ISSN: 2577 - 8005

Case Report

Medical & Clinical Research

Poor Adherence and Limited Treatment Support are Risk Factors for Second Line Treatment Failure among HIV Children Under 15 Years, 2022: A Case Control Study

Kudzai Fortunate Vongai Chokuona[1,2*], Munyaradzi Mukuzunga[2], Gerald Shambira[1], Tsitsi Patience Juru[1], Addmore Chadambuka[1], Notion Tafara Gombe[3] and Mufuta Tshimanga[1]

[1]*Department of Global Public Health and Family Medicine, Faculty of Medicine and Health Sciences, University of Zimbabwe, Harare, Zimbabwe.*

[2]*Manicaland Provincial Medical Directorate, Mutare, Zimbabwe*

[3]*African Field Epidemiology Network, Harare, Zimbabwe*

***Corresponding Author**

Kudzai Fortunate Vongai Chokuona, Department of Global Public Health and Family Medicine, Faculty of Medicine and Health Sciences, University of Zimbabwe, Harare, Zimbabwe.

Submitted: 2024, Aug 06; **Accepted**: 2024, Aug 14; **Published**: 2024, Aug 29

Citation: Chokuona, K. F. V., Mukuzunga, M., Shambira, G., Juru, T. P., & Chadambuka, A., et al. (2024). Poor Adherence and Limited Treatment Support are Risk Factors for Second Line Treatment Failure among HIV Children Under 15 Years, 2022: A Case Control Study. *Med Clin Res, 9*(8), 1-12.

Abstract

Title: *Poor adherence and limited treatment support are risk factors associated with second line treatment failure among children under 15 years at Victoria Chitepo provincial hospital, 2022: a case control study.*

Background: *New HIV resistance mutations have been emerging and frequently changing. HIV positive people switching to third line have been increasing in Manicaland Province. Third line anti-retroviral therapy (ART) combinations are not always available. We sort to determine the factors associated with second line treatment failure among HIV positive patients.*

Methods: *We conducted a 1:1 unmatched case-control study among 107 case-control pairs. A case was any HIV positive individual with treatment failure confirmed by 2 viral load of ≥1000 copies/ml while a control was any HIV positive individual with a viral load of <1000/ml copies; on second line therapy at Victoria Chitepo Provincial Hospital (VCPH), in 2022. Systematic random sampling was used to select cases and controls from the line-list. Administered questionnaires were used to ascertain risk factors to second line treatment failure. Patient booklets were reviewed for demographic and clinical characteristics. Frequencies, means, medians and odds ratios were generated. Multivariate analysis and stratified analysis was performed to identify independent risk factors. Permission to proceed was sought from relevant authorities and all ethical considerations were observed.*

Results: *Defaulting treatment (aOR=2.42, 95% CI: 1.03-5.93), missing a viral load test (aOR=5.52, 95% CI: 2.30-13.26) and being under 15 years of age (aOR=6.18, 95% CI: 1.46-26.20) were independent risk factors associated with second line treatment failure. Having a treatment support was an independent protective factor (aOR=0.30, 95% CI: 0.10-0.86).*

Conclusion: *Poor adherence is the key drive to second line treatment failure. Good adherence is critical in children under 15 years. Treatment support promotes viral load suppression.*

Keywords: Virologic failure, Second line antiretroviral therapy, Adherence, Children, Manicaland

Abbreviations

AHD: Advanced HIV Disease; AIDS: Acquired Immunodeficiency Syndrome; ATB: AIDS and TB; ART: Antiretroviral Therapy; CD4: Cluster of Differentiation; DHIS: District Health Information System; HIV: Human Immunodeficiency Virus; HSO: Health Studies Office; INH: Isonicotinic Acid Hydrazide; INSTI: Integrase Strand Transfer Inhibitor; JREC: Joint Research Ethics Committee; NRTI: Nucleoside Reverse Transcriptase Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; PI: Protease Inhibitor; PLHIV: People Living with HIV; TB: Tuberculosis; UNAIDS: United Nations Acquired Immunodeficient Syndrome Program; USD: United States Dollars; VCPH: Victoria Chitepo Provincial Hospital; VL: Viral Load; WHO: World Health

Organisation; ZWD: Zimbabwean Dollar.

1. Introduction

The purpose of Antiretroviral Therapy (ART) is to inhibit Human Immunovirus (HIV) replication, maintaining undetectable Viral Load (VL) levels. The immune system, typically Cluster of Differentiation (CD4) T cell count, improves with suppressed VL by reducing the disease progression to Acquired Immunodeficiency Syndrome (AIDS) [1].

Antiretroviral treatment failure occurs when the regimen is not able for a variety of reasons to control the viral replication [2]. World Health Organization (WHO) recommends scaling up of HIV treatment, intensive monitoring and improvement on quality of ART delivery to minimize the spread for HIV drug resistance [3]. The antiretroviral therapy use has increased rapidly in the past decade [4]. HIV drug resistance has also increased with the increased use of HIV medicines [4]. HIV can change its genetic structure (mutation) affecting the ability of ART in blocking viral replication. This results in emergence of drug resistant HIV affecting the global target of ending AIDS pandemic [5].

In all regions, antimicrobial resistance has been identified and it is killing at least a million people each year globally making it an urgent public health threat [6]. The middle and low income countries are affected disproportionately by antimicrobial resistance partly due to the high burden of communicable diseases [7]. In high-income countries, the transmitted drug resistance prevalence ranges from 9-14% [8]. By the end of 2015, an estimate of two million HIV infected people globally were initiated on second line treatment [9]. There has been high levels of HIV drug resistance affecting nearly half of the newly diagnosed infants of less than 18 months of age in recent studies in the middle and low income countries [4,10]. According to WHO; Zimbabwe, Uganda and Namibia reached the critical level of >10% of nucleoside reverse transcriptase inhibitor (NRTI) related drug resistance in 2017 [11]. In 2020, Zimbabwe met the second and third 90-90-90 targets and is well positioned to achieve United National Acquired Immunodeficiency Syndrome (UNAIDS) goal of ending AIDS by 2030 [12].

