PREVALENCE, RATE AND PREDICTORS OF VIROLOGIC FAILURE AMONG ADULT HIV-INFECTED CLIENTS ON SECOND-LINE ANTIRETROVIRAL THERAPY (ART) IN TANZANIA (2018-2020)

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By

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A Dissertation Submitted in (Partial) Fulfilment of the Requirements for the Degree of Master of Science (Epidemiology and Laboratory Management) of

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CERTIFICATION

The undersigned certify that they have read and hereby recommend for acceptance by Muhimbili University of Health and Allied Sciences a dissertation entitled; **‘‘Prevalence, rate and predictors of virologic failure among adult HIV-infected clients on second-line antiretroviral therapy (ART) in Tanzania (2018-2020)’’,** in (partial) fulfilment of the requirements for the degree of Master of Science (Epidemiology and Laboratory Management) of Muhimbili University of Health and Allied Sciences.

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DECLARATION AND COPYRIGHT

I, **Ester T. Mwavika**, declare that this **dissertation** is my original work and that it has not been presented and will not be presented to any other University for a similar or any other degree award.

Signature……. **Date**……..

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DEDICATION

I would like to dedicate this work to my husband, Daniel Laswai, and our children Dinah and Dalvin.

ABSTRACT

Background: Antiretroviral Therapy (ART) has been proven to be highly effective in reducing the impact of Human Immunodeficiency Virus (HIV) infection. However, as more people receive initial ART treatment, the risk of developing resistance and eventual treatment failure increases, leading to the need for second-line treatment regimens. Understanding the factors that contribute to virologic failure to second-line ART is crucial in preventing switching to the more expensive and toxic third-line regimens. This study provides information on the prevalence, rate, and predictors of virologic failure (VF) among clients on second-line ART in Tanzania.

Results: We followed 4,718 clients for 15,100 person-years (PY) of observations. Of them, 1,402(29.72%) experienced virologic failure, at a rate of 92.85 per 1000 PY of observations (95% CI 88.11, 97.84). Factors that were associated with VF included: having a viral load count of ≥1000 copies/mL during first-line ART, with adjusted hazard ratio (aHR) 4.65 (95% CI 3.57, 6.07), using lopinavir (LPV/r) as a protease inhibitor during second-line ART aHR 4.20 (95% CI 3.12, 7.10), having a CD4 count <200 cells/mm^3 during second-line ART aHR 1.89 (95% CI 1.46, 2.44), and being on ART for 13-35 months aHR 8.22 (95% CI 2.21, 30.61). Paradoxically, having a CD4 count <200 cells/mm^3 during first-line ART treatment was associated with a reduced risk of virologic failure aHR 0.77 (95% CI 0.60, 0.99).

Conclusions: In Tanzania, approximately 30% of the adult clients on second-line ART experience VF at a rate of 92.71 per 1000 person-years. This high virologic failure rate highlights the need for targeted interventions for HIV-infected clients on second-line ART to reduce the need for switching to the more costly and relatively more toxic third-line ART therapy and help to achieve the third UNAIDS goal of achieving viral suppression for 95% of those treated by 2030.

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ABBREVIATIONS

ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ATV/r	Atazanavir/Ritonavir
AZT	Zidovudine
CI	Confidence Interval
CTC	Care and Treatment Centre
D4T	Stavudine
DDI	Didanosine
DRMs	Drug Resistance Mutations
DTG	Dolutegravir
EAC	Enhanced Adherence and Counselling
EFV	Efravirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HIVDR	HIV Drug Resistance
HVL	HIV Viral load
HR	Hazard Ratio
INSTIs	Integrase Strand Transfer Inhibitors
IQR	Inter Quartile range
LPV/r	Lopinavir

NASHCoP	National AIDS, STIs and Hepatitis Control Programme
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NVP	Nevirapine
PIs	Protease Inhibitors
PLHIV	People Living With HIV/AIDS
PMTCT	Prevention of Mother To Child Transmission
PY	Person Years
SD	Standard Deviation
SSA	Sub-Saharan Africa
TB	Tuberculosis
TDF	Tenofovir Disoproxil Fumarate
UNAIDS	United Nations Program on HIV and AIDS
USD	United State Dollar
VF	Virological Failure
VL	Viral Load
WHO	World Health Organization

DEFINITION OF TERMS

Antiretroviral Therapy: The standard treatment consists of a combination of drugs, often called highly active antiretroviral therapy (HAART) that suppress Human Immunodeficiency Virus (HIV) replication(1).

Enhanced Adherence and Counselling (EAC): This is an innovative program that offers specialized adherence counselling to HIV-positive patients taking antiretroviral medication who have viral loads that have not been suppressed(2).

Option B+ facilities: offer lifelong treatment of all HIV-positive pregnant mothers to prevent mother-to-child transmission of HIV (3).

Virological Failure: Refers to viral loads that are detectable and greater than 1,000 copies/mL on two occasions, spaced three to six months apart and with adherence support in between, and this occurs at least six months after beginning a new antiretroviral treatment (ART) regimen(4)

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

Worldwide, as of 2022, nearly 39.0 million individuals were living with the Human Immunodeficiency Virus (HIV), with 25.6 million of them residing in Sub-Saharan Africa (SSA) (5)

In Tanzania, approximately 1,548,000 adults are living with HIV, with an annual incidence rate of 0.18%, corresponding to around 60,000 new cases of HIV each year (6) . Regional HIV prevalence ranges from 0.5% in Zanzibar to 11.4% in Njombe (7).

For people living with HIV (PLHIV), early initiation of Antiretroviral Therapy (ART) is crucial for improving viral suppression and increasing life expectancy (8–10). Currently, it is estimated that 29.8 million PLHIV are receiving ART, 15 million of them in SSA and 1.2 million in Tanzania (6).

Tanzania's Care and Treatment Plan for PLHIV is a crucial component of the country's health sector response to the HIV and AIDS epidemic (11). The initiative that offers free access to ART commenced in September 2004, as part of the HIV/AIDS Treatment and Care Plan for the years 2003 to 2008 (12). Presently, more than 6,000 health facilities are authorized to provide HIV care and treatment services, including ART(13), benefiting a total of 1,616,952 individuals by 2023(14).

To achieve optimal ART treatment outcomes, clients undergo monitoring for adherence, scheduled viral load, and/or CD4 count. Additionally, they receive management for opportunistic infections and the integration of care for other ailments (13). Clients are typically switched to second-line regimens in the event of treatment failure (virologically, immunologically, or clinically), drug adverse effects (such as acidosis or rash), or during pregnancy(15,16).

1.2 Problem Statement

With the increased availability of ART and more individuals starting first-line ART, the risk of viral resistance and eventual treatment failure has escalated (17–19), necessitating the need to switch to second-line treatment regimens. Studies conducted in African countries have found the proportion of individuals switching to second-line treatment to range between 62.2% and 67.45% (20,21), and this number is projected to increase significantly by 2030 (10).

Failure to second line ART regimens pose a specific problem, especially those in low-income countries since their access to third-line treatment regimens is very limited due to financial and logistic constraints (22). Third-line ART regimens are estimated to cost seven times as much as second-line ART regimens and require more resources for the provision of care and treatment (23,24).

Most of the studies in Tanzania have focused on virologic failure (VF) among PLHIV who are on first-line ART (25) and have shown an increase in prevalence rates, from 14.9% in 2016 to 23% and 32.8% in 2021 (26,27). Information on VF among clients on second-line ART is limited and pertains to specific regions of the country. A study conducted in north-western Tanzania reported a prevalence of 12.18%, while another study in the Morogoro region found a prevalence of 13.1% (28,29). A more recent Tanzania Health Indicator Survey (THIS), which was conducted in 2022, revealed significant regional variations, ranging from 6.5% in Tanga to 34.2% in Tabora (6). Unfortunately, nationwide estimates of failure to second line ART regimens is missing. We conducted this study, to provide national estimates on the prevalence, rate, and factors associated with VF among adult HIV-positive clients on second-line ART in Tanzania. Unlike many previous studies, we also explored possible factors during first-line treatment that could predict failure in the second line. We hypothesized that with the increased use of second-line ART regimens, the likelihood of having clients experiencing VF will increase.

