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Predictors of Virologic Failure among Adults on Second Line ART in the Northwest Region of Cameroon

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Abstract

Background: An increasing number of first line Anti-retroviral therapy (ART) patients in resource limited countries are experiencing regimen failure and are switched to second line ART. However, predictors of second line ART virologic failure in Cameroon are scarce. This study aimed at investigating the predictors of virologic failure of second line ART regimen amongst adult patients in the Northwest Region of Cameroon.

Method: A cross-sectional study was conducted among adults on second line ART between January 2018 and December 2021 at 3 purposefully selected health facilities. Study participants were systematically selected to include participants on second line ART with documented first line and second line viral load information. Data was extracted from clients' files and analyzed using SPSS version 25.

Results: A total of 157 second line ART clients were sampled with majority (69%) being males. The median time to switch to second line ART from the time of first high viral load on first line ART was 18 months (SD=8). The second line ART virologic failure rate was estimated at 16%. Significant predictors of second line ART virologic failure were baseline CD4 >200 copies/ml (AOR: 5.06, 95% CI: 1.54-16.61, p = 0.007) and fair adherence AOR: 19.21, 95% CI: 5-75.37, p = 0.001).

Conclusion: Baseline CD4 counts greater than 200 cells/mL and fair adherence were significant predictors of virologic failure of second-line ART. The Midian duration from first high viral load to switch was high at 18 months. Strategies to improve adherence with more attention on the 18-30 years age group will help reduce virologic failure rate of second line ART. Patients on first line ART with high viral load should be closely monitored and provided with treatment support to ensure that those with a persistent high viral load are identified and switched to second line earlier than 12 months to improve their treatment outcomes.

Keywords: Second Line Anti-Retroviral Therapy; Virologic failure; Predictors

Introduction

Human Immunodeficiency Virus (HIV) treatment and prevention has evolved remarkably in recent years but limitations still exist. Globally, nearly 38 million people are living with HIV [1]. Sub-Saharan Africa (SSA) is the hardest hit region in the world, accounting for more than two-thirds of all people living with HIV [2]. Current antiviral treatments can reduce HIV-associated morbidity, prolong survival, and prevent HIV transmission. Combination antiretroviral therapy containing preferably three active drugs from two or more classes is required for durable virologic suppression. Therefore, maximizing the safety and tolerability of ART is a high priority.

Emergence of resistance and/or lack of tolerability in individual patients requires the availability of a range of treatment options [3]. There are many options for first-line antiretroviral therapy, but second-line therapy is necessary for people who fail the first-line treatment [4]. A growing proportion of patients in resource-limited countries who have initiated ART have experienced first-line regimen failure and are switching to second-line therapy [5,6].

One of the critical clinical decisions made in ART is when to switch from an initial regimen to another due to treatment failure [6]. Identification of treatment failure is frequently determined by clinical and immune changes, which may occur long before or long after the

loss of virological suppression [7]. A delay in recognizing treatment failure can result in the accumulation of resistance mutations that jeopardize next-line options and efficacy leading to a greater risk in mortality and may increase the transmission of resistant HIV [8]. On the other hand, switching to second-line ART before it is indicated unnecessarily increases the use of expensive and less tolerated second-line agents and may result in quicker progression to treatment exhaustion [8]. HIV-1 drug-resistance mutations may limit subsequent drug options and constitutes a source for onward transmission [8].

Second-line ART regimens are used when patients develop treatment failure for first-line drug regimens. It is costly unaffordable and it is not widely available for patients in resource limited setting [9]. Second-line HIV treatment failure has become highly prevalent in SSA and it is associated with base line high viral load, low CD4, advance HIV stage and suboptimal adherence [10].

In 2016, the United Nations General Assembly's Political Declaration on Ending Acquired Immunodeficiency Syndrome (AIDS) committed countries to the 90–90–90 targets, which aim to bring HIV testing and treatment to the vast majority of people living with HIV by the end of 2020 and to reduce the amount of HIV in their bodies to undetectable levels, so they keep healthy and to prevent the further spread of the virus. In December 2020, UNAIDS released a new set of ambitious targets calling for 95% of all people living with HIV to know their HIV status, 95% of all people with diagnosed HIV infection to receive sustained antiretroviral therapy, and 95% of all people receiving antiretroviral therapy to have viral suppression by 2025[11]. Globally, there have been remarkable gains across the HIV testing and treatment cascade but the global target of 95% of people on ART having a suppressed viral load is unlikely to be met as only 86% (72-92%) people on ART were virologically suppressed in 2019and 93% (74–>98%) in 2023 [11].