The morbidity and mortality related to HIV and the HIV incidence has been reduced by ART drastically making the chronic HIV infection manageable and increasing the HIV positive people's life expectancy closer to that of people living without HIV [13, 14]. To maximize duration on first line ART, it is important to assess VL suppression with routine VL while on first line ART [15]. Patients who fail second line therapy should receive intensified adherence counselling and constant support [8]. Patients with high VL while on second line treatment should undergo resistance testing and the choice of the third line combination should be made by an HIV expert [8].

There has been a notable increase of non-nucleoside reverse transcriptase (NNRTI) resistance across all WHO regions from recent studies, with prevalence close to or above 10% in Southern Africa, Eastern Africa and Latin America [5]. It is important to understand the VL levels and HIV drug resistance levels to optimize treatment outcomes [16].. Early treatment initiation is recommended in acute or recently infected individuals, in HIV positive pregnant women and in people who are willing to be initiated on ART soon after HIV diagnosis. The regimen can then be modified after receipt of results [17].

A preliminary assessment of the DHIS2: ATB HIV D3 for Manicaland province shows an increasing proportion of HIV positive individuals who failed second line treatment; 4/10000, 22/10000 and 32/10000 people per year on second line ART in 2020, 2021 and 2022 respectively. Patients who fail on third-line therapy which is the final option in management of people living with HIV (PLHIV) are at high risk of succumbing to HIV which can result in death and have a high risk of transmitting the resistant variant. HIV treatment failure precipitates the high HIV related morbidity and mortality. Switching regimens to third line ART combinations might not be sustainable in our resource limited country owing to high costs and unavailability of these medicines. The minimum cost of third line combination consisting of Darunavir/ritonavir, Dolutegravir and Raltegravir costs $70.00USD, for an adult one month course, against an average income of 218000 ZWD ($43.60USD at prevailing interbank rate) [18]. Virologic failure may indicate poor care and management of the HIV positive patients and findings from the study can assist in identifying gaps and finding ways of improving their care. Multi drug resistant HIV is difficult to treat, expensive to genotype and the medication is expensive. Investigation of the factors associated with second line ART failure can assist in the management of HIV positive patients to prevent development of resistance.

2. Research Question

What are factors associated with second-line therapy failure in HIV positive patients presenting at VCPH?

3. Broad Objective

To determine the factors associated with second-line therapy failure in HIV positive patients presenting at VCPH in 2022.

4. Specific Objectives

- To determine the socio-demographic characteristics associated with second line therapy failure in HIV positive patients presenting at VCPH in 2022.
- To determine the behavioral factors associated with second line therapy failure in HIV positive patients presenting at VCPH in 2022.
- To determine the clinical factors associated with second-line therapy failure to HIV at VCPH in 2022.
- To determine the biological factors associated with second-line therapy failure to HIV at VCPH in 2022.

5. Study Hypothesis

5.1 Null Hypothesis

H0: There is no association between poor adherence and second-line therapy treatment failure to HIV.

5.2 Alternative Hypothesis

H1: There is an association between poor adherence and second-

line therapy treatment failure to HIV.

6. Materials and Methods

6.1 Study Design

An unmatched case control study was conducted where: a case was any HIV positive individual on second-line therapy; who had ART failure confirmed by repeated viral load tests of ≥1000 copies/ml as defined in Table 1. A control was any HIV positive individual on second-line therapy; who had a viral load test of <1000/ml copies; at VCPH in 2022.

Table 1: Second line treatment failure confirmed by two viral load tests by categories, 2022 guidelines

Category	First VL	Second VL
Pregnant women already on ART	>1000 copies/ml VL result at first ANC visit	>1000 copies/ml of repeated VL test after a month from the first ANC visit
Breastfeeding mothers regardless of when ART was started	>1000 copies/ml VL result after 3 months of delivery (with adherence counselling)	>1000 copies/ml of a repeated VL test after a month from the adherence counselling session
Routine viral load monitoring for treatment failure	>1000 copies/ml VL result (followed by three 4 week intervals enhanced adherence counseling)	>1000 copies/ml of repeated VL test after 3 months of adherence counseling

6.2 Study Setting

The study was conducted at Victoria Chitepo Provincial Hospital (VCPH), a referral facility for Manicaland Province. VCPH is situated in Mutare City 3.4km north of Mutare town along the Mutare-Harare highway. Mutare is the third biggest city in Zimbabwe (after Harare and Bulawayo). The province has a population in excess of two million people according to the census, 2022. In 2022, 127038 people were currently on first line ART, 5500 were on second line ART and 217 were on third line ART, in Manicaland Province (DHIS2).

6.3 Study Population

The study was done among HIV positive people on second-line ART who presented at VCPH in 2022.

6.4 Inclusion Criteria

The study included HIV positive individuals who provided informed consent, and who had been on second line antiretroviral therapy for at least 6 months and were still on ART on enrolment, regardless of the site where therapy was initiated.

6.5 Exclusion Criteria

The study excluded HIV positive individuals who did not consent and patients with unknown second line start date.

6.6 Sampling

6.6.1 Sample Size Calculation

A minimum sample size of 107 cases and 107 controls was calculated using Stat Cal function in Epi Info 7, at 95% confidence interval using 80% power as presented in **Table 2.**

Table 2: Sensitivity Analysis-Sample Size Calculation.

