERO, ATHANASIUS LUTTA – 3520556 – UNIVERSITY OF THE WESTERN CAPE

The aforementioned is a student at the University of the Western Cape, MPH program and has been granted permission to access, review patient health records at the ART Clinic. He will abide by Patient Health Information Privacy and Confidentiality.

May you accord him the support required.

Yours Faithfully,

Samuel Soita

WESTERN PROVINCIAL GENERAL HOSPITAL
MEDICAL SUPERINTENDENT
Tel: 30052
Date:.....
P.O. Box 15 - 50100, KAKAMEGA

Health Records and Information Officer In Charge

Kakamega County General Hospital

Appendix IV: BMREC Letter

UNIVERSITY of the WESTERN CAPE

OFFICE OF THE DIRECTOR: RESEARCH
RESEARCH AND INNOVATION DIVISION

Private Bag X17, Bellville 7535
South Africa
T: +27 21 959 2988/2948
F: +27 21 959 3170
E: research-ethics@uwc.ac.za
www.uwc.ac.za

19 January 2017

Mr AI Maero
School of Public Health
Faculty of Community and Health Sciences

Ethics Reference Number: BM/17/1/11

Project Title: Treatment Events of Patients on antiretroviral therapy in Kakamega County General Hospital in Kenya.

Approval Period: 15 December 2016 – 15 December 2017

I hereby certify that the Biomedical Science Research Ethics Committee of the University of the Western Cape approved the scientific methodology and ethics of the above mentioned research project.

Any amendments, extension or other modifications to the protocol must be submitted to the Ethics Committee for approval. Please remember to submit a progress report in good time for annual renewal.

The Committee must be informed of any serious adverse event and/or termination of the study.

Ms Patricia Josias
Research Ethics Committee Officer
University of the Western Cape

PROVISIONAL REC NUMBER -130416-050