HIV Viral Non-Suppression Trends in Siaya County: 2015-2021

BARCLAY ACHIENG` OBIERO

H56/34328/2019

A RESEARCH DISSERTATION SUBMITTED TO THE DEPARTMENT OF MEDICAL MICROBIOLOGY IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE AWARD OF A MASTER OF SCIENCE DEGREE IN MEDICAL MICROBIOLOGY AT THE UNIVERSITY OF NAIROBI.

DECEMBER 2023

DECLARATION

1. I declare that this dissertation is my original work and has not been submitted elsewhere for examination, award of a degree, or publication. Where other people's work or my work has been used, this has adequately been acknowledged and referenced per the University of Nairobi's requirements.
2. I have not sought or used the services of any professional agencies to produce this work.
3. I have not allowed and shall not allow anyone to copy my work to pass it off as his/her work.
4. I understand that any false claim regarding this work shall result in disciplinary action according to the University's Plagiarism Policy.

MSc Student

Barclay Achieng` Obiero (H56/34328/2019)

Signature:  Date: 05.12.2023

This research dissertation has been submitted with our approval as University Supervisors.

Dr. Martin Mulinge (BSc, MSc, PhD),
Lecturer, Department of Biochemistry,
University of Nairobi, Kenya.

Signature: …..  ……. Date: 07.12.2023

Dr. Moses Masika (MBChB, MSc, PhD),
Lecturer, Department of Medical Microbiology,
University of Nairobi, Kenya.

Signature:  Date: 05.12.2023

DEDICATION

This thesis is dedicated to the individuals whose support and encouragement have been crucial in making this research possible.

To my parents Paul, Edwina, and my entire family, I am eternally grateful for your boundless love, sacrifice, and belief in my abilities. Your unwavering support has been the foundation of my academic journey.

ACKNOWLEDGMENT

I express gratitude to God for guiding me through the entire process of completing this thesis. I owe a debt of gratitude to my supervisors Dr. Martin Mulinge and Dr. Moses Masika for their expertise, guidance, and patience, which have shaped this research and transformed me into a better scholar. I also extend my appreciation to my friends and classmates Kevin, Jeff, Betty, Halima, Paul, and Justin for their inspiration and motivation during the highs and lows of this research endeavor. To my home county Siaya, thank you for your valuable contributions that have made this research insightful and impactful. Lastly, I want to acknowledge all the individuals who have contributed to my intellectual and personal growth. Your friendship, mentorship, and encouragement have made a significant impact on my life and this thesis.

TABLE OF CONTENTS

DECLARATION ii

DEDICATION iii

ACKNOWLEDGMENT iv

TABLE OF CONTENTS v

LIST OF TABLES x

LIST OF FIGURES xi

ABSTRACT xii

CHAPTER 1: INTRODUCTION 1

1.1. Background 1

1.2. Problem statement 2

1.3. Justification of the Study 3

1.4. Objectives 4

1.4.1. Broad objective 4

1.4.2. Specific objectives 4

CHAPTER 2: LITERATURE REVIEW 5

2.1. HIV Origin 5

2.1.1. The HIV genome 6

2.1.2. HIV-1 life cycle and antiretroviral drug targets 6

2.2. HIV Epidemiology 8

2.3. HIV Pathogenesis 10

2.3.1. Transmission 10

2.3.2. HIV Progression 11

2.3.3. WHO clinical staging of HIV 12

2.3.4. Treatment Guidelines. 13

2.3.5. Drug resistance in HIV 14

2.3.6. HIV Testing Schemes 15

2.4. Viral load suppression 16
2.4.1. HIV viral suppression in infants, adolescents, and adults 17
2.4.2. Predictors of HIV viral non-suppression 17
2.4.2.1. Socio-demographic correlates of HIV viral non-suppression 17
2.4.3. Correlates of patients' health and viral non-suppression 19
2.4.4. Viral non-suppression and health systems 20
2.5. Summary and the gap 21
CHAPTER 3: MATERIALS AND METHODS 23
3.1. Study setting 23
3.1.1. Study area 23
3.1.2. Study population 24
3.2. Study design 25
3.3. Sample size 25
3.4. Data analysis plan 26
3.4.1. Variable definitions 26
3.4.2. Statistical analysis 26
3.5. Ethical Considerations 27
CHAPTER 4: RESULTS 28
4.1. Patient characteristics 28
4.2. Trends of HIV Viral non-suppression for the period 2015 to 2021 30
4.3. Time difference in months since initial VL test from 2015 to 2021 32
4.4. Distribution of age, gender, and viral non-suppression and justification of VL test across the sub-counties in Siaya 32
4.5. Clinical and socio-demographic predictors of viral non-suppression. 34
4.5.1. Age category 35
4.5.2. Sex 35
4.5.3. Sub-county 35

4.5.4. Years 35
4.5.5. Sample type 36
4.5.6. Justification 36
4.5.7. Regimen 37
CHAPTER 5: DISCUSSION 39
Study limitations and strengths 44
Conclusion and Recommendations 44
REFERENCES 46

LIST OF ABBREVIATIONS

AIDS	Acquired immunodeficiency virus.
ART	Anti-retroviral therapy
ARV	Antiretroviral
AUC	Area under the curve
AZT	Zidovudine
CI	Confidence interval
DBS	Dry Blood Spot
DNA	Deoxyribonucleic acid
DRVr	Darunavir
DTG	Dolutegravir
EFV	Efavirenz
ETV	Etravirine
IQR	Inter-quartile range
INSTI	Integrase strand transfer inhibitor
LPVr	Lopinavir
LTR	Long terminal repeats
NASCOP	National AIDS Control Programmed
NNRTI	Non-nucleoside reverse transcription inhibitor
NRTI	Nucleoside reverse transcription inhibitor
NVP	Nevirapine
OR	Odds ratio
PI	Protein inhibitor
3TC	Lamivudine
PLLV	Prolonged low-level viremia
PLWHIV	People living with HIV
RAL	Raltegravir
RNA	Ribonucleic acid
RTI	Reverse transcription inhibitor
TDF	Tenofovir
UNAIDS	Joint United Nations Programme on HIV/AIDS
VL	Viral load
WHO	World Health Organization

DEFINITION OF TERMS

Acquired drug resistance refers to the virus's ability to divide because of drug selection pressure caused by mutations in treatment individuals.

Antiretroviral therapy: medication used to prevent other types of retroviruses or HIV from proliferating in the human body.

ARV adherence: entails initiating HIV treatment, attending all scheduled visits, and taking HIV medications consistently and as directed.

HIV drug resistance refers to HIV's ability to replicate despite being treated with antiretrovirals.

People Living With HIV: HIV/AIDS-positive infants, children, adolescents, and adults.

Polymerase chain reaction: a laboratory technique used to multiply a segment of DNA into multiple copies of millions or billions that can be used for further analysis.

Pre-treatment drug resistance occurs when viral replication is not suppressed during treatment.

Transmitted drug resistance occurs in treatment-naive people who become infected with a virus that already has HIV drug resistance-related mutations.

Undetectable viral load: when a viral load test is unable to detect the presence of HIV in the blood because the viral copies are too low. When a person's viral load is still undetectable at least six months following a first undetectable test result, it is said to be "durably undetectable."

Viral load: the quantity of virus particles found in each milliliter of blood is referred to as HIV viral load.

Viral non-suppression: viral load copies > =1000 per milliliter of blood six months after initiation of antiretroviral therapy.

Viral load suppression: having <1000 viral copies per milliliter of blood.

LIST OF TABLES

Table 1. PLWHIV demographics 28
Table 2. Clinical characteristics of patients in the VL database (2015–2021) 29
Table 3. Year vs time difference in months since the initial VL test.....32
Table 4. Predictors of non-suppressed VLs among PLWHIV in Siaya County. 34

LIST OF FIGURES

Figure 1. Geographical distribution of HIV-1 recombinants and subtypes 5
Figure 2. The HIV-1 genome 6
Figure 3. HIV-1 life cycle and antiretroviral drug targets. 8
Figure 4. Health facilities in Siaya County. 10
Figure 5. Location, size, and sub-counties in Siaya County. 24
Figure 6. Trends of viral non-suppression in Siaya County (A), among infants (B), among children (C), among adolescents (D), and among adults (E) from 2015–2021. 31
Figure 7. Participant age distribution (A), gender (B), viral status (C), and justification of VL testing (D) across the six sub-counties. 33
Figure 8. Frequency of treatment regimens. 37
Figure 9. Receiver operating characteristics curve of the logistic regression model. 38

ABSTRACT

Background: Siaya County in Kenya remains among the top five counties with the leading burden of HIV/AIDS. Understanding trends and predictors of unsuppressed viral load can help manage transmission and reduce associated burdens.

Methodology: Data from Kenya's national viral load database (2015–2021) in Siaya County was retrospectively analyzed. A total of 444,389 tests were analyzed to evaluate the trends in viral non-suppression using the Mann-Kendall trend test. Univariate and multivariate logistic regression models were employed to identify the predictors of viral non-suppression and the prediction model was validated using the K-fold cross-validation technique.

Results: The number of viral load tests increased each year, from 7,618 in 2015 to 30,178 in 2021. The highest proportion of viral non-suppression was observed in 2017 (21%). Non-suppression decreased from 19% in 2015 to 5% in 2021. Most tested patients were female (296,866; 67%), and the most common sample type was fresh plasma (324,502; 73%) with most of the samples being for routine viral load tests (396,650; 90%). Viral non-suppression decreased from 19% in 2015 to 5% in 2021, with a significant negative trend (tau = -081, *p*-value = 0.016; Sen's slope = -2.6, *p*-value = 0.016). Males had a higher likelihood of non-suppression. Viral non-suppression in children, adolescents, and adults significantly declined over time, while among infants it increased but the trend was not statistically significant (tau = 0.23, *p*-value = 0.548; Sen's slope = 3.03, *p*-value = 0.548). Recency testing was strongly associated with increased odds of non-suppressed VLs (aOR = 20.00, 95% CI: 7.88–51.45, $p < 0.001$) while breastfeeding mothers and pregnant mothers had no significant associations with non-suppressed viral loads. The 2 NRTI + 1 NNRTI regimen combination increased the odds of viral non-suppression (aOR = 1.26, 95% CI: 1.15–1.39, $p < 0.001$).

Conclusion: While viral non-suppression rates decreased over time, they remained below the Joint United Nations Programme on HIV/AIDS targets specifically in infants and children. Concerns arise regarding increasing non-suppression among infant patients. The choice of antiretroviral regimen was strongly associated with non-suppression. Further investigation is needed to understand resistance patterns and their impact on treatment response, especially with different regimen combinations.

CHAPTER 1: INTRODUCTION

1.1. Background

From the onset of the HIV epidemic, an estimated 85.6 million individuals have contracted HIV, resulting in approximately 40.4 million deaths attributed to HIV-related causes. As of the close of 2022, the global tally of individuals living with HIV reached approximately 39.0 million. About 0.7% of adults aged 15–49 worldwide are presently living with HIV, though the extent of the epidemic's impact varies significantly among nations and regions (WHO, 2023). Through better diagnosis and treatment, death and morbidity have been reduced among people living with HIV/AIDS (Maartens *et. al*., 2014). To end the HIV AIDS pandemic by 2030, the Joint United Nations Programme on HIV/AIDS (UNAIDS) current goals are that 95% of people living with HIV must be aware of their HIV status, 95% of the people who know their status must be placed on management, and 95% of those already on management must be virally suppressed (UNAIDS, 2015). UNAIDS claims that there has been inconsistent progress made in reaching the initial target of 90-90-90 across the various nations. However, by the end of 2017, the world had achieved 75-79-81, meaning that 75% of people who tested for HIV were aware of their status, 79% had started antiretroviral therapy (ART) and 81% of persons with HIV had their viral load (VL) suppressed (UNAIDS, 2017).

As reported by UNAIDS, countries in the Gulf Region, Northern Africa, West Africa, and Central Africa have seen an increase in viral suppression levels. Awareness creation has also increased in Eastern Europe and Central Asia. According to the UNAIDS 2017 report, South Africa had increased the number of people receiving treatment, bringing the country closer to meeting the UNAIDS objective at 85, 71, and 86. Notwithstanding all the hurdles, countries like the Netherlands, Denmark, Botswana, Cambodia, Eswatini, and Namibia met the UNAIDS 90-90-90 targets (UNAIDS, 2017). Despite constituting 12% of the global population, Sub-Saharan Africa still bears 71% of the global HIV/AIDS burden (UNAIDS, 2014a). Nearly 90% of people who have tested positive for HIV in Kenya can now undergo ART, and 76% of those on ART have attained viral suppression (WHO, 2016).

Regardless of the efforts to implement ART, approximately 81% of patients globally have attained viral suppression, compared to ~9% of People Living With HIV (PLWHIV) on ART who have not (WHO, 2016). Studies have been conducted to understand the factors that affect

viral suppression (Pepfar, 2018). Many have revealed that a key obstacle to optimum adherence to treatment is the cost of traveling to health facilities (Jobanputra et al., 2015a).

According to the 2018 Kenya Population-Based HIV Impact Assessment, Kenya has an HIV prevalence of 5%. However, despite attempts to scale up HIV treatment and care, there has been a modest reduction in new infections. HIV infection rates are high in men and women aged 25–44, with women aged 15–24 having the highest risk of contracting the virus due to new infections, necessitating urgent action for this population group (Kenya-NASCOP, 2018). In Kenya, 1.6 million people live with HIV, and as of December 2017, 1.14 million people were receiving care and new infections had decreased by 15% (Mwau et al., 2018a). To concentrate on population impact and geographical effectiveness while ramping up evidence-based prevention efforts, Kenya has stratified the HIV epidemic (Musyoki et al., 2021). Due to low ART uptake, a high rate of transmission from mother to child, and subpar care, the majority of HIV-related deaths in 2014 occurred among children and adolescents, accounting for a quarter of all deaths related to HIV that year in Western Kenya (Nyakeriga et al., 2022). In Kenya, retention in care at 12 months for adolescents aged 15–24 is 68%, compared to 75% for adults, and 82% for children (Mwau et al., 2018a).

1.2. Problem statement

According to The Kenya Population-based HIV Impact Assessment, Siaya County has a 24.8% HIV prevalence, with an estimated 126,411 PLWHIV (Kenya-NASCOP, 2018). The Ministry of Health is collaborating with other partners to ensure that Siaya meets the 95-95-95 UNAIDS targets for reducing the HIV epidemic. To improve the health outcomes and well-being of people living with HIV, rapid HIV diagnosis, ideal linkage, retention to care, expanded coverage of ART, and viral suppression are crucial (Githuka *et al*., 2014). Siaya County`s cascade of care needs to be improved further to close the remaining gaps in the UNAIDS 95:95:95 strategies for viral suppression, identification, and linkage. This can only be done with the help of a skilled, driven, and adequately trained healthcare workforce providing HIV services (Mutambo & Hlongwana, 2019). All other efforts will be undermined by the gap in viral load suppression since PLWHIV who are virally non-suppressed will increase the rate of viral transmission, resulting in newer HIV infections (Rajasingham et al., 2017).

The 4,056 PLWHIV with high viral loads from Siaya reported by (Mwau et al., 2018b) in 2018 should cause the county's health sector great concern. After all, they will raise the county's rates of HIV/AIDS-related morbidity and mortality, causing a significant strain on the country's

health system through the purchase of drugs and a potential increase in the likelihood of resistance to existing ARVs. HIV/AIDS resistance may be experienced in the increase of opportunistic infections that will ultimately impact the county's productivity, health outcomes, and quality of healthcare systems (Janssen *et. al*., 1989).

Since 4,056 of the PLWHIV in Siaya were non-suppressed in 2018, there is a significant risk of viral transmission (Mwau *et. al*., 2018). There is a need for more knowledge on the correlates of the variation in HIV viral non-suppression in Siaya County. This study aims to examine the trends of HIV viral non-suppression in Siaya County from 2015 to 2021.

1.3. Justification of the Study

HIV viral non-suppression is a significant public health challenge globally, with an estimated 20% of PLWHIV not achieving viral suppression despite the availability of effective ART. In Kenya, 57% of all new infections are from the eight high-burden counties including Siaya. Siaya County has a 24.8% HIV prevalence in comparison to the national prevalence of about 5%. There are approximately 126,411 PLWHIV in Siaya and about 4000 new infections annually. Identification of more precise geographic locations for HIV interventions is becoming more important as governments make strides in containing the HIV epidemic. Therefore, assessing the trends of viral non-suppression and mapping the geographic hot spots of viral non-suppression in Siaya is vital for developing targeted interventions.

Similarly, recent studies in Siaya have mapped out hot spots of new infections within the county, this study will add to the knowledge of non-suppression trends of PLWHIV in Siaya with a particular advantage of knowing the pattern the county is heading to and other researchers can utilize the results to build models for predicting the future and identify predictors of changes within a time frame.

The results of this study may also be valuable to health management stakeholders working on viral suppression programs by providing information about the non-suppression status of HIV-positive patients in Siaya. These results could also help identify areas where monitoring and evaluating patients' adherence to their antiretroviral treatment plans are lacking.

Furthermore, this research provides a baseline for researchers who wish to conduct additional investigations on this subject and may assist Siaya County in developing policies that will spur progress in achieving the third Sustainable Development Goal of ensuring healthy lives and improving the well-being of residents of all ages.

1.4. Objectives

1.4.1. Broad objective

To determine the trends and factors associated with HIV viral non-suppression in Siaya County from 2015 to 2021.

1.4.2. Specific objectives

1. To assess the trends of HIV viral non-suppression in infants, children, adolescents, and adults from Siaya County between 2015-2021
2. To determine the clinical and socio-demographic predictors of viral non-suppression in HIV-positive patients in Siaya County

CHAPTER 2: LITERATURE REVIEW

2.1. HIV Origin

The cause of HIV is presumed to be the Simian immunodeficiency virus which infected primates and then spread to people in West and Central Africa (Hahn *et. al*., 2000). Several HIV lineages (M, N, O, and P groups of HIV-1 and A to H of HIV-2) have emerged due to the independent zoonotic spread from primates to humans. Each is associated with an epidemic but they differ greatly in size (Hemelaar, 2012). Group M HIV-1 infection has infected 33 million people globally, group O causes just a few tens of thousands of infections in West-Central Africa, while group N has been found among a small number of Cameroon nationals (Tee et al., 2019). HIV-2 is less infectious than HIV-1, has only a few known recombinants, and limited information on its subtypes (Hahn *et. al*., 2000). Recombination is a crucial factor in viral diversity; it enables the virus to elude the host immune system and antiretroviral therapy. A viral sequence known as a recombinant comprises parts from two or more different parental strains. A circulating recombinant form is generated when two infected individuals combine viral genomes of distinct subtypes to produce a mosaic genome made up of portions from each subtype. These recombinants are identified as circulating strains in the HIV epidemic and are categorized as circulating recombinant forms if they are transmitted and spread within a community (Cheong et al., 2015).