Variable	Study by	Odds ratio (CI)	Minimum sample size
Non-disclosure of HIV status	Sithole et al	5.88(2.94-11.11)	31 cases and 31 controls
CD4 <100 cells/mm^^{3}	Jaleta et al	0.20(0.10-0.41)	107 cases and 107 controls
History of TB treatment	Musana et al	5.65(1.76-18.09)	86 cases and 86 controls

6.6.2 Sampling Procedure

Systematic random sampling of 107 cases was done on the 217 patients who failed second line ART, where every 2nd unit from the line list was picked and enrolled into the study. The first case was chosen by the toss of a coin to consider picking either an odd number or even number. Systematic random sampling of 107 controls was also done on the 5500 patients on second line ART, where every 50th unit on the line list of patients was enrolled into the study. If the selected case or control failed to be enrolled, the next number was picked without distorting the sampling scheme. Purposive sampling of key informants (nurses and doctors who work in the Opportunistic Infection department) was done.

6.6.3 Data Collection

A pre-tested interviewer administered questionnaire was used for data collection. The questionnaires were used to collect data from the HIV positive patients on second line ART and from the healthcare workers. Verbally, the questionnaire was used to collect information assessing the factors associated with second line ART failure which include the demographic characteristics, type of regimen taken, number of years on ART, ART treatment history, TB treatment history and adherence factors. Adherence was measured using the Morisky 4 mark scale and objective assessment of counting the pills of each patient against the documented pills in the patient book was done. Review of patient records for the WHO stage, CD4 cell count, viral load results, appointment visits and type of regimens taken was done. Opportunistic Infection department registers were reviewed

for demographic characteristics of patients and patient number of years on ART. Patient booklets and pharmacy records were reviewed to check for any missed appointments and a pill identification test was done where each patient identified the pills they were taking.

6.64 Data Capture and Analysis

Data was captured using Epi Info 7 software. Incomplete and missing variables were checked by running frequencies for all variables thereby cleaning the data. Data entry mistakes were corrected using the questionnaires. Univariate analysis was performed through the calculation of proportions, means and frequencies. Bivariate analysis was performed using the same software, measuring against the outcome of interest: second line treatment failure. Odds ratios with 95% confidence intervals were generated and recorded from the bivariate analysis. Multivariate analysis was performed to identify independent risk factors and stratified analysis was done to control for confounding. All the variables with a p-value ≤ 0.25 were added in the logistic regression model and all the variables with a p-value <0.05 were regarded statistically significant.

6.7 Ethical Considerations

Permission to carry out the study was sought from the Manicaland Provincial Medical Directorate, Medical Superintendent and Health Studies Office (HSO). Ethical approval was sought from the Joint Research Ethics Committee (JREC); approval number JREC/280/2023. Individuals were treated as autonomous agents. Confidentiality of participants was ensured and informed written consent was obtained from all participants. Participants signed consent forms as part of enrolment. Records of data collected are secured under lock and key. The researcher will share the data with the field and academic supervisors only.

7. Results

A total of 107 cases and 107 controls were recruited into the study. The demographic characteristics of the respondents are shown in **Table 3.**

7.1 Demographic Characteristics of Respondents

Table 3: Socio-demographic characteristics of study participants presenting at VCPH, 2022.

Variable	Cases n=107 (%)	Controls n=107 (%)	p value
Sex			
Female	46 (43.0)	65 (60.8)	
Male	61 (57.0)	42 (39.2)	0.009
Age			
≤15 years	13 (12.1)	4 (3.7)	
16-24 years	43 (40.2)	15 (14.0)	
30-45 years	23 (21.5)	47 (43.9)	<0.001
>45 years	28 (26.2)	41 (38.3)	
Median age (Q1=;Q3=)	22 (Q_1=17; Q_3=50)	44 (Q_1=28; Q_3=53)	
Marital status			
Single	57 (53.3)	31 (29.0)	
Married	33 (30.8)	48 (44.8)	0.004
Divorced	10 (9.4)	14 (13.1)	
Widowed	7 (6.5)	14 (13.1)	
Level of education			
Primary	25 (23.4)	13 (12.2)	
Secondary	71 (66.4)	72 (67.2)	
Never attended school	5 (4.6)	3 (2.8)	0.010
Tertiary	6 (5.6)	19 (17.8)	
Employment status			
Formal	22 (20.4)	49 (45.8)	
Informal	21 (19.6)	17 (15.9)	<0.001
Unemployed	64 (60.0)	41 (38.3)	
Residence			
Rural	27 (25.2)	17 (15.9)	0.092
Urban	80 (74.8)	90 (84.1)	

The cases and controls were comparable on the residential status. There were statistical significant differences with regards to gender, age, level of education, marital status and employment status as presented in Table 3. This means that these factors were to undergo bivariate and multivariate analysis to check if they are significant factors associated with second line ART failure.

Bivariate and multivariate analysis was performed to investigate the factors associated with second line treatment failure.

7.2 Factors Associated with Second-Line ART Failure Among HIV Positive Patients Presenting at VCPH in 2022

Table 4: Socio-demographic factors associated with second-line ART failure among HIV positive patients presenting at VCPH in 2022 (bivariate and multivariate analysis).

