PREVALENCE AND PREDICTORS OF VIROLOGIC FAILURE AMONG HIV-1 PATIENTS ON ANTIRETROVIRAL THERAPY IN MAKUENI COUNTY, KENYA: A CROSS-SECTIONAL STUDY

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Among HIV-1 Patients on Antiretroviral Therapy in Makueni County, Kenya: A Cross-Sectional Study

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ABBREVIATIONS

AIDS – Acquired Immuno-Deficiency Syndrome

ART – Antiretroviral therapy ABC

– Abacavir

ATV/r – Atazanavir/ritonavir

AZT – Zidovudine

3TC – Lamivudine

DTG – Dolutegravir

DRT – Drug resistance testing

EFV – Efavirenz

EID – Early Infant Diagnosis

LPV/r – Lopinavir/ritonavir

NVP –Nevirapine

TDF –Tenofovir

HIV – Human Immunodeficiency Virus

KP – Key Populations

MoH – Ministry of Health

NACC – National AIDS Control Council

NASCOP – National AIDS and STIs Control Programme

PEPFAR – United States President's Emergency Plan for AIDS Relief

PLHIV– People Living with HIV

UNAIDS – Joint United Nations Programme on HIV and AIDS

VF – Virologic failure

VL – Viral load

WHO – World Health Organization

OPERATIONAL DEFINITIONS

Adherence refers to the agreement of a person's conduct – taking medication, following a diet, or lifestyle changes– with the recommendations from a healthcare provider.

ART (antiretroviral therapy) is a combination of three or more ARV drugs taken for treating HIV infection. It may also be referred to as highly active ART or combination ART and involves lifelong treatment.

Key Populations are people that have a high burden of HIV or that have a higher risk of acquiring HIV in all epidemic settings. These people experience social and legal constraints that increase their vulnerability to HIV infection, including factors impeding access to HIV care, treatment, prevention, and other health and social services. Key populations include (1) persons who inject drugs, (2) men who have sex with men, (3) sex workers, (4) prisoners and (5) transgender people.

Virologic failure happens when ART fails to suppress the viral load below a certain threshold. It is defined as a persistently detectable viral load exceeding 1000 copies/mL after at least 6 months of using ART; based on two successive measurements done within three months with adherence reinforcement between measurements.

Viral suppression is the reduction of a patients' viral load to undetectable levels by using effective ART.

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ABSTRACT

Background: The rising number of people on antiretroviral therapy (ART) in Kenya has led to a decrease in HIV morbidity and mortality. However, emerging virologic failure (VF) threatens to reverse these gains. In Makueni County, existing data indicate challenges in achieving viral load suppression among persons living with HIV (PLHIV). Few studies have been carried out investigating VF in the area despite being listed among the counties that failed to meet the global and national targets of reducing new HIV infection by 75% between 2013 and 2021.

Objectives: This study sought to assess the status of VF in Makueni County by estimating the prevalence of VF among PLHIV in the county during the period of October 2018 to June 2019. The study also investigated the socio-demographic risk factors and regimen-related factors that contributed to VF in the area.

Methods: An analytical cross-sectional study was conducted among PLHIV in Makueni County to investigate the determinants and estimate the prevalence of VF in the area. The prevalence of VF and its associated 95% exact binomial confidence interval were estimated, and a mixed-effects logistic regression model used to evaluate the relationship between the predictors and VF.

Results: A total of 16360 PLHIV in Makueni County who were enrolled in the national VL/EOD database and who met the inclusion criteria for the study and were included in the data analysis. Male patients represented 30.4% (n=4975) of the database while 69.6% (n=11365) were female. The patients' ages ranged between 0-93 years with a median age of 43 and IQR of 19 years. The estimated period prevalence of VF between October 2018 and June 2019 was 13.2% (n=2162). From the results of the multivariable analysis, being 15 years or older (aOR=0.53; 95% CI: 0.44 – 0.645) and having blood samples collected for reasons other than baseline viral load measurement breastfeeding mothers (aOR=0.1; 95% CI: 0.01 – 0.97); clinical failure (aOR=0.08; 95% CI: 0.01

– 0.44); confirmation of VF (aOR=0.2; 95% CI: 0.07 – 0.62); no VL data (aOR=0.06; 95% CI: 0.01 – 0.31); routine VL (aOR=0.04; 95% CI: 0.01 – 0.12); drug substitution (aOR=0.03; 95% CI: 0.01 – 0.08), was significantly associated with lower odds of VF. Taking ABC-based, AZT-based, or other regimens increased the odds of VF (aOR)=1.61; 95% CI: 1.34 – 1.94), (aOR)=1.75; 95% CI: 1.52 - 2.01), and (aOR)=1.55; 95% CI: 0.99 - 2.44) respectively.

Conclusion: This study showed that over 13% of HIV patients on ART in Makueni County had VF between October 2018 and June 2019. The significant risk factors associated with VF were found to be age lower than 15 years, take a non-TDF based ART regimen, and blood sampling for baseline VL measurement.

1 CHAPTER ONE: INTRODUCTION

This chapter describes the background of the study, the justification, problem statement as well as the research objectives.

1.1 Background

Over the last decade, Kenya has made tremendous strides towards the control of the HIV epidemic, reporting a 68.5% reduction in HIV incidence between 2013 and 2021 (MOH, 2021; NASCOP, 2020). This reduction has been attributed to the dramatic increase in antiretroviral therapy (ART) coverage from 5000 in 2003 to 1,199,101 in 2021 among people living with HIV (PLHIV) (MOH, 2021; PEPFAR, 2005; Waruru et al., 2016). Emerging virologic failure could reverse these gains especially in areas where virologic monitoring has not been implemented in concert with ART scale-up (Hassan et al., 2014; Wamalwa et al., 2013; Waruru et al., 2016). Virologic failure (VF) refers to a persistently detectable viral load (VL) exceeding 1000 copies/ml after at least six months of ART based on two successive measurements done within a three-month interval (with adherence support between measurements) (WHO, 2017a).

The prevalence of VF is an important metric for the global control of HIV (WHO, 2016). In sub-Saharan Africa, the overall proportion of patients experiencing VF has been reported as 14% with a range from 0–43% (Barth et al., 2010; Bulage et al., 2017; Kiweewa et al., 2019; Mutwa et al., 2014). A study in Malawi reported VF in 32% of inpatients on ART between 2015 and 2017 (Gupta-Wright et al., 2020). A VF rate of 11.5% was reported in Northern Ethiopia after a median time on ART of 36 months (Hailu et al., 2018). In Tanzania 25.4% of children on ART for four years experienced VF (Muri et al., 2017). In Kenya, 24% of adult patients on ART had VF between 2008 and 2011 (Hassan et al., 2014; Waruru et al., 2016). A failure rate of 34% has been reported among children 18 months to 12 years on first-line combination ART followed for a median 49 months (Wamalwa et al., 2013). The main attributing factors for VF in Kenya have been identified as younger age and unsatisfactory adherence (Hassan et al., 2014).

The predictors of VF have been largely grouped into patient and regimen-related factors (J. Cutrell et al., 2020; Meshesha et al., 2020). Among the patient-related factors, age, WHO stage, CD4

count, clinician skill level, suboptimal adherence, and treatment history have been highlighted as important predictors of VF (Ahmed et al., 2019; Burch et al., 2016; Henerico et al., 2022; Kiweewa et al., 2019; Paterson et al., 2000; Wendie & Workneh, 2020). A meta-analytic study reported that about 70% of patients with VF would be virally suppressed following an adherence intervention (Bonner et al., 2013). Additional factors including rural residency, gender, treatment interruption, opportunistic infections and tuberculosis (TB) co-infection were significantly associated with VF (Demsie et al., 2020; Penot et al., 2014; Samizi et al., 2021). Regimen-related factors including the potency and tolerability of the ART regimen have been reported as predictors of VF (Geretti et al., 2008; Meshesha et al., 2020; Meyers et al., 2015). These factors affect the plasma drug concentrations causing VF (WHO, 2017b). On potency, patients on efavirenz-based combination therapy had lower prevalence of VF compared to those on nevirapine (Huibers et al., 2018; Tang et al., 2012; Zoufaly et al., 2013). Poor tolerability due to unpalatable formulations, toxicity and adverse drug events, large ART pill burden, high frequency dosing and complex handling of drugs increased the odds of VF (Ahonkhai et al., 2018; Ahoua et al., 2009; Bassett et al., 2001; J. Cutrell et al., 2020; Samizi et al., 2021; Schlatter et al., 2016).