1.3 Conceptual framework

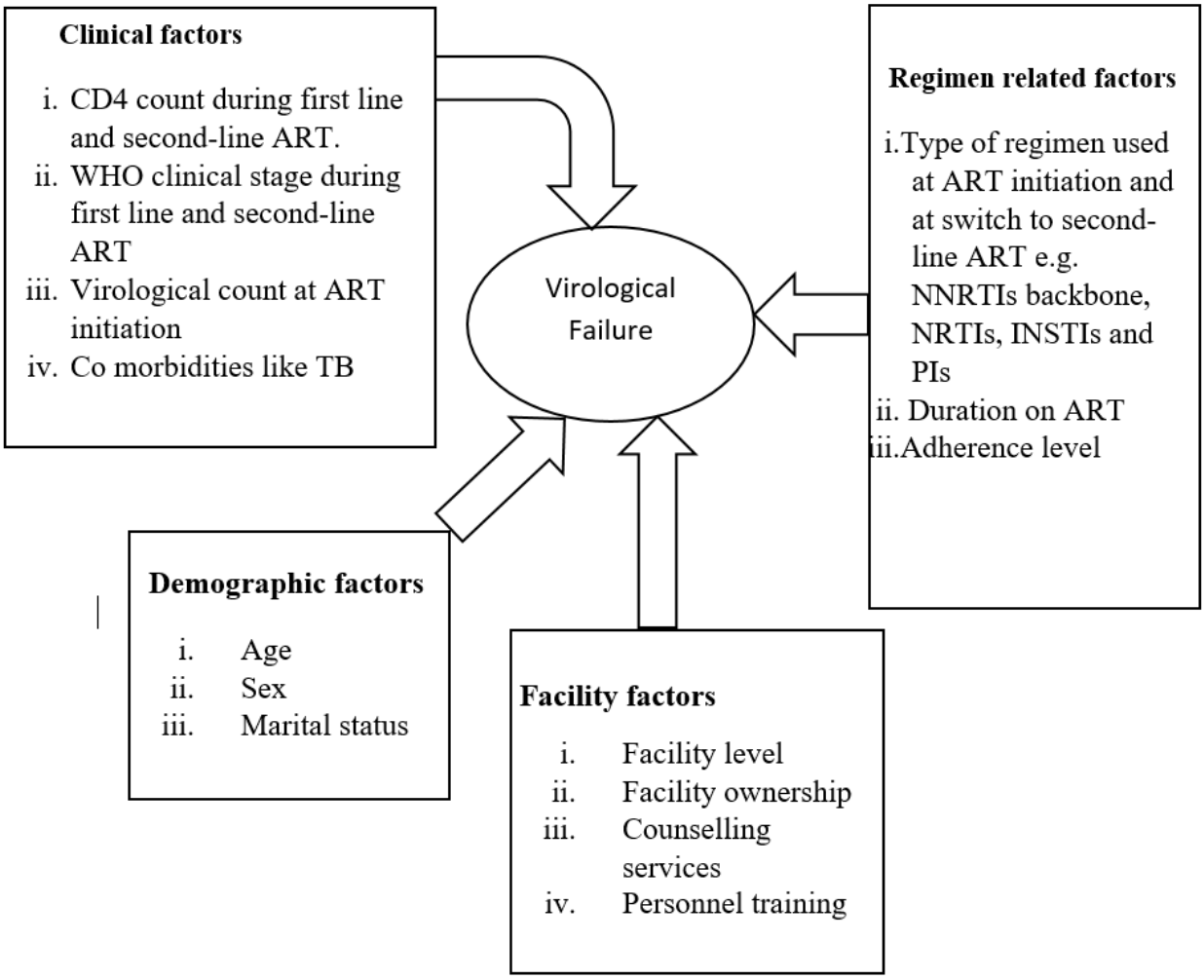


Figure 1: Conceptual framework for factors associated with virological failure among HIV clients on Antiretroviral Therapy

1.4 Rationale

This study aims to assess the rate and predictors of virological failure (VF) among PLHIV receiving second-line ART in Tanzania. The findings are expected to provide nationally representative data, informing the Ministry of Health, health policymakers, and Implementing Partners (IPs) about the burden, rate, and predictors of virologic failure to second line ART among adult clients in Tanzania. Additionally, it will guide the development of cost-effective strategies to decrease the rate of virological failure among clients using second-line ART and help achieve the third 95 UNAIDS goal as a nation and avoid switching to the more toxic and expensive third-line ART regimens (30).

1.5 Research Questions

1.5.1 Main Research Question

What is the prevalence, rate and predictors of virological failure to second line ART among adult HIV clients in Tanzania?

1.5.2 Specific research questions

1. What is the prevalence of virological failure to second line ART among adult HIV clients in Tanzania?
2. What is the rate of virological failure to second line ART among adult HIV clients in Tanzania?
3. What are the predictors of virological failure to second line ART among adult HIV clients in Tanzania?

1.6 Objectives

1.6.1 Broad Objectives

To determine the prevalence, rate and predictors of virological failure to second line ART among adult HIV clients in Tanzania from January 2018 to December 2020.

1.6.2 Specific Objectives

1. To determine the prevalence of virological failure to second line ART among adult HIV clients in Tanzania between January 2018 and December 2020.
2. To determine the rate of virological failure to second line ART among adult HIV clients in Tanzania between January 2018 and December 2020.
3. To determine predictors of virological failure to second line ART among adult HIV clients in Tanzania between January 2018 and December 2020.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 Virological failure to second-line ART regimens among adult HIV clients.

Virological failure, the most revealing biomarker of treatment failure(31), has become a common public health problem among HIV patients on ART(13). WHO defines virological failure as a viral load above 1000 copies/mL of blood based on two consecutive viral load measurements three months apart, with adherence support following the first viral load test (4).

According to the World Health Organization (WHO) 2016 global report, 70% of patients experienced virological failure (32) .In Asia and Europe it was reported in 7% of adult patients (33), while other studies in the same region have reported a VF of between 9.5% and 17.7% (34,35). A comprehensive evaluation and meta-analysis of 19 studies in Sub-Saharan Africa (SSA), reported second-line failure rates between 21% and 38% for 6 to 36 months, respectively. According to studies conducted in East Africa, VF on second-line ART ranges from 12% to 23% (24,28,29,36,37). Noticed variation might be due to, definitions of VF used, subpopulations studied and measurement time points(33). Furthermore, level of care and resources to support VL monitoring and drug resistance testing, as well as support for treatment adherence which varies from one setting to another(38) might have also contributed to the noted variation.

2.2 Predictors of virological failure among Adult HIV clients on second-line ART

ART failure can be predicted by considering a wide array of factors, which range from patient-related, program-related, facility related to aspects(37). The discussion of these factors follows below;

Age

Children and adolescents have been shown to exhibit a high proportion of failure that has been associated by distinct behavioural and emotional elements such as fear, stigma, and lack of disclosure, as well as low socioeconomic status and poor ART medication adherence(39). Additional challenges include the difficulty of ARV administration and the requirement for

ART dose adjustment as children grow (37). In contrast, older patients had a greater risk of virological failure due to extended exposure to first-line medications, some of which are recycled to be used in second-line regimens(40).

Sex

It has been shown that men on ART have poorer outcomes than females (41). This has been correlated with the fact that HIV patients who are male are more likely to be admitted with advanced illness to HIV care facilities due to poor health seeking behaviour (24,42,43), have poor medication adherence and excessive alcohol use while taking ART(44).

Facility type/level

In East Africa, a study exploring factors influencing the retention of patients in HIV care revealed good performance in secondary-level facilities compared to primary care facilities whereby that this was explained by factors like staffing, physical accessibility, available resources, and services provided(45). A study conducted in South Africa revealed a disengagement from HIV care when patients are treated at their local primary health care due to stigma, suggesting a poor virological outcome in primary health facilities(46). In Ethiopia likelihood of developing viral non-suppression in patients from nonmilitary healthcare facilities was 1.47 times higher when compared with patients from military healthcare facilities this might be due to strictness in drug adherence as well as better nutritional access among the army staff members(47).

ART Regimen used

There is a significant association between the type of regimen used/in use with treatment outcome (38,48–50). A difference in combination of drugs in a regime has shown to differ in their efficacy. Among clients on second-line ART, the odds of experiencing treatment failure were lower among who switched to ATV/r or utilized a TDF-based regimen while on first-line ART(37).