Variables	Case n=107 (%)	Control n=107 (%)	COR(CI)	AOR (CI)
Age in years				
≤15	13 (12.1)	4 (3.7)	3.81 (1.22-11.88)	**6.18 (1.46-26.20)**
16-24	43 (40.2)	15 (14.0)	4.20 (1.96-8.97)	2.81 (0.88-8.97)
25-49	23 (21.5)	47 (43.9)	0.72 (0.36-1.47)	0.53 (0.18-1.53)
>49	28 (26.2)	41 (38.3)	Ref	
Sex				
Male	61 (57.0)	42 (39.2)	2.05 (1.19-3.54)	1.85 (1.00-3.44)
Female	46 (43.0)	65 (60.8)		
Marital status				
Single	57 (53.3)	31 (29.1)	2.67 (1.43-4.98)	0.30 (0.06-1.59)
Widowed	7 (6.5)	14 (13.0)	0.73 (0.27-2.00)	0.61 (0.13-3.01)
Divorced	10 (9.4)	14 (13.0)	1.04 (0.41-2.62)	0.62 (0.14-2.83)
Married	33 (30.8)	48 (44.9)	Ref	
Level of education				
Primary	25 (23.4)	13 (12.2)	5.77 (1.84-18.06)	4.05 (0.78-21.14)
Secondary	71 (66.4)	72 (67.2)	2.92 (1.10-7.77)	1.57 (0.40-6.14)
None	5 (4.6)	3 (2.8)	5.00 (0.91-27.5)	1.75 (0.13-23.45)
Tertiary	6 (5.6)	19 (17.8)	Ref	
Employment status				
Informal	21 (19.6)	17 (15.9)	2.75 (1.22-6.20)	1.16 (0.33-4.03)
Unemployed	64 (59.8)	41 (38.3)	3.48 (1.84-6.58)	1.13 (0.39-3.25)
Formal	22 (20.6)	49 (45.8)	Ref	

In bivariate analysis, being under 15 years, being between 16-24 years, being a male, being single, lower levels of education and unemployment were risk factors associated with second –line treatment failure. However, being under 15 years of age was the only independent risk factor associated second-line ART failure (aOR=6.18, 95% CI: 1.46-26.20).

Table 5: Biological factors associated with second-line ART failure among HIV positive patients presenting at VCPH in 2022 (bivariate and multivariate analysis).

Variables	Case n=107 (%)	Control n=107 (%)	COR(CI)	AOR (CI)
Missed viral load test				
Yes	61 (57.0)	17 (15.9)	7.02(3.69-13.37)	**5.52 (2.30-13.26)**
No	46 (43.0)	90 (84.1)		
History of TB treatment				
Yes	19 (17.8)	8 (7.5)	2.67 (1.11-6.41)	10.91 (0.98-60.06)
No	88 (82.2)	99 (92.5)		

History of an opportunistic infection Yes No	 8 (7.5) 99 (92.5)	 7 (6.5) 100 (93.5)	 1.15 (0.40-3.30)	 0.47 (0.11-2.08)
CD4 cell count at switch (cells/mm^3) CD4>200 CD4≤200	 71 (66.4) 36 (33.6)	 89 (83.2) 18 (16.8)	 0.40 (0.21-0.76)	 **0.21 (0.08-0.55)**

Missing a viral load test was an independent risk factor associated with second-line ART failure while having a CD4 cell count >200 cells/mm^3 was an independent protective factor associated with second line treatment failure.

Table 6: Clinical factors associated with second-line ART failure among HIV positive patients presenting at VCPH in 2022 (bivariate and multivariate analysis).

Variables	Case n=107 (%)	Control n=107 (%)	COR(CI)	AOR (CI)
Disclosure of previous ART history Yes No	 93 (86.9) 14 (13.1)	 106 (99.1) 1 (0.9)	 0.06 (0.01-0.49)	 0.07 (0.01-1.12)
Period of years on 2nd line ART <2 years ≥2 years	 7 (6.5) 100 (93.5)	 11 (10.3) 96 (89.7)	 0.61 (0.23-1.64)	 0.32 (0.08-1.23)
WHO stage at ART initiation WHO stage II WHO III WHO stage IV WHO I	 33 (30.8) 56 (52.3) 8 (7.5) 10 (9.4)	 61 (57.1) 28 (26.2) 1 (0.9) 17 (15.6)	 0.92 (0.38-2.24) 3.46 (1.40-8.53) 11.88 (1.27-111.09) Ref	 0.75 (0.22-2.50) 1.53 (0.43-5.39) 2.65 (0.13-54.31)

There was no statistical significant difference between being on second line ART for less than 2 years and for being on second-line ART for more than 2 years.

Table 7: Behavioural factors associated with second-line ART failure among HIV positive patients presenting at VCPH in 2022 (bivariate and multivariate analysis).

Variables	Case n=107 (%)	Control n=107 (%)	COR(CI)	AOR (CI)
Defaulting treatment Yes No	 71 (66.4) 36 (33.6)	 30 (28.0) 77 (72.0)	 4.83 (2.71-8.62)	 **2.47 (1.03-5.93)**
Missing appointments Yes No	 41 (38.3) 66 (61.7)	 10 (9.3) 97 (90.7)	 6.03 (2.82-12.82)	 **3.22 (1.16-8.92)**

Adherence Good Poor	 81 (75.7) 26 (24.3)	 103 (96.3) 4 (3.7)	 0.23 (0.13-0.40)	 0.01 (0.01-1.00)
Treatment support Yes No	 75 (70.1) 32 (29.9)	 95 (88.8) 12 (11.2)	 0.30 (0.14-0.61)	 0.30 (0.10-0.86)
Correct and consistent condom use Yes No	 40 (78.4) 11 (21.6)	 78 (91.8) 7 (8.2)	 0.33 (0.12-0.91)	 0.72 (0.01-6.30)
Alcohol intake Yes No	 16 (15.0) 91 (85.0)	 9 (8.4) 98 (91.6)	 1.91 (0.81-4.55)	 1.76 (0.53-5.90)
Smoking Yes No	 4 (3.7) 103 (96.3)	 1 (0.9) 106 (99.1)	 4.12 (0.45-37.45)	 2.41 (0.18-32.70)
Taking herbs or alternative medication Yes No	 7 (6.5) 100 (93.4)	 1 (0.93) 106 (99.1)	 3.68 (0.75-18.11)	 3.27 (0.55-19.49)

On the behavioral factors; defaulting treatment and missing appointments were independent risk factors associated with second-line ART failure.

Table 8: Antiretroviral regimen related factors associated with second-line ART failure among HIV positive patients presenting at VCPH in 2022 (bivariate and multivariate analysis).