A systematic review on the treatment outcomes of patients on second line antiretroviral therapy in resource limited settings showed that virologic failure was high with 21.8% failure rate in the polled population [5]. High viral load is becoming a threat in different African countries, like in Burkina Faso (6.4%), Ghana (15.7%) and Tanzania (14.9%). In Ethiopia, virological failure is found to be about 11.5% [12]. In the setting of sustained viral suppression, individuals with HIV do not transmit HIV to sexual partners (described as "undetectable = untransmissible" [U = U]) [13]. Missed medical care visits are consistently associated with poor HIV outcomes as missed visits in the prior year predicts future risk for missing future appointments, reducing the opportunities for clinic-level intervention [13].

In another systematic review conducted in SSA to estimate the burden of second line treatment failure, it was revealed that the pooled second-line HIV treatment failure rate was 15.0 per 100 PYs (95% CI: 13.0-18.0). It was slightly higher at 12-18 months of follow-up (19.0/100 PYs; 95% CI: 15.0-22.0), in children (19.0/100 PYs; 95% CI: 14.0-23.0) and in southern SSA (18.0/100 PYs; 95% CI: 14.0-23.0). Baseline values (high viral load (OR: 5.67; 95% CI: 13.40-9.45); advanced clinical stage (OR: 3.27; 95% CI: 2.07-5.19); and low CD4 counts (OR: 2.80; 95% CI: 1.83-4.29)) and suboptimal adherence to therapy (OR: 1.92; 95% CI: 1.28-2.86) were the factors associated with increased failure rates [14].

In Amhara Region in Northem Ethiopia, the results of a retrospective study revealed that the overall incidence of second-line treatment failure was 9.86 per 100 person-years and it was high during the first and last year of follow up and was found to be lower for patients who were under WHO clinical stage III at switch [9]. A study involving 394 adults on lopinavir/ritonavir-based second-line regimen in Kenya revealed that, 21% had viral load more than 1000 copies/ml, associated with younger age, tuberculosis treatment, shorter time on second-line, lower CD4count/percentage, longer first-line treatment interruption and pregnancy [15].

Increased second-line ART failure rate narrows future options for HIV/AIDS treatment and contributes to the spread of resistant HIV strains. It has critical implications in resource-limited settings; including sub-SSA where the burden of HIV-infection is immense [10]. In Northern Ethiopia, second line ART treatment failure incidence in adolescents and adults on second line ART was estimated at 25.1% [16]. Emergence of resistance and/or lack of tolerability in individual patients require availability of a range of treatment options [3]. Therefore, maximizing the safety and tolerability of ART is a high priority.

In the Northwest region of Cameroon, an increasing number of patients on second line ART are virologically unsuppressed. This, coupled with limited access to resistance testing and third line ART options, resulting to undesirable outcomes such as increased HIV related morbidity and mortality.

Understanding the factors associated with second line treatment failure is paramount in maximizing treatment opportunities on second line regimen. This study aims to investigate the predictors of virologic failure for patients on second line ART regimen in the Northwest Region of Cameroon.

Methods

The study setting

The study was carried out in the Northwest region of Cameroon. The region comprises of 7 divisions with 20 health districts and 415 health facilities. By mid-2020, 153 health facilities were providing comprehensive ART treatment in the region. The study was conducted in three purposefully selected health facilities (Mbingo Baptist Hospital, Banso Baptist Hospital and Nkwen Baptist Hospital) with a high number of patients on second line ART and routine viral load monitoring.

Study design

We conducted across-sectional study among adults (18 years and above) who were initiated on second line ART between January 2018 and December 2021 in the selected treatment centers. Patients on second line ART who did not start treatment in the selected treatment centers were excluded from the study as well as those without documented viral load follow up information.

Study population

The source population for this study were adult HIV patients (greater than 18 years) who initiated second line ART between January 2018 and Dec 2021 and must have been on second line ART for at least 1 year.

Sampling technique

Study sites were purposively selected, including facilities with >1500 patients on ART, routine viral load monitoring and the availability of patient clinical records. Patients on second line ART with documented first line and second line viral load were systematically included in the study.

Data collection and management

The data used in this study was extracted from patient's files using a case review form and entered into an excel spreadsheet. The form was divided into 3 sections to capture patient's demographic information, risk factors of virologic failure at initiation and during first line treatment and risk factors of virologic failure at switch and during second line treatment.

Data analysis

Factors associated with virologic failure of second line ART were assessed using Chi 2 test. After controlling for confounders, logistic regression analysis was used to determine predictors of virologic failure of second line ART by computing significant variables from the bivariate analysis.

Ethical considerations

This study received Ethical Clearance from the CBCHB Internal Review Board (IRB study number: IRB2023-27).Data was coded to maintain confidentiality and only those involved in the study had access to the data. Furthermore, data was collected by health care providers who have been involved in HIV services and are conscious of issues of confidentiality.