Compared to other PIs, ATV/r typically has a lower pill burden, better oral bioavailability, low risk of lipid abnormality, and insulin sensitivity(37,51). However, usage of Zidovudine (AZT) in the first line is linked to an accumulation of Thymidine Analogue mutations(TAMs) that

confer resistance to TDF and Abacavir (ABC), which are the choices in the NRTI base of second-line ART (37).

CD4 count

CD4 T lymphocytes (CD4 cells) help coordinate the immune response by stimulating other immune cells, such as macrophages, B lymphocytes (B cells), and CD8 T lymphocytes (CD8 cells), to fight infection (52). If left untreated, HIV virus, kills infected cells both directly and indirectly via immunological responses that induce cell death. This gradual decrease of CD4+ T cells weakens the immune system over time, even after antiretroviral treatment (cART) in HIV-infected persons(53). Numerous studies have associated CD4 count with viral load, opportunistic infections and clinical well-being of HIV-infected individuals (41,54,55). Clients with extremely low CD4 counts (200 cells/mm3) are more prone to acquire opportunistic infections, such as TB, which further impairs their response to treatment(15).

Adherence Level

Adherence level is the degree to which a person complies with the agreed-upon suggestions from a health care professional in terms of their behaviour, such as taking medicine, following a diet, and/or modifying their lifestyle(4). The adherence rates for ART must be nearly excellent(as high as 95%)(56). Poor adherence(below 85%) has detrimental effects, including rising viremia that may accelerate the progression of the disease, the emergence of drug-resistant HIV strains, and their spread to other people(48). Indeed, suboptimal adherence which is defined as, an average of at least 1 missed ART dose per month over the previous three months(57), result in inadequate drug exposure and increases the likelihood of immunological and virological failure, resistance, and leads to disease progression(55). Those who skip more than three twice-day doses or more than one daily dosage of ART per month are forced to experience virological failure due to a decreased medication concentration in plasma(39). Poor adherence has been pointed out as the major reason for failing virologically among clients on ART, including those on second-line regimens (48,50,58).

Duration on ART

Several studies have demonstrated that participants who had received ART for a longer time could fail treatment due to insufficient drug potency, development of resistance, and pharmacological incompatibilities(50). Longer time on ART was associated with treatment "tiredness" but as well prolonged asymptomatic condition which led to questioning the necessity of continuing with strict adherence, hence treatment failure(59). However other studies have revealed improved virological outcomes with a longer duration of ART(60,61). Furthermore, duration of ART use during the first line has been marked as a significant predictor of treatment failure on second-line ART which is explained by possible cross-resistance(28).

In summary, each of the above-mentioned factors must be thoroughly investigated for an improved therapy success rate. This will prevent clients on second-line ART from being unnecessarily switched to the more costly third-line regimens, which are not readily available in Low and Middle Income Countries, like Tanzania. The cost of third-line is eighteen times and seven times higher than the lowest price of first and second-line ART, respectively(62). Furthermore, a third-line ART regimen is more intolerable, and costs more in terms of resources required for its provision (23)

CHAPTER THREE

3.0 METHODOLOGY

3.1 Study Design and setting

This retrospective cohort study that involved data analysis of data from the CTC2(63) database, an electronic system for HIV/AIDS Care and Treatment clinics. The analysis covered all 26 regions of mainland Tanzania and included 6026 health facilities that offer ART services, of them 2,103 were care and treatment centres (CTCs) and 4,103 were Prevention of Mother to Child Transmission (PMTCT) facilities. The latter facilities do provider Option B + services, which refers to the provision of ART to all breastfeeding and pregnant women living with HIV, regardless of CD4 count or clinical stage. As of December 2018, approximately 3800 facilities had submitted data to the CTC2 database.

3.2 Study Area

This study involved all 26 regions of Tanzania's mainland. At present an estimated 6,206 health facilities are offering ART services, of which 2103 are care and treatment centres (CTCs), and 4103 are Prevention of Mother to Child Transmission (PMTCT) facilities offering Option B+ i.e. provision of life-long ART to all breastfeeding and pregnant women living with HIV Regardless of CD4 count or clinical stage. As of December 2018, about 3800 facilities submitted data to the CTC2 database(64).

3.3 Study Participants

We enrolled all adult clients aged 15 years and older, and who were receiving second-line ART between January 2018 and December 2020. We excluded clients on second-line ART for less than six months and those missing HIV viral load results.

3.4 Sample size estimation

The sample size estimation was calculated using the Open-Epi Version 3.1.01. Based on a study conducted in Tanzania that reported a VF of 12.18%(28) the estimated minimum sample size was 1,147. As shown in Figure 2 below we enrolled a total of 4,718 clients.

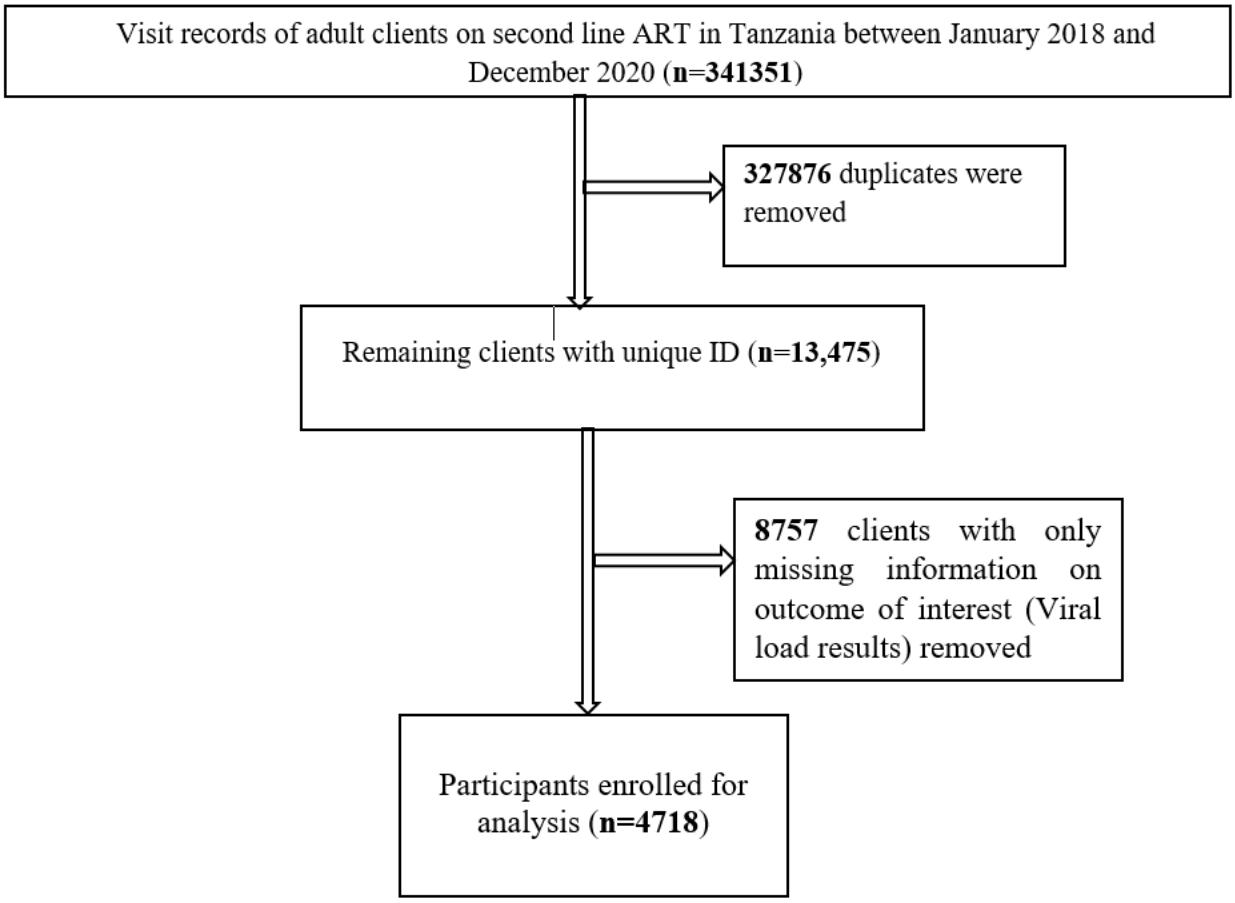


Figure 2: Schematic presentation of the sampling procedure of the study participants

3.5 Power of the study

The assumption for the calculation of power was as follows;

- From the literature a study conducted in Ethiopia looking at virological failure among clients on second-line ART(65), TB was independently predicting virological failure and so in this study it was a variable for.