Variables	**Case n=107 (%)**	**Control n=107 (%)**	**COR(CI)**	**AOR (CI)**
Regimen type PI based Efavirenz based DTG based Nevirapine based	 49 (45.8) 5 (4.7) 46 (43.0) 7 (6.5)	 55 (51.4) 8 (7.5) 43 (40.2) 1 (0.9)	 0.13 (0.02-1.29) 0.09 (0.01-1.00) 0.15 (0.02-1.29) Ref	 0.32 (0.02-6.48) 0.25 (0.01-8.34) 0.41 (0.02-8.01) Ref
Switching regimens on first line ART No change ≥1 change	 32 (29.9) 75 (70.1)	 75 (70.1) 32 (29.9)	 0.18 (0.10-0.33)	 **0.15 (0.06-0.34)**

The antiretroviral regimen related independent protective factor associated with second line ART failure was not switching regimens on first line ART ($p<0.05$).

7.3 Perceived Institutional Factors Associated with Second Line Treatment Failure

Delay in viral load monitoring and limited stock of some of the second line treatment regimens were among the perceived reasons associated with second line treatment failure. Summary of the institutional factors associated with second line treatment failure is presented in **Table 9.**

Table 9: Perceived institutional factors associated with second line treatment failure, at VCPH, 2022.

Variable	Description
Availability of ART drugs	Second line treatment sometimes in short supply
Availability of ART treatment guidelines	Available
Availability of Job aids /SOPs on HIV management	Available
Interventions in place to minimise second line treatment failure	• performed adherence counselling sessions on patients with high VL • followed up defaulters • monitored high viral load results
Availability of treatment, care and support programs	Available
Training on VL results interpretation	Done on the opportunistic infection department nurses
Availability of VL testing	Delay in receiving VL results

A total of 5 key informants were interviewed who included one doctor, 2 nurses, one counsellor and one pharmacist. The opportunistic infection (OI) department had treatment guidelines and standard operating procedures for HIV management. The OI staff were trained on interpretation of high viral loads and on viral load monitoring, patient enhanced adherence counselling and following up on defaulters. However, most of the time the viral load results were received late for review of patients from the laboratory. The pharmacy department reported that the second line antiretroviral drugs were sometimes in short supply increasing the number of patient visits.

7.4 Perceived Barriers to Second Line Treatment Uptake

The participants were asked some of the barriers they were facing in taking second line treatment and the frequencies of their responses are summarized in **Figure 2.**

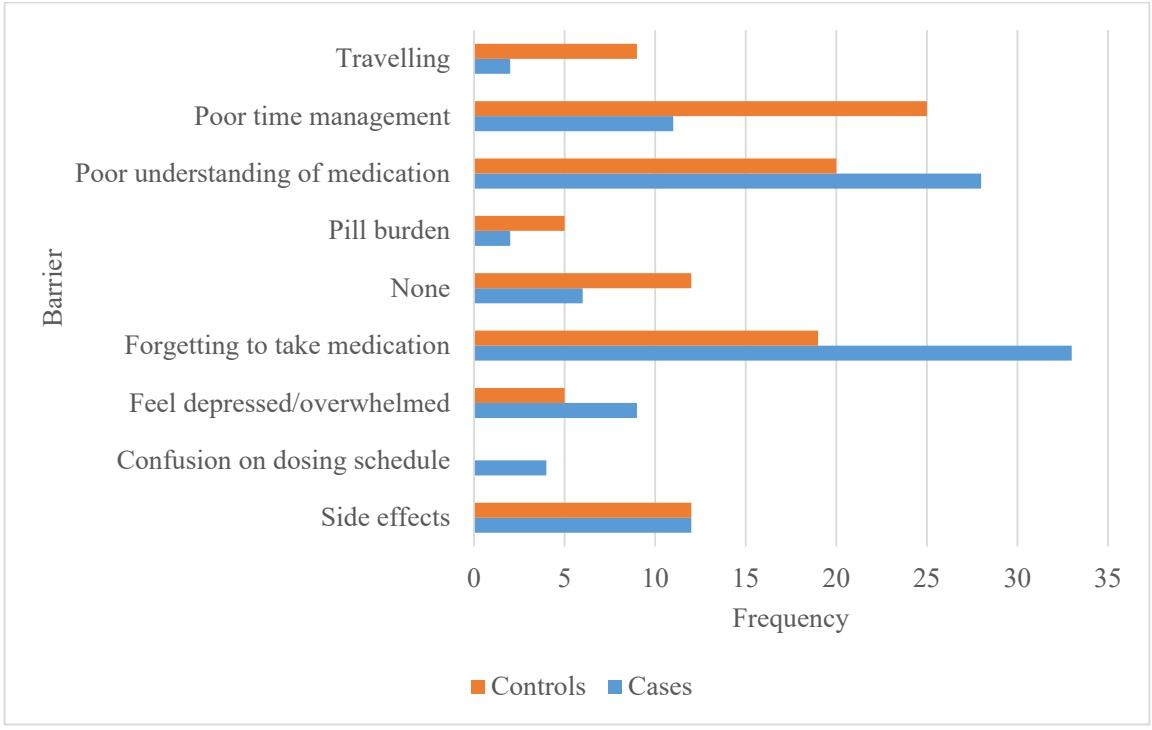

Figure 2: Perceived barriers to second line treatment uptake.

A total of 33 (30.8%) cases forgot taking their medicines and 28 (26.2%) of them had poor understanding of the ART medication. Majority of the controls 25 (23.4%) had poor time management due to busy schedules.