Operational definition

Adherence: In this study, adherence was assessed retrospectively based on clients' compliance with their ART pick-up appointments during the study period. Clients who respected at least 80% of their appointments were classified as adherent, those who respected between 60% and 79% were considered to have fair adherence, and those with less than 60% respect attendance were categorized as having poor adherence. However, there is potential for bias, as some classification decisions may have relied on subjective judgment by the data collectors.

Virologic failure: According to WHO, virologic failure is defined as plasma viral load greater than 1000 copies/ML based on two consecutive viral load measurements after 3 months with enhanced adherence support. In this study, virologic failure was considered as two consecutive viral loads greater than 1000 copies/ML within three to six months following successful enhanced adherence counseling.

Results

A total of 157 adults who initiated second line ART between January 2017 and December 2021were included in the study. The mean age of study participants was 47 years (SD=11years) and a majority were females (69%). About half (54%) of the study participants were switched to second line ART at 31-45 years age group. The patients were predominantly switched at clinical stage 1and 3, 38% and 34% respectively. The baseline CD4 cells were less than 200 cells/UL for 77% of participants. Majority of the study participants were initiated on ATV/R (75%) and they mostly received their ARVs at the facility 83% than in the community. Adherence was fair for the majority of patients (80%). Majority (78%) delayed for more than 12 months after first high viral load on first line ART before switching to second line ART.

In the bivariate analyses, a significant relationship was observed between age at switch (P=0.043), baseline CD4 (P=0.027), adherence to second line ART (P=0.001) and virologic failure of second line ART. Though there was no significant difference in the proportion of males to females failing second line ART, there was a slightly higher treatment failure rate in males than females (17%/16%). Majority of those experiencing second Line ART failure were initiated at WHO clinical stage 1 and 2. A slightly higher failure rate was observed in those initiated on LPV/r than those initiated on ATV/r (18%/15%). A greater proportion of patients experiencing second line ART failure were receiving ARVs in the community than in the facility (22% and 15 % respectively). Concerning the delayed time to switch from the first high viral load on first line ART, we observed that a greater proportion 4(31%) of clients were switched between 7-12 months. It is also important to observe that in terms of absolute numbers, a majority of that experiencing second line treatment failure delayed for more than 12 months before switching to second line ART 16(13%) (Table 1).

Significant variables from the bivariate analysis were put into a logistic regression model to predict specific predictors of second line ART failure. The analysis showed that Baseline CD4 counts of greater than 200 cells/UL, and fair adherence are significant predictors of virologic failure of second line ART.

Patients aged 31-45 years showed significantly lower odds of experiencing virologic failure compared to those aged 18-30 years (COR: 0.28, 95% CI: 0.09-0.91, p = 0.034). However, after adjustment, this association was no longer statistically significant (AOR: 0.42, 95% CI: 0.09-1.95, p = 0.253). Similarly, patients aged 46 years and above had significantly lower odds of virologic failure in the unadjusted model (COR: 0.23, 95% CI: 0.06-0.84, p = 0.026), but this effect was not significant after adjusting for other factors (AOR: 0.44, 95% CI: 0.08-2.18, p = 0.315).

There was no statistically significant association between WHO clinical stage at ART initiation and virologic failure or suppression. All clinical stages (Stage 2, 3, and 4) did not significantly differ from Stage 1 in their association with virologic outcomes. Patients with a baseline CD4 count greater than 200 had significantly higher odds of virologic failure compared to those with a CD4 count of less than 200 (COR: 2.71, 95% CI: 1.10-6.74, p = 0.031). This association remained strong and statistically significant in the adjusted model (AOR: 5.06, 95% CI: 1.54-16.61, p = 0.007). There was no significant association between community ART dispensation and virologic outcomes.

Patients with fair adherence had significantly higher odds of virologic failure compared to those with good adherence (COR: 14.9, 95% CI: 4.39-50.33, p = 0.001; AOR: 19.21, 95% CI: 5-75.37, p = 0.001). On the other hand, patients with poor adherence showed no statistically significant difference in virologic failure rates compared to those with good adherence (COR: 1.14, 95% CI: 0.28-4.68, p = 0.853; AOR: 1.17, 95% CI: 0.26-5.32, p = 0.834).

The delay in time to switch from first-line ART after the first detection of high viral load did not show a significant impact on virologic outcomes. Although patients who delayed switching for more than 12 months had increased odds of virologic failure (COR: 1.94, 95% CI: 0.63-6.02, p = 0.25), this result was not statistically significant (Table 2).