- The proportion of clients with TB (**exposed**) was 88.33% and those with no TB (**unexposed**) were 11.67%.
- From the above study proportions, the number of exposed and unexposed calculated from this study sample size was 550 and 4168, respectively.
- Calculating K, we obtained 7.6, so n1=550, n2=4,168
- From a referred study, the risk of virological failure among the exposed group is 61.9% and 5.77%.
- Using a formula below, this study had a power of **100%** calculated in open Epi software version 3.01 which can be assessed at https://www.openepi.com/Menu/OE_Menu.html.

$$Power = \Phi\left(\frac{\sqrt{(n_1 * \Delta^2)} - z_{1-\alpha/2}\sqrt{(1+1/\kappa) * p * q}}{\sqrt{(p_1 * q_1) + (p_2 * q_2 / \kappa)}} \right)$$

The notations for the formulae are:

Δ = difference of risk of disease between exposed group and non-exposed group

κ = ratio of sample size: non-exposed group / exposed group

p1= risk of disease among the exposed group;

p2= risk of disease among the non-exposed group;

p = (p1*n1+p2*n2) / (n1+n2)

q= 1-p

n1= available sample size among the exposed group;

3.6 Dependent and independent variables

Dependent Variable

In this study, the dependent variable was virologic failure, which was defined as having two consecutive viral load results of ≥ 1000 virus copies per mL of blood.

3.7 Independent Variables

The independent variables were demographic characteristics (age, sex, marital status, facility details, and geographical location within the country), medical and clinical characteristics as follows: Regimens were categorized as Nucleoside Reverse Transcriptase Inhibitors (NRTI) backbone, Integrase Strand Transfer Inhibitors (INSTI), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) and Protease Inhibitors (PI) (2019). Adherence was considered to be good if it was≥95 %(< 2 doses of 30 doses or <30 doss of 60 doses is missed)(66) and cumulative duration on ART was categorized as ≤12 months, 13-35 months, and ≥60 months.

Further, categorization of clinical characteristics was based on WHO stages (I, II, III, and IV), CD4 count (≥200 cells/mm3 and < 200 cells/mm3), and TB diagnosis.

Observations were censored at death, loss to follow-up, or when second-line ART was discontinued for reasons other than failure.

3.8 Data collection method

The study used secondary programmatic data available in the CTC-3 Macro system, which is a component of the HIV case-based surveillance system. This electronic patient monitoring system captures information/records of patients in every attendance to clinics. Therefore, all clinical and laboratory records are uploaded and updated on every visit. Because of the amount of data found in this system and for security purposes data analysis of data is commanded directly from the server.

3.9 Data Pre-testing

Sample data was shared by NASHCOP for the preparation of do file for analysis. The data sample helped to verify the planned analysis command in the do file before final analysis from NASHCOP server.

3.10 Data Analysis

For continuous and categorical variables we calculated frequencies, median, interquartile ranges (IQR), means, and standard deviations (SD). Person-time at risk was calculated as the time interval from when a patient switched to the second-line regimen to the end of follow-up. The rate of VF was calculated as number of clients with virologic failure per total person-time at risk for the follow-up period, while the prevalence of VF was calculated as the proportion of clients on second-line ART who experienced failure.

We used the multivariable Cox proportional hazard models to assess independent causes of VF, including age, sex, marital status, facility level, facility ownership, regimen use history, TB co-infection, WHO stage, CD4 count, and adherence level. Bivariate analysis was used to assess the potential determinant factors of VF, and those with a p value of less than or equal to 0.2 were included in the multivariable model. Factors with a $p \leq 0.05$ were considered to be significantly associated with VF in clients receiving second-line ART.

3.11 Ethical Consideration

The Institutional Research Board (IRB) of Muhimbili University of Health and Allied Sciences (MUHAS) provided ethical clearance (MUHAS-REC-05-2023-1697). Permission to use patients' data was obtained from the Permanent Secretary of MOH through NASHCOP (Ref. No. HD/MUH/T.650/2021). To ensure participant data confidentiality, client identifications including ID numbers, names, phone numbers, and household identifiers were removed from the extracted database by NASHCOP data officers. Each medical record was assigned a unique study identification code which was linked to the client's ID. According to the nature of the study, there was no interaction with clients so waiver of consent was requested from MUHAS IRB.

CHAPTER FOUR

4.0 RESULTS

Socio-demographic characteristics of clients on second-line ART

The study reviewed the records of 4718 adult HIV-positive clients who were on second-line ART. The average age of the clients was 42.08 (±15.47) years. Of them, 2817 (59.71%) were females, and 2440 (51.72%) were married. Most clients 4360 (92.65%) received care in public health facilities, and most of the 3025 (64.12%) were attending clinic-level health facilities. Geographically the Eastern zone contributed 1719 (36.53%) of the enrolled clients (Table 1).

Table 1: Socio-demographic characteristics of clients on second-line ART in Tanzania from January 2018 to December 2020 (n= 4718)

Characteristics	Frequency (n)	Percentage (%)
Sex		
Male	1901	40.29
Female	2817	59.71
Age group(years)		
15-24	0	0
25-34	313	9.24
35-44	920	27.16
45-54	1233	36.40
≥55	921	27.19
Marital status		
Married	2440	62.77
Single	1447	37.23
Facility ownership		
Private	346	7.35
Public	4360	92.65
Facility level		
Dispensary	110	2.34
Health center	564	11.99
Hospital	1006	21.38
Clinic	3025	64.29
Geographical zones		
Central Zone	254	5.40
Eastern	1719	36.53
Lake	420	8.92
Northern	1060	22.52
Southern Highlands	616	13.09
Southern	215	4.57
Southern West Highland	340	7.22
Western	82	1.74

Virological, immunological, and clinical characteristics of HIV clients during first-line and second-line ART

During the first-line ART, 2160 (46.39%) clients were in WHO clinical stage III, and 2050 (61.10%) had viral load count of <1,000 cp/mL, with 2126 (53.01%) having a CD4 count of less than <200 cells/mm^3. When initiating second-line ART, half of the clients (2396 or 50.78%) were in WHO clinical stage III, and 1690 (59.93%) had a CD4 count of ≥200 cells/mm^3. During the first-line ART 107 (2.30%) clients had a history of TB, compared to 44 (0.93%) during the second-line ART (Table 2).

Table 2: Virological, immunological, and clinical characteristics of HIV clients during first-line and second-line ART

Characteristic	Frequency (n)	Percentage (%)
During First-line ART		
CD4 count (First test since Initiation of first-line ART)		
<200 cells/mm^3	2126	53.01
≥200 cells/mm^3	1885	46.99
Viral load count (First test since Initiation of first-line ART)		
<1000 cp/mL	2050	61.10
≥1000 cp/mL	1305	38.90
WHO stage at first-line ART initiation		
Stage I	506	10.87
Stage II	1235	26.52
Stage III	2160	46.39
Stage IV	755	16.22

Characteristic	Frequency (n)	Percentage (%)
Tuberculosis diagnosis during first-line ART		
No	4554	97.70
Yes	107	2.30
During second-line ART		
CD4 count (First CD4 After switching to second-line ART) *		
<200 cells/mm^3	1130	40.07
≥200 cells/mm^3	1690	59.93
WHO-stage at the switch to second-line ART		
Stage I	241	5.11
Stage II	713	15.12
Stage III	2396	50.81
Stage IV	1366	28.97
Tuberculosis diagnosis during second-line ART		
No	4674	99.07
Yes	44	0.93

ART regimens offered to HIV Positive Clients on Second-line ART (Insights from First-line Therapy)

In this study, most clients, 4438 (94.07%), had been on antiretroviral therapy (ART) for 60 months or more, with 1854 (41.14%) clients initiated on AZT as part of their NRTI backbone, while 3317 (74.39%) were initiated on EFV/NVP (NNRTI). On switching to second-line ART regimens, 2274 (51.18%) clients took lopinavir, and 2339 (56.63%) used TDF as their NRTIs, and adherence was good (>95%) during both first and second-line ART (Table 3)

Table 3: Type of regimen given and the level of adherence during the first and second-line ART (n=4718)