1.2 Statement of the problem

In the year 2018, Makueni County contributed 3.9% of the total HIV prevalence in Kenya (NASCOP, 2020). Previous data reported that among PLHIV in the county, 56% were diagnosed and enrolled in care, 94% of those diagnosed were receiving ART and only 33% of those on ART were virally suppressed (NACC, 2016). Viral suppression is a measure of an individual's risk for transmitting HIV, (WHO, 2016) thus the picture in Makueni County is likely to translate to a high VF rate which could increase transmission risk. This is supported by findings from the Ministry of Health that reported Makueni among the counties that failed to meet the global and national targets of reducing new HIV infection by 75% between 2013 and 2021 (MOH, 2021; UNAIDS, 2018).

To address the high incidence of HIV infections in Makueni County, treatment optimization for VL suppression is needed complemented by the implementation of HIV prevention interventions

(MOH, 2021; PEPFAR, 2020). The primary goal of ART is the suppression of HIV viral replication to undetectable levels (Deeks et al., 2013; UNAIDS, 2018; WHO, 2016). Suppression of VL to undetectable levels prevents the onward transmission of HIV and AIDS-related illnesses (Penot et al., 2014; Shroufi et al., 2019; UNAIDS, 2018). High viral suppression rates often help PLHIV to lead long and healthy lives.

A proportion of PLHIV develop VF despite being maintained on ART. Previous studies done in Kenya have identified predictors of VF among them poor drug adherence, young age, male gender, being married, low socio-economic status and clinical stage of disease (Hassan et al., 2014; Jain et al., 2017; Waruru et al., 2016). In Makueni County, challenges remain in suppressing children, adolescents, and young adults (NACC, 2016; NASCOP, 2020). The development of VF has implications for the individual patient and is strongly predictive of higher risk of advanced disease and death (Gupta-Wright et al., 2020; UNAIDS, 2018). An additional concern is the urgency to change patients from failing first-line regimens to second-line drugs which are more expensive (Waruru et al., 2016). Moreover, the economic burden associated with VF presents a challenge to the ART programs involved and has potential serious public health implications for Kenya's HIV response which is heavily dependent on external resources (MOH, 2021).

1.3 Justification for the Study

Although there are previous studies evaluating the prevalence and determinants of VF, local factors associated with VF and the magnitude of VF are not well understood in Makueni County. The epidemic analysis of HIV in the country shows geographical diversity with counties displaying heterogenous epidemic patterns. Insights into viral suppression at the population-level can assist programmes dealing with HIV treatment and prevention by revealing the demographic groups most burdened with detectable VL. The generation of granular data could identify areas of high HIV transmission where there is a high burden of detectable viraemia and increase focus on those counties and sub-populations. A national household survey designed to estimate the prevalence of VF in Kenya was conducted from 2018-2019. However, the survey was not powered to characterize VF in smaller geographical regions but provided national estimates. This study

analyzed HIV VL data from Makueni county during the same period to determine whether the geographical variation in VF mirrors the prevalence in the country and may improve the corresponding efforts to reduce HIV incidence in the county. These insights could help programmes to intensify HIV programme support and efficiently target resources to regions and people most burdened with VF.

2 CHAPTER TWO: LITERATURE REVIEW

Introduction

This review of literature focuses on studies reporting the burden and determinants of VF. The prevalence and economic burden of VF have been reviewed as well as the predictors associated with VF.

2.1 Burden of virologic failure

Several studies in sub-Saharan Africa have reported a prevalence of VF ranging 11–50% (Emmett et al., 2010; Fassinou et al., 2004; Kekitiinwa et al., 2008). A study in Ethiopia found that the prevalence of VF among inpatients was 12.47% between September and December 2019 (Negash et al., 2020). In South Africa 16.9% of patients had VF by the fifth year of ART (Fox et al., 2012). A study in Cameroon found that 17% of children living with HIV experienced VF after 28 months on ART (Njom et al., 2017), while in Tanzania 25.4% had VF after 4.3 years on ART (Muri et al., 2017). A study following adult ART patients in Kenya, Uganda, Tanzania and Nigeria from 20132017 showed a prevalence of VF ranging 11–24% (Kiweewa et al., 2019). More data from Kenya reported that 24.6 % of adult patients on ART experienced VF after a median duration of 13.9 months (Hassan et al., 2014) while 34% among children on first-line combination ART had VF after 49 months (Wamalwa et al., 2013).

On the economic burden of VF, a study in the US reported that VF resulted in an increase in costs of at least $US250 per patient per month, with costs rising further as patients experienced multiple VF (Chaix-Couturier et al., 2000). VF resulted in 0.54 million disability adjusted life-years (DALYs) costing nations up to $500 million in losses (Phillips et al., 2015). Monitoring VL has been proven to increase the life-expectancy gain at 6-monthly and 12-monthly testing (Bendavid et al., 2008; Hamers et al., 2012). The financial benefit of point of care VL testing rose when a higher detection limit of >1000 copies/ml was used (ESTILL et al., 2013). This translates to more persons with non-nucleoside reverse-transcriptase inhibitor resistance being switched to secondline ART (ESTILL et al., 2013; Shroufi et al., 2019) and the aversion of more than 10,000 AIDs related deaths annually (Shroufi et al., 2019).

2.2 Risk factors associated with VF

These include socio-demographic factors, patient factors and regimen-related risk factors.

2.2.1 Socio-demographic risk factors

These include marital status, age, sex, education, body mass index (BMI) and socio-economic status.

2.2.1.1 Socio-economic status

Several countries in sub-Saharan Africa report that the burden of VF is heavier in certain geographic areas and in certain key population groups. The geographic hotspots for VF have been reported to include transportation routes, markets and bars (Jain et al., 2017). Sex workers, farmers, fishermen, construction workers and HIV positive partners in discordant couples have been reported as key populations associated with VF (Jain et al., 2017; Meshesha et al., 2020; Plymoth et al., 2020). It was found that in a predominantly urban population, working in multiple locations outside of a person's residential district and low household wealth were associated with VF among PLHIV who were on ART (Plymoth et al., 2020). Additional indicators of socio-economic disadvantage such as homelessness, financial hardship and unemployment were associated with VF in high-income countries (Burch et al., 2016; Raho-Moussa et al., 2019).

2.2.1.2 Age

Younger age has been found to be significantly associated with VF (Jobanputra et al., 2015; Marconi et al., 2013; Penot et al., 2014). Data indicates that the VF rate for children on first-line ART after a median time of 24 months is 15% to 40% (Njom et al., 2017; Wamalwa et al., 2013). The odds of HIV VF have been reported to be two times higher in patients younger than 35 years (Meshesha et al., 2020). Similarly, VF has been shown to be more prevalent in adolescents and young adults (between ages 15-25) compared to older adults (Ahonkhai et al., 2018) This could be explained by their vulnerability to emotional instability with depression, causing suboptimal adherence, defaulted continuum of care (James Mburu et al., 2020), emerging drug resistance and early treatment failure (Sutcliffe et al., 2008; Wachira et al., 2012).

2.2.1.3 Sex

Male gender has been associated with VF both in adults and children on ART (Marconi et al., 2013). Studies report that the odds of VF among male children were twice as much as those of female children (Njom et al., 2017). Among patients 15 years and older, males were more vulnerable to VF than females (Penot et al., 2014). One possible explanation could be gender differences in adherence to HIV care and treatment. Gender-based socio-cultural norms have been associated with poorer male adherence (Braitstein et al., 2008). Data indicates that health-seeking behaviors are poorer among men, causing them to present late with higher baseline VL and advanced disease. Men also experience inadequate retention in care with lower ARV concentrations (Bila & Egrot, 2009; Marconi et al., 2013; Plymoth et al., 2020).