7.5 Perceived Reasons for First Line Treatment Failure

The respondents were asked the cause of first line treatment failure and their responses are summarized in **Figure 3.**

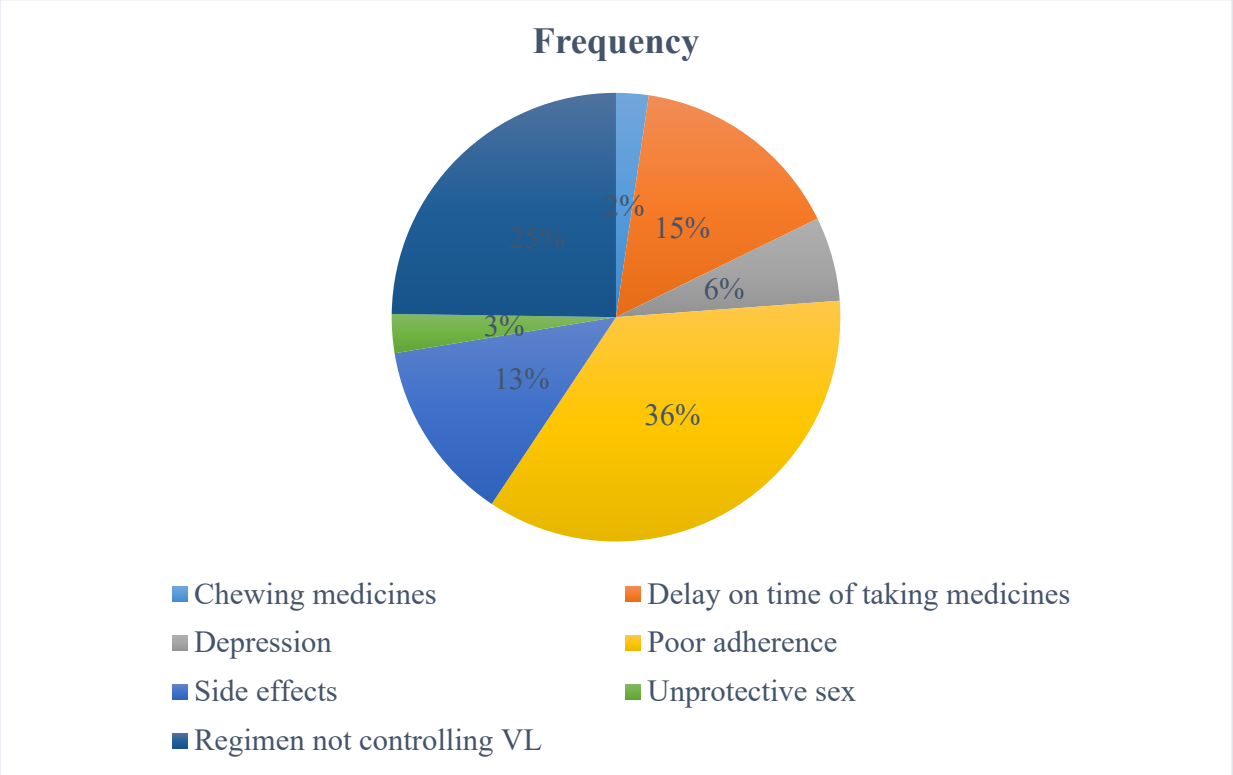

Figure 3: Perceived reasons for first line treatment failure.

Participants predominantly failed first line treatment due to poor adherence 76 (35.5%). A total of 88 (82.2%) cases had the same perceived reasons to first line treatment failure affecting them in second line treatment failure.

8. Discussion

In this study, being at advanced HIV disease (AHD) on second line therapy initiation was associated with second line treatment failure. Patients with AHD are at an increased risk of rapid disease progression thereby resulting in virologic failure. Consistent findings have been reported by Haftu et al who mentioned that patients with a low CD4 cell count are immune deficient which increases the rate of virus replication. He also added that patients on WHO stage 4 were significantly associated with second line treatment failure [19].

Defaulting treatment was an independent risk factor as also found to be associated with second line ART failure. This could be due to the reduced second line ART concentration to below therapeutic levels thereby allowing the virus to thrive and with increasing viral replication comes medicine resistance development. Similarly, Seid et al discovered that poor adherence reduced the patient immunity as the viral load increased leading to second line treatment failure [20.. Our study also evidenced that constant treatment support through participating in HIV support groups or having a support system was significantly protective against second line ART failure. This is supported by Sithole et al in another Zimbabwean study where he reported that treatment support promotes viral load suppression [21]. Good adherence to second line treatment ensures there is virologic suppression and hence diminishes the risk of development of treatment failure. The less there is viral multiplication the less the development of resistant mutations.

Missing an appointment or viral load test when due was a significant risk factor to developing second line virologic failure. Similar study findings were reported by Johnson et al. [22]. Missing a routine viral load test and /or review denies the opportunity for the healthcare workers to assess adherence and virological control leading to a person living with HIV continue on a failing regime for a long time without early intervention to avoid further development of ART resistance and deterioration of patient thereby increasing risk of dying.

Switching the first line regimen more than once was significantly associated with second line treatment failure. On the contrary, Bahir Dah et al discovered that there is no association between regimen change and virologic failure [23]. However, history of regimen change or regimen substitution was similarly significantly associated with virologic failure in a study by Jatela et al in Adama town, Ethiopia [24]. Switching of first line ART several times is driven by toxicity and/or poor availability of

medicines rather than poor adherence, however, the changes to different first ART regime exposes the virus to various ART medicines within one class and/or different classes with the possibility of stimulating mutations by the virus which can drive development of resistance.

Children who were under 15 years of age were significantly associated with second line treatment failure. This is concurrence with a Ethiopian study that reported children at higher risk of virologic failure as they are initiated on ART when their immune system is still developing causing rapid replication of the virus [24]. This could be due to limited knowledge on ART medication as some of them chewed the medicines while some had poor adherence. Children also potentially receive an inadequate dose in vitro and through breast milk increasing the risk of viral replication. As the children grow older, the onset of the adolescent stage and effects of the adolescent hormones could also contribute to the change of the attitude to being rebellious, shyness in taking medication, treatment exhaustion and stigma which drives poor adherence. However in contrast, Chimbetete et al in another Zimbabwean study reported that patients older than 25 years were associated with PI drug resistance due to longer exposure on ART resulting in virologic failure [25]. Children need constant support and monitoring due to their perceived negative behavior towards medication.