Characteristic	Frequency (n)	Percentage (%)
During First-line		
NRTI backbone at initiation		
Tenofovir (TDF)	787	17.46
Zidovudine (AZT)	1854	41.14
Abacavir (ABC)	13	0.29
Others (d4t, ddi)	1853	41.11
NNRTIs/INSTIs based regimen at initiation		
EFV/NVP	3317	74.39
DTG	637	14.29
Others	505	11.33
ART Adherence		
Good (>95%)	4546	97.93
Poor (<95%)	96	2.07
During second-line		
PI at switch		
Lopinavir/Ritonavir (LPV/r)	2274	51.18
Atazanavir/Ritonavir(ATV/r)	1848	41.59
Other	321	7.22
NRTI backbone at switch		
Tenofovir (TDF)	2339	56.63
Zidovudine (AZT)	347	8.40
Abacavir (ABC)	1444	34.96
ART Adherence		
Good (>95%)	4494	95.29
Poor (<95%)	222	4.71
Total duration of ART (Months)		
≤12 months	3	0.06
13–35months	64	1.36
36–59 months	213	4.51
≥60 months	4438	94.07

The rate of virological failure among HIV-positive adult clients on second-line ART

This study observed 4718 clients for a total of 15100 person-years (PY), of whom 1402 (29.72%) experienced virological failure during second-line ART. The overall rate of VF was 92.85 (95% CI 88.11-97.84) per 1000 PY of observations.

The rate of VF was high among clients aged 35-44 years, 118.99(95% CI 106.34-133.14), and was lower among those aged ≥ 55 years, 52.52 (95% CI 45.38, 60.78). Single clients had a higher failure rate of 122.61 (95% CI 112.64, 133.46) than those who were married 78.48 (95% CI 72.49, 84.96).

There was no significant VF between clients receiving care from private facilities 94.87 (95% CI 79.02, 113.89) and those receiving services in public facilities 92.71 (95% CI 87.77, 97.92). In comparison, clients receiving care in health centers had the highest VF at 135.53 (95% CI 117.57, 156.24) compared to those attending clinics at 78.22 (73.11, 83.69) (Table 4).

Table 4: Virological Failure Rates/1000 Person-Years in HIV-Positive Adult Clients on Second-Line ART (2018-2020)

Variable	Person-years	Number Failed	Failure rate/1000 person years(95% CI)
Crude failure rate	**15100**	**1402**	**92.85 (88.11, 97.84)**
Age group (years)			
25 – 34	1001	101	100.86 (82.97, 122.58)
35 – 44	2555	304	118.99 (106.34, 133.14)
45 – 54	4086	282	69.02 (61.42, 77.56)
≥ 55	3428	180	52.52 (45.38, 60.78)
Sex			
Male	6278	592	94.29 (87.00, 102.20)
Female	8822	810	91.82 (85.71, 98.37)
Marital status			
Married	7773	610	78.48 (72.49, 84.96)
Single	4355	534	122.61 (112.64, 133.46)
Facility level			
Dispensary	313	39	124.53 (90.99, 170.44)
Health center	1402	190	135.53 (117.57, 156.24)
Hospital	2596	329	126.73 (113.75, 141.19)
Clinic	10751	841	78.22 (73.11, 83.69)
Facility Ownership			
Private	1212	115	94.87 (79.02, 113.89)
Public	13850	1284	92.71 (87.77, 97.92)

Rate of virological failure to second-line ART across regions of Tanzania

Geographically, Ruvuma and Mtwara regions had the highest rates of VF, 140-154 per 1000 person-years, followed by Pwani and Songwe regions (120 per 1000 person-years) while Kagera had the lowest rate (48-59 per 1000 person-years)

Virological Failure rates across Immunological, Virological, and Clinical Characteristics during First and Second-line Antiretroviral Therapy

During first-line ART, a higher rate of VF was observed among clients with an initial viral load count of ≥1000cp/mL 235.99 (95% CI 216.70, 257.01) VF than those with an initial viral load count < 1000/mL 62.75 (95% CI 57.23, 68.81). Clients with TB had a higher failure rate of 112.55 (95% CI 81.54, 155.33) than those without TB, 92.48 (95% CI 87.67, 97.54).

During the second line, the rate of VF was two times higher among those who used ATV/r 135.10 (95% CI 124.16, 147.02) than those on LPV/r 73.21 (95% CI 67.78, 78.98). Moreover, clients who were on ART for 13-35 months had a higher VF rate of 331.93(95% CI 22.48, 495.22) than other groups, with the lowest rate reported among those on ART for > 60 months was 89.01(95% CI 84.49, 94.15) (Table 5).

Table 5: Virological Failure rates according to Immunological, Virological, and Clinical Characteristics during First and Second-line Antiretroviral Therapy (n=1402)

Variable	Person years	Number Failed	Failure rate/1000 person-years (95% CI)
CD4 at first-line ART			
< 200 cells/mm^3	7626	599	78.55 (72.50, 85.10)
≥ 200 cells/mm^3	5598	577	103.08 (95.00, 111.84)
HVL at first-line ART			
< 1000 cp/ml	7203	452	62.75 (57.23, 68.81)
≥ 1000 cp/ml	2237	528	235.99 (216.70, 257.01)
WHO stages at first-line initiation			
Stage I	1471	136	92.45 (78.15, 109.37)
Stage II	3928	350	89.09 (80.23, 98.93)
Stage III	6789	694	102.23 (94.90, 110.13)
Stage IV	2727	207	75.92 (66.25, 87.00)
TB at first-line ART			
No	14609	1351	92.48 (87.67, 97.54)
Yes	329	37	112.55 (81.54, 155.33)
CD4 count at second-line			
<200 cells/mm^3	4702	413	87.84 (79.76, 96.73)
≥200 cells/mm^3	6575	353	53.69 (48.37, 59.59)
WHO stage at second-line ART			
Stage I	637	67	105.15 (82.76, 133.60)
Stage II	2293	184	80.25 (69.46, 92.73)
Stage III	7390	762	103.11 (96.04, 110.70)
Stage IV	4767	388	81.39 (73.68, 89.90)
Tb at second-line ART			
No	14956	1382	92.41 (87.66, 97.41)
Yes	144	20	139.02 (89.69, 215.49)

Virological failure rates classified by regimen use history in first and second-line Antiretroviral Therapy

During the first line ART, clients who were on TDF, an NRTI had higher failure rates at 135.39 (95% CI 118.74, 154.38) compared to those on AZT 104.04 (95% CI 94.09, 111.66) and ABC 105 at 123.24 (39.50, 280.41). In addition, those who used NNRTI had a two-fold higher failure rate at 100.56 (95% CI 94.47, 107.05) than those who used INSTI at 62.02 (95% CI 53.14, 72.38).

During the second line, the rate of VF was two times higher among those who used ATV/r 135.10 (95% CI 124.16, 147.02) than those on LPV/r 73.21 (95% CI 67.78, 78.98). Moreover, clients who were on ART for 13-35 months had a higher VF rate of 331.93(95% CI 22.48, 495.22) than other groups, and the lowest rate reported among those on ART for > 60 months was 89.01(95% CI 84.49, 94.15) (Table 6).

Table 6: Virological failure rates/1000 person-years by type of regimen during first and second-line ART (n=1402)

Variable	Person years	Number Failed	Failure rate/1000 person-years (95% CI)
NRTI backbone during first-line ART			
TDF	1647	223	135.39 (118.74, 154.38)
AZT	5774	595	103.04 (94.09, 111.66)
ABC	38	4	105.24 (39.50, 280.41)
d4t, ddi	7203	487	67.60 (61.86, 73.88)
NNRTIs/INSTIs at first line			
NNRTI	9785	984	100.56 (94.47, 107.05)
DTG	2596	161	62.02 (53.14, 72.38)
Other	2126	145	68.22 (57.97, 80.28)
ART Adherence			
Good (>95%)	14605	1,349	92.37 (87.57, 97.43)
Poor (<95%)	270	34	125.85 (89.93, 176.13)
Protease Inhibitors during second-line ART			
Lopinavir/Ritonavir (LPV/r)	9124	668	73.21 (67.78, 78.98)
Atazanavir/Ritonavir (ATV/r	3982	538	135.10 (124.16, 147.02)
Other	1391	73	52.47 (41.72, 66.00)
NRTI backbone during second-line ART			
Tenofovir (TDF)	6725	624	92.78 (85.78, 100.36)
Zidovudine (AZT)	937	118	125.94 (105.15, 150.84)
Abacavir (ABC)	5510	465	84.38 (77.05, 92.41)
ART Adherence			
Good (>95%)	14619	1,315	89.95 (85.22, 94.94)
Poor (<95%)	478	87	189.76 (147.32, 224.27)
Duration of ART (Months)			
≤12 months	1	2	1337.91 (334.61, 5349.56)
13–35months	72	24	331.93 (22.48, 495.22)
36–59 months	327	65	198.55 (155.70, 253.19)
≥60 months	14698	1,311	89.19 (84.49, 94.15)

Predictors of virological failure among adult HIV clients on second-line ART in Tanzania from 2018 to 2020.