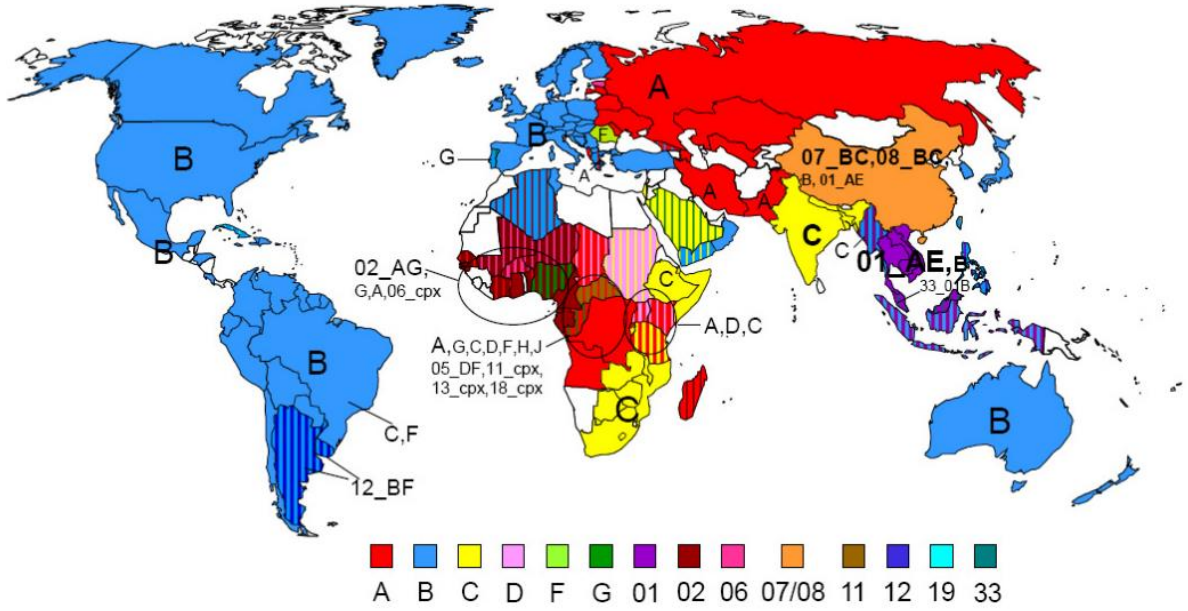

Figure 1. Geographical distribution of HIV-1 recombinants and subtypes

2.1.1. The HIV genome

HIV is an RNA virus whose genome has identical copies of positive-sense single-stranded RNA (Mahlen *et. al*., 2012a). On either side of the genome are long terminal repeats (LTR) sandwiching three structural genes and six accessory genes (McLaren & Fellay, 2021). The structural genes include *gag*, *pol*, and *env*. *Gag*, classified as a group-specific gene, is situated as the initial gene reading frame following the LTR on the 5' end (McLaren & Fellay, 2021). It encodes for proteins found in the outer core membrane, including the p24 capsid protein, the p17 matrix protein, and the p7 nucleocapsid protein (McLaren & Fellay, 2021; Seitz, 2016a). Next to the *gag* gene is the *pol* gene, responsible for encoding three viral enzymes: reverse transcriptase, protease, and integrase. After the *pol* gene is *env*, from which the surface proteins gp120 and gp41 originate (McLaren & Fellay, 2021; Seitz, 2016a). Following *env* in the reading frame are accessory viral genes, which include *vif*, *vpr*, *vpu, tat, rev,* and *nef* (McLaren & Fellay, 2021; Seitz, 2016a). HIV-2 has *vpx* instead of *vpu* in its genetic coding. (Seitz, 2016a).

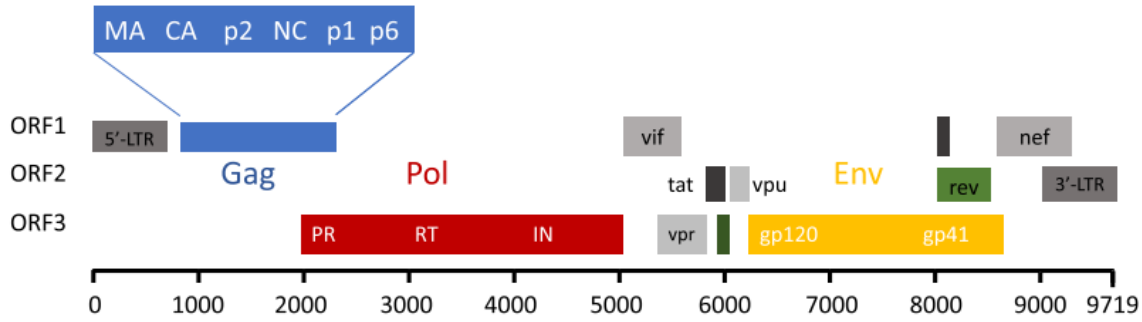

Figure 2. The HIV-1 genome

The genome's 3' and 5' end has LTRs serving as sites for host transcription factors. After the 5' LTR, is the *gag* gene, responsible for coding viral nucleocapsid core and matrix proteins. Next is the *pol* gene, encoding the viral enzymes IN, RT, and PR. Situated between the genes encoding regulatory factors *vif, vpr, vpu, tat, rev*, and *nef* is the *env* gene, which encodes glycoproteins gp120 and gp41 (Abbas et al., 2017).

2.1.2. HIV-1 life cycle and antiretroviral drug targets

Seven steps make up the HIV life cycle: binding, fusion, entry of virions into the host cell membrane; release of single-stranded RNA into the cytoplasm; transcription from RNA to DNA by reverse transcription; translocation of DNA to the nucleus and integration with the host DNA; transcription of mRNA coding for viral proteins; translation to proteins and post-

translational cleavage by HIV protease; and viral maturation and budding (Atta et al., 2019). Combination antiviral therapy medicines fall into five broad categories and target various stages of the HIV-1 cycle. Drugs from one class, known as entry inhibitors, block the attachment and entry of viruses into CD4 cells through two distinct phases of viral entry: cellular chemokine receptor 5 binding and membrane fusion. These agents bind to viral envelope proteins (Greene et al., 2008). Agents from the second class prevent viral replication by terminating the growing chain during transcription (nucleoside reverse transcription inhibitors [NRTIs]). The third category of drug called non-nucleoside reverse transcription inhibitors (NNRTIs) inhibits reverse transcription similarly to NRTIs, but by binding reverse transcription at a different site, hence they do not share cross-resistance with the NRTI family (Greene et al., 2008).

Integrase strand transfer inhibitors (INSTIs), the fourth class of drugs functions by preventing the integration of viral DNA into the host cell's genome. Drugs from the fifth category known as protease inhibitors (PIs) suppress the protease enzyme, which is necessary for the creation of new virus particles (Atta et al., 2019).

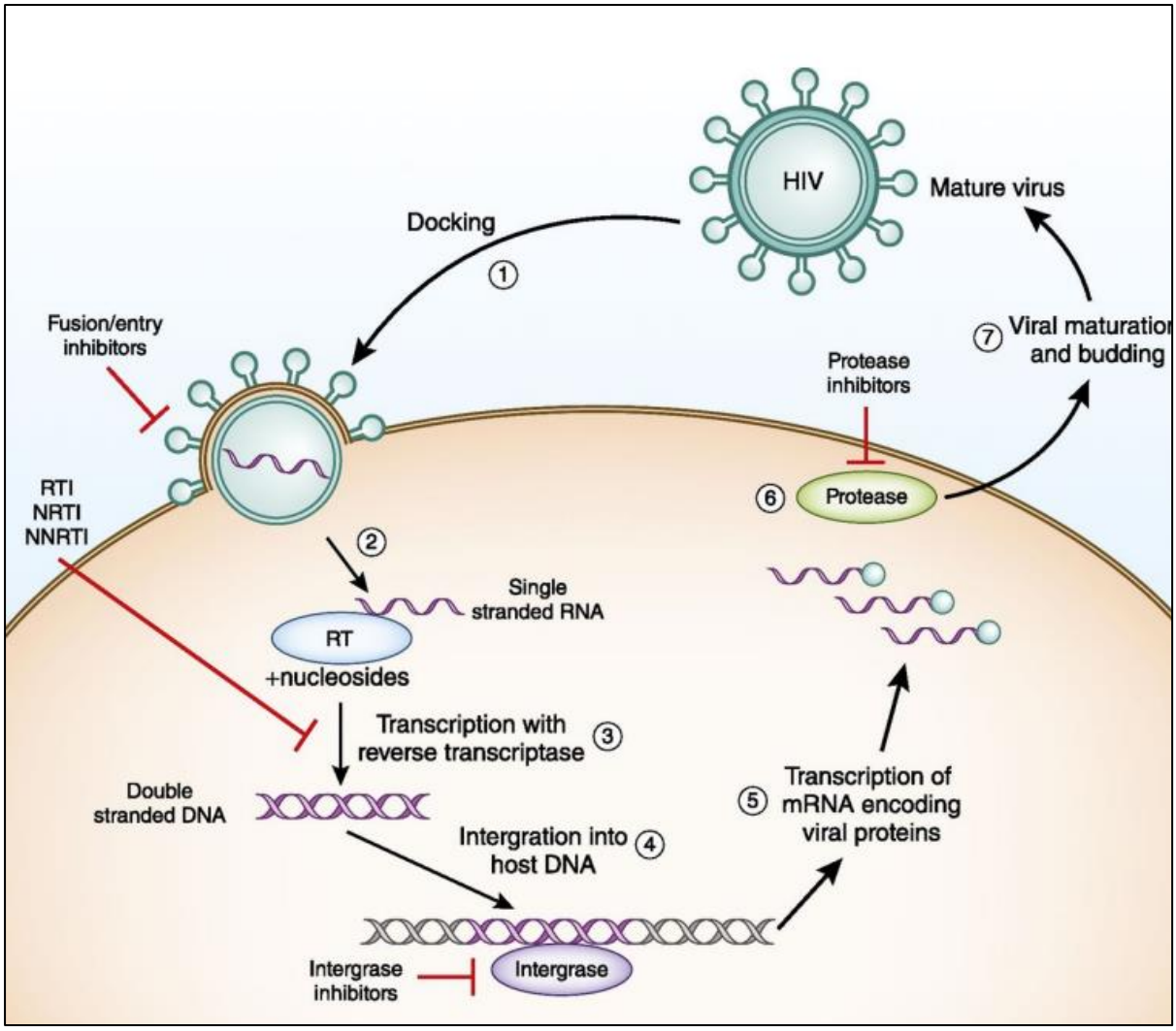

Figure 3. HIV-1 life cycle and antiretroviral drug targets.

Numbered circles denote the seven stages of the HIV lifecycle. Antiretroviral medication classes are represented as red lines close to the life cycle stage they impede (Atta et al., 2019).

2.2. HIV Epidemiology

Around 37.9 million individuals worldwide, including 1.5 million from Kenya, had HIV-1 infection by the end of 2017 (UNAIDS, 2022). Overall, 75 million people have acquired HIV since the epidemic began, and 32 million have died. The UNAIDS launched an ambitious 90-90-90% HIV prevention strategy to end the AIDS pandemic by 2025. However, 1.7 million new HIV infections were recorded by the end of 2017 (UNAIDS, 2014b). It was anticipated that by 2020, 90% of people with HIV would be aware of their status, 90% of HIV-infected persons would be on continuous antiretroviral medication, and 90% of those taking ART would be virally suppressed (UNAIDS, 2014b). The World Health Organization (WHO)'s recommended public health method for starting HIV therapy has now been used in efforts to

reach 90% of individuals on treatment. The strategy has now been amended so that everyone is tested and treated, irrespective of their CD4 count at the time of diagnosis (WHO, 2015).

In Kenya, patients starting ART therapy after the 90-90-90 HIV prevention plan have increased significantly in the past 14 years, with a total population of 1,121,938 by the end of 2017, including 1,035,615 adults and 86,323 children (Waruru et al., 2018). Since then, the progression of clinical illness and VL monitoring have guided this therapeutic approach (Puthanakit et al., 2010). Data from Kenya show that by the end of 2019, 79% of people living with HIV were aware of their status, 96% were receiving treatment, and 88% had achieved viral suppression (Kenya-NASCOP, 2018). These results demonstrate overall national success toward implementing the new HIV prevention strategy, which has resulted in a 5% national HIV prevalence (Kenya-NASCOP, 2018). However, some counties like Siaya, which has one of the highest incidences of HIV, may not follow this pattern (Mutabari, 2017). This is a problem, particularly in Kenyan settings where we lack regular individualized therapy monitoring that includes information on genotypic drug resistance, which may limit the success of this HIV preventive approach (Johnson et al., 2017).

When the patient has a poor response to treatment, the virus may be subjected to drug pressure and produce a drug-associated mutation. HIV medication resistance occurs more frequently because HIV replication is mistake-prone, leading to a high mutation rate, combined with persistent drug-selective pressures (Rusine et al., 2013). Patients who had previously been uninfected can become infected with strains that emerge at the start of treatment (often recognized as secondary or acquired HIV drug resistance) (referred to as primary or transmitted HIV drug resistance). Transmitted HIV drug resistance reduces the effectiveness of first-line ART regimens and raises the probability of virological therapy failure. This is significant given the lack of available treatments (Anderson et al., 2019).

Effective HIV infection pandemic control is still elusive despite ART discoveries that have revolutionized the treatment of HIV disease. Kenya is one of the African nations with several HIV subtypes. Although HIV incidence is declining thanks to current interventions, the diversity of the circulating subtypes may be growing as a result of mixed-up or superinfections that result in the creation of viral recombinants (Rowland-Jones & Andrews, 2017). Numerous viral strains are anticipated to have an impact on viral tropism, replication fitness, treatment response, and vaccine design (Cohen et al., 2008). The potential utilization of particular second-line regimens and drug cross-resistance may be impacted by resistance mechanisms in

various subtypes (Johnson et al., 2017). Even patients taking newer medications need to be monitored as pre-treatment drug resistance in HIV-1 is on the rise. There`s uncertainty in the possibility of new kinds of ARV medications developing resistance. However, it is anticipated that resistance will undoubtedly emerge as nations whose NNRTI resistance is high adjust their ART first-line regimens, which also include the recently adopted ones, and this needs to be constantly watched (Epidemic, 2017). This study will focus on viral non-suppression in Siaya County. The various health facilities in Siaya where data will be extracted are shown in the map below.

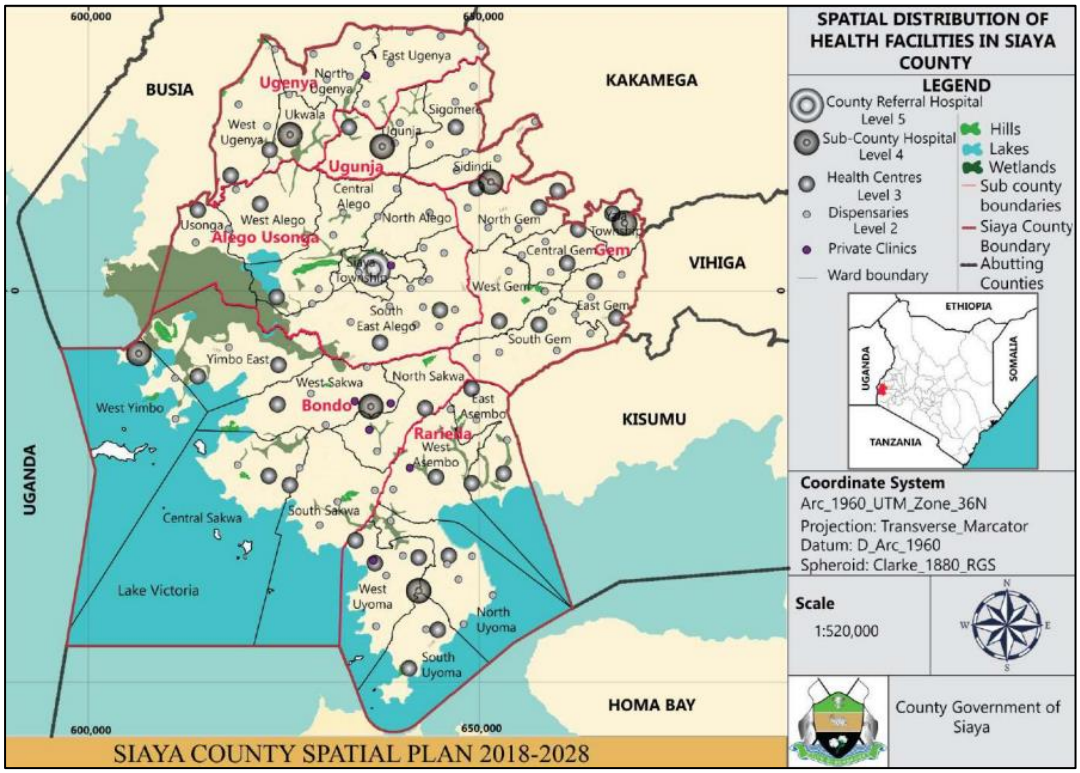

Figure 4. Health facilities in Siaya County.