Being a male was associated with second line treatment failure compared to being a female although it was not statistically significant. In contrast, in a Tanzanian study by Muri et al and in a South African study by Meintjes et al. females were associated with virologic failure [26, 27]. However, in Kenya Mwangi et al discovered that gender and viral load suppression had no significant association [28]. The differences with our study could be possibly due to difference in the maturity of the HIV epidemic in the different countries with South Africa and Tanzania in the infancy ART roll out as compared to Kenya and Zimbabwe. Early in roll out of ART disproportional access to ART drive by various factors including health seeking behavior could explain the significance of male and female differences.

There was no statistical significance between the type of regimen being taken on second line and second line treatment failure. A Zimbabwean study by Chimbetete et al revealed that drug resistant mutations had one or more NNRTI and/or NRTI mutations [25]. Another study in Uganda reported that Zidovudine based first line regimen (NRTI regimen) was associated with second line therapy failure [29]. Alene et al evidenced that Tenofovir and Zidovudine, second-line based regimens, were associated with treatment failure in comparison with Abacavir second-line based regimen [30]. Historically Zidovudine (AZT) was used as single then subsequently as dual therapy later on in mother to child transmission prevention meaning exposure of circulating virus to the medicines had some degree of resistance development. Therefore those countries which used AZT in second line were likely to register second line resistance with this type of regimen whereas countries like Zimbabwe who shied away from using AZT in the second line would not bear the brunt of resistance from prior exposure.

9. Limitations

There was 8.3% refusal rate among the cases with a limited sampling frame of 217 units. This resulted in non-response bias which could possibly affect our findings in missing the target population with risk factors which the study is seeking.

Conclusion and Recommendations

Good adherence is critical particularly in the younger individuals (under 15 years) to minimize the risk of developing second line treatment failure. It is of paramount importance to have adherence counselling sessions before and during course of ART while monitoring the patient viral loads so as to minimize ART regimen switches related to poor adherence. Maintaining regimens on first line ART minimize the risk of second-line treatment failure. Routine viral load testing in monitoring is the milestone in reducing second line treatment failure. PLHIV need to be encouraged to adhere to medication so as to reduce the risk of developing AHD which is difficult to manage and which can lead to virologic failure. Constant treatment support enhances the uptake of ART medications thereby promoting viral load suppression. The number of years on second line ART, the second-line regimen type and the WHO stage at ART initiation did not have a significant effect to patients on second line ART. We recommended the expansion of the adolescent support groups into the younger age group (under 15 years) so as to enhance good adherence and hence promoting viral load suppression. Enforcement of existing updated 2016 guidelines (test and treat) is recommended for early diagnosis and intensifying the adherence counselling sessions for all the HIV positive patients to reduce virologic failure. Healthcare workers were recommended to continue educating PLHIV on factors associated with treatment failure, specifically updating patients on second line on significant risk factors associated with second line ART failure. This helps on the management of patients on second line ART reducing their chance to second line virologic failure.

Competing Interests

The authors declare that they have no competing interests both financial and non-financial.

Funding

The study was funded by Manicaland Provincial Medical Directorate for fuel.

Acknowledgement

The authors acknowledge the Manicaland Provincial Medical Directorate for their support in conducting this study. The authors are also thankful to the Zimbabwe MPH-FETP program and Centers for Disease Control and Prevention (CDC) Zimbabwe for technical assistance.

Authors' Contributions

KC: conception, design, acquisition, analysis and interpretation of data and drafting the manuscript. MM: conception, design, acquisition, analysis and interpretation of data and drafting the manuscript. GS: conception, design, data collection, analysis, interpretation and reviewing of several drafts of the manuscript

for important intellectual content. NG: conception, design, data collection, analysis, interpretation and reviewing of several drafts of the manuscript for important intellectual content. AC: conception, design, data collection, analysis, interpretation and reviewing of several drafts of the manuscript for important intellectual content. TJ: conception, design, data collection, analysis, interpretation and reviewing of several drafts of the manuscript for important intellectual content. MT: conception, design, data collection, analysis, interpretation and reviewing of several drafts of the manuscript for important intellectual content. All authors read and approved the final manuscript.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author, KC. The data are not publicly available as it contains privacy of research participants.