2.2.1.4 Marital status

Studies have reported varying data on the association between marital status and the risk of VF. One study conducted in Ethiopia showed that the odds of VF were 3 times higher among divorced individuals than those who were single, possibly due to social drug use, sedentary lifestyle and other risky behaviors that undermined adherence and health seeking (Wendie & Workneh, 2020). In Tanzania, the median time to VF was higher among those who were single than in those who were married/ co-habiting or those widowed/separated (Samizi et al., 2021). One study reported that cases of VF were more likely among those who were single or divorced than among married individuals (Plymoth et al., 2020)

2.2.1.5 Education

The odds of VF decrease as the level of education increases (Ayele et al., 2018). A study in Uganda showed that lack of formal education and primary level education among adolescents was associated with higher risk of VF in comparison to secondary or university education (Maena et al., 2021). In the UK, non-university education contributed to higher risk of VF (Burch et al., 2016). This may be because educated patients understand more the importance of taking medicine and adherence (Burch et al., 2016; Maena et al., 2021). Increasing patients' treatment literacy through counselling led to a decreased in VF rate among HIV-1 patients in Thailand (Wilson et al.,

2009). By contrast, a study in Burkina Faso reported that the level of education was not significantly associated with VF (Penot et al., 2014).

2.2.1.6 Body mass index (BMI)

Malnourished and overweight PLHIV have been shown to be at higher risk of VF than individuals with normal BMI (Negash et al., 2020). Low BMI was reported as an important risk factor for VF (Gupta-Wright et al., 2020). In Ethiopia, VF was 4.2 times higher in patients whose current BMI was < 16 kg/m2 versus those with BMI > 18.5 kg/m2 (Ahmed et al., 2019). On the contrary, a study in the US reported that high BMI individuals (≥30 kg/ m2) were at higher risk of VF compared to those with lower BMI (A. G. Cutrell et al., 2021)

2.2.2 Patient-related risk factors

These include advanced immunosuppression, adherence to ART and longer duration on ART

2.2.2.1 Advanced immunosuppression

The odds of virological failure have been shown to increase with advanced disease at ART initiation (Penot et al., 2014). Patients initiated on ART with severe disease (WHO stage 3 & 4), and low baseline CD4 counts (CD4 < 350 cells/mm3) had increased risk of VF as compared to those in WHO stage 1 or 2 and those with higher CD4 counts (Jobanputra et al., 2015; Sithole et al., 2018). A study in Ethiopia revealed that among TB co-infected individuals VF was 6 times more likely than in those without TB (Negash et al., 2020). In Kenya, viral suppression decreased from 23% to 5% for those with CD4 count <250 cells/ mm3 at baseline (Okonji et al., 2012).

2.2.2.2 ART adherence

VF has been shown to be robustly associated with adherence and is more prevalent in patients with suboptimal adherence than those with optimal adherence (Bezabhe et al., 2016; Demsie et al., 2020; Rupérez et al., 2015; Sithole et al., 2018; Zoufaly et al., 2013). A thorough investigation of barriers to ART adherence should be undertaken before other causes are considered. Potential

barriers may include co-existing mental health disorders and substance abuse, and psychosocial factors, such as unstable housing, inaccessible care, or issues of non-disclosure of HIV status (J. Cutrell et al., 2020; Jobanputra et al., 2015; Sithole et al., 2018) One study reported that VF was more prevalent among those who defaulted taking ART, those who defaulted their clinical appointments and those who failed to honor their refill appointments (James Mburu et al., 2020). This confirms that the Achilles' heel of successful virologic outcomes lies in achieving long-term optimal adherence.

2.2.2.3 Longer duration on ART

The likelihood of VF has been reported to increase with time on ART (Jobanputra et al., 2015; Penot et al., 2014). A in Ethiopia, patients on ART longer than five years were likely to develop VF (Emagnu et al., 2020). This was supported by data from China where patients on longer term ART had VF and drug resistance mutations (Ma et al., 2010). Additional data from resource limited settings reported VF prevalence of 11%, 15% and 21% in patients on ART for 12– 23 months, 24–36 months and >36 months respectively (Hassan et al., 2014; Stadeli & Richman, 2013). Possible reasons could be reduced efficacy as a result of prior exposure to suboptimal regimens (Meshesha et al., 2020) and persistent replication of the virus during ART (Emagnu et al., 2020).

2.2.3 Regimen- related risk factors

These include pharmacologic factors of the drug and resistance mutations.

2.2.3.1 Drug resistance

Combination ART largely consists of three classes of HIV medications— nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). The HIV-1 reverse transcriptase (RT) is highly errorprone, with a high replication rate and a lack of proof-reading in its activity, which causes high rates of mutation and drug resistance during viral replication (J. Cutrell et al., 2020; Roberts et al., 1988). A large number of drug resistant strains have developed following ART intake in low resource settings, and these counteract the benefits from treatment programs (Yuan et al., 2020) (Table 1

below). Sub-Saharan Africa estimates a prevalence of 10–15% for resistance to NNRTIs in drug naive patients (transmitted drug resistance), and 50–80% in patients taking ART (Gupta-Wright et al., 2020). One study showed that a single VL ≥1000copies/ml was associated with high rates of resistance associated mutations (Henerico et al., 2022). In Togo, 94 % of patients with VF had drug resistance strains (Salou et al., 2016) while in Kenya, about 67% of the children with VF had resistance detectable at the point of failure (Wamalwa et al., 2013). In Mozambique 89% of subjects with VF presented with at least one HIV drug resistance mutation (Rupérez et al., 2015).

2.2.3.2 Pharmacological factors

Suboptimal pharmacokinetics of the drug related to poor absorption of ART, drug toxicity, drugdrug or drug-food interactions inhibit adequate drug levels in the blood (J. Cutrell et al., 2020). Interrupted therapy (Demsie et al., 2020) and a reduction in the potency of ART have been associated with VF (Havlir et al., 2001). Gene polymorphisms of cytochrome enzymes and transporter proteins affect ART metabolism and distribution altering the concentration and efficacy of the drug (Calcagno et al., 2016). Diseases such as chronic diarrhea or poor intestinal absorption cause impaired drug absorption that may cause VF (J. Cutrell et al., 2020; McCluskey et al., 2019). Prescribing errors and errors during drug administration especially during transition into care may jeopardize viral suppression (A. G. Cutrell et al., 2021; Meshesha et al., 2020; Mocroft et al., 2001). System-level factors also contribute to suboptimal drug levels, due to medication stockouts common in low resource settings (McCluskey et al., 2019).

2.3 Research Questions

This study attempted to answer the following questions:

1. What is the prevalence of virologic failure among HIV-1 patients in Makueni County?
2. Are socio-demographic factors associated with virologic failure among HIV-1 patients in Makueni County?
3. What regimen-related factors are associated with virologic failure among HIV-1 patients in Makueni County?

2.4 Aim and objectives

2.4.1 General objective

The broad objective of this study was to estimate the prevalence of virologic failure and identify its determinants among HIV-1 patients in Makueni county.

2.4.2 Specific objectives

1. To estimate the prevalence of virologic failure in HIV-1 patients in Makueni County during the period of October 2018 and June 2019,
2. To identify the socio-demographic risk factors (age, sex, residence) of virologic failure among HIV-1 patients in Makueni County,
3. To identify the regimen-related risk factors (drug regimen, treatment implementing partner) for virologic failure among HIV-1 patients in Makueni County.