2.3. HIV Pathogenesis

2.3.1. Transmission

Most new HIV infections are spread through sexual contact (Cohen et al., 2008). Parenteral drug delivery is another epidemiologically significant method, as is drug snorting with epistaxis. HIV can be found within one to two days of infection in local lymphatic tissue, and local lymph nodes within five to six days. HIV spreads in the entire body, including the neurological system, 10 to 14 days after the initial infection (Mahlen *et. al*., 2012b). HIV can spread through blood or transplanted organs, including bone, starting about 5–6 days after the

donor becomes infected. Mother-to-child transmission has been observed as earlier than usual at the first 12 weeks of pregnancy, however, it is more common (>90%) within the last trimester, particularly just before or at delivery (Seitz, 2016b). Breast milk can be a source of HIV transmission too (Adetokunboh & Oluwasanu, 2016). Whatever the method, HIV-1 transmission is dependent on the "index case's" (the individual who transmits the virus) infectiousness and the host's susceptibility. HIV-1 must be present in relevant body fluids (blood or genital tract secretions) and must be transmitted for an infection to be contagious (Mahlen *et. al*., 2012b). A complete understanding of these quick and intricate biological activities is necessary for the development of biological ways to stop the transfer of HIV-1 to the host (Cohen *et. al*., 2008).

2.3.2. HIV Progression

Most HIV-infected individuals can have a range of clinical symptoms, including fever, lymph node enlargement, fatigue, malaise, a rash with small, hardly perceptible lesions, and/or digestive problems, and the humoral immune response to HIV begins to manifest after 3–6 weeks (Seitz, 2016b). These general symptoms can also be seen in other viral diseases like influenza and mononucleosis caused by Epstein-Barr virus and cytomegalovirus. The acute phase frequently includes acute neuropathy. The symptoms last for two to six weeks (Burin-des-Roziers *et. al*., 1995). Blood virus titers of 10^5–10^9 are produced in the blood at the start of the infection; in rare circumstances, up to 10^{14} genome copies/mL are seen. As a result, blood donations are very contagious in this acute phase. The VL may decrease to 10^2 genome copies/ml or undetectable levels during the asymptomatic phase. Infected people can still transmit the virus at this stage through their blood and any cervicovaginal secretions or seminal fluids (Seitz, 2016b).

Several different HIV protein epitopes trigger a targeted T-cell response (Kunwar *et. al*., 2013). At the beginning of the immune response, there are low titers of immunoglobulin M and G antibodies, primarily directed against p24 and the surface glycoproteins gp120 and gp41. High-avidity immunoglobulin G antibodies are then produced in a matter of weeks against all HIV proteins. Some of the antibodies can neutralize the gp120, gp41, or group-specific proteins p24/p17 of the invading virus. The gp120 V3 loop is the target of a sizable part of the neutralizing antibodies. These strain-specific antibodies cannot entirely eradicate all the HIV quasispecies that the sick person is continuously creating. The immunological response causes viruses with a variable V3 loop to be chosen (Herndier *et. al*., 1994). Like other viral infections,

the early immune response triggers an immunoglobulin M antibody response that can extend for months (Kunwar *et. al*., 2013).

Initially, vague symptoms may appear throughout the HIV infection according to the CD4 cell count. They may include transient episodes of fever, diarrhea, malaise, exhaustion, and weight loss (symptoms of the so-called AIDS-related complex, ARC) (Kong & Sattentau, 2012). When immunodeficiency advances, which is usually seen when the CD4 levels are below 300 cells /mm^3, opportunistic infections and cancers arise. Periods of health followed by sickness, which occur more frequently and last longer throughout the infection, are the defining features of an HIV infection. Before immunodeficiency signs appear, 2 to 25 years or more may have passed (Kong & Sattentau, 2012).

Salmonella species, pneumococci, human polyomavirus JC, cytomegalovirus, and herpes simplex virus are examples of opportunistic infections that are widespread. These infections include atypical mycobacteria, *Toxoplasma gondii*, *Cryptosporidium parvum*, *Pneumocystis jirovecii*, and *Mycobacterium tuberculosis*. Kaposi's sarcoma and non-Hodgkin lymphomas are two typical neoplasms connected to human herpes virus type 8 infections. B-cell lymphoma is linked to the Epstein-Barr virus (Coelho et al., 2014).

2.3.3. WHO clinical staging of HIV

After confirming an infection by HIV through rapid diagnostic antibody tests, immunoassays, or polymerase chain reaction tests (WHO, 2007), the next step involves clinical staging. The WHO classifies HIV into 4 stages, denoted as stage 1 through stage 4. Each stage requires the presence of at least one clinical feature (WHO, 2007). Placement into any stage requires the presence of at least one classical feature. Stage 1 patients are asymptomatic, primarily exhibiting persistent generalized lymphadenopathy lasting more than six months (WHO, 2007). The second clinical stage is characterized by mild symptoms, including marginal weight loss, typically not exceeding 10% of total body weight. Patients in this stage may experience recurrent upper respiratory tract infections such as sinusitis, tonsillitis, pruritic eruptions, pharyngitis, sporadic oral ulcerations, and fungal nail infections (WHO, 2007). Stage 3 patients present with advanced symptoms as their immune systems further deteriorate. Significant weight loss exceeding 10% of their body mass, along with neutropenia, chronic thrombocytopenia, unexplained anemia, chronic fever, and persistent diarrhea for more than a month, are observed. Oral manifestations include oral candidiasis, oral leukoplakia, periodontitis, and gingivitis (WHO, 2007).

Opportunistic bacterial infections, with pulmonary tuberculosis being the most prevalent, begin to emerge, leading to a variety of infections such as meningitis, bacteremia, and pneumonia (WHO, 2007). In the last clinical stage, stage 4, AIDS is diagnosed. Patients experience extensive body wasting (HIV wasting syndrome) and recurrent severe disseminated opportunistic infections, including extrapulmonary tuberculosis, severe bacterial pneumonia, HIV encephalopathy, disseminated mycosis, disseminated non-tuberculous mycobacterial infection, cryptococcosis, cryptosporidiosis, non-typhoidal salmonella bacteremia, and malignancies such as Kaposi's sarcoma (WHO, 2007).

2.3.4. Treatment Guidelines.

Despite the abundance of drugs targeting various phases of the HIV-1 cycle, current worldwide recommendations now advise a combination regimen based on the Integrase Strand Transfer Inhibitor (INSTI) medication class in conjunction with reverse transcription inhibitors (RTIs) as the primary therapy for the majority of persons with HIV (Günthard et al., 2016). NNRTIs and PIs should occasionally be taken with cytochrome P4503A (CYP3A) inhibitors or pharmaco-enhancers in clinical settings. The fundamental objectives of these recommendations include preventing HIV transmission, restoring and maintaining the immunologic function, minimizing HIV-1-associated morbidity, and extending the duration and quality of the survival (Pepping et al., 2014). Existing ART programs adhere to the test-and-treat principle for all PLWHIV patients (Kuznik et al., 2016). According to recent Kenyan guidelines, first-line therapy should consist of Zidovudine dosed with Lamivudine and Nevirapine for infants, Abacavir combined with Lamivudine and Efavirenz for children under 15 years, Abacavir combined with Lamivudine and Lopinavir for teens, and Tenofovir and Lamivudine combined with either Dolutegravir or Efavirenz for all above 15 years (Pepfar, 2018).

Antiretroviral drugs remain the cornerstone of HIV therapy and prevention. HIV-positive people whose plasma has detectable virus should get treatment, starting with an INSTI and two NRTIs being recommended. Pre-exposure prophylaxis should be considered part of an HIV prevention strategy for those who are at risk. Effective usage of the ARVs that are now on the market can maintain HIV suppression and stop the spread of HIV. The survival rates of HIV-positive persons who are kept in care can approach 90% with various treatment regimens (Chan, 2018).

2.3.5. Drug resistance in HIV

HIV drug resistance refers to HIV's ability to replicate despite being treated with ARVs (WHO, 2019a). It is typically the result of mutations within the genes that code for viral proteins that the ARVs act on. Primary mutations reduce the drug's ability to bind the target enzyme, whereas secondary mutations augment primary mutations by enhancing the fitness of variants with primary mutations (Holec *et. al*., 2017; WHO, 2001). HIV drug resistance is divided into three types: acquired drug resistance, transmitted drug resistance, and pre-treatment drug resistance (WHO, 2019a). Acquired drug resistance refers to the virus's ability to divide because of drug selection pressure caused by mutations in individuals undergoing treatment (Coetzee *et. al*., 2017; WHO, 2019a). Transmitted drug resistance occurs in treatment-naive people who become infected with a virus that already has HIV drug resistance-related mutations (WHO, 2019a). Pre-treatment drug resistance occurs when viral replication is not suppressed during treatment. It can be transmitted drug resistance, acquired drug resistance, or both in ART-naive patients or treatment-experienced patients re-initiating ART (Chimukangara *et. al*., 2019; WHO, 2019a).

Antiretroviral drug use before the start of ART is now recognized as a concern in Low and middle-income countries since those who have taken antiretrovirals in the past run a significant risk of developing HIV drug resistance and may be more at risk of treatment failure when beginning or restarting an NNRTI-containing first-line ART regimen (Gupta et al., 2018). A growing number of people starting NNRTI-containing ART, now that ART is more widely accessible in low and middle-income countries are not antiretroviral-naive but rather have previously disclosed or unreported exposure to antiretroviral medications either as a treatment for the prevention of mother-to-child transmission of HIV or previously disengaging from care (Hamers et al., 2010). In a major study from South Africa, 24% of the 326 people who started first-line ART reported prior use of antiretroviral medications (Phillips et al., 2017).

It has also been observed that failure to systematically monitor first-line ART resistance leads to the buildup of viral variants (Avino et al., 2019). Previous research in sub-Saharan Africa, including Tanzania, South Africa, and Uganda, found that individuals on first-line ART exhibited rates of treatment failures of 11%, 15%, and 14.9%, respectively (Hawkins et al., 2016). Among 874 HIV-infected people on first-line ART in Ethiopia, a multicenter cohort study found that treatment failure rates were 23.3% and 33.9% at 6 and 12 months (Telele et al., 2018). In Dar es Salaam city, a 2017 study evaluating pre-treatment and acquired HIV drug

resistance mutations found that 30% of clients without ART had pre-treatment drug resistance mutations (Samizi et al., 2021).

The following were significant findings from a Kenyan cohort study: Resistance to pre-treatment drugs resistance increases the likelihood of (1) viral non-suppression in a few months of initiating NNRTI, (2) an increase in the number of mutant codons, (3) an increase in the number of mutant variants within a person's HIV quasispecies, and (4) resistance occurring at a greater rate with Nevirapine regimen when compared with Efavirenz regimen (5) Patients who were virally non-suppressed after 12 months of ART seemed to have numerous mutations in both NRTI and NNRTIs, regardless of whether they had pre-treatment drug resistance or wild-type genotype before enrollment (Beck et al., 2020).

2.3.6. HIV Testing Schemes

HIV rapid diagnostic tests are the main tools for the diagnosis and screening of HIV in places with limited resources (Case et al., 2019a). HIV diagnosis must be performed using both sensitive and specific tests due to the potential of growing misleading findings from HIV testing, as well as the negative social, emotional, and health consequences of HIV wrong diagnosis in various contexts (Shanks et al., 2013). WHO recommends utilizing a mix of rapid diagnostic tests and/or enzyme immunoassays to offer an HIV testing approach or algorithm with at least a 99% positive predictive value. Prior WHO guidelines indicate that settings with a national HIV prevalence of 5% or above should use two consecutive reactive tests to make an HIV-positive diagnosis to maintain at least a 99% positive predictive value. In locations with a national HIV prevalence under 5%, the WHO advocated utilizing three consecutive reactive tests to confirm an HIV-positive diagnosis to maintain at least a 99% positive predictive value (WHO, 2014).

In the past, CD4 cell count, a measure of the immunological state, was utilized by national HIV programs in resource-constrained areas to track patient response to HIV antiretroviral therapy. A more accurate indicator of treatment response is the VL measurement of plasma HIV concentration. In high-income nations, VL testing has long been used to assess viral response to therapy and identify patients who might be treatment refractory. VL has the advantage of detecting treatment failure more quickly and reliably than CD4 testing, allowing healthcare personnel to provide patients with the care they need by providing more in-depth adherence counseling or moving to second-line medications. Because VL testing has unreasonably high costs and resource needs for both infrastructure and employees, scaling it up has proven to be

difficult in the past (Mwau et al., 2018b). Despite these obstacles and doubts regarding their viability in low-resource environments, Kenya's national VL program was first launched in 2012 and has since expanded (Roberts et al., 2016).

The national VL database in Kenya has made it possible to track program expansion, keep track of how patient and treatment parameters change over time, and pinpoint regions with problems (Mwau et al., 2018b). Similarly, results of a study in Western Kenya showed that future research should aim at maximizing VL suppression rates for children living with HIV by combining an improved point-of-care VL and drug resistance mutation monitoring algorithm with evidence-based socio-behavioral therapies (Patel et al., 2020). In 2018, data from the national VL database was utilized for a study in Kenya that reported that males, adolescents, and children were more likely to have elevated VL and similarly, Nairobi and Central Kenya had a higher likelihood of being suppressed compared to other regions of the country (Mwau et al., 2018b).

2.4.Viral load suppression

There are three primary methods for HIV testing: virologic, antigen/antibody, and antibody (Fabri et al., 2015). VL, which measures the quantity of viral copies per microliter of blood, is the preferred approach for monitoring patients' ARV treatment. VL suppression is typically defined as having fewer than 1000 viral copies per microliter of blood. The most common technique for VL determination involves using an enzyme in the polymerase chain reaction, which amplifies the HIV amount in a blood sample. During the reaction, certain markers determine the virus concentration, yielding a positive result if a chemical reaction occurs. The Branched DNA method is another approach commonly employed in qualitative research, while Nucleic Acid Sequence-Based Amplification is used to quantify viral proteins (Deeks et al., 2015).

Depending on the test's sensitivity, a VL test that is undetected indicates a very small number of viral copies in the body. In research settings, VL tests are used to diagnose HIV, particularly in the early stages of infection, track the progression of the disease, and evaluate the efficacy of treatment. The risk of HIV transmission is eliminated by HIV therapy, which inhibits HIV viral replication. Most patients respond effectively to treatment within three to six months of beginning it, as evidenced by their undetectable virus loads (Deeks et al., 2015). According to scientific evidence, HIV-positive individuals who are receiving treatment and have a VL that is not detectable may not transfer the virus to their partners or unborn children (Lu et al., 2020).

People with HIV/AIDS are more susceptible to opportunistic infections such as cryptococcal meningitis, which affects the brain and spinal cord and is an indication of insufficient immunity (Khadka et al., 2021).

Before enrolling in care, those with HIV/AIDS should have their CD4-Count and opportunistic illnesses such as cancer, hepatitis, tuberculosis, and cryptococcal meningitis evaluated, according to the Kenya Quality HIV Framework (Kenya Quality Improvement HIV Framework, 2014). As part of the clinical and laboratory tests used to identify the pathogen, blood is analyzed; culture and sensitivity tests with the detection of antigens for Cryptococcal Meningitis are also performed. There are specialized CD4 counting machines available for CD4 counts, which typically range from 500 to 1200 cells/mm3. The Kenya Anti-Retroviral Therapy Guidelines state that people with CD4 counts of 100 cells/mm^3 or lower should be screened for Cryptococcal Meningitis (Kenya HIV Prevention and Treatment Guidelines, 2022).

2.4.1. HIV viral suppression in infants, adolescents, and adults

The main monitoring strategy to identify and validate ARV treatment failure is VL. 95% of persons living with HIV should be aware of their status, 95% of those who have been diagnosed with HIV should start antiretroviral therapy, and 95% of those who are receiving treatment should achieve VL suppression, according to the Global Health Sector Strategy on HIV, with a major focus on adolescents (UNAIDS, 2022). A study conducted in South Africa found that 5% of young adults and 8% of adolescents experienced virological failure. This emphasizes that virological failure occurs more frequently in adolescents than in young adults as also reported in another study in Cape Town, South Africa (Nglazi et al., 2012).

2.4.2. Predictors of HIV viral non-suppression

2.4.2.1.Socio-demographic correlates of HIV viral non-suppression

The socioeconomic condition and general well-being of an individual are considered to be socio-demographic factors (Reagan & Barkley, 2015). It has been demonstrated that baseline socio-demographic characteristics influence the suppression of VL in patients who use facilities (Rajasingham et al., 2017). The age of patients enrolled in facilities was discovered to be a significant predictor of VL suppression in a study of the prediction of high VL in Swaziland; in this case, the researchers discovered that the majority associated with VL suppression was among children, adolescents, and adults with advanced disease (Jobanputra et al., 2015b).

For the (Nobile et al., 2010) study, participants were chosen from seven different countries, including South Africa, Pakistan, Mexico, India, Cambodia, and the United States. To increase the volume and quality of the data, the study was only done utilizing qualitative instruments, such as focus groups and interview guides. The study's target population was 1200 PLWHIV, The study's key conclusion was that 7 out of 8 patients in the cohort were female; however, according to a different study carried out in Canadian prisons, gender was unrelated to viral suppression (Rajasingham et al., 2017). A study by (May et al., 2014) also indicated that age was closely correlated with VL suppression in cohorts from Malawi, Zimbabwe, and South Africa.

In a study conducted in Uganda's Busia District, cohorts of high VL children aged 5 to 12 years, adolescents aged 12 to 15 years, and adults aged over 20 were compared. An in-depth interview served as the method for gathering the study's data. In addition, the study found that contrary to past findings, young adolescents and children aged 1 to 5 years were substantially more likely to have higher VLs than any other age group and this was because it is challenging to monitor children's ARV dosage and adjust it as they grow, as the probable explanation for the high VL in children. The study also concluded that when compared to the other adult age groups, young women have a higher likelihood of not being virally suppressed due to poor equality (Bulage et al., 2017).

In a study that examined PLWHIV in the Ugenya Sub-County in Siaya County, the researchers sought to identify the specific socioeconomic factors, patient characteristics, and structural aspects of the hospital facilities that could be used to forecast ARV adherence and high viral suppression. The socioeconomic status of the patients, including their occupation, income group, and level of education is said to have an impact on VL. In that study, it was found that the cost of care had very substantial effects on the treatment strategy and, concurrently, income security had a significant effect on treatment adherence and was a determinant of elevated VL (Adino, 2020). In addition, a study by Diaz *et. al* found that a patient's socioeconomic position, including their willingness to adhere to their medication, is influenced by their career, level of income, and literacy rate level. This is significant because Botswana's treatment costs used to be of significant influence on HIV medication adherence (Diaz et al., 2016). In Uganda, a study was conducted that found a link between patients' socioeconomic status and high VLs. Food security was discovered to significantly affect patients' compliance with treatment and in addition, increase its adverse impacts. The suppression of VL was also connected to aspects related to access to healthcare, particularly patient proximity to a healthcare facility. Patients

who were closest to the healthcare facility were found to have the best odds of adhering to ARV with an odd ratio of 3, while those who were farther away were found to adhere with 1 as the odds ratio. Some other factors that were determined to be significant included the HIV status of partners, difficulties in integrating treatment into daily living schedules, and the stigma involved (Chandler et al., 2015).