On bivariate analysis, individuals aged 35-44 years had a 2.35-fold increased risk (95% CI 1.95, 2.82) of virologic failure, while clients receiving care from health centers had a 1.83-fold increase (95% CI 1.56, 2.14). Regarding the type of ART regimen, clients who were on TDF (NRTI) had a 2.25 times increase (95% CI 1.19, 2.65), and those on NNRTI during first-line ART had a 1.56-fold increase (95% CI 1.31, 1.86). Clients with poor adherence during second-line ART had a 2.13 times higher risk of failing (95% CI 1.71, 2.65). However, these associations did not remain significant after adjusting for confounders in multivariate analysis.

Upon adjusting for confounders, clients with increased risk of VF were those with; an initial viral load of ≥1000 copies/mL during first-line ART 4.65 (95% CI 3.57, 6.07), using lopinavir during second-line ART 4.20 (95% CI 3.12, 7.10), being on ART for 13-35 months 8.22 (95% CI 2.21, 30.61), having TB during first-line ART 2.21 (95% CI 1.05, 4.64), receiving care at the dispensary 2.48 (95% CI 1.12, 5.48), and having <200 cells/mm^3 CD4 count during second-line ART 1.89 (95% CI 1.46, 2.44). Paradoxically, individuals with a CD4 count of <200 cells/mm^3 during first-line ART had a reduced risk of VF 0.77 (95% CI 0.60, 0.99) (Table 7).

Table 7: Bivariate and multivariate analysis of predictors of virological failure among adult HIV clients on second-line ART in Tanzania from 2018 to 2020

Covariate	Proportion failed (%)	Bivariate analysis		Multivariate analysis	
		Crude hazard ratio (95% CI)	*p*-value	Adjusted hazard ratio (95% CI)	*p*-value
Age group (years)					
25-34	7.20	1.95 (1.53, 2.49)	<0.001*	1.55 (0.88, 73)	0.132
35-44	21.68	2.35 (1.95, 2.82)	<0.001*	1.50 (1.00, 2.24)	0.050
45-54	20.11	1.33 (1.11, 1.61)	0.003	0.92 (0.63, 1.32)	0.645
55>	12.84	1		1	
Sex					
Male	42.23	1		1	
Female	57.77	0.98 (0.88 , 1.09)	0.755	0.86 (0.66 , 1.13)	0.295
Marital status					
Married	43.51	1		1	
Single	38.09	1.57 (1.40, 1.77)	0.932	1.02 (0.76, 1.38)	0.295
Facility Ownership					
Private	8.20	1		1	
Public	91.58	0.98 (0.81, 1.19)	0.863	1.31 (0.83, 2.09)	0.879
Facility Level					
Dispensary	2.78	1.64 (1.19, 2.27)	0.002	2.48 (1.12, 5.48)	0.025*
Health center	13.55	1.83 (1.56, 2.14)	<0.001*	1.30 (0.79, 2.13)	0.299
Hospital	23.47	1.70 (1.49, 1.93)	<0.001*	1.22 (0.86, 1.70)	0.251
Clinic	59.99	1		1	
Initial HVL after first-line Initiation of ART					
<1000	76.35	1		1	
≥1000	6.00	4.29 (3.76, 4.89)	<0.001*	4.65 (3.57, 6.07)	<0.001*
NRTI backbone during first-line ART					
Tenofovir (TDF)	15.91	2.25 (1.91, 2.65)	<0.001*	1.76 (1.06, 2.90)	0.028

Covariate	Proportion failed (%)	Bivariate analysis		Multivariate analysis	
		Crude hazard ratio (95% CI)	*p*-value	Adjusted hazard ratio (95% CI)	*p*-value
Zidovudine (AZT)	42.44	1.5 (1.41, 1.79)	<0.001*	1.37 (0.97, 1.96)	0.078
Abacavir (ABC)	0.29	1.56 (0.58, 4.17)	0.377	6.8 (0.92, 50.66)	0.060
Others (d4t, ddi)	34.74	1		1	
NNRTIs/INSTIs during first-line ART					
EFV/NVP	70.19	1.56 (1.31, 1.86)	<0.001*	1.43 (0.83, 2.48)	0.203
DTG	11.48	0.93 (0.74, 1.17)	0.543	1.45 (0.82, 2.55)	0.199
Other	10.34	1		1	
PI during second line					
LPV/r	47.65	1.36 (1.06, 1.74)	<0.001*	4.20 (3.12, 7.10)	<0.001*
ATV/r	38.37	2.96 (2.31, 3.79)	<0.001*	1.07 (0.94, 2.35)	0.213
Other	5.21	1		1	
NRTI backbone during the second line ART					
Tenofovir (TDF)	44.51	1.14 (1.01, 1.30)	0.036	1.22 (0.91, 1.64)	0.186
Zidovudine (AZT)	8.42	1.56 (1.27, 1.92)	<0.001*	1.14 (0.67, 1.83)	0.670
Abacavir (ABC)	33.17	1		1	
CD4 count during first-line ART					
≥200 cells/mm^3	41.16	1		1	
<200 cells/mm^3	42.72	0.75 (0.67, 0.84)	<0.001*	0.77 (0.60, 0.99)	0.040*
CD4 count during second-line ART					
≥200 cells/mm^3	25.18	1		1	
<200 cells/mm^3	29.46	1.59 (1.38, 1.84)	<0.001*	1.89 (1.46, 2.44)	<0.001*
WHO stage during the first line ART					
Stage 1	9.70	1		1	
Stage 2	24.96	0.96 (0.79, 1.17)	0.711	1.44 (0.77, 2.69)	0.256
Stage 3	49.50	1.10 (0.91, 1.32)	0.312	1.47 (0.82, 2.63)	0.191

Covariate	Proportion failed (%)	Bivariate analysis		Multivariate analysis	
		Crude hazard ratio (95% CI)	*p*-value	Adjusted hazard ratio (95% CI)	*p*-value
Stage 4	14.76	0.81 (0.65, 1.00)	0.052	1.26 (0.68, 2.36)	0.460
WHO stage during the second line ART					
Stage 1	4.78	1		1	
Stage 2	13.12	0.75 (0.57, 0.99)	0.043	0.80 (0.34, 1.84)	0.601
Stage 3	54.35	0.97 (0.75, 1.23)	0.787	1.19 (0.56, 2.53)	0.648
Stage 4	27.67	0.76 (0.58, 0.98)	0.034	1.16 (0.55, 2.44)	0.698
TB during first-line ART					
No	96.36	1		1	
Yes	2.64	1.23 (0.88, 1.70)	0.221	2.21 (1.05, 4.64)	0.037*
TB during second-line ART					
No	98.57	1		1	
Yes	1.43	1.50 (0.97, 2.34)	0.069	0.88 (0.21, 3.79)	0.869
Adherence to first-line ART					
Good (≥95%)	96.22	1		1	
Poor (<95%)	2.43	1.37 (0.98, 1.93)	0.068	0.93 (0.42, 2.06)	0.855
Adherence to second-line ART					
Good (≥95%)	93.79	1		1	
Poor (<95%)	6.21	2.13 (1.71, 2.65)	<0.001*	1.31 (0.79, 2.18)	0.293
Total duration on ART					
≤12 months	0.14	41.39 (10.23, 167.36)	<0.001*		
13–35months	1.71	4.6 (3.07, 6.94)	<0.001*	8.22 (2.21, 30.61)	0.002*
36–59 months	4.64	2.53 (1.97, 3.26)	<0.001*	1.59 (0.72, 3.50)	0.248
≥60 months	93.51	1		1	

*p-value ≤ 0.05 statistically significant

CHAPTER FIVE

5.0 DISCUSSION

The study provides nationwide estimates of the prevalence, rate, and predictors of virological failure among clients on second-line antiretroviral therapy (ART) in Mainland Tanzania. In addition, the study also examined predictors of VF in the first-line ART that could have contributed to VF during the second-line ART.