References

1. Lange C (NIH/NCI). Handbook on HIV DRug resistance Testing Availability, accessibility and capacity for caribbean states. 58.
2. Treatment Failure, NIH. Available from: https://clinicalinfo.hiv.gov/en/glossary/treatment-failure.
3. HIV drug resistance surveillance guidance. Available from: https://www.who.int/publications-detail-redirect/978-92-4-151009-7.
4. Fact Sheet: HIV Drug Resistance. Available from: https://www.who.int/news-room/fact-sheets/detail/hiv-drug-resistance.
5. World Health Organization. Regional Office for Africa. Preventing and responding to HIV drug-resistance in the African Region: regional action plan 2019-2023. Brazzaville: World Health Organization. Regional Office for Africa; 2019 [cited 2022 Nov 9]. Available from: https://apps.who.int/iris/handle/10665/312176.
6. Centers for Disease Control and Prevention. 2022 [cited 2023 May 24]. Antibiotic Resistance Spreads Across the World. Available from: https://www.cdc.gov/drugresistance/across-the-world.html.
7. Sulis, G., Sayood, S., & Gandra, S. (2022). Antimicrobial resistance in low- and middle-income countries: current status and future directions. Expert review of anti-infective therapy, 20(2), 147–160.
8. SAHCS. Available from: https://sahivsoc.org.
9. Antiretroviral medicines in low- and middle-income countries: forecasts of global and regional demand for 2020-2024. Available from: https://www.who.int/publications-detail-redirect/9789240041264.
10. Bertagnolio, S., Jordan, M. R., Giron, A., & Inzaule, S. (2022). Epidemiology of HIV drug resistance in low- and middle-income countries and WHO global strategy to monitor its emergence. Current opinion in HIV and AIDS, 17(4), 229–239.
11. Kouamou, V., & McGregor, A. M. (2021). High Levels of Pre-Treatment HIV Drug Resistance in Zimbabwe: Is this a Threat to HIV/AIDS Control?. Journal of AIDS and HIV Treatment, 3(3), 42-45.
12. ZIMPHIA-2020-Summary-Sheet_Web.pdf. Available from: https://phia.icap.columbia.edu/wp-content/uploads/2020/11/ZIMPHIA-2020-Summary-Sheet_Web.pdf
13. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV :585.
14. HIV drug resistance report 2021.
15. World Health Organization. Surveillance of HIV drug resistance in adults receiving ART (acquired HIV drug resistance): concept note. Geneva: World Health Organization; 2014, 46 p.
16. World Health Organization, Global Fund, US Centers for Disease Control and Prevention. HIV drug resistance report 2017. Geneva: World Health Organization; 2017.
17. Drug-Resistance Testing, NIH. Available from: https://clinicalinfo.hiv.gov/en/guidelines/hiv-clinical-guidelines-adult-and-adolescent-arv/drug-resistance-testing
18. Average Salary in Zimbabwe 2023 - The Complete Guide.
19. Zenebe Haftu, A., Desta, A. A., Bezabih, N. M., Bayray Kahsay, A., Kidane, K. M., Zewdie, Y., & Woldearegay, T. W. (2020). Incidence and factors associated with treatment failure among HIV infected adolescent and adult patients on second-line antiretroviral therapy in public hospitals of Northern Ethiopia: Multicenter retrospective study. PloS one, 15(9), e0239191.
20. Seid, A., Cherie, N., & Ahmed, K. (2020). Determinants of Virologic Failure Among Adults on Second Line Antiretroviral Therapy in Wollo, Amhara Regional State, Northeast Ethiopia. HIV/AIDS (Auckland, N.Z.), 12, 697–706.
21. Sithole, Z., Mbizvo, E., Chonzi, P., Mungati, M., Juru, T. P., Shambira, G., Gombe, N. T., & Tshimanga, M. (2018). Virological failure among adolescents on ART, Harare City, 2017- a case-control study. BMC infectious diseases, 18(1), 469.
22. Johnson, L. F., Stinson, K., Newell, M. L., Bland, R. M., Moultrie, H., Davies, M. A., Rehle, T. M., Dorrington, R. E., & Sherman, G. G. (2012). The contribution of maternal HIV seroconversion during late pregnancy and breastfeeding to mother-to-child transmission of HIV. Journal of acquired immune deficiency syndromes (1999), 59(4), 417–425.
23. Gelaw, B., Mulatu, G., Tesfa, G., Marew, C., Chekole, B., & Alebel, A. (2021). Magnitude and associated factors of virological failure among children on ART in Bahir Dar Town public health facilities, Northwest Ethiopia: a facility based cross-sectional study. Italian journal of pediatrics, 47(1), 84.
24. Jaleta, F., Bekele, B., Kedir, S., Hassan, J., Getahun, A., Ligidi, T., Garoma, G., Itefa, K., Gerenfes, T., Botore, A., Kenate, B., Dagafa, G., & Muleta, D. (2022). Predictors of unsuppressed viral load among adults on follow up of antiretroviral therapy at selected public and private health facilities of Adama town: unmached case-control study. BMC public health, 22(1), 1770.
25. Chimbetete, C., Katzenstein, D., Shamu, T., Spoerri, A., Estill, J., Egger, M., & Keiser, O. (2018). HIV-1 Drug Resistance and Third-Line Therapy Outcomes in Patients Failing Second-Line Therapy in Zimbabwe. Open forum infectious diseases, 5(2), ofy005.
26. Muri, L., Gamell, A., Ntamatungiro, A. J., Glass, T. R.,

Luwanda, L. B., Battegay, M., Furrer, H., Hatz, C., Tanner, M., Felger, I., Klimkait, T., Letang, E., & KIULARCO Study Group (2017). Development of HIV drug resistance and therapeutic failure in children and adolescents in rural Tanzania: an emerging public health concern. AIDS (London, England), 31(1), 61–70.

27. Meintjes, G., Dunn, L., Coetsee, M., Hislop, M., Leisegang, R., Regensberg, L., & Maartens, G. (2015). Third-line antiretroviral therapy in Africa: effectiveness in a Southern African retrospective cohort study. AIDS research and therapy, 12, 39.
28. Mwangi, A., & van Wyk, B. (2021). Factors Associated with Viral Suppression Among Adolescents on Antiretroviral Therapy in Homa Bay County, Kenya: A Retrospective Cross-Sectional Study. HIV/AIDS (Auckland, N.Z.), 13, 1111–1118.
29. Sam, M., Masaba, J. P. M., Alio, D., & Byakika-Tusiime, J. (2021). Treatment Failure and Associated Factors among Individuals on Second Line Antiretroviral Therapy in Eastern Uganda: A Retrospective Cohort Study. Infectious diseases, 14, 11786337211014518.
30. Alene, M., Awoke, T., Yenit, M. K., & Tsegaye, A. T. (2019). Incidence and predictors of second-line antiretroviral treatment failure among adults living with HIV in Amhara region: a multi-centered retrospective follow-up study. BMC infectious diseases, 19(1), 599.