2.4.3. Correlates of patients' health and viral non-suppression

Antiretroviral therapy adherence is moderately correlated with viral suppression, according to a study carried out in Cambodia. In this country, the study determined that, as reported within 30 days of treatment, total self-reported ART adherence was 96%. It also looked at how many virally non-suppressed patients were reported during the shorter period. Study results revealed that the employment of stringent client assessment measures before enrollment in the study and the start of ARV may have been the precondition for VL suppression rather than the cause of suppression itself (Chhim et al., 2018). Huerga *et. al* conducted a study with 400 patients in remote South Africa in KwaZulu-Natal, employing mixed methods. They discovered that nearly half of the individuals regarded lifestyle and sexual concerns as important predictors of VL non-suppression (Huerga et al., 2017).

Stigma is a significant factor in predicting VL suppression. One Indonesian study that solely used secondary data discovered that stigma and disclosure were the most crucial factors in reducing VL (Vetrova et al., 2022). A study in the United States of America investigated the clinical associations between drug addiction, smoking, and alcohol consumption among lorry drivers. 84.0% of the respondents in the cohort of 100 HIV-positive individuals who took drugs and got ART participated in the study. According to the study, there is no connection between VL and cigarette smoking (Sullivan et al., 2015).

Another study, which focused on PLWHIV in France, discovered that clients on treatment who acknowledged routine consumption of alcohol had an approximately four times greater chance of HIV viral non-suppression than clients on treatment who were non-alcoholics (Nolan et al., 2017). There are strong relationships between `feeling healthy,` a history of drug injection, conflicts between work and school, detention or imprisonment, perceived distance to the clinic, and receiving care later than expected, according to a study carried out in Vietnam (Grau et al., 2017). The ability of patients to adhere to prescriptions and related instructions is correlated with their ability to follow through with treatment concerning the management of HIV hence reduced compliance is linked to a decreased possibility of booking doctor

appointments for medical prescriptions, which is also linked to compliance to medication, whereas higher compliance is linked to a greater probability of suppression of the virus (Olivieri-Mui et al., 2020).

In a study of the factors that influence treatment compliance in Nairobi, questionnaires were utilized to assess participants' comfort levels in using coping mechanisms when confronted with challenges in life. 94.5% of participants reported not skipping medication within the preceding four days. Explanations offered due to skipping dosages included patients being too occupied, forgetting, fear of other people watching them take their medication, being unwell, and the assumption of `being all right.` According to the study, there is a strong correlation between adherence and coping self-efficacy. Drug side effects are important in medication adherence, especially when it comes to ARV, asserts Ronen *et. al*. Redistribution of fat, excruciating diarrhea, vomiting, and drug-related allergies are typical adverse effects of medications (Ronen et al., 2017).

Difficulty in taking medicine as prescribed despite side effects, barriers relating to attitudes about medications, and beliefs about them might also contribute to poor adherence. These obstacles include side effects that are actual or anticipated, complementary therapies, adherence to rigid or complex regimens, varying dosages, and frequent medication changes (Parry et al., 2005). BMI was also found to be linked to mortality in PLWHIV when starting ARV medication as well as suppression of the virus according to a study in KwaZulu Natal, South Africa (Gupta et al., 2018).

2.4.4. Viral non-suppression and health systems

Health promotion, restoration, and maintenance are the core goals of the structures and procedures that make up health systems. These networks of systems directly contribute to bettering the results of medical care, making them the primary determinant of health (Ogunbajo et al., 2019). Policy, guidelines, regulatory requirements, and funds on health care (including financial, physical facilities and sites as well as health workers' education) are all factors that have an impact on health systems (Tobergte & Curtis, 2013). Different levels of structures, infrastructure, and commodities have an impact on a facility's diagnostic operations, according to a Brazilian study (Landmann et al., 2015).

A research study in Southern New England identified important parameters that have an impact on HIV healthcare. A group of on-call and off-call clinicians in this study were subjected to qualitative instruments. The study's goal was to pinpoint the key health system elements that

enable a facility to create an environment that boosts the likelihood of viral suppression. The study concluded that infrastructure, adherence to procedures and regulations, commodity availability, personnel training to handle HIV care, and infrastructure are crucial in guaranteeing the quality of HIV care (Grau et al., 2017). Protocols and procedures in the health system assist the management of healthcare facilities in periodically analyzing, enhancing, and benchmarking the processes that take place in those institutions (Amstutz et al., 2020). The purpose of the guidelines or recommendations for HIV/AIDS quality management is to enhance interventions, aid in locating care, and increase access to medications for virally non-suppressed persons together with care for people with opportunistic infections. These recommendations as well as the procedures aspire to improve overall health outcomes by reducing loss along the diagnostic-to-treatment continuum. The application of the recommendations is still in its infancy in many countries, despite all the effort put into developing them to assure quality assurance in healthcare for HIV/AIDS patients (Rowland-Jones & Andrews, 2017).

Facilities with outstanding access to healthcare, strict governance, high worker satisfaction, socio-consecutiveness at work, and work-life balance have a lower HIV VL. To guarantee service delivery, standardizations, and space for comparison with the highest standards of care, healthcare facilities should use guidelines and protocols to assess policy gaps concerning the WHO and UNAIDS framework for effective HIV/AIDS care (Case et al., 2019b). There is not enough data on how global guidelines and national HIV regulations are implemented at the level of health facilities, given that the practices at the level of the facility will have an impact on health outcomes through a variety of mechanisms, such as availability and coverage, level of quality care, care coordination and tracking of patients, as well as aid for PLWHIV, and continuous monitoring of patient treatment. Acknowledging the gaps in policies regarding HIV in association with guidelines from WHO, and disparities between nationwide programs involved mentorship could be beneficial to those who are having trouble providing informed HIV service.

2.5.Summary and the gap

Sub-Saharan Africa, has 12% of the world's population but still bears 71% of the burden of HIV/AIDS globally. According to NASCOP statistics, ART is now accessible to about 90% of those with HIV, with 76% of those receiving the treatment experiencing viral suppression. Like previous studies, this study is comprehensive in that it examines factors related to the health system, patients, and socio-demographics that are related to VL non-suppression. Previous

studies have focused on elements that are linked to viral suppression. This study will focus on the trends of HIV viral non-suppression in Siaya county from 2015 to 2021 with the particular advantage of knowing the pattern the county is heading to and other researchers can utilize the results to build models for predicting the future.

CHAPTER 3: MATERIALS AND METHODS

3.1. Study setting

3.1.1. Study area

Siaya is located in Nyanza and is surrounded to the Northwest by Busia County, to the Northeast by Kakamega County, to the East by Vihiga and Kisumu County, and to the South by Lake Victoria. The current population is 842,304 and a population density of 33 people per Km^2 with an area of 2,530 km2 (Chs-Kenya, 2017). The county is divided into six sub-counties and thirty wards. Rarieda, Ugenya, and Ugunja sub-counties each have five, four, and three wards, respectively; Alego Usonga is the largest sub-county with approximately an area of 605.8 Km^2, whereas Ugunja is the smallest with just an approximate area of 200.9 Km^2 (Siaya, 2018).

According to the existing population allocation by a residential area, 89% percent of residents in Siaya reside in rural areas (Siaya, 2018). In 2017, there were 434.2 Km of basic tarmac roads in the county, gravel roads 1,297.41 Km long, murram roads 532.78 Km long, and 1,170 Km of additional narrow roads (Siaya, 2018). Inadequate and poor infrastructure, inadequate supply of water, unpredictable supply of electricity, high HIV/AIDS prevalence, and massive unemployment are the main development challenges; as a result, approximately 48% of the overall population in the county presently lives beneath the poverty line (Siaya, 2018). In 2018, the county had 220 registered health facilities, including 11 level-4 hospitals, 50 level-3 health centers, and 159 dispensaries (Nyangueso et al., 2018).

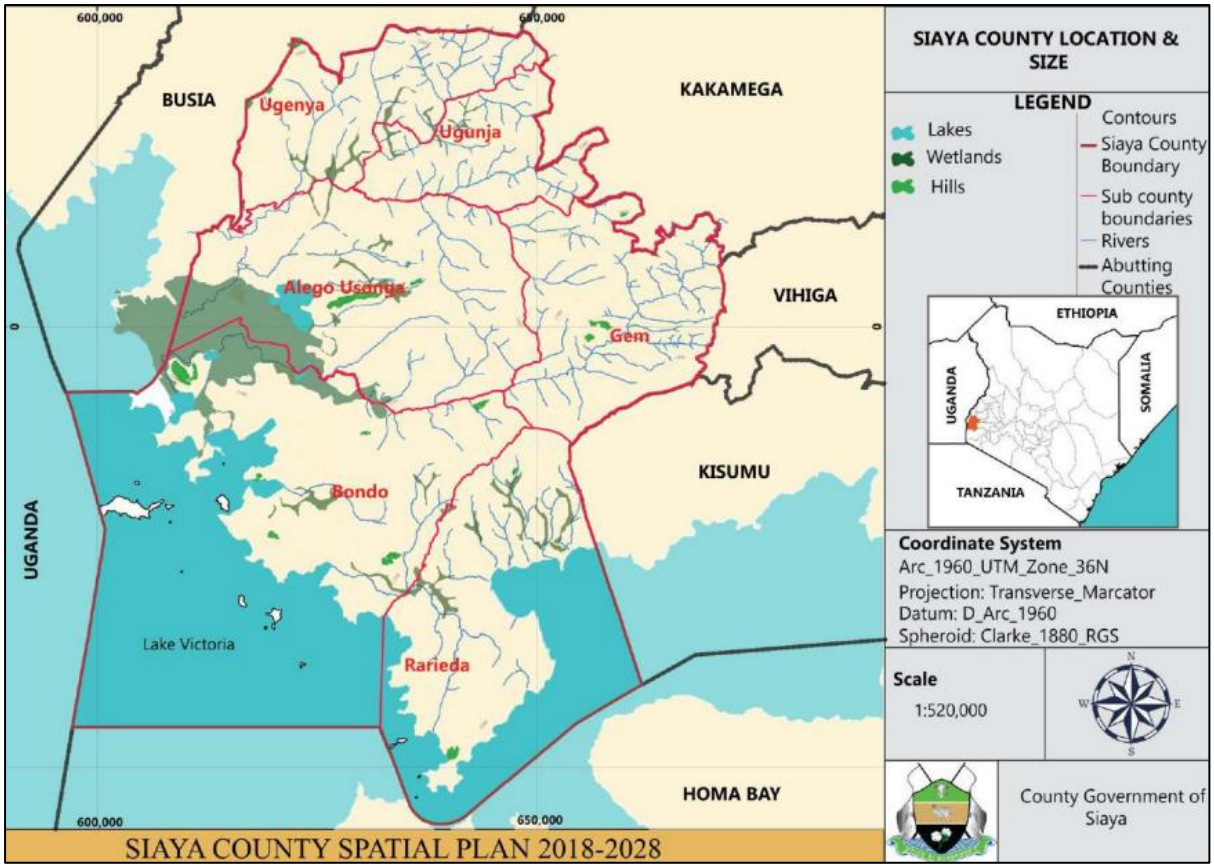

Figure 5. Location, size, and sub-counties in Siaya County.

3.1.2. Study population

The study population included PLWHIV in Siaya County receiving care and management from the health facilities within the county. According to KENPHIA (Kenya-NASCOP, 2018), Siaya County has a 24.8% HIV prevalence rate, with an estimated 126,411 PLWHIV and a viral suppression of 79%. Data points from individuals of all ages were included in this study. The analysis unit was data points for the patients on care from 2015–2021. The population sample was all data points across the health facilities available on KMFHL/VL databases. All the health facilities were purposively selected as the focus for data abstraction. KMFHL/VL databases is a national viral load database that is managed by the Ministry of Health/NASCOP, therefore enhancing the credibility and validity of the acquired data.

3.2. Study design

This study employed a retrospective cross-sectional study design to conduct a time trend analysis of VL non-suppression from 2015 to 2021 in Siaya County.

3.2.1. Data abstraction and management

Data was obtained from KMFHL/VL databases over the seven years. Information of interest that was extracted including VL was transferred to an electronic Excel format; a pre-made file extraction and collection guideline. The electronic data was examined to make sure that each data item was properly formatted and that every data point was recorded. The sites were contacted for evaluation and correction of any inaccurate/unidentified data. Data was combined all over the sites to create a multi-site database. The data retrieved from these databases was stratified yearly from 2015 to 2021. Within each year, the data was further categorized for (0–23 months), children (2–14 years), adolescents (15–24 years), and adults (> 25 years). The data was further stratified per sub-county and the dataset of interest included variables such as viral non-suppression, HIV regimen, age, sex, sample type for VL, and justification for VL testing. The information was gathered by the investigator and was assisted by experienced assistants and a biostatistician. Research assistants included individuals from the National HIV Reference Lab, who were familiar with the databases. A biostatistician was consulted for data cleaning and the generation of codes for data analysis.

3.3. Sample size

The main aim of the study was to determine trends of viral non-suppression over the 7 years of 2015 to 2021. A census was employed with the aim of surveying and collating all the data points available in the KMFHL/VL databases. The estimated number of PLWHIV in Siaya is 126,411, while the proportion of those virally non-suppressed in the county is not specifically reported in available sources, but it is likely to be high given the high overall HIV prevalence in the county (Kenya-NASCOP, 2018). The National AIDS Council's annual HIV estimates on PLWHIV provided a good comparison for the yearly data from 2015 to 2021 that was retrieved from the databases.

The seven years were considered because of the completeness of data available from the databases dated back to 2015 and since the study was conceptualized in 2022, these data were fully available up to 2021. The total population in each age group (infants, children, adolescents, and adults) was first analyzed together to determine general trends in HIV viral non-suppression across the years then separately for individual non-suppression trends per

group across the years. This analysis plan was necessary because studies have shown that HIV viral non-suppression rates vary across different age groups. Several factors may contribute to these age-related differences in viral non-suppression rates, and it is also important to note that these rates may vary depending on geographic location, race/ethnicity, and other demographic factors (Nwangwu-Ike *et. al*., 2021).

3.4. Data analysis plan

3.4.1. Variable definitions

HIV viral non-suppression was defined as PLWHIV with viral copies >1000/mL of blood. The HIV regimen was not categorized as per the line of treatment because this information was not available in the database. Sample types for VL testing included either Dry Blood Spot (DBS) or plasma.

3.4.2. Statistical analysis

To analyze the trends of HIV viral non-suppression across seven years, the Mann-Kendall trend test; a non-parametric test for time series analysis was employed. As an ordered time series, the data values were evaluated. Each data value was compared with all data values that came after it. When $x_{1,}\, x_{2,}\, x_3 \ldots\, x_n$ comprises n sets of data, and x_j shows the data point at the time J. Kendall`s tau statistic and Sens slope were calculated to determine the significance of the trends in viral non-suppression in infants, children, adolescents, and adults. The difference in time from the initial VL test over the seven years was analyzed by the Kruskal-Wallis Test. By employing a sample median and a nonparametric statistic, the difference in time from the initial VL test across the years was measured by this nonparametric test.

The data was visualized through a pictorial representation of a summary of the variables of interest across the sub-counties in Siaya. The variables included the Sub-county, Age, the proportion of virally non-suppressed, and Justification of testing. Stacked bar charts were used for pictorial representation of the differences in these variables across the sub-counties.

To investigate the predictors of viral non-suppression i.e., age, sex, regimen, sub-county, and justification for VL testing, logistic regression was used, and the prediction model was validated using K=2 folds cross-validation. All the statistical analyses were performed in R package.

3.5. Ethical Considerations

Ethical approval was given by Kenyatta National Hospital-University of Nairobi Ethics and Research Committee #P49/01/2023. The investigator requested a waiver for individual informed consent because this study was presumed to pose only a negligible risk to PLWHIV in Siaya. The waiver had no negative consequences on participants' rights or well-being. All the required information was obtained from the Kenya Master File Health Facility List and VL databases. To maintain confidentiality, all patient identifiers were excluded, and each patient was assigned a unique identifier. All records were saved on password-protected computers and folders containing data were encrypted. The retrieval of identifiers was restricted to the principal investigator and co-investigators. In the final reports and publications of this work, no identifying information will be disclosed.

CHAPTER 4: RESULTS

4.1. Patient characteristics

The entire dataset from 2015 to 2021 for Siaya was analyzed to provide information on trends of HIV viral non-suppression within the County as shown in Table 1 and 2. The data included the number of VL tests for each year, sub-county, age, sex, sample type, justification, and regimen. The analysis also included the result category for VL in each sample tested and this was used to determine virological non-suppression defined as having >1000 copies of viral RNA/ml of blood. Over the course of the seven-year period, a total of 444,389 VL tests were performed and recorded in the county, with the number of tests increasing each year from 7,618 in 2015 to 30,178 in 2021.

Table 1. PLWHIV demographics

.