Overall, the proportion of VF was found to be 29.72%, at a rate of 92.71 per 1000 person-years, with the highest rates being observed in Mtwara and Ruvuma regions, on the southern part of the country as elaborated in Fig. 3.

Several factors were found to be significantly associated with VF including, initial viral load count of ≥1000 copies/mL during first-line ART, using lopinavir as a protease inhibitor during second-line treatment, receiving care in dispensaries (which is the lowest level of caregiving facilities), being on ART for 13-35 months, TB infection during first-line ART, and having CD4 counts <200 cells/mm^3 during second-line ART. Interestingly, clients with CD4 counts <200 cells/mm^3 during first-line ART were found to have a reduced risk of failure.

Comparatively, the proportion of clients experiencing virological failure in this study (30%) over a two-year follow-up period is notably higher than previous findings due to variations in the follow-up periods. Earlier studies in Tanzania reported a virological failure proportion of 12.18% over six months (Gunda et al. 2019), while in Rwanda, virological failure was 12% for 26 months. Our findings are alarming when compared to those of studies conducted in Uganda showing a VF of 23% after five years of follow-up (Sam et al. 2021). The observed magnitude aligns with published data emanating from South Africa showing that 25% of clients receiving second-line ART experience treatment failure, citing poor adherence, delayed switching, and accumulation of PI-resistance mutations as the main determinants (Naidoo et al. 2022).

The rate of VF found in this study (92.71 per 1000 PY) is similar to a study conducted in Ethiopia that reported 98.6 per 1000 PY (Alene et al. 2019), but slightly higher rates of 129 per 1000 PY are reported in South Africa and 150 per 1000 person-years reported in the sub-Saharan Africa region (Collier et al. 2017; Edessa et al. 2019). On the other hand, significantly lower rates have been reported in Northern (61.7 per 1000 PY) and Northwest Ethiopia (72.3 per 1000 PY) (Tsegaye et al. 2016; Haftu et al. 2020). There are several possible explanations for variations seen between studies. We noted differences between studies in defining virological failure. In this study, VF was defined as two consecutive viral load results of ≥1000 copies/ml after ≥ six months on second-line ART (WHO 2021), while another study described it as a viral load of>1000 copies/mL on at least one occasion after ≥6 months, finding a VF rate of 129 per 1000 PY (Collier et al. 2017). Another study included both clinical, immunological, mortality, and loss of follow-up factors in defining treatment failure, and ended up with a rate of 61.7 per 1000 PY (Tsegaye et al. 2016). Other possible reasons include geographic differences i) in HIV subtypes (Nastri et al. 2023) and HIV-drug resistance (HIVDR) levels and patterns (Mazzuti et al. 2020), ii) the quality of care and community/social support, and iv) levels of adherence to ART (Fokam et al. 2020). Within Tanzania, the highest rate of VF were observed in Mtwara and Ruvuma, regions that have the highest prevalence of HIV in the country and the highest use of antiretroviral drugs (THIS 2022).

Regarding the treatment regimen, we observed a higher failure rate among clients prescribed LPV/r than those on ATV/r. This finding is similar to the findings of a study conducted in Ethiopia, where ATV/r showed a 13% lower risk of failure than LPV/r (Tigabu et al. 2020). ATV/r has been shown to lower the risk of mortality and the incidence of AIDS-defining illness and to have a more significant 12-month increase in CD4 cell count and less risk of virologic failure at 12 months than LPV/r (Cain 2015). In addition, ATV/r is a well-tolerated drug with a lower pill burden compared to other Protease inhibitors, such as LPV (Sam et al. 2021), and has better oral bioavailability compared with other protease inhibitors (Tigabu et al. 2020).

We observed that clients with a history of TB while on the first-line ART had a significantly higher rate of VF, supporting the findings of a South African study, that reported an eleven times higher rate of VF in clients with TB (Collier et al. 2017), and those of another study

conducted in Ethiopia that showed a 2.46 times higher rate of VF among clients with HIV-TB coinfection(Getaneh et al. 2022). This finding is expected since TB has been shown to enhance HIV viral replication and to be associated with poor treatment outcomes (Bell and Noursadeghi 2017; Getaneh et al. 2022). In addition, many clients with TB-HIV co-infection experience adverse side effects due to the high pill burden (Daftary et al. 2014).

In our study, we observed higher VF among clients receiving care at dispensary level 2.48 (1.12, 5.48) compared to those receiving care in health centers 1.30 (95% CI 0.79, 2.13) and hospitals 1.22 (95% CI 0.86, 1.70). This finding is consistent with those of a study conducted in Kenya that reported a high likelihood of failure 1.87 (95% CI 1.29, 2.72) among clients attending lower-level facilities (Masaba et al. 2023). Often, lower facilities are located in less privileged rural areas with relatively poor services such as counselling, community/social support, and quality of healthcare workers, which may impact treatment outcomes (Chakravarty et al. 2015; Diress et al. 2020; Nastri et al. 2023).

We discovered that clients with an initial viral load count of ≥1000 cp/mL during the first-line ART had a 4.30 (95% CI 3.43, 5.48) higher risk of failing. A study from Ethiopia reported similar findings, where clients with an initial viral load count of ≥5000 cp/mL had a lower probability of suppressing viral load, 0.44 (95% CI 0.28, 0.71) after enhanced adherence counselling (EAC) (Diress et al. 2020). The same findings were also reported in Asia, with a risk of 2.90 (95% CI 1.17-7.18), and in India with an odds ratio of 3.4 (Boettiger et al. 2015; Chakravarty et al. 2015). This collective evidence supports the theory that a high baseline viral load causes delayed or incomplete HIV suppression and a higher risk of viral rebound (Chen et al. 2020).

This study found a significantly greater risk of virological failure in clients who have been on ART for 13-35 months, representing an 8-fold increase compared to those on ART for more than 60 months (HR 8.22, 95% CI 2.21, 30.61). There are significant variations concerning the duration of ART and VF. A study conducted in central Ethiopia reported a 7-fold increase in the risk of virological failure (HR 6.93, 95% CI 2.62, 18.33) among clients on ART for 12-23 months compared to those on ART for more than 48 months (Endebu et al. 2018). Another study conducted in northeast Ethiopia (Diress et al. 2020) observed a high risk of failure among those on ART for 36-59 months 0.35 (95% CI 0.130, 0.9491). The

observed variations can be explained by differences in the distribution of clients among covariates.

We observed a high likelihood of treatment failure among clients with a CD4 count of less than 200 cells/mm^3 during the second-line ART, with a relative risk of 1.77 (95% CI 1.41, 2.22). This supports previous findings that clients with low CD4 T-cell counts experience slower viral clearance and have higher levels of virological failure (Crowell et al. 2021). Interestingly, clients with a CD4 count of less than 200 cells/mm^3 during the first-line of ART had a 30% reduction in the likelihood of treatment failure among the clients. These clients probably received intensive care and monitoring due to their medical history while on first-line ART which prompted healthcare workers to pay more attention to them during second-line ART.

Our findings have potential implications for the country. According to the study, 30% of clients receiving second-line ART in Tanzania require switching to the third-line ART regimens. With an estimated 24,000 clients currently on second-line ART (based on unpublished program data), 7,200 clients will need this change. The switch to third-line ART will require expensive phenotypic and genotypic HIVDR testing, expensive and rather toxic ARV drugs, and intensive clinical and laboratory monitoring (Gachogo et al. 2020). The estimated cost of HIV Drug Resistance (HIVDR) is approximately 272 USD per test (Gachogo et al. 2020), while the annual cost of third-line ART for the commonly used regimen such as ritonavir with darunavir, dolutegravir (DTG) and NRTI is close to 920 USD(Naidoo et al. 2022), bringing a total of 1192 USD for laboratory expenses and medication alone. For the estimated number of clients in Tanzania, this would cost the country 8.6 m USD which is equivalent to 0.94% of the entire budget allocated for health in the 2023/2024 budget per year. Additional costs would involve tracking the clients to ensure their clinical and virological outcomes, and regular monitoring and recording of severe adverse reactions.