Discussions

This study estimated a second line ART virologic failure rate of 16% with a greater proportion of males failing second line ART than females 8(17%). This is lower than the21% rate established in a similar study in Kenya [15] but higher than the rates in Burkina Faso (6.4%), Tanzania (14.9%) and Ethiopia 11.5% [12] but very close to that established in Ghana (15.7%) [12]. Another study conducted in Northern Ethiopia, amongst adolescents and adults on second line ART estimated a second

Table 1: Sociodemographic and Clinical characteristics of study participants and association with virologic failure of second line ART.

Variable	Total	Virologic Failure	Virologic Suppression	P-Value
	n=157	n=25	n=132	
	n (%)	n (%)	n (%)	
SEX				0.87
Female	109(69)	17(16)	92(84)	
Male	48(31)	8(17)	40(83)	
Age at switch				0.043*
17-30 years	16(10)	6(38)	10(62)	
31-45 years	84(54)	12(14)	72(86)	
46 years and above	57(36)	7(12)	50(88)	
WHO clinical stage at initiation				0.766
Stage 1	59(38)	8(14)	51(86)	
Stage 2	32(20)	7(22)	25(78)	
Stage 3	54(34)	8(15)	46(85)	
Stage 4	12(8)	2(17)	10(83)	
Baseline CD4				0.027*
Less than 200	121(77)	15(12)	106(88)	
Greater than 200	36(23)	10(28)	26(72)	
PI Component of second line Regimen				
LPV/r	39(25)	7(18)	32(82)	0.69
ATV/r	118(75)	18(15)	100(85)	
How many NRTI drugs changed				0.436
One NRTI drug changed	74(47)	10(14)	64(86)	
Two NRTI drugs changed	83(53)	15(18)	68(82)	
Community ART Dispensation				0.33
Yes	27(17)	6(22)	21(78)	
No	130(83)	19(15)	111(85)	
Adherence on second line ART				0.001*
Good	15(10)	8(53)	7(47)	
Fair	126(80)	9(7)	117(93)	
Poor	16(10)	8(50)	8(50)	
Time to switch from the first high viral load on first line ART				0.164
1-6 months	22(14)	5(23)	17(77)	
7-12 months	13(8)	4(31)	9(69)	
Greater than 12 months	122(78)	16(13)	106(87)	

Table 2: Predictors of virologic failure of second line ART.

Variable	Outcome on second line ART		COR (95% CI)	P-value	AOR (95%CI)	P-Value
	Virologic Failure	Virologic Suppression				
Age group at switch						
18-30 years	6	10	1		1	
31-45 years	12	72	0.28(0.09-0.91)	**0.034**	0.42(0.09-1.95)	0.253
46 years and above	7	50	0.23(0.06-0.84)	**0.026**	0.44(0.08-2.18)	0.315
WHO clinical stage at initiation						
Stage 1	8	51	1			
Stage 2	7	25	0.56(0.18-1.72)	0.31		
Stage 3	8	46	0.90(0.31-2.59)	0.85		
Stage 4	2	10	0.78(0.145-4.26)	0.78	-	-
Baseline CD4						
Less than 200	15	106	1		1	
Greater than 200	10	26	2.71(1.10-6.74)	**0.031***	5.06(1.54-16.61)	**0.007***
Adherence on second line ART						
Good	8	7	1		1	
Fair	9	117	14.9(4.39-50.33)	**0.001***	19.21(5-75.37)	**0.001***
Poor	8	8	1.14(0.28-4.68)	0.853	1.17(0.26-5.32)	0.83
Delay time to switch from first high viral load on first line ART						
1-6 months	5	17	1			
7-12 months	4	9	0.66(0.14-3.09)	0.6		
Greater than 12 months	16	106	1.94(0.63-6.02)	0.25	-	-

line ART treatment failure rate of 25.1% [16] which is higher than that estimated in this study. These are all PEPFAR-supported countries with similar approaches to HIV care and treatment. However, the difference between the second line treatment failure rate in this study and that of other studies could be due to differences in health seeking behaviours across these countries, religious and cultural believes and the functionality of the health system.

Age at switch was an important factor in the unadjusted analysis, with older patients being less likely to experience virologic failure, but this effect diminished after adjustment for other factors (COR: 0.28, 95% CI: 0.09-0.91, p = 0.034). These results are similar to those of a study conducted in Kenya where younger age was a major risk factor of virologic failure [15]. The younger age is usually crowded with many adventures and distractions and it is likely that patients in this age group turn to be busier with their social adventures than issues concerning their health. This could be a pointer that patients in this age group needs more strategic adherence support than older patients.

Second line ART virologic failure did not significantly vary with respect to the WHO clinical stage. All clinical stages (Stage 2, 3, and 4) did not significantly differ from Stage 1 in their association with virologic outcomes. This