Characteristics	Category	Overall (N = 444,389)	Viral suppression (n = 390,720)	Viral non-suppression (n = 53,669)
Age category	0-23 m (Infants)	1,508 (0%)	901 (56%)	607 (40%)
	2-14 y (Children)	42,513 (10%)	32,026 (75%)	10,487 (25%)
	15-24 y (Adolescents)	34,234 (8%)	28,488 (83%)	5,746 (17%)
	≥25 y (Adults)	366,134 (82%)	329,305 (90%)	36,829 (10%)
Sex	Female	296,866 (67%)	263,724 (89%)	33,142 (11%)
	Male	147,135 (33%)	126,673 (86%)	20,462 (14%)
Year	2015	7,618 (2%)	6,159 (81%)	1,459 (19%)
	2016	27,053 (6%)	21,308 (79%)	5,745 (21%)
	2017	88,095 (20%)	69,558 (79%)	18,537 (21%)
	2018	93,045 (21%)	81,707 (88%)	11,338 (12%)
	2019	125,981 (28%)	115,877 (92%)	10,104 (8%)
	2020	72,419 (16%)	67,364 (93%)	5,055 (7%)
	2021	30,178 (7%)	28,747 (95%)	1,431 (5%)
Subcounty	Alego Usonga	105,310 (24%)	93,173 (89%)	12,137 (12%)
	Bondo	87,745 (20%)	77,297 (88%)	10,448 (12%)
	Gem	78,214 (18%)	68,789 (88%)	9,425 (12%)
	Rarieda	80,808 (18%)	68,789 (88%)	9,837 (12%)
	Ugenya	43,302 (10%)	37,604 (87%)	5,698 (13%)
	Ugunja	49,010 (11%)	42,886 (88%)	6,124 (13%)

The highest proportion of individuals with viral non-suppression was observed in 2017 (21%). In infants, the highest proportion of viral non-suppression of 40% (n = 607) was observed while the adults ≥ 25 years group experienced the lowest proportion of 10% (n = 36,829). Most patients who were tested for VL over the entire period (296,866; 67%) were female and in comparison, to the male, the proportion of virally non-suppressed females was lower at 11% (n = 126,673) while that of males was 14% (n = 20,462).

Table 2. Clinical characteristics of patients in the VL database (2015–2021)

Characteristics	Category	Viral suppression (n = 390,720)	Viral non-suppression (n = 53,669)	Overall (N = 444,389)
Sample type	DBS	548 (58%)	394 (42%)	942 (0%)
	Frozen Plasma	103,888 (87%)	15,057 (13%)	118,945 (27%)
	Fresh plasma	286,284 (88%)	38,218 (12%)	324,502 (73%)
Justification	Baseline	1,527 (82%)	344 (18%)	1,871 (0%)
	Breast Feeding Mothers	174 (85%)	31 (15%)	205 (0%)
	Clinical Failure	235 (73%)	89 (28%)	324 (0%)
	Confirmation of PLLV	1,782 (91%)	180 (9%)	1,962 (0%)
	Pregnant Mother	147 (81%)	35 (19%)	182 (0%)
	Recency Testing	11 (44%)	14 (56%)	25 (0%)
	Repeat VL	18,687 (64%)	10,697 (36%)	29,384 (7%)
	Routine VL	355,417 (90%)	41,233 (10%)	396,650 (89%)
	Single Drug Substitution	10,926 (95%)	529 (5%)	11,455 (3%)
	Other	169 (78%)	48 (22%)	217 (0%)
Regimen	ABC+3TC+ATVr	513 (78%)	147 (22%)	660 (0%)
	ABC+3TC+DRVr+RAL	12 (71%)	5 (29%)	17 (0%)
	ABC+3TC+DTG	1,520 (93%)	109 (7%)	1,629 (0%)
	ABC+3TC+EFV	6,780 (77%)	2,013 (23%)	8,793 (2%)
	ABC+3TC+LPVr	7,422 (74%)	2,633 (26%)	10,055 (2%)
	ABC+3TC+NVP	3,363 (64%)	1,881 (36%)	5,244 (1%)
	ABC+3TC+RAL	83 (94%)	5 (6%)	88 (0%)
	AZT+3TC+ABC	1 (33%)	2 (67%)	3 (0%)
	AZT+3TC+ATVr	16,166 (82%)	3,481 (18%)	19,647 (4%)
	AZT+3TC+DRVr+RAL	8 (67%)	4 (33%)	12 (0%)
	AZT+3TC+DTG	314 (83%)	64 (17%)	378 (0%)
	AZT+3TC+EFV	873 (75%)	290 (25%)	1,163 (0%)
	AZT+3TC+LPVr	5236 (77%)	1,537 (23%)	6,773 (2%)
	AZT+3TC+NVP	33,429 (80%)	8,344 (20%)	41,773 (9%)
	TDF+3TC+ATVr	10,578 (82%)	2,292 (18%)	12,870 (3%)
	TDF+3TC+DTG	93,743 (97%)	3,334 (3%)	97,077 (22%)
	TDF+3TC+DTG+ATVr	2 (100%)	0 (0%)	2 (0%)
	TDF+3TC+DTG+DRVr	3 (100%)	0 (0%)	3 (0%)
	TDF+3TC+DTG+ETV+DRVr	4 (100%)	0 (0%)	4 (0%)
	TDF+3TC+EFV	160235 (89%)	18,998 (11%)	179,233 (40%)
	TDF+3TC+LPVr	4,305 (84%)	830 (16%)	5,135 (1%)
	TDF+3TC+NVP	42,551 (86%)	7,193 (15%)	49,744 (11%)
	TDF+3TC+RAL+DRVr	2 (100%)	0 (0%)	2 (0%)
	Other	3,295 (88%)	456 (12%)	3,751 (1%)

Among the sub-counties, Alego Usonga had the lowest viral non-suppression rate of 12% (n = 12,137). The other sub-counties, including Bondo, Gem, Rarieda, Ugenya, and Ugunja,

exhibited viral non-suppression rates of 12% (n = 10,448), 12% (n = 9,425), 12% (n = 9,837), 13% (n = 5,698), and 13% (n = 6,124), respectively.

The most common sample type for VL testing was fresh plasma (324,502; 73 %), followed by frozen plasma (118,945; 27%) and DBS (942; 0.2%). Most of the samples were for routine VL tests (396,650; 90%), repeat VL and ARV class substitution were other observations observed albeit with smaller proportions. Analyzing the results by justification, recency testing, and clinical failure had the highest viral non-suppression rate of 56% and 26% respectively, with other justifications, such as repeat VL testing, single drug substitution, confirmation of prolonged low-level viremia (PLLV), and "other" category, exhibiting viral non-suppression rates ranging from 5% to 36%. The most common regimen combination used were TDF+3TC+EFV (40%), TDF+3TC+DTG (22%), and AZT+3TC+NVP (11%). Other regimens had lower utilization rates. Among the different regimens, there was a higher viral non-suppression rate of 67% with the use of AZT+3TC+ABC. Similarly, other regimens such as TDF+3TC+NVP, AZT+3TC+LPVr, ABC+3TC+EFV, and ABC+ 3TC+ NVP exhibited viral non-suppression rates ranging from 15–36% as shown in Table 2.

4.2. Trends of HIV Viral non-suppression for the period 2015 to 2021

Viral non-suppression was 19% in 2015, peaked in 2016 and 2017 at 21%, and decreased from 21% in 2017 to 5% in 2021 as shown in Figure 6 below. The Mann Kendall and Sen's Slope tests were further conducted to assess the presence and significance of trends in the data. The overall tau statistic value over the entire study period was -0.81 (p-value = 0.016), indicating the presence of a significant negative trend. Furthermore, Sen's slope was determined to be

-2.6 (p-value = 0.016), supporting the conclusion of a significant negative or downward trend of viral non-suppression from 2015 to 2021 in Siaya county. The calculated tau statistic and Sen`s slope values for the different age groups i.e., infants, children, adolescents, and adults with their corresponding p-values are indicated in Figure 7 below. Both adults, adolescents, and children show a significant downward trend in viral non-suppression. However, infants indicate an upward trend in viral non-suppression but this trend is statistically not significant.

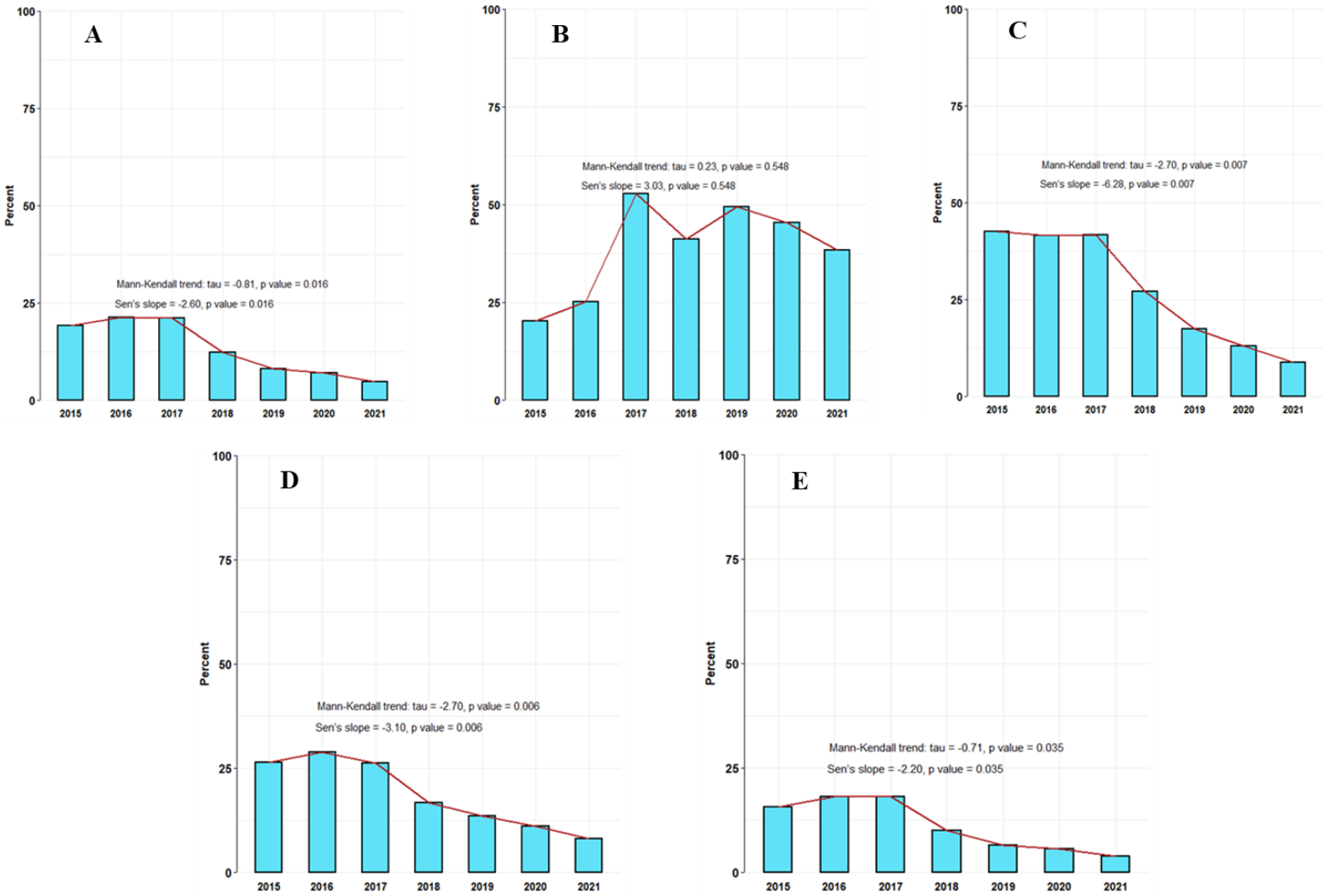

Figure 6. Trends of viral non-suppression in Siaya County (A), among infants (B), among children (C), among adolescents (D), and among adults (E) from 2015–2021.

4.3. Time difference in months since initial VL test from 2015 to 2021

The time difference in months since the initial VL test across different years was evaluated using the Kruskal-Wallis test. The results are summarized below in Table 3 in the form of median and interquartile ranges (IQR) for each year from 2015 to 2021.

In 2015, the median time difference since the initial VL test was 37 months with an IQR of 15 to 57 months. The median increased in subsequent years with 40 months (IQR: 19, 66) in 2016, 43 months (IQR: 21, 75) in 2017, 51 months (IQR: 26, 86) in 2018, 60 months (IQR: 34, 98) in 2019, 67 months (IQR: 38, 106) in 2020, and 72 months (IQR: 40, 111) in 2021.

The Kruskal-Wallis test was significant (p <0.001), indicating a statistically significant difference in the median time difference since the initial VL test between at least two of the years under consideration. The results suggest that the proportion of VL tests conducted has been increasing over the years from 2015 to 2021.

Table 3. Year vs time difference in months since the initial VL test

Year	Median [IQR]	Kruskal-Wallis Test
2015	37 [15, 57]	<0.001
2016	40 [19, 66]	
2017	43 [21, 75]	
2018	51 [26, 86]	
2019	60 [34, 98]	
2020	67 [38, 106]	
2021	72 [40, 111]	

4.4. Distribution of age, gender, and viral non-suppression and justification of VL test across the sub-counties in Siaya

Figure 7 underlines the distributions of age, gender, viral non-suppression, and the rationale behind VL testing. A glance at the figures reveals that the age spread among the sub-counties is relatively balanced. Overall, a higher proportion of females compared to males had VL testing, and this pattern is proportionately reflected across all six sub-counties. The data also shows an equal distribution of both viral non-suppression/suppression and the justification for VL testing.

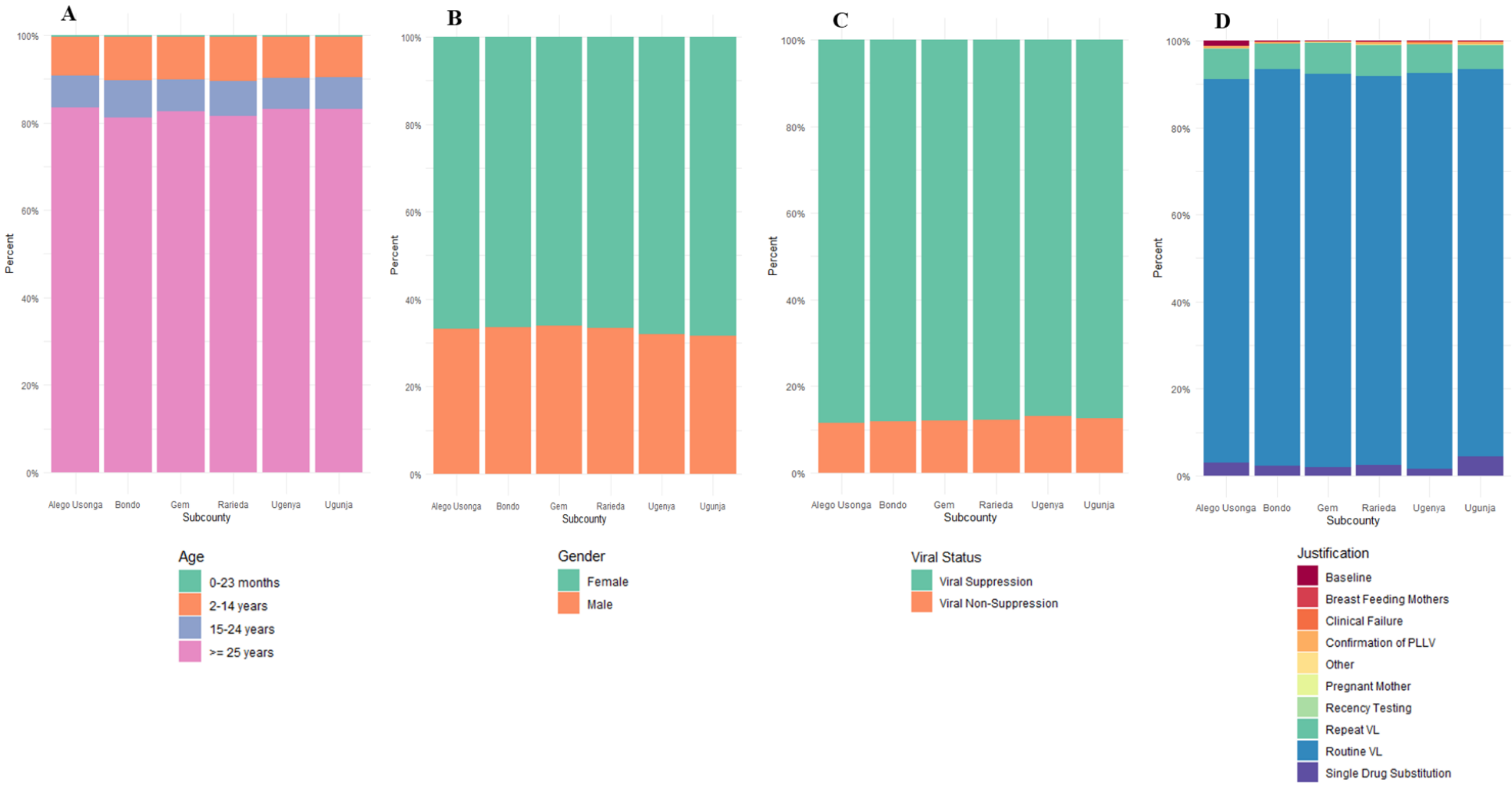

Figure 7. Participant age distribution (A), gender (B), viral status (C) and justification of VL testing (D) across the six sub-counties.

4.5. Clinical and socio-demographic predictors of viral non-suppression.

Table 4 shows univariate and multivariate logistic regression model results for viral non-suppression risk factors. Odds ratios (OR) and adjusted odds ratio (aOR) with their corresponding 95% confidence intervals (CIs) and *p*-values are presented below.

Table 4. Predictors of non-suppressed VLs among PLWHIV in Siaya County.