3 CHAPTER THREE: METHODOLOGY

3.1 Study area

The study site was Makueni County, one of the 47 counties in Kenya located on the Southeastern part of the country. The county covers an approximated area of 8,176.7 Km^2 with a human population of about one million people made up predominantly of the Akamba community (KNBS, 2020). The county is arid to semi-arid, and the main economic activities include beekeeping, dairy farming, ecotourism, subsistence agriculture, small-scale trade, commercial businesses and coffee growing (KNBS, 2020). Administratively, there are six constituencies in Makueni County namely, Kilome, Mbooni, Makueni , Kaiti, Kibwezi East, and Kibwezi West (KNBS, 2020). There are 142 functional public health facilities in Makueni County and the average distance to the nearest health facility is six kilometers (MOH, 2015; Mutiso et al., 2020). In 2020 the prevalence of HIV in Makueni County was 3.5 % (NACC, 2020), with the county displaying a mixed epidemic pattern where HIV prevalence varied between 3% - 10% among the general population and 23-30% among key populations (MOH, 2021). Data indicate that challenges faced with HIV epidemic control in Makueni County include moderate ART coverage with 21% unmet need, moderate testing inefficiencies, high mother to child transmission and low VL suppression among children (PEPFAR, 2020). HIV services in Makueni County include HIV testing and treatment, prevention, and care services. These services are available for high risk populations, PLHIV and their partners, families and caregivers, according to the Kenya national guidelines (MoH, 2018).

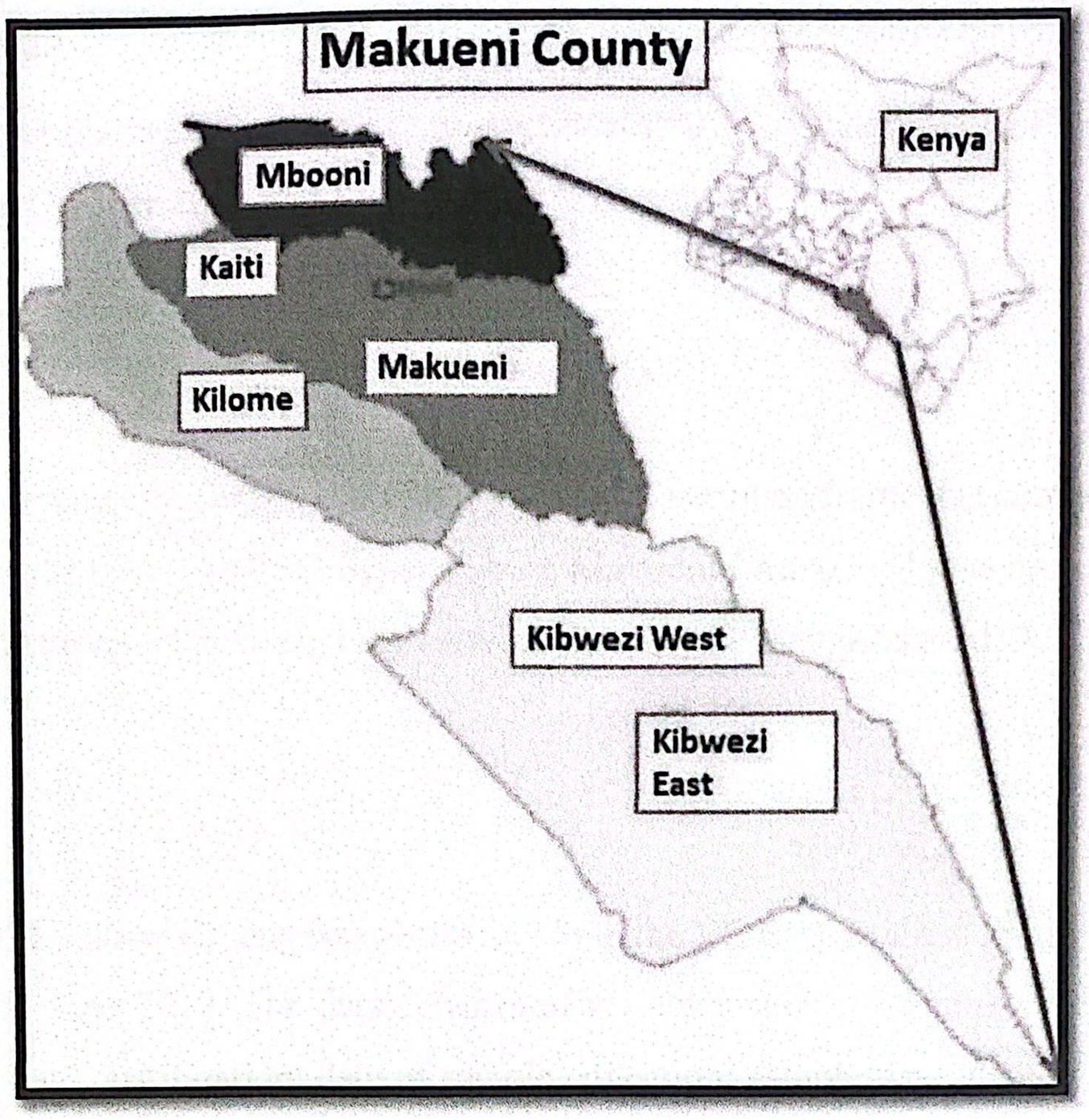

Figure 1: Map of the Makueni County

3.2 The National Viral Load/EID system

Data from this study was abstracted from the National Viral Load/EID monitoring system. This system is a repository of HIV VL and early infant diagnosis (EID) data and is managed by the National AIDS and STI Control Programme (NASCOP). Briefly, NASCOP spearheads the Ministry of Health's interventions in tackling HIV/AIDS through policy formulation, coordination of procurement and supply chain management, training and monitoring and evaluation of the HIV response (NASCOP, 2018). The national VL/EID system is an electronic data management system for monitoring patients. It contains patient information on medication and ART history and demographic data. Health facilities feed data into the system which is available publicly via an interactive computer interface tool that graphically represents program indicators (Mwau et al., 2018; NASCOP, 2022).

3.2.1 Study design

This was a population-based analytical cross-sectional study conducted among PLHIV in Makueni County between October 2018 and June 2019.

3.2.2 Sampling

A simple random sampling design was employed with a sampling frame that comprised all PLHIV with VL test results from point of care centers in Makueni County and who were enrolled in the national VL/EID monitoring framework between October 2018 and June 2019.

3.2.3 Data

HIV VL data for Makueni County was abstracted from the VL/EID database for the period between October 2018 to June 2019. The data consists of variables such as administered ART regimen, ART initiation date, justification, date of sample collection, sample type, date of sample testing, VL outcome (copies/ml) and date of result dispatch. The database also stores facility information and has variables such as location (county and sub-county), facility name, Master Facility List (MFL) code, facility type, owner type, and the regulatory body.

3.3 Study population

Inclusion criteria

All PLHIV across all ages, resident in Makueni County and who had VL tests done between October 2018 and June 2019 in point of care facilities under the national VL/EID monitoring system were included. Additionally, those classified as receiving ART by either having detectable blood levels of selected ART or by reporting current ART use were also included in the study.

Exclusion Criteria

All PLHIV in Makueni County on ART for six months or less and those with missing information on key variables and/or invalid VL outcomes were excluded.

3.4 Case definition

For this study, cases were defined as those with VF identified as detectable viral load $\geq$ 1,000 copies/ml after a minimum of six months on ART, as per the Kenya national treatment guidelines (MoH, 2018).

3.5 Sample size

All PLHIV in Makueni County and enrolled in the national VL/EID database were assessed for eligibility. An initial screening of the database showed that 23,067 entries were made between 2018 and 2019 from health facilities in Makueni County. A total of 16,340 eligible participants met the inclusion criteria and were selected for this study. Among those included, 15,014 were adolescents and adults aged ≥15 years, and 1,326 were children aged 0-14 years.