The present study has several strengths. The study presents, for the first time, nationwide estimates of virological failure among clients on second-line ART, involving all facilities providing HIV care and treatment in Tanzania. Secondly, the data came from a diverse population of clients across various facilities at different levels of health service delivery.

Such information is important to the National AIDS, STIs and Hepatitis Control Programme (NASHCoP) and other stakeholders involved in the provision of HIV services in Tanzania to investigate at community, district, regional, and national levels i) the reasons for the magnitude of VF, ii) assess the health service quality at different levels, iii) find the reasons for inadequate individuals' ART adherence level, and iv) determine social and behavioral factors that hinder HIV viral load suppression.

However, we do acknowledge, as a limitation, that this is a retrospective study dependent on the completeness of the records. Hence, information bias might have occurred because of underreporting/missing data elements, including CD4 count and viral load, and under-reporting of clinical conditions. Furthermore, the information present in the NASHCoP database lacked information about HIV drug resistance, as this is not done routinely. This information might have furnished more information on VF among the clients.

CHAPTER SIX

6.0 CONCLUSION AND RECOMMENDATION

6.1 Conclusions

This study offers valuable insights into the frequency and causes of VF among clients receiving second-line ART in Tanzania. It reveals that approximately 30% of clients on second-line ART experience VF, which hinders progress toward achieving the UNAIDS third 95% target. Addressing the factors associated with VF identified in this study could help reduce the need to switch to more expensive and toxic third-line ART regimens. Tanzania should establish national guidelines for managing clients on third-line ART that consider funding, sustainability, and equitable access for those needing third ART regimens. Furthermore, the type(s) of the third-line ART regimen should be based on the phenotypic and genotypic HIVDR test results.

6.2 Recommendations

- This study found about 30% of adult clients on second-line ART failing virologically and therefore there is an urgent need to implement targeted interventions to improve virological suppression among clients on second-line ART
- Noticed regional variations, which signifies possibility of differences on quality of care among these clients. Call for standardization the quality of care including access to guideline at each level of facility, uniform access to medications, and continuous healthcare provider training. Targeted interventions are recommended to regions with higher rates i.e. Ruvuma and Mtwara
- Ministry of Health through the Quality Division should continue conducting routine onsite supportive supervision to all levels of facilities including dispensaries to ensure that personnel adherence to treatment guides and standardized quality of care is provided to clients on second line ART.
- For those individuals with first viral load count of ≥1000cp/ml during first line ART as well as CD4 of <200cells/mm^3 at switch to second line ART. Close follow up and monitoring is needed for improved outcome.

- Clients who are prescribed with lopinavir as protease inhibitor during second line ART, should be monitored for their response to treatment. This intensified a need to perform drug resistance testing to clients failing on first line before switching to second line. Drug resistance will help in identifying the resistance strain as well will guide on proper choice of regimen for better patient outcome
- For those clients on ART for more than one year, monitoring adherence is recommended. Longer time on ART was associated with treatment “tiredness” but as well prolonged asymptomatic condition which lead to questioning the necessity of continuing with strict adherence, hence treatment failure(59).
- The high rates of treatment failure among HIV-positive patients on second-line ART necessitate enhanced efforts to monitor and evaluate existing interventions to improve patient outcomes. A prospective study should be conducted to capture all relevant variables in real-time, along with a survey assessing the quality of care services across the country

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APPENDICES

Appendix I: Data collection tool

For HIV infected clients on second line 2018-2020(Retrospective data collection)

Data extraction sheet
Patient ID
Age
Sex
Facility level
Region
Date of enrollment to ART
During First line
Regimen used
Initial HVL Results (6 months after starting on ART)
Initial CD4 count
WHO stage at initiation of ART
TB diagnosis
During second line
HVL Results
CD4 count at switch
WHO stage at switch
TB diagnosis
Adherence level
Length of time on ART

Appendix II: Approval for ethical clearance

UNITED REPUBLIC OF TANZANIA

MINISTRY OF EDUCATION, SCIENCE AND TECHNOLOGY

MUHIMBILI UNIVERSITY OF HEALTH AND ALLIED SCIENCES

OFFICE OF THE DIRECTOR – RESEARCH, PUBLICATIONS AND INNOVATION

In reply quote;
Ref. No.DA.282/298/01.C/1697

Date: 29/05/2023

MUHAS-REC-05-2023-1697
Ester Timothy Mwavika
School of Public Health and Social Sciences
MUHAS.

RE: APPROVAL FOR ETHICAL CLEARANCE FOR A STUDY TITLED: "VIROLOGICAL FAILURE AND ASSOCIATED FACTORS AMONG ADULT HIV CLIENTS ON SECOND LINE ANTIRETROVIRAL THERAPY IN TANZANIA"

Reference is made to the above heading.

I am pleased to inform you that the Chairman has on behalf of the University Senate approved ethical clearance of the above-mentioned study, on recommendations of the Senate Research and Publications Committee meeting accordance with MUHAS research policy and Tanzania regulations governing human and animal subjects research.

APPROVAL DATE: 29/05/2023
EXPIRATION DATE OF APPROVAL: 29/05/2024

STUDY DESCRIPTION:
Purpose:
The purpose of this cohort study is to determine the extent of Virological failure and its associated factors among adult clients on second line ART in Tanzania.

The approved protocol and procedures for this study is attached and stamped with this letter, and can be found in the link provided:
https://irb.muhas.ac.tz/storage/Certificates/Certificate%20-%201098.pdf and in the MUHAS archives.

The PI is required to:

1. Submit bi-annual progress reports and final report upon completion of the study.
2. Report to the IRB any unanticipated problem involving risks to subjects or others including adverse events where applicable.
3. Apply for renewal of approval of ethical clearance one (1) month prior its expiration if the study is not completed at the end of this ethical approval. You may not continue with any research activity beyond the expiration date without the approval of the IRB. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.
4. Obtain IRB amendment (s) approval for any changes to any aspect of this study before they can be implemented.
5. Data security is ultimately the responsibility of the investigator.
6. Apply for and obtain data transfer agreement (DTA) from NIMR if data will be transferred to a foreign country.
7. Apply for and obtain material transfer agreement (MTA) from NIMR, if research materials (samples) will be shipped to a foreign country,
8. Any researcher, who contravenes or fail to comply with these conditions, shall be guilty of an offence and shall be liable on conviction to a fine as per NIMR Act No. 23 of 1979, PART III section 10 (2)
9. The PI is required to ensure that the findings of the study are disseminated to relevant stake holders.
10. PI is required to be versed with necessary laws and regulatory policies that govern research in Tanzania. Some guidance is available on our website https://drp.muhas.ac.tz/

Dr. Nahya Salim Masoud
Chairman, MUHAS Research and Ethics Committee

Muhimbili University of Health and Allied Sciences
DIRECTOR
Research & Publications
Box 65001

Appendix III: Permission to collect data at National AIDS

THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

Telegrams: "AFYA", DODOMA
Telephone: +255 026 2323267
Email:ps@afya.go.tz
(All letters should be addressed to The Permanent Secretary)

Government City-Mtumba,
Afya Road,
P.O.BOX 743,
40478 DODOMA.

Ref. No.GA.134/209/01D/038 **5th June, 2023**

Vice Councillor,
Muhimbili University of Health and Allied Science (MUHAS),
P.O Box 65001,
DAR ES SALAAM.

RE: PERMISSION TO USE DATA FROM NATIONAL AIDS CONTROL PROGRAM

Reference is made to the letter with HD/MUH/T.650/2021 dated 29th May, 2023.

2. The Minister of Health is grateful for the efforts made by your organization to improve quality of health services delivery in Tanzania.

3. The Ministry of Health has accepted the request to use the data from National AIDS Control Program for the study titled **"Rate and Predictors of Virological failure among adult's clients on second line ART in Tanzania from 2018 to 2020"** as requested.

4. The Ministry will require to receive a copy of final report soon after completion of the Study.

5. Thank you for your continued collaboration. For any clarification please don't hesitate to communicate with Mr. Veryeh Sambu, phone number +255 743 517 460, and email: veryeh77@hotmail.com.

Dr. Werner Maokola
For. PERMANENT SECRETARY

C.C: Permanent Secretary,
Ministry of Health
DODOMA — For Information