Characteristics	Category	Univariate model		Multivariate model	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age category	0–23 months	1		1	
	2–14 years	0.47 (0.41 - 0.53)	<0.001	0.59 (0.52-0.68)	<0.001
	15–24 years	0.29 (0.26 - 0.33)	<0.001	0.53 (0.46-0.61)	<0.001
	≥25 years	0.16 (0.14 - 0.18)	<0.001	0.30 (0.27-0.35)	<0.001
Sex	Female	1		1	
	Male	1.28 (1.26 - 1.31)	<0.001	1.26 (1.23-1.28)	<0.001
Year	2015	1		1	
	2016	1.13 (1.05 - 1.22)	0.001	1.09 (1.01-1.18)	0.021
	2017	1.12 (1.04 - 1.19)	0.001	1.02 (0.94-1.10)	0.645
	2018	0.58 (0.54 - 0.62)	<0.001	0.51 (0.47-0.55)	<0.001
	2019	0.37 (0.34 - 0.39)	<0.001	0.32 (0.30-0.35)	<0.001
	2020	0.31 (0.29 - 0.34)	<0.001	0.25 (0.23-0.27)	<0.001
	2021	0.21 (0.19 – 0.22)	<0.001	0.17 (0.16-0.19)	<0.001
Subcounty	Alego Usonga	1		1	
	Bondo	1.04 (1.01-1.07)	0.012	1.05 (1.01-1.08)	0.009
	Gem	1.05 (1.01-1.08)	0.006	1.05 (1.01-1.08)	0.01
	Rarieda	1.06 (1.03-1.09)	<0.001	1.02 (0.98-1.05)	0.37
	Ugenya	1.15 (1.11-1.20)	<0.001	1.08 (1.04-1.12)	<0.001
	Ugunja	1.09 (1.05-1.13)	<0.001	1.06 (1.02-1.10)	0.005
Sample type	DBS	1		1	
	Frozen Plasma	0.19 (0.17-0.22)	<0.001	0.43 (0.36-0.51)	<0.001
	Fresh plasma	0.18 (0.15-0.21)	<0.001	0.41 (0.34-0.48)	<0.001
Justification	Baseline	1		1	
	Breast Feeding Mothers	0.77 (0.48-1.19)	0.256	0.55 (0.34-0.86)	0.011
	Clinical Failure	1.66 (1.22-2.25)	0.001	1.37 (0.99-1.87)	0.055
	Confirmation of PLLV	0.45 (0.36-0.56)	<0.001	0.96 (0.77-1.21)	0.756
	Other	1.35 (0.92-1.93)	0.115	0.97 (0.66-1.43)	0.896
	Pregnant Mother	1.08 (0.69-1.63)	0.731	0.75 (0.48-1.15)	0.199
	Recency Testing	4.91 (1.96-12.48)	0.001	20.0 (7.88-51.45)	<0.001
	Repeat VL	2.55 (2.23-2.92)	<0.001	2.68 (2.31-3.13)	<0.001
	Routine VL	0.51 (0.45-0.59)	<0.001	0.58 (0.50-0.67)	<0.001
	Single Drug Substitution	0.22 (0.18-0.25)	<0.001	0.41 (0.34-0.49)	<0.001
Regimen	1 NRTI + 1 NNRTI + 1 PI	1		1	
	1 NRTI + 2 NNRTI	0.69 (0.63-0.75)	<0.001	0.83 (0.76-0.91)	<0.001
	2 NRT1 + 1 NNRTI	1.50 (1.38-1.64)	<0.001	1.26 (1.15-1.39)	<0.001
	2NRTI + 1 INSTI	0.20 (0.18-0.21)	<0.001	0.43 (0.39-0.47)	<0.001
	2NRTI+1 PI	1.35 (1.24-1.47)	<0.001	1.32 (1.20-1.45)	<0.001
	Other	0.73 (0.64-0.84)	<0.001	0.82 (0.70-0.94)	0.006

4.5.1. Age category

In the univariate analysis, compared to the reference category (0-23 months), all age categories showed significantly lower odds of having non-suppressed VLs. The odds decreased progressively from 0–23 months to the ≥25-year age group. Specifically, children (2–14 years) had an OR of 0.47 ($p < 0.001$), adolescents (15–24 years) had an OR of 0.29 ($p < 0.001$), and adults (≥ 25 years) had an OR of 0.16 ($p < 0.001$). After adjusting for other variables in the multivariate analysis, these associations remained statistically significant as shown in Table 4. The aOR for children was 0.59 ($p < 0.001$), for adolescents was 0.53, and for adults was 0.30 ($p < 0.001$).

4.5.2. Sex

In the univariate and multivariate models, being male was associated with higher odds of non-suppressed VLs compared to females. In the univariate analysis, the OR for males was 1.28. After adjusting for other variables, the aOR for males was 1.26. (Table 4).

4.5.3. Sub-county

Among the different sub-counties, Bondo, Gem, Ugenya, and Ugunja exhibited significantly higher odds of non-suppressed VLs compared to the reference subcounty (Alego Usonga). However, after adjusting for potential confounders, only Bondo, Gem, and Ugenya remained significantly associated with non-suppressed VLs. In the univariate analysis, the ORs for Bondo, Gem, Rarieda, Ugenya, and Ugunja were as follows: Bondo (OR: 1.04,), Gem (OR: 1.05, $p = 0.006$), Rarieda (OR: 1.06, $p < 0.001$), Ugenya (OR: 1.15, $p < 0.001$), and Ugunja (OR: 1.09, $p < 0.001$). After adjusting for other variables, the aORs for Bondo, Gem, and Ugenya were as follows: Bondo (aOR: 1.05, $p = 0.009$), Gem (aOR: 1.05, $p = 0.010$), and Ugenya (aOR: 1.08, $p < 0.001$).

4.5.4. Years

The univariate analysis revealed a significant association between the year of observation and non-suppressed VLs. Odds ratios decreased over time, indicating a decreasing trend in non-suppressed VLs. Specifically, compared to the reference year (2015), the ORs for subsequent years were as follows: 2016 (OR: 1.13, $p = 0.001$), 2017 (OR: 1.12, $p = 0.001$), 2018 (OR: 0.58, $p < 0.001$), 2019 (OR: 0.37, $p < 0.001$), 2020 (OR: 0.31, $p < 0.001$), and 2021 (OR: 0.21, $p < 0.001$). This trend remained significant even after adjusting for other variables in the multivariate analysis.

4.5.5. Sample type

In both the univariate and multivariate analyses, using frozen or fresh plasma as the sample type was associated with significantly lower odds of non-suppressed VLs compared to DBS. In the univariate analysis, the ORs for frozen plasma and fresh plasma were as follows: frozen plasma (OR: 0.19, $p < 0.001$) and fresh plasma (OR: 0.18, $p < 0.001$). After adjusting for other variables, the aORs for frozen plasma and fresh plasma were as follows: frozen plasma (aOR: 0.43, $p < 0.001$) and fresh plasma (aOR: 0.41, $p < 0.001$).

4.5.6. Justification

In comparison to the reference category (baseline), for the various reasons for VL testing, the logistic regression analysis revealed the following associations with viral non-suppression: Breastfeeding mothers had an OR of 0.77 (p =0.256), indicating a potential decrease in the odds of non-suppressed VLs compared to the baseline justification. However, this association did not have statistical significance. Similarly, pregnant mothers did not show significant associations with non-suppressed VLs in either the univariate or multivariate models.

Clinical failure was associated with increased odds of non-suppressed VLs, with an OR of 1.66 (p = 0.001). However, in the multivariate logistic model, the adjusted odds ratio (aOR) for clinical failure was 1.37 (p = 0.055), which did not have statistical significance. Confirmation of previous low-level viremia was strongly associated with decreased odds of non-suppressed VLs, with an OR of 0.45 ($p < 0.001$). After adjusting for potential confounders, the aOR for this justification remained similar at 0.96 (p = 0.756), but the association lost statistical significance.

Recency testing was strongly associated with increased odds of non-suppressed VLs, with an OR of 4.91 (p = 0.001). This indicates that individuals who were recently infected had almost five times higher odds of having non-suppressed VLs compared to the reference justification (baseline). In the multivariate logistic model, this association remained significant, with an aOR of 20.00 ($p < 0.001$). Repeat VL testing was also strongly associated with increased odds of non-suppressed VLs. In the univariate analysis, the OR for repeat VL testing was 2.55 ($p <$ 0.001), indicating more than double the odds of non-suppressed VLs compared to the reference. After adjusting for potential confounders, the aOR for repeat VL testing was 2.68 ($p < 0.001$), suggesting a similar magnitude of association.

Routine VL testing showed a significant association with decreased odds of non-suppressed VLs. The univariate analysis revealed an OR of 0.51 ($p < 0.001$), indicating a protective effect.

This association remained significant in the multivariate analysis, with an aOR of 0.58 ($p < 0.001$). Single-drug substitution was also associated with decreased odds of non-suppressed VLs. In the univariate analysis, the OR for single drug substitution was 0.22 ($p < 0.001$), indicating a strong protective effect. After adjusting for potential confounders, the aOR for single drug substitution was 0.41 ($p < 0.001$), suggesting a similar level of protection.

4.5.7. Regimen

The choice of antiretroviral regimen was also associated with non-suppression. Before fitting the regimen in the logistic model, we categorized them into various categories, and the frequency of each combination is shown in Figure 8 below. Different regimens showed varying associations with non-suppression compared to the reference regimen (1 NRTI + 1 NNRTI + 1 PI). While most regimens exhibited decreased odds of non-suppression, other combinations like 2 NRTI + 1 NNRTI and 2 NRTI + 1 PI showed increased odds of viral non-suppression in both the univariate and multivariate analyses with significant p values indicating an increased risk of non-suppressed. In the univariate and multivariate analysis, the ORs and aORs are as indicated in Table 4 above.

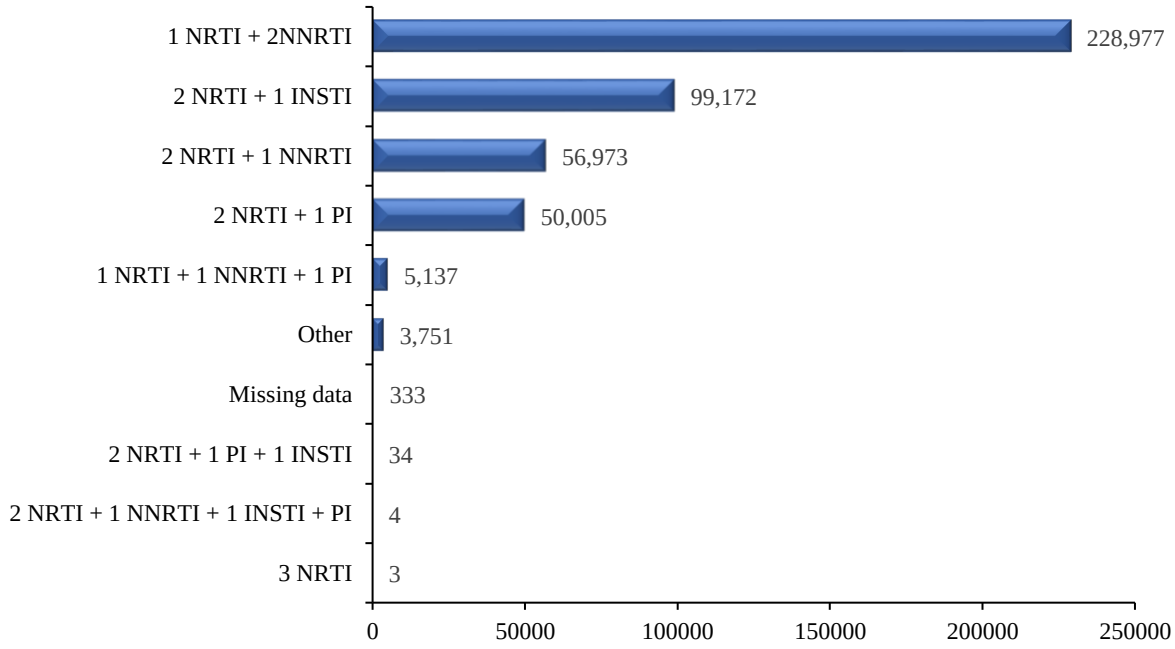

Figure 8. Frequency of treatment regimens.

To validate the prediction model, a K=2 folds cross-validation technique was employed. The results demonstrated an Area under the Receiver Operating Characteristics curve (AUC) of 0.69, indicating that the model possesses the ability to effectively classify patients into either

viral non-suppression or viral suppression categories. The overall AUC of the logistic model is depicted in Figure 9.

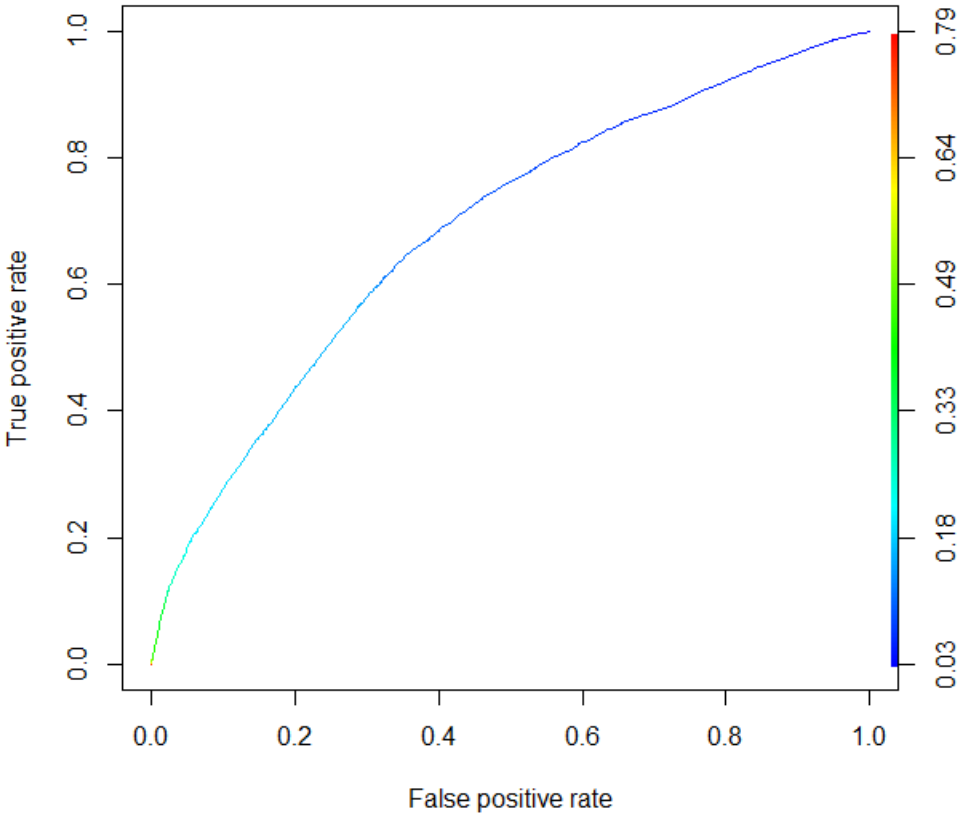

Figure 9. Receiver operating characteristics curve of the logistic regression model.

CHAPTER 5: DISCUSSION

The implementation of Kenya's national VL database has enabled the monitoring and expansion of HIV programs, tracking the evolution of patient and treatment characteristics over time, and identifying specific areas in need of improvement (Mwau *et. al*., 2018b). Our study used this data to assess the trends in viral non-suppression among individuals in Siaya County from 2015 to 2021. The results revealed that the percentage of individuals with viral non-suppression substantially declined from 21% in 2017 to 5% in 2021. While the decline in viral non-suppression is promising, the overall proportion of viral non-suppression in certain age categories including infants and children remained below the 95.95.95 UNAIDS targets throughout this period. Nevertheless, considering the declining trend in viral non-suppression rates observed, it is evident that with further improvement and strengthening of existing strategies, the county has the potential to achieve the current UNAIDS targets specifically in infants and children. Notably, the highest proportion of individuals with viral non-suppression (21%) was observed in 2017. This indicates a potential period of concern for HIV management in Siaya County. The reasons behind the higher rates of viral non-suppression in 2017 could be multifactorial with a major impact contributed by a nurses' strike `that happened around the same period and lasted for about 5 months (Kenya council of governors, 2017).

Similarly, in our study, there was a high likelihood of viral non-suppression in the years 2016 and 2017 implying that there may have been challenges or factors contributing to the increase in viral non-suppression during these years. However, from 2018 onwards, we observed a substantial decrease in the odds ratios, indicating a significantly lower likelihood of viral non-suppression. These results imply an improvement in treatment outcomes and a higher proportion of individuals achieving viral suppression in subsequent years. This trend aligns with global efforts to enhance access to antiretroviral therapy, promote adherence support programs, and strengthen healthcare infrastructure. Continued monitoring and implementation of targeted interventions are crucial to maintaining and further improving viral suppression rates in the population.

Examining different age groups—adults, adolescents, and children—a significant downward trend in viral non-suppression was observed suggesting that efforts targeted at these age groups (adherence support programs and age-appropriate interventions) have been effective in decreasing viral non-suppression. However, an increase in viral non-suppression was observed among the infant population. Although this trend was not found to be statistically significant,

it raises concerns about treatment outcomes and management interventions among infant patients. This requires further investigation and targeted interventions to address the challenges faced by infant patients in achieving viral suppression. These findings align with previous studies by (Umar *et. al*., 2019) and (Kadima *et. al*., 2019) in Zimbabwe and the western part of Kenya respectively which highlighted that there is a notable deficiency in subsequent testing and achieving virologic suppression among infants who experience virologic failure in the initial routine viral load test. These studies emphasize that it is imperative to urgently enhance the management and viral load monitoring protocols for infants and children living with HIV facing treatment failure, to ensure enhanced long-term outcomes and optimize the overall care for affected children.

We observed an increasing trend in the median time difference from each patient`s initial VL test from 2015 to 2021. This difference suggests a notable increase in the proportion of tests conducted over time and supports a study by Mwau *et. al*., (2018b) which indicated an increase in the proportion of tests that appeared to be subsequent tests from the same patients. Similar studies examining the time difference since the initial VL test are scarce. However, a study by (Swannet *et. al*., 2017) investigated the journey toward VL monitoring in Mozambique and reported a similar pattern of increasing time intervals between VL tests over time. Regarding demographic distribution, VL testing was more frequently undertaken by females compared to males, consistent with gender disparities in health-seeking behavior. Exploring the reasons for VL testing, we found an equal distribution of justifications, including treatment monitoring and identification of treatment failure, in line with WHO recommendations (WHO, 2017).

Our study also examined the distributions of age, sex, viral non-suppression, and the rationale behind VL testing in Siaya County. In terms of age distribution, there was a relatively balanced spread across the sub-counties within Siaya County. This finding suggests that the sample population used in this study is representative and captures a diverse range of age groups within the county. Regarding sex, a higher proportion of females compared to males underwent VL testing in Siaya County. This pattern was consistently reflected across all six sub-counties. This gender discrepancy in seeking VL testing aligns with previous research, such as the study by (Tomescu *et. al*., 2023), which highlighted gender disparities in health-seeking behavior. While our study indicated a higher proportion of females undergoing testing, a study in Maputo Mozambique by (Swannet *et. al*., 2017) reported a higher uptake of testing among males. These differences may be attributed to contextual factors, cultural norms, or variations in healthcare-seeking behavior across different regions or populations. It is essential to further explore the

underlying factors contributing to these gender differences and address potential barriers that may hinder males from accessing VL testing services.