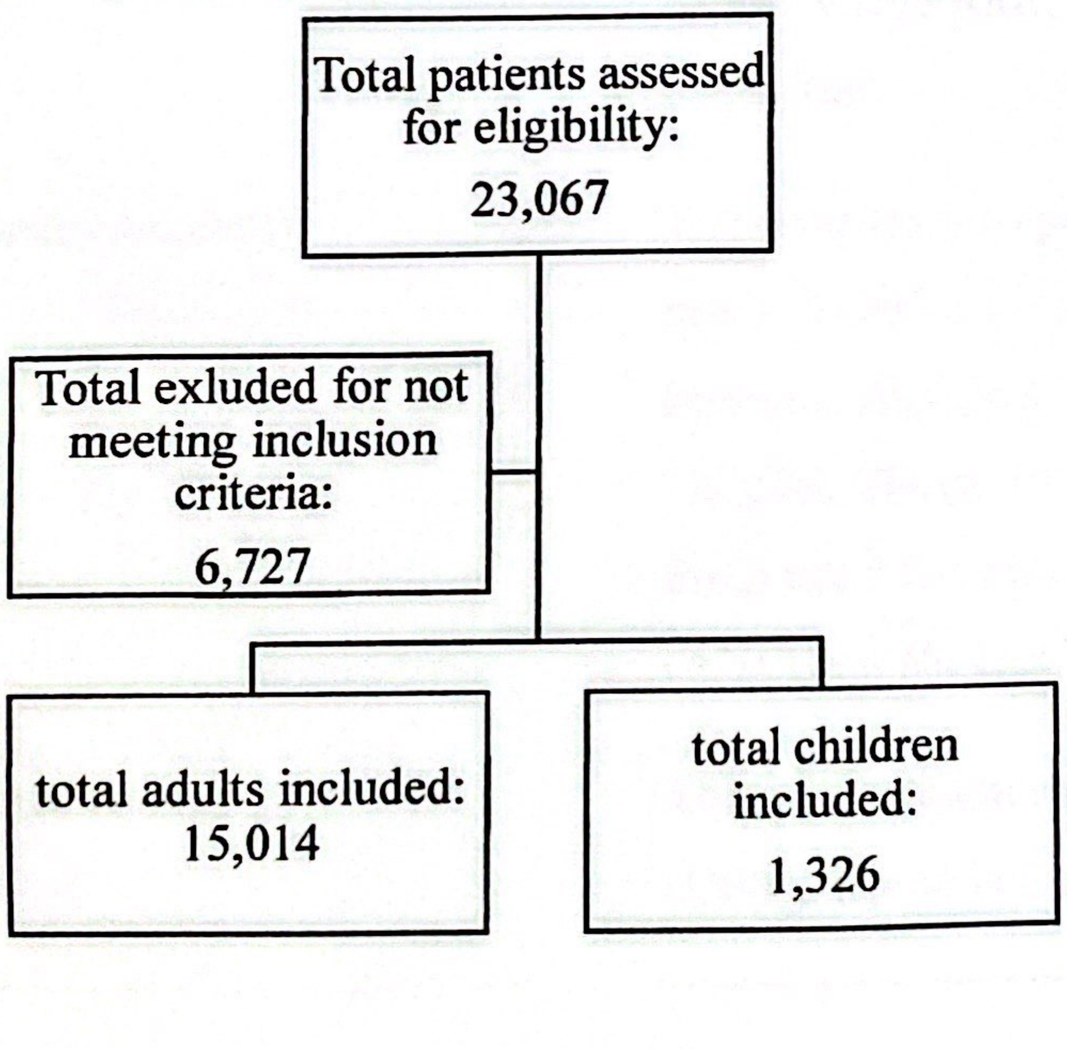

Figure 2: Flow chart of the sample size description

3.6 Study variables

The outcome variable was virologic failure which is a binary outcome: suppressed or virologic failure. The predictor variables were the sociodemographic factors of the participants including age sex, and residence. Additional variables included health facility, implementing partner, type of sample collected, justification for sample collection, ART regimen and date of initiation on ART.

Table I: Predictor variables and their measurements

Variables	**Measurement of the predictor variables**
Age (continuous)	This will be captured in years
Sex (nominal)	This will be captured as male or female
Residence (nominal)	The sub-county where the participant is domiciled
Health Facility (nominal)	One among the 82 facilities captured in the dataset where participant VL results were dispatched.
Implementing partner (nominal)	The organizations partnering with the health facilities to provide HIV care and services. These will be categorized as CHS - Naishi, CHAK-CDC HIV AIDs Program, AIDs Healthcare Foundation (AHF) and No Partner
Sample type collected (nominal)	This will be captured as dried blood spots (DBS), Whole blood, and Frozen Plasma

ART Regimen (nominal)	This is the participant combination therapy. The possible combinations of ART regimen combinations for newborns, infants, children, adolescents, and adults include: Abacavir (ABC) Based regimens ABC+3TC+LPV/r; ABC+3TC+EFV; ABC+3TC+DTG; ABC+3TC+ATV/r; or ABC+3TC+NVP Zidovudine (AZT) Based regimens AZT+3TC+NVP; AZT+3TC+LPV/r; AZT+3TC+EFV; AZT+3TC+ATV/r; or AZT+3TC+DTG Tenofovir (TDF) Based regimens TDF+3TC+DTG; TDF+3TC+EFV TDF+3TC+NVP; TDF+3TC+ATV/r or TDF+3TC+ LPV/r Other Drug resistance testing based second-line

3.7 Conceptual framework

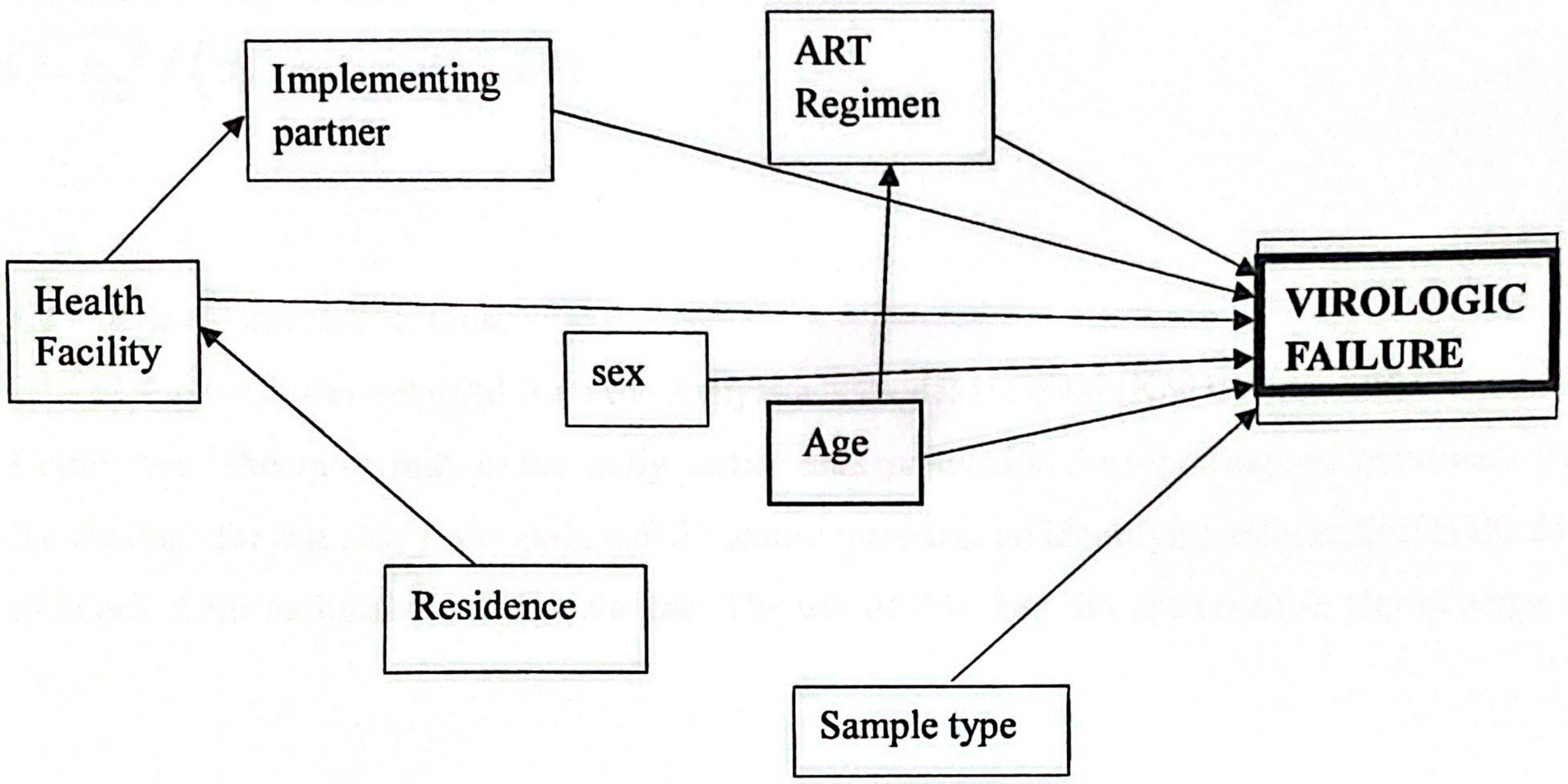

Figure 3: Causal diagram of potential factors affecting the occurrence of VF among PLHIV in Makueni County.

3.8 Statistical Analysis

Descriptive statistics for the continuous variables were summarized using median and range. For qualitative variables, the frequencies and proportions were computed. The frequency of VF and its associated 95% exact binomial confidence interval were estimated. This was followed by a univariable mixed-effects logistic regression analysis to assess the effect of each predictor on VF. The variables "sub-county", "facility" and "individual" were included as random effects to account for clustering of the outcome within these levels. At this stage, a likelihood ratio test (LRT) at $P<0.20$, which is a liberal p-value (Dohoo et al., 2012) helping to rule out a negative confounding, was used to evaluate the significance of each of the predictors. The variables found to be significant in the univariable analysis were included in a multivariable model where a backward stepwise approach was used to eliminate variables at $P<0.05$. This was only done if their exclusion from the

model resulted in a less than 30% change in the effects of the remaining variables (Dohoo et al., 2012). Two-way interactions were fitted between the remaining variables of the final model and assessed for significance. The proportion of variance at the sub-county and facility level known as the intra-cluster correlation coefficient (ICC/ρ) was estimated by the following formula: $ICC = \rho = \sigma_g^2 / (\sigma_r^2 + \sigma_g^2 + 3.29)$.

3.9 Ethical considerations

Ethical approval was obtained from the Kenyatta National Hospital (KNH)-UoN Ethics Research Committee. The anonymity of the study participants included in the reporting and presentation of the findings for this study was maintained because there was no identifying information in the data obtained from national VL/EID database. The use of this data did not result in any damage or distress.

4 CHAPTER FOUR: STUDY RESULTS

This chapter provides the study findings in detail. It gives the descriptive statics that summarize the data and shows the prevalence of VF and the results of the univariable, and multivariable analyses based on the mixed-effects logistic regression models.

4.1 Descriptive statistics of the research data

A total of 16360 PLHIV in Makueni County who were enrolled in the national VL/EID database and who met the inclusion criteria for the study and were included in the data analysis. The table II shows the descriptive statistics of the study. During the study period, HIV-1 patients in Makueni County were aged 0-93 years with a median age of 43 years. Male patients represented 30.4% (n=4975) of the database while 69.6% (n=11365) were female. Many patients were resident in Kibwezi West 25.8% (n=4217), Makueni 23.6% (n=3860) (n=3073) and Kibwezi East 18.8% sub counties. The estimated period prevalence of VF between October 2018 and June 2019 was 13.2% (n=2162).

Table II. Descriptive statistics of HIV-1 patients on ART in Makueni county for the period of October 2018 and June 2019

VARIABLE	Values	Median	Range	Frequency n(%)
Sex	Male	-		4975 (30.4)
	Female	-		11365 (69.6)
Age	0.0 -93	43	33; 52	
Subcounty	Kaiti	-		1639 (10.0)
	Kibwezi East	-		3073 (18.8)
	Kibwezi West	-		4217 (25.8)
	Kilome	-		1119 (6.8)
	Makueni	-		3860 (23.6)

	Mbooni	-	2432 (14.9)
Partner	AHF	-	1311 (8.0)
	CHAK-CDC	-	945 (5.8)
	CHS - Naishi	-	13343 (81.7)
	No Partner	-	741 (4.5)
Sample type	DBS	-	16059 (98.3)
	Frozen Plasma	-	239 (1.5)
	Whole Blood	-	42 (0.3)
Justification For VL Testing	Baseline	-	18 (0.1)
	BF Mothers	-	8 (0.05)
	Clinical Failure	-	13 (0.08)
	Confirmation of VF	-	867 (5.3)
	No Data	-	17 (0.1
	Other	-	4 (0.02)
	Routine VL	-	13811 (84.5)
	Single Drug Substitution	-	1602 (9.8)
ART- Regimen	ABC	-	1016 (6.2)
	AZT	-	1575 (9.6)
	Other	-	136 (0.8)
	TDF	-	13613 (83.3)

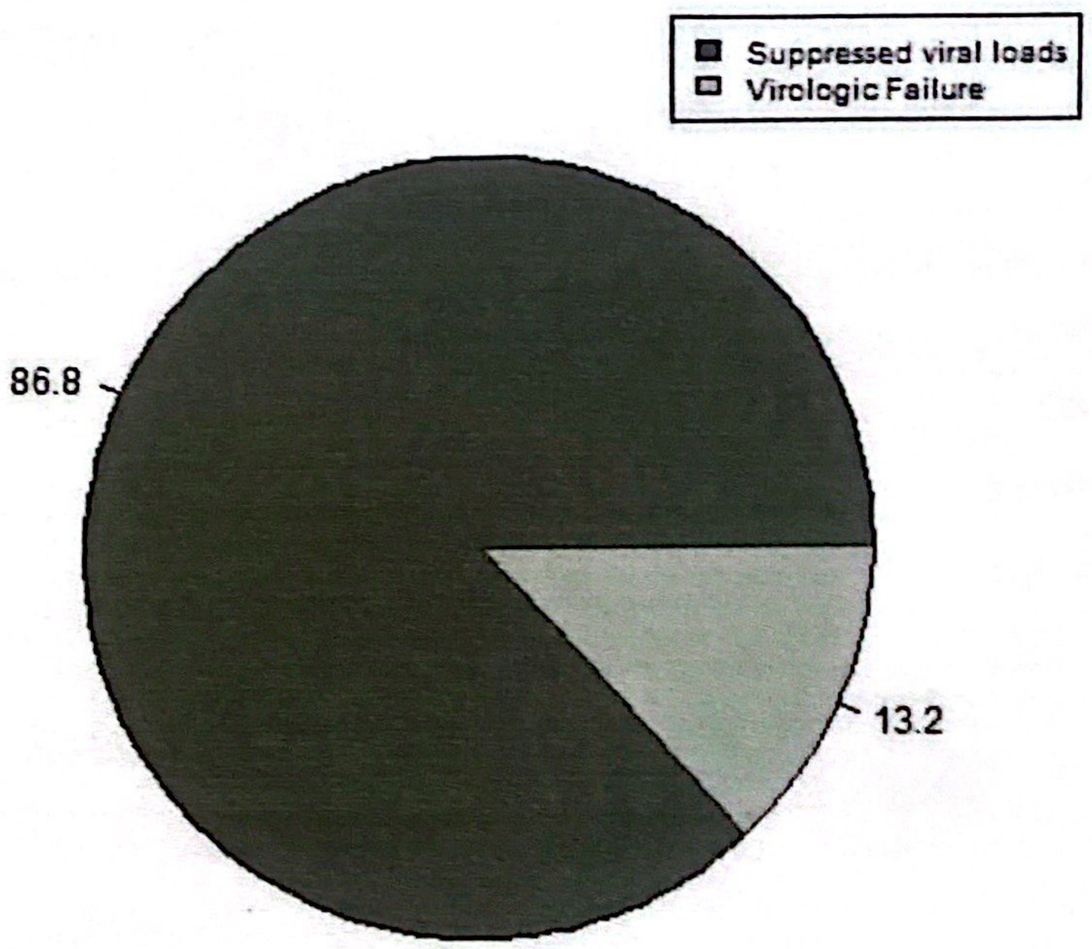

Figure 4: Prevalence of virologic failure among HIV-1 patients in Makueni County from October 2018 to June 2019 (n=16340)

4.2 Results of the logistic regression analysis

From the results of the univariable analysis of the risk factors of VF (table III), sex, age, partner, sample type, ART-regimen, and Justification were found to be significantly associated with VF among HIV-1 patients in Makueni County at 20% significance level.

Male patients had 1.2 times higher odds of VF compared to female patients, *p-value* ≤0.001. For every additional year in age, the odds of VF were multiplied by a factor of 0.98 $p= \leq 0.001$. The odds of VF were lower for all patients who visited a facility with an implementing partner for HIV services compared to those with no partner $p= 0.068$. The odds of VF were reduced for all patients whose samples were collected for reasons other than baseline measurement $p= \leq 0.001$.

Patients who had different sample types taken other than DBS samples had higher odds of VF. For example, the odds of VF in patients who had whole blood samples taken for measurement were

two times higher compared to those who gave DBS samples $p= 0.072$. Compared to patients taking ART regimens that were TDF-based, those who were enrolled on other regimens had two times higher odds of VF $p=\leq 0.001$.

Table III: Univariable analysis of the determinants of virologic failure among HIV-1 patients on ART in Makueni county during the period of October 2018 and June 2019

VARIABLE	Values	VF frequency (n=2162)	OR	95% CI Lower Upper	P-value
Sex	Male	716 (14.4)	1.16	1.05 -1.28	< 0.001
	Female	1446 (12.7)	Ref		
Age	>= 15 years	372 (28.1)	0.98	0.97 -0.98	< 0.001
	< 15 years	1790 (11.9)			
Partner	AHF	192 (14.6)	0.71	0.43 -1.17	0.068
	CHAK-CDC	130 (13.8)	0.66	0.45 - 0.98	
	CHS - Naishi	1722 (12.9)	0.66	0.49 - 0.90	
	No Partner	118 (15.9)	Ref		
Sample type	Whole Blood	8 (19)	2.01	0.92 - 4.38	0.072
	Frozen Plasma	34 (14.2)	1.42	0.96 - 2.09	
	DBS	2120(13.2)	Ref		
Justification for VL testing	BF Mothers	2 (25)	0.1	0.01 - 0.97	< 0.001
	Clinical Failure	3 (23.1)	0.08	0.01 - 0.44	
	Confirmation of VF	349 (40.3)	0.20	0.07 - 0.62	
	No Data	3 (17.6)	0.06	0.01 - 0.31	
	Routine VL	1671(12.1)	0.04	0.01 - 0.12	
	Drug	120 (7.5)	0.03	0.01 - 0.08	

	Substitution				
	Baseline	14 (77.8)	Ref		
ART- Reg	ABC based	271 (26.7)	2.95	2.54 - 3.42	< 0.001
	AZT based	348 (22.1)	2.29	2.01 - 2.61	
	Other	27 (19.9)	2.13	1.39 - 3.26	
	TDF based	1516(11.1)	Ref		

These six variables *sex, age, sample type, justification, partner,* and *ART regimen* were significantly associated with VF in the univariable analysis and were subsequently included in the multivariable mixed-effects logistic regression model (table IV). In the multivariable model only *age, justification* and *ART-regimen* were found to be significant predictors of VF at 5% significance level. For further clarity, age was stratified into two categories, <15 years and ≥15years and remained significantly associated with VF. Exclusion of the non-significant variables from the model resulted in < 30% change in the effects of the remaining variables.

Being 15 years or older reduced the odds of VF by a factor of 0.53 (aOR=0.53; 95% CI: 0.44 – 0.645) compared to patients younger than 15 years, controlling for the ART regimen and the justification for VL testing. Compared to patients taking a TDF-based ART-regimens, those taking ABC-based, AZT-based, or other regimens had about two times higher odds of VF (aOR)=1.61; 95% CI: 1.34 – 1.94), (aOR)=1.75; 95% CI: 1.52 - 2.01), and (aOR)=1.55; 95% CI: 0.99 - 2.44) respectively, controlling for age and the justification for VL testing. Compared to patients whose blood samples were taken for baseline viral load measurement, those who gave samples for other reasons had lower odds of VF: breastfeeding mothers (aOR=0.1; 95% CI: 0.01 – 0.97); clinical failure (aOR=0.08; 95% CI: 0.01 – 0.44); confirmation of VF (aOR=0.2; 95% CI: 0.07 – 0.62); no VL data (aOR=0.06; 95% CI: 0.01 – 0.31); routine VL (aOR=0.04; 95% CI: 0.01 – 0.12); drug substitution (aOR=0.03; 95% CI: 0.01 – 0.08), controlling for their age and ART regimen.

Table IV. Results of multivariable analysis of determinants of virologic failure among HIV-1 patients on ART in Makueni county during the period of October 2018 and June 2019

VARIABLE	Values	aOR	95% CI		P-value
			Lower	Upper	
Age	>= 15 years	0.53	0.44 – 0.645		< 0.001
	< 15 years	Ref			
ART- Regimen	ABC based	1.61	1.34 – 1.94		< 0.001
	AZT based	1.75	1.52 - 2.01		
	Other	1.55	0.99 - 2.44		
	TDF based	Ref			
Justification for VL testing	BF Mothers	0.16	0.02 – 1.19		< 0.001
	Clinical Failure	0.12	0.02 – 0.69		
	Confirmation of VF	0.34	0.11 – 1.07		
	No Data	0.11	0.02 – 0.61		
	Routine VL	0.08	0.02 – 0.24		
	Drug Substitution	0.05	0.02 – 0.17		
	Baseline	Ref			

5 CHAPTER FIVE: DISCUSSION

The objectives of this study were to estimate the prevalence of VF and investigate the sociodemographic and regimen-related risk factors associated with VF among HIV-1 patients in Makueni County during the study period. This chapter describes the study findings and compares the results to other authors' findings to identify their similarities or differences.

5.1 Prevalence of virologic failure

In this study the VF rate was 13.2% among HIV-1 patients in Makueni County. This was an improvement in the VF rate compared to the national reports from 2015 where more than 60% of adults receiving ART in Makueni County had VF (NACC, 2016). This prevalence of VF is comparable with the findings of a national cross-sectional survey in Uganda that found a VF rate of 11% (Bulage et al., 2017). Similar burden has been observed elsewhere in sub-Saharan Africa: in Rwanda 12%, in Ethiopia 12.5%, in South Africa 17%, in Cameroon 17%, and in Kenya, Uganda, Tanzania and Nigeria a prevalence of VF ranging 11-24% (Fox et al., 2012; Hassan et al., 2014; Kiweewa et al., 2019; Ndahimana et al., 2016; Negash et al., 2020; Njom et al., 2017). This prevalence was lower than that reported in Zimbabwe 30.6% (Makadzange et al., 2015) and Togo 51.6% (Salou et al., 2016), which may be attributed to differences in the study design, the study participants and the duration of follow-up.

5.2 Risk factors for virologic failure

This study revealed that younger age was associated with higher odds of VF. This was similar to the findings of a national household-based survey in Kenya where decreasing age was associated with higher risk of VF (NASCOP, 2020). A possible explanation for this finding could be that the youth face a complex myriad of challenges including behavioural and psychosocial factors like peer-related stigma, anxiety, lack of disclosure, sexual, reproductive and gender health concerns that may undremine adherence (Maena et al., 2021; Marconi et al., 2013; Natukunda et al., 2019; Ndahimana et al., 2016; Nglazi et al., 2012). Similarly, a study in South Africa showed that

adolescents aged <15 years had higher risk of VF compared to older patients (Joseph Davey et al., 2018). High pill burden among adolescents could also explain the lack of adherence leading to VF (Maena et al., 2021). These challenges if applicable may indirectly contribute to the burden of VF in the area. Several studies have reported similar findings with younger patients having poor adherence or higher levels of drug resistance mutations (Kiweewa et al., 2019; Maena et al., 2021; Marconi et al., 2013; Muri et al., 2017; Nglazi et al., 2012; Plymoth et al., 2020).

In this study, patients taking Tenofovir (TDF) based ART regimens had lower odds of VF compared to those on zidovudine (AZT) or abacavir (ABC) based or other regimens. This corresponds to the research findings of a study in Uganda which showed that patients who initiated on AZT-based regimens compared with TDF-based regimen were more likely to have VF (Ssemwanga et al., 2020). TDF-based regimens have been shown to be better tolerated with fewer side effects and hence better adherence (Tang et al., 2012). Nonetheless, one study reported that patients experiencing VF on a TDF-based regimen had higher rates of the NRTI-resistance mutation K65R emerged (Marconi et al., 2013). Some studies reported that ART-experienced patients have higher odds of VF compared to ART-naïve patients (Greig et al., 2013; Rutstein et al., 2015). Data suggests that drug resistance testing should be done for all patients with VF of HIV RNA levels >1000 copies/ml (J. Cutrell et al., 2020). The absence of drug resistance in these patients indicates poor adherence. Drug-related reasons such as toxicity, frequency of dosing and pill burden should be investigated and strategies of optimizing ART adherence discussed.

Patients tested for VF because of suspected clinical failure, repeat testers after suspected virologic failure, breastfeeding mothers, those with no VL data, those undergoing routine viral loads and those with drug substitutions had overall reduced odds of VF compared to those tested at baseline. This could be collaborated by the finding that patients on routine monitoring registered the lowest levels of VF (Bulage et al., 2017), due to enhanced adherence counselling and support. A national analysis done in Kenya showed that patient suppression increased as viral load monitoring increased (Mwau et al., 2018). Contrary findings were reported from a study in Uganda where adolescents who had detectable VL in their initial viral load were more likely to have VF upon a

repeat viral load regardless of their adherence level and change in ART regimen (Natukunda et al., 2019). Moreover, repeat testers who had active tuberculosis co-infection had higher odds of VF (Bulage et al., 2017).

Sex was not a risk factor for VF in this study (Table IV). The fact that the data consisted of older patients might explain this finding. This is agrees with the findings of previous studies in resource limited settings which found no association between sex and VF (Badri et al., 2008; Izudi et al., 2016; Plymoth et al., 2020). On the contrary, several studies reported that being male was associated with higher risk of VF due to reluctance to access healthcare and poor adherence compared to women (Maena et al., 2021; Njom et al., 2017; Penot et al., 2014). One study in rural Cameroon found that men had higher odds of VF, independently of their adherence behaviors, associated with biological differences where men took longer to regenerate their CD4 count while on ART compared to women (Boullé et al., 2015). Reports of a study in Tanzania and another in the UK showed that females were more likely to experience VF than males (Geretti et al., 2008; Muri et al., 2017).

Patients receiving HIV care in facilities that had an implementing partner were shown to have reduced odds of VF compared to those that attended facilities with no partner (table III) although this relationship was not statistically significant in the multivariable analysis. This may have been attributed to the different levels of quality of care that the partners offer to the patients, program level differences or factors such as variations in policy and their implementation (Kiweewa et al., 2019; Marconi et al., 2013). Moreover, this could have been a result of task shifting comprising of the redistribution of tasks from highly qualified to less specialized healthcare workers where appropriate, to efficiently utilize the available human resources for health (Grimsrud et al., 2016; WHO, 2008). Task shifting was shown to be most successful in areas where the community health workers provided care under the supervision of experienced ART providers (Ma et al., 2010; WHO, 2008).

The sample type collected was not independently associated with VF in this study. This was collaborated by the findings of several studies that showed that using DBS samples and plasma samples to quantify the HIV viral loads resulted in findings that were reliable and comparable (Garrido et al., 2009; Johannessen et al., 2009; Rutstein et al., 2015). In Malawi, one study reported that using plasma samples increased the precision of VL monitoring but was associated with more logistical and financial barriers making it unappealing in resource limited settings (Rutstein et al., 2015). On the other hand, DBS samples were shown to be cost effective and easy to transport at ambient temperature but were shown to have reduced sensitivity with viral loads <5000 copies/ml (Phillips et al., 2015; Ssemwanga et al., 2020).

There were several limitations inherent in the present study. The usage of routine data that was not collected for research purposes handicapped the research regarding the exposure variables that could be studied. The study did not analyze data on variables like income, education, or distance to the health facility that would have allowed for the control of more concealed demographic confounders, because these are not routinely collected in public health facilities. Additionally, some important factors leading to VF such as ART adherence, should be considered as potential factors in the study, but such information was not available. This may have led to residual confounding that could have biased the estimated odds ratios towards null. Furthermore, the study was based on outcome data collected at a single time point. Therefore, we might have overestimated the virologic failure rate due to individual temporal variability in biological markers or possible measurement errors. Nevertheless, the strength of this study rests on its sizeable statistical power afforded by the large sample size. Further, investigations using cohort studies may be necessary to validate the study's findings.

6 CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

This chapter highlights the details of the major finding of the study. Recommendations resulting from this study are suggested with a view of preventing and controlling the burden of VF in Makueni County

6.1 Conclusion

This study showed that over 13% of HIV-1 patients on ART in Makueni County had virologic failure (VF) during the period of October 2018 and June 2019. The data on samples derived from the National Viral Load/EID monitoring system provides a critical outlook on the challenge of VF amongst different populations receiving ART. The significant risk factors associated with VF among HV-1 patients in Makueni County during the study period were found to be lower age, the type of ART regimen and the justification for viral load measurement. The strength of this study was its large sample size. Further investigations using cohort and case-control studies may be required to validate the findings of this study.

6.2 Recommendations

Based on the research findings from this study, the recommendations listed are key in increasing the effort to reduce the burden of VF in Makueni county among HIV-1 patients on ART:

1. Given that younger age was associated with the risk of VF, the study recommends that youth-friendly ART initiatives are warranted in this setting to reduce the VF prevalence among younger patients.
2. Adherence support in patients taking regimens that are not TDF-based should also be prioritized, particularly in cases of suspected VF and before treatment switches.
3. Routine viral load measurements should be conducted to ensure treatment success and prevent VF. However, if VF is confirmed, targeted HIV drug resistance testing to prevent unnecessary/premature switches should be considered.

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APPENDICES

1. Plagiarism report
2. KNH/UoN – ERC APPROVAL LETTER

10/8/2023

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14th December, 2022

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Dept. of Public & Global Health
Faculty of Health Sciences
University of Nairobi

KENYATTA NATIONAL HOSPITAL APPROVED 14 DEC 2022 KNH/UoN-ERC P.O. Box 20723 - 00202, NAIROBI

Dear Yvonne,

RESEARCH PROPOSAL: PREVALENCE AND PREDICTORS OF VIROLOGIC FAILURE AMONG HIV-1 PATIENTS ON ANTIRETROVIRAL THERAPY IN MAKUENI COUNTY: A CROSS-SECTIONAL STUDY (P707/09/2022)

This is to inform you that KNH-UoN ERC has reviewed and approved your above research proposal. Your application approval number is **P707/09/2022.** The approval period is 14th December 2022 – 13th December 2023.

This approval is subject to compliance with the following requirements;

i. Only approved documents including (informed consents, study instruments, MTA) will be used.
ii. All changes including (amendments, deviations, and violations) are submitted for review and approval by KNH-UoN ERC.
iii. Death and life threatening problems and serious adverse events or unexpected adverse events whether related or unrelated to the study must be reported to KNH-UoN ERC 72 hours of notification.
iv. Any changes, anticipated or otherwise that may increase the risks or affected safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH-UoN ERC within 72 hours.
v. Clearance for export of biological specimens must be obtained from relevant institutions.
vi. Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. Attach a comprehensive progress report to support the renewal.
vii. Submission of an executive summary report within 90 days upon completion of the study to KNH-UoN ERC.