Our study further found that males had higher odds of viral non-suppression compared to females, indicating an increased likelihood of viral non-suppression among males. Our findings are consistent with previous studies that have examined the relationship between sex and viral suppression outcomes. A study by (Penot *et. al*., 2014) and (Hailu *et. al*., 2018) in Burkina Faso and Ethiopia respectively conducted a similar analysis and reported higher odds of viral non-suppression among males compared to females. This suggests that gender may play a role in determining viral suppression outcomes, with males being more vulnerable to experiencing viral non-suppression. Several factors may contribute to the observed gender disparity in viral non-suppression rates. Firstly, differences in adherence to ART regimens between males and females might explain the variation in viral suppression outcomes. Studies have shown that adherence to ART is influenced by various factors such as social support, stigma, and healthcare access, which may differ between genders. Females may have better adherence due to higher engagement in healthcare, greater social support, or other contextual factors that contribute to better treatment outcomes. Furthermore, societal, and cultural factors may also contribute to the observed gender disparity. Gender norms and roles may influence healthcare-seeking behavior, access to treatment, and engagement in care (Desta *et. al*., 2020).

Age was found to be inversely related to viral non-suppression, with older individuals less likely to be non-suppressed. These findings suggest that older individuals may be more likely to achieve viral suppression compared to younger age groups and this is supported by several previous studies, providing valuable context for our results. A study by (Tomescu *et. al*., 2023) conducted a similar analysis and found a similar inverse relationship between age and viral non-suppression, with higher age categories associated with lower odds of non-suppression. There are several plausible explanations for the observed relationship between age categories and viral non-suppression. Older individuals may have had longer exposure to ART and therefore more time to achieve viral suppression (Rashighi & Harris, 2017). Since many research studies have explored the age-viral non-suppression relationship, future studies should aim to assess the impact of the age-targeted interventions that have been put in place e.g., Starting in 2016, Kenya initiated the procurement of heat-stable LPV/r pellets, which present an easier swallowing option for the younger demographic and the impact of these measures should further be assessed.

There were slight variations in viral non-suppression observed, with a higher proportion of patients from Bondo, Gem, Rarieda, Ugenya, and Ugunja experiencing viral non-suppression compared to Alego Usonga. These findings indicate that factors specific to each sub-county may play a role in influencing viral non-suppression outcomes. A study in Ethiopia by (Emagnu *et. al*., 2020) observed that geographic factors may contribute to differences in viral non-suppression rates within different regions. Regions located in remote or rural areas might face challenges related to healthcare access, transportation, and availability of specialized healthcare services, and these factors could impact timely access to ART, regular VL monitoring, and overall treatment adherence, potentially leading to higher rates of viral non-suppression. This pattern was also evident in our study, where Alego Usonga, situated near Siaya town, exhibited more favorable outcomes in terms of viral non-suppression compared to other sub-counties within the county. This pattern can also be attributed to a difference in the distribution of health facilities within the sub-counties with Alego Usonga having more registered health facilities compared to the other sub-counties (Siaya, 2018). To further investigate the factors contributing to the slight differences in viral non-suppression within sub-counties, future research should consider a comprehensive approach. Longitudinal studies, including both quantitative and qualitative analyses, could provide deeper insights into the dynamics of viral non-suppression and help identify the specific factors driving the observed disparities.

Although DBS as a sample type offers a practical alternative for VL testing in resource-limited settings, our study demonstrated a significant association between using DBS for VL testing and viral non-suppression. It is important to consider the possible underlying reasons for the above observation. DBS is a frequently collected sample type for Early Infant Diagnosis and from our findings, there was a higher proportion of viral non-suppression among the younger populations hence these populations are more likely to be unsuppressed in comparison to older populations. To further explain the association between DBS and viral non-suppression, a recent systematic review by (Vojnov *et. al*., 2022) indicated that the performance of DBS samples is not flawless, leading to the possibility of some misclassification. This means that a small percentage of patients who are successfully achieving undetectable VLs may be erroneously classified as treatment failures. Additionally, the selection and implementation of technologies specifically designed for use with DBS can be challenging due to variations in performance and the need for regulatory approvals.

The study also highlighted associations between different reasons for VL testing and viral non-suppression. Clinical failure and repeat testing were strongly associated with increased likelihoods of non-suppression, while single drug substitution, routine testing, and confirmation of potential low-level viremia were associated with reduced likelihoods of non-suppression. To contextualize our findings, we refer to (Bulage *et. al*., 2017b) and (Mwau *et. al*., 2018b) who reported that patients undergoing routine monitoring had the lowest proportion of non-suppressed patients, whereas those who underwent repeat testing following suspected treatment failure had the highest proportion of non-suppressed patients. Specifically, repeat testers after suspected treatment failure, being indicative of suspected treatment failure itself, exhibited the highest likelihood of viral non-suppression. These findings contribute to our understanding of the factors influencing treatment outcomes and underscore the importance of targeted interventions for individuals at higher risk of viral non-suppression. Future research should continue to explore the mechanisms underlying these associations and develop strategies to optimize treatment response and achieve sustained viral suppression in persons living with HIV.

The choice of antiretroviral regimen was associated with viral non-suppression. While most regimens demonstrated decreased odds of non-suppression, certain combinations, such as 2 NRTI + 1 NNRTI and 2 NRTI + 1 PI, showed increased odds of viral non-suppression in both the univariate and multivariate analyses. These associations were statistically significant, indicating an elevated risk of non-suppressed VLs. This potential variation in treatment effectiveness among NRTI and NNRTI-based combinations has been reported in several studies with the latest studies exploring the increasing pre-treatment drug resistance (the presence of HIV strains with resistance mutations in individuals who have never received antiretroviral therapy) in the above-mentioned drug combinations (Boyce *et. al*., 2022; Njuguna *et. al*., 2020). The presence of pre-existing resistance mutations in the HIV population has been shown to compromise the effectiveness of NNRTI-based regimens. Individuals infected with NNRTI-resistant strains may experience suboptimal viral suppression and reduced treatment response when initiated on a 2 NRTI + 1 NNRTI regimen, leading to an increased risk of viral non-suppression (Boyce *et. al*., 2022). Further research is needed to explore the specific mutations associated with viral non-suppression and resistance to NNRTIs, NRTIs, and PIs within the context of the observed regimen associations. Understanding the underlying mechanisms of resistance development can inform the development of more effective treatment strategies and help preserve the long-term efficacy of antiretroviral therapy.

Study limitations and strengths

Acknowledging the limitations despite the valuable insights gained from this study, it is important to note that the utilization of VL data exclusively from Siaya County may restrict the applicability of the findings to other populations or regions. The characteristics of the study population and healthcare system in Siaya County may differ from those in other areas, potentially impacting the observed associations. Second, the study relied on retrospective data, which is subject to inherent limitations such as incomplete or missing information which can affect the accuracy of the results. Third, the study utilized a cross-sectional design, which limits the ability to establish causality. Longitudinal studies or randomized controlled trials would provide stronger evidence of the associations identified in this study. Lastly, the study had limited control over the variables studied because only the documented information from the database was utilized. Future research should consider potential factors that are not routinely documented on the VL databases to provide a better understanding of the topic.

Notwithstanding the limitations mentioned, this study also possesses several notable strengths. A sufficient sample size was utilized, enhancing the statistical power, and increasing the reliability of the findings. Similarly, the study employed rigorous statistical analysis, including both univariate and multivariate logistic regression models, to examine the associations between predictors and non-suppressed VLs. Adjustments were made for potential confounding variables, providing a more accurate estimation of the associations. The research utilized a nationally validated viral load database managed by the Ministry of Health/NASCOP, ensuring the credibility of the acquired data. Additionally, examining viral non-suppression trends across infants, children, adolescents, and adults offers intriguing analyses, considering the distinctive HIV care requirements and varied factors influencing treatment outcomes within these specific populations.

Conclusion and Recommendations

In conclusion, this study utilized data from Kenya's national VL database to assess trends in viral non-suppression among individuals in Siaya County from 2015 to 2021. While there has been a promising decline in viral non-suppression rates over time, the overall proportion of viral non-suppression in the various age categories remained below the current UNAIDS targets. The study revealed variations in viral non-suppression among different age groups, with a concerning upward trend observed among the infant population. Gender disparities were also evident, with males being more likely to experience viral non-suppression compared to

females. Additionally, there were slight differences in viral non-suppression rates among sub-counties, indicating the influence of geographic factors on treatment outcomes. Similarly, this study also explored the predictors of viral non-suppression among which the choice of ART regimen combination used was found to be highly associated with viral non-suppression. Further research is needed to explore specific resistance patterns and their impact on treatment response within the context of these regimen combinations. Based on these findings, several recommendations can be made. Efforts should be focused on reducing viral non-suppression outcomes among infant patients, addressing gender disparities, and tailoring interventions to specific sub-counties with higher rates of viral non-suppression and strategies should be enhanced for regular monitoring of drug resistance patterns among people on ART.

REFERENCES

Abbas, A., Lichtman, A., & Pillai, S. (2017). Cellular and Molecular Immunology. In *Journal of Chemical Information and Modeling* (9th ed., Vol. 8, Issue 9). Elsiever. https://doi.org/10.1017/CBO9781107415324.004

Adino, D. (2020). Dynamics of Management of HIV and AIDS in Kenya with Special Reference to the Challenges Facing People on Antiretroviral Therapy in Siaya County. *Journal of African Interdisciplinary Studies*, *4*(12), 21–40. http://cedred.org/jais/index.php/issues

Amstutz, A., Lejone, T. I., Khesa, L., Muhairwe, J., Bresser, M., Vanobberghen, F., Kopo, M., Kao, M., Nsakala, B. L., Tlali, K., Klimkait, T., Battegay, M., Labhardt, N. D., & Glass, T. R. (2020). Home-based oral self-testing for absent and declining individuals during a door-to-door HIV testing campaign in rural Lesotho (HOSENG): a cluster-randomised trial. *The Lancet HIV*, *7*(11), e752–e761. https://doi.org/10.1016/S2352-3018(20)30233-2

Anderson, D. R., Morgano, G. P., Bennett, C., Dentali, F., Francis, C. W., Garcia, D. A., Kahn, S. R., Rahman, M., Rajasekhar, A., Rogers, F. B., Smythe, M. A., Tikkinen, K. A. O., Yates, A. J., Baldeh, T., Balduzzi, S., Brozek, J. L., Etxeandia-Ikobaltzeta, I., Johal, H., Neumann, I., … Dahm, P. (2019). American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. *Blood Advances*, *3*(23), 3898–3944. https://doi.org/10.1182/BLOODADVANCES.2019000975

Atta, M. G., De Seigneux, S., & Lucas, G. M. (2019). Clinical Pharmacology in HIV Therapy. *Clinical Journal of the American Society of Nephrology*, *14*(3), 435–444. https://doi.org/10.2215/CJN.02240218

Avino, M., Ndashimye, E., Lizotte, D. J., Olabode, A. S., Gibson, R. M., Meadows, A. A., Kityo, C. M., Nabulime, E., Kyeyune, F., Nankya, I.-M., Quiñones, M. E., Quiñones-Mateu, Q.,

Arts, E. J., & Poon, A. F. Y. (2019). Detection of novel HIV-1 drug resistance mutations by support vector analysis of deep sequence data and experimental validation. *BioRxiv*, 804781. https://doi.org/10.1101/804781

Beck, I. A., Levine, M., McGrath, C. J., Bii, S., Milne, R. S., Kingoo, J. M., So, I., Andersen, N., Dross, S., Coombs, R. W., Kiarie, J., Chohan, B., Sakr, S. R., Chung, M. H., & Frenkel, L. M. (2020). Pre-treatment HIV-drug resistance associated with virologic outcome of first-line NNRTI-antiretroviral therapy: A cohort study in Kenya. *EClinicalMedicine*, *18*, 100239. https://doi.org/10.1016/J.ECLINM.2019.100239

Bulage, L., Ssewanyana, I., Nankabirwa, V., Nsubuga, F., Kihembo, C., Pande, G., Ario, A. R., Matovu, J. K. B., Wanyenze, R. K., & Kiyaga, C. (2017). Factors Associated with Virological Non-suppression among HIV-Positive Patients on Antiretroviral Therapy in Uganda, August 2014-July 2015. *BMC Infectious Diseases*, *17*(1). https://doi.org/10.1186/s12879-017-2428-3

Case, K. K., Johnson, L. F., Mahy, M., Marsh, K., Supervie, V., & Eaton, J. W. (2019a). Summarizing the results and methods of the 2019 Joint United Nations Programme on HIV/AIDS HIV estimates. *AIDS (London, England)*, *33*(Suppl 3), S197. https://doi.org/10.1097/QAD.0000000000002440

Case, K. K., Johnson, L. F., Mahy, M., Marsh, K., Supervie, V., & Eaton, J. W. (2019b). Summarizing the results and methods of the 2019 Joint United Nations Programme on HIV/AIDS HIV estimates. *AIDS (London, England)*, *33*(Suppl 3), S197. https://doi.org/10.1097/QAD.0000000000002440

Chan, R. K. (2018). Can We End the Human Immunodeficiency Virus (HIV) in Singapore? *Annals of the Academy of Medicine, Singapore*, *47*(12), 499–501. https://doi.org/10.47102/annals-acadmedsg.v47n12p499

Chandler, R. K., Kahana, S. Y., Fletcher, B., Jones, D., Finger, M. S., Aklin, W. M., Hamill, K.,

& Webb, C. (2015). Data collection and harmonization in HIV research: The seek, test, treat, and retain initiative at the national institute on drug abuse. *American Journal of Public Health*, *105*(12), 2416–2422. https://doi.org/10.2105/AJPH.2015.302788

Cheong, H. T., Chow, W. Z., Takebe, Y., Chook, J. B., & Chan, K. G. (2015). *Genetic Characterization of a Novel HIV-1 Circulating Recombinant Form (CRF74 _ 01B) Identified among Intravenous Drug Users in Malaysia : Recombination History and Phylogenetic Linkage with Previously Defined Recombinant Lineages*. 1–10. https://doi.org/10.1371/journal.pone.0133883

Chhim, K., Mburu, G., Tuot, S., Sopha, R., Khol, V., Chhoun, P., & Yi, S. (2018). Factors associated with viral non-suppression among adolescents living with HIV in Cambodia: a cross-sectional study. *AIDS Research and Therapy*, *15*(1). https://doi.org/10.1186/S12981-018-0205-Z

Chs-Kenya. (2017). *Siaya County Profile*. www.crakenya.org

Coelho, L., Veloso, V. G., Grinsztejn, B., & Luz, P. M. (2014). Trends in overall opportunistic illnesses, Pneumocystis carinii pneumonia, cerebral toxoplasmosis and Mycobacterium avium complex incidence rates over the 30 years of the HIV epidemic: A systematic review. *Brazilian Journal of Infectious Diseases*, *18*(2), 196–210. https://doi.org/10.1016/j.bjid.2013.10.003

Cohen, M. S., Hellmann, N., Levy, J. A., Decock, K., & Lange, J. (2008). The spread, treatment, and prevention of HIV-1: evolution of a global pandemic. *J Clin Invest*, *118*(4), 1244. https://doi.org/10.1172/jci34706

Deeks, S. G., Overbaugh, J., Phillips, A., & Buchbinder, S. (2015). HIV infection. *Nature Reviews Disease Primers 2015 1:1*, *1*(1), 1–22. https://doi.org/10.1038/nrdp.2015.35

Diaz, C. M., Segura, E. R., Luz, P. M., Clark, J. L., Ribeiro, S. R., De Boni, R., Eksterman, L., Moreira, R., Currier, J. S., Veloso, V. G., Grinsztejn, B., & Lake, J. E. (2016). Traditional

and HIV-specific risk factors for cardiovascular morbidity and mortality among HIV-infected adults in Brazil: A retrospective cohort study. *BMC Infectious Diseases*, *16*(1), 1–13. https://doi.org/10.1186/S12879-016-1735-4/TABLES/3

Epidemic, W. R. O. T. G. T. (2017). *Tobacco use kills more than 7 million people each year*.

Fabri, M., Ingabire, C., Cohen, M., Donenberg, G., & Nsanzimana, S. (2015). The mental health of HIV-positive adolescents. *The Lancet Psychiatry*, *2*(8), e21. https://doi.org/10.1016/S2215-0366(15)00291-6

Grau, L. E., Griffiths-Kundishora, A., Heimer, R., Hutcheson, M., Nunn, A., Towey, C., & Stopka, T. J. (2017). Barriers and facilitators of the HIV care continuum in Southern New England for people with drug or alcohol use and living with HIV/AIDS: Perspectives of HIV surveillance experts and service providers. *Addiction Science and Clinical Practice*, *12*(1), 1–14. https://doi.org/10.1186/S13722-017-0088-7/TABLES/1

Greene, W. C., Debyser, Z., Ikeda, Y., Freed, E. O., Stephens, E., Yonemoto, W., Buckheit, R. W., Esté, J. A., & Cihlar, T. (2008). Novel targets for HIV therapy. *Antiviral Research*, *80*(3), 251–265. https://doi.org/10.1016/J.ANTIVIRAL.2008.08.003

Günthard, H. F., Saag, M. S., Benson, C. A., Del Rio, C., Eron, J. J., Gallant, J. E., Hoy, J. F., Mugavero, M. J., Sax, P. E., Thompson, M. A., Gandhi, R. T., Landovitz, R. J., Smith, D. M., Jacobsen, D. M., & Volberding, P. A. (2016). Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2016 Recommendations of the International Antiviral Society–USA Panel. *JAMA*, *316*(2), 191–210. https://doi.org/10.1001/JAMA.2016.8900

Gupta, R. K., Gregson, J., Parkin, N., Haile-Selassie, H., Tanuri, A., Andrade Forero, L., Kaleebu, P., Watera, C., Aghokeng, A., Mutenda, N., Dzangare, J., Hone, S., Hang, Z. Z., Garcia, J., Garcia, Z., Marchorro, P., Beteta, E., Giron, A., Hamers, R., … Bertagnolio, S. (2018). HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy

in low-income and middle-income countries: a systematic review and meta-regression analysis. *The Lancet Infectious Diseases*, *18*(3), 346–355. https://doi.org/10.1016/S1473-3099(17)30702-8

Hamers, R. L., Siwale, M., Wallis, C. L., Labib, M., Van Hasselt, R., Stevens, W. S., Schuurman, R., Wensing, A. M. J., Van Vugt, M., & De Wit, T. F. R. (2010). HIV-1 drug resistance mutations are present in six percent of persons initiating antiretroviral therapy in Lusaka, Zambia. *Journal of Acquired Immune Deficiency Syndromes*, *55*(1), 95–101. https://doi.org/10.1097/QAI.0B013E3181E544E0

Hawkins, C., Ulenga, N., Liu, E., Aboud, S., Mugusi, F., Chalamilla, G., Sando, D., Aris, E., Carpenter, D., & Fawzi, W. (2016). HIV virological failure and drug resistance in a cohort of Tanzanian HIV-infected adults. *Journal of Antimicrobial Chemotherapy*, *71*(7), 1966–1974. https://doi.org/10.1093/JAC/DKW051

Hemelaar, J. (2012). The origin and diversity of the HIV-1 pandemic. *Trends in Molecular Medicine*, *18*(3), 182–192. https://doi.org/10.1016/j.molmed.2011.12.001

Huerga, H., Ferlazzo, G., Bevilacqua, P., Kirubi, B., Ardizzoni, E., Wanjala, S., Sitienei, J., & Bonnet, M. (2017). Incremental Yield of Including Determine-TB LAM Assay in Diagnostic Algorithms for Hospitalized and Ambulatory HIV-Positive Patients in Kenya. *PLOS ONE*, *12*(1), e0170976. https://doi.org/10.1371/JOURNAL.PONE.0170976

Jobanputra, K., Parker, L. A., Azih, C., Okello, V., Maphalala, G., Kershberger, B., Khogali, M., Lujan, J., Antierens, A., Teck, R., Ellman, T., Kosgei, R., & Reid, T. (2015a). Factors Associated with Virological Failure and Suppression after Enhanced Adherence Counselling, in Children, Adolescents and Adults on Antiretroviral Therapy for HIV in Swaziland. *PLOS ONE*, *10*(2), e0116144. https://doi.org/10.1371/JOURNAL.PONE.0116144

Jobanputra, K., Parker, L. A., Azih, C., Okello, V., Maphalala, G., Kershberger, B., Khogali, M.,

Lujan, J., Antierens, A., Teck, R., Ellman, T., Kosgei, R., & Reid, T. (2015b). Factors Associated with Virological Failure and Suppression after Enhanced Adherence Counselling, in Children, Adolescents and Adults on Antiretroviral Therapy for HIV in Swaziland. *PLOS ONE*, *10*(2), e0116144. https://doi.org/10.1371/JOURNAL.PONE.0116144

Johnson, L. F., May, M. T., Dorrington, R. E., Cornell, M., Boulle, A., Egger, M., & Davies, M. A. (2017). Estimating the impact of antiretroviral treatment on adult mortality trends in South Africa: A mathematical modelling study. *PLOS Medicine*, *14*(12), e1002468. https://doi.org/10.1371/JOURNAL.PMED.1002468

Kenya-NASCOP. (2018). Kenya Population-based HIV Impact Assessment: Preliminary Report: KENPHIA 2018. *Nascop*, *August*, 1–26.

Kenya council of governors. (2017). *Council of Governors statement on Nurses strike*.

Kenya HIV Prevention and Treatment Guidelines. (2022). *No* http://applications.emro.who.int/dsaf/EMROPUB_2014_EN_1689.pdf?ua=1

Kenya Quality Improvement HIV Framework. (2014). Ministry of Health. *Nature*, *188*(4749), 452–453. https://doi.org/10.1038/188452b0

Khadka, S., Kandel, S., Pandit, R., Manjhi, R., Dhital, S., Bahadur Baniya, J., Kumar Mishra, S., & Kumar Mahato, R. (2021). Sero-prevalance of Cryptococcal Antigenemia in HIV Positive Individual having CD4 Counts <100 Cells/mm3. *Nepal Journal of Biotechnology*, *9*(2), 29–32. https://doi.org/10.54796/njb.v9i2.41912

Kuznik, A., Iliyasu, G., Habib, A. G., Musa, B. M., Kambugu, A., & Lamorde, M. (2016). Initiation of antiretroviral therapy based on the 2015 WHO guidelines. *Aids*, *30*(18), 2865–2873. https://doi.org/10.1097/QAD.0000000000001251

Landmann, C., Fundação, S., Cruz, O., Landmann Szwarcwald, C., Roberta, A., Pascom, P., & Roberto De Souza Júnior, P. (2015). Estimation of the HIV Incidence and of the Number

of People Living With HIV/AIDS in Brazil. *Article in Journal of AIDS*, *6*, 430. https://doi.org/10.4172/2155-6113.1000430

Lu, X., Sun, H., Li, H., Xia, W., Wu, H., Chen, D., Tan, M., Yu, S., Zhang, T., Sheng, H., & Zhu, Z. (2020). Validation of the BD FACSPresto system for the measurement of CD4 T-lymphocytes and hemoglobin concentration in HIV-negative and HIV-positive subjects. *Scientific Reports 2020 10:1*, *10*(1), 1–11. https://doi.org/10.1038/s41598-020-76549-6

May, M. T., Gompels, M., Delpech, V., Porter, K., Orkin, C., Kegg, S., Hay, P., Johnson, M., Palfreeman, A., Gilson, R., Chadwick, D., Martin, F., Hill, T., Walsh, J., Post, F., Fisher, M., Ainsworth, J., Jose, S., Leen, C., … Glabay, A. (2014). Impact on life expectancy of HIV-1 positive individuals of CD4+ cell count and viral load response to antiretroviral therapy. *AIDS (London, England)*, *28*(8), 1193. https://doi.org/10.1097/QAD.0000000000000243

Musyoki, H., Bhattacharjee, P., Sabin, K., Ngoksin, E., Wheeler, T., & Dallabetta, G. (2021). A decade and beyond: learnings from HIV programming with underserved and marginalized key populations in Kenya. *Journal of the International AIDS Society*, *24*(S3), 53–58. https://doi.org/10.1002/jia2.25729

Mutabari, D. (2017). *Assessment of virological failure among Hiv patients on first line antiretroviral at Kenyatta National Hospital Comprehensive Care Centre, Nairobi Kenya*. http://erepository.uonbi.ac.ke/handle/11295/101998

Mwau, M., Syeunda, C. A., Adhiambo, M., Bwana, P., Kithinji, L., Mwende, J., Oyiengo, L., Sirengo, M., & Boeke, C. E. (2018a). Scale-up of Kenya's national HIV viral load program: Findings and lessons learned. *PLOS ONE*, *13*(1), e0190659. https://doi.org/10.1371/JOURNAL.PONE.0190659

Mwau, M., Syeunda, C. A., Adhiambo, M., Bwana, P., Kithinji, L., Mwende, J., Oyiengo, L., Sirengo, M., & Boeke, C. E. (2018b). Scale-up of Kenya's national HIV viral load

program: Findings and lessons learned. *PLOS ONE*, *13*(1), e0190659. https://doi.org/10.1371/JOURNAL.PONE.0190659

Nglazi, M. D., Kranzer, K., Holele, P., Kaplan, R., Mark, D., Jaspan, H., Lawn, S. D., Wood, R., & Bekker, L. G. (2012). Treatment outcomes in HIV-infected adolescents attending a community-based antiretroviral therapy clinic in South Africa. *BMC Infectious Diseases*, *12*(1), 1–7. https://doi.org/10.1186/1471-2334-12-21/FIGURES/1

Nobile, C., Rudnicka, D., Hasan, M., Aulner, N., Porrot, F., Machu, C., Renaud, O., Prévost, M.-C., Hivroz, C., Schwartz, O., & Sol-Foulon, N. (2010). HIV-1 Nef Inhibits Ruffles, Induces Filopodia, and Modulates Migration of Infected Lymphocytes. *Journal of Virology*, *84*(5), 2282–2293. https://doi.org/10.1128/JVI.02230-09/ASSET/A3D9945E-9AB8-4319-9A5C-CA5765CEBF72/ASSETS/GRAPHIC/ZJV9990928830006.JPEG

Nolan, S., Walley, A. Y., Heeren, T. C., Patts, G. J., Ventura, A. S., Sullivan, M. M., Samet, J. H., & Saitz, R. (2017). HIV-infected individuals who use alcohol and other drugs, and virologic suppression. *Https://Doi.Org/10.1080/09540121.2017.1327646*, *29*(9), 1129–1136. https://doi.org/10.1080/09540121.2017.1327646

Nyakeriga, E., Waruiru, W., Opollo, V., Waruru, A., Kingwara, L., Onyango, D., Junghae, M., Muuo, S., Macharia, T., Ngugi, C., Mwangome, M., & Ali, H. (2022). Mortuary and hospital-based HIV mortality surveillance among decedents in a low-resource setting: lessons from Western Kenya. *BMC Public Health*, *22*(1), 1–13. https://doi.org/10.1186/s12889-022-12909-3

Nyangueso, S., Hayombe, P., & Owino, F. (2018). Spatial Equity in Devolved Healthcare: Geospatially Exploring Local Disparities in Maternal Healthcare Uptake After Devolution in Kenya. *European Scientific Journal, ESJ*, *14*(27), 378. https://doi.org/10.19044/esj.2018.v14n27p378

Ogunbajo, A., Leblanc, N. M., Kushwaha, S., Boakye, F., Hanson, S., Smith, M. D. R., & Nelson,

L. R. E. (2019). Knowledge and Acceptability of HIV pre-exposure prophylaxis (PrEP) among men who have sex with men (MSM) in Ghana. *Https://Doi.Org/10.1080/09540121.2019.1675858*, *32*(3), 330–336. https://doi.org/10.1080/09540121.2019.1675858

Olivieri-Mui, B., McGuire, J., Griffith, J., Cahill, S., & Briesacher, B. (2020). Assessing the Quality of Human Immunodeficiency Virus Care in Nursing Homes. *Journal of the American Geriatrics Society*, *68*(6), 1226–1234. https://doi.org/10.1111/jgs.16359

Parry, M. F., Wright, P., Stewart, J., McLeod, G. X., Tucker, J., & Weinberg, A. R. (2005). Impact of an adherence program on the health and outlook of HIV-infected patients failing antiretroviral therapy. *Journal of the International Association of Physicians in AIDS Care*, *4*(3), 59–65. https://doi.org/10.1177/1545109705281897

Patel, R. C., Oyaro, P., Odeny, B., Mukui, I., Thomas, K. K., Sharma, M., Wagude, J., Kinywa, E., Oluoch, F., Odhiambo, F., Oyaro, B., John-Stewart, G. C., & Abuogi, L. L. (2020). Optimizing viral load suppression in Kenyan children on antiretroviral therapy (Opt4Kids). *Contemporary Clinical Trials Communications*, *20*, 100673. https://doi.org/10.1016/J.CONCTC.2020.100673

Pepfar. (2018). *Kenya Country Operational Plan (COP/ROP) 2018 Strategic Direction Summary*.

Pepping, J. K., Otvos, L., Surmacz, E., Gupta, S., Keller, J. N., & Bruce-Keller, A. J. (2014). Designer adiponectin receptor agonist stabilizes metabolic function and prevents brain injury caused by HIV protease inhibitors. *Journal of Neuroimmune Pharmacology*, *9*(3), 388–398. https://doi.org/10.1007/s11481-014-9529-1

Phillips, A. N., Stover, J., Cambiano, V., Nakagawa, F., Jordan, M. R., Pillay, D., Doherty, M., Revill, P., & Bertagnolio, S. (2017). Impact of HIV Drug Resistance on HIV/AIDS-Associated Mortality, New Infections, and Antiretroviral Therapy Program Costs in Sub–

Saharan Africa. *The Journal of Infectious Diseases*, *215*(9), 1362–1365. https://doi.org/10.1093/INFDIS/JIX089

Puthanakit, T., Aurpibul, L., Louthrenoo, O., Tapanya, P., Nadsasarn, R., Insee-Ard, S., & Sirisanthana, V. (2010). Poor Cognitive Functioning of School-Aged Children in Thailand with Perinatally Acquired HIV Infection Taking Antiretroviral Therapy. *Https://Home.Liebertpub.Com/Apc*, *24*(3), 141–146. https://doi.org/10.1089/APC.2009.0314

Rajasingham, R., Smith, R. M., Park, B. J., Jarvis, J. N., Govender, N. P., Chiller, T. M., Denning, D. W., Loyse, A., & Boulware, D. R. (2017). Global burden of disease of HIV-associated cryptococcal meningitis: an updated analysis. *The Lancet Infectious Diseases*, *17*(8), 873–881. https://doi.org/10.1016/S1473-3099(17)30243-8

Reagan, R., & Barkley, T. W. (2015). *Neuropathic Pain Management: A Reference for the Clinical Nurse*. *24*(6).

Roberts, T., Cohn, J., Bonner, K., & Hargreaves, S. (2016). Scale-up of Routine Viral Load Testing in Resource-Poor Settings: Current and Future Implementation Challenges. *Clinical Infectious Diseases*, *62*(8), 1043–1048. https://doi.org/10.1093/CID/CIW001

Ronen, K., Unger, J. A., Drake, A. L., Perrier, T., Akinyi, P., Osborn, L., Matemo, D., O'Malley, G., Kinuthia, J., & John-Stewart, G. (2017). SMS messaging to improve ART adherence: perspectives of pregnant HIV-infected women in Kenya on HIV-related message content. *Https://Doi.Org/10.1080/09540121.2017.1417971*, *30*(4), 500–505. https://doi.org/10.1080/09540121.2017.1417971

Rowland-Jones, S., & Andrews, S. M. (2017). Recent advances in understanding HIV evolution. *F1000Research*, *6*, 597. https://doi.org/10.12688/F1000RESEARCH.10876.1

Rusine, J., Ondoa, P., Asiimwe-Kateera, B., Boer, K. R., Uwimana, J. M., Mukabayire, O., Zaaijer, H., Mugabekazi, J., Reiss, P., & van de Wijgert, J. H. (2013). High

Seroprevalence of HBV and HCV Infection in HIV-Infected Adults in Kigali, Rwanda. *PLOS ONE*, *8*(5), e63303. https://doi.org/10.1371/JOURNAL.PONE.0063303

Samizi, F. G., Panga, O. D., Malugu, S. S., Gitige, C. G., & Mmbaga, E. J. (2021). Rate and predictors of HIV virological failure among adults on first-line antiretroviral treatment in Dar Es Salaam, Tanzania. *Journal of Infection in Developing Countries*, *15*(6), 853–860. https://doi.org/10.3855/JIDC.13603

Shanks, L., Klarkowski, D., & O'Brien, D. P. (2013). False Positive HIV Diagnoses in Resource Limited Settings: Operational Lessons Learned for HIV Programmes. *PLOS ONE*, *8*(3), e59906. https://doi.org/10.1371/JOURNAL.PONE.0059906

Siaya. (2018). *Siaya county integrated development plan*.

Sullivan, P. S., Rosenberg, E. S., Sanchez, T. H., Kelley, C. F., Luisi, N., Cooper, H. L., Diclemente, R. J., Wingood, G. M., Frew, P. M., Salazar, L. F., del Rio, C., Mulligan, M. J., & Peterson, J. L. (2015). Explaining racial disparities in HIV incidence in black and white men who have sex with men in Atlanta, GA: a prospective observational cohort study. *Annals of Epidemiology*, *25*(6), 445–454. https://doi.org/10.1016/J.ANNEPIDEM.2015.03.006

Tee, K. K., Thomson, M. M., & Hemelaar, J. (2019). *Editorial : HIV- genetic diversity , volume II*.

Telele, N. F., Kalu, A. W., Marrone, G., Gebre-Selassie, S., Fekade, D., Tegbaru, B., & Sönnerborg, A. (2018). Baseline predictors of antiretroviral treatment failure and lost to follow up in a multicenter countrywide HIV-1 cohort study in Ethiopia. *PLOS ONE*, *13*(7), e0200505. https://doi.org/10.1371/JOURNAL.PONE.0200505

Tobergte, D. R., & Curtis, S. (2013). *SQUIRE guidelines*. *53*(9), 1689–1699.

UNAIDS. (2014a). The Gap Report. *Geneva: UNAIDS*.

UNAIDS. (2014b). To help end the AIDS epidemic. *United Nations*, 40.

UNAIDS. (2015). Understanding Fast-Track Targets. Accelerating action to end the AIDS epidemic by 2030. *UNAIDS Reference*, 12. https://www.unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf

UNAIDS. (2017). Data 2017. *Programme on HIV/AIDS*, 1–248. http://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf

UNAIDS. (2022). *Global HIV statistics People living with HIV People living with HIV accessing antiretroviral therapy New HIV infections AIDS-related deaths*.

Vetrova, M., Lodi, S., Rateau, L., Patts, G., Blokhina, E., Palatkin, V., Yaroslavtseva, T., Toussova, O., Bushara, N., Bendiks, S., Gnatienko, N., Krupitsky, E., Lioznov, D., Samet, J. H., & Lunze, K. (2022). Stigma and ART initiation among people with HIV and a lifetime history of illicit drug use in Saint-Petersburg, Russia–A prospective cohort analysis. *International Journal of Drug Policy*, *102*, 103600. https://doi.org/10.1016/J.DRUGPO.2022.103600

Waruru, A., Achia, T. N. O., Tobias, J. L., Ng'Ang'A, J., Mwangi, M., Wamicwe, J., Zielinski-Gutierrez, E., Oluoch, T., Muthama, E., & Tylleskär, T. (2018). Finding Hidden HIV Clusters to Support Geographic-Oriented HIV Interventions in Kenya. *Journal of Acquired Immune Deficiency Syndromes (1999)*, *78*(2), 144. https://doi.org/10.1097/QAI.0000000000001652

WHO. (2014). Use of rapid HIV tests in HIV testing strategies. In *WHO Regional Publications, Eastern Mediterranean Series* (Vol. 36). http://applications.emro.who.int/dsaf/EMROPUB_2014_EN_1689.pdf?ua=1

WHO. (2015). *WHO*.

WHO. (2016). *WHO Progress Report 2016*. *c*, 16.

http://ec.europa.eu/research/era/pdf/era_progress_report2016/era_progress_report_2016_com.pdf

WHO, 2023. (2023). *Epidemiological fact sheet HIV statistics , globally and by WHO region , 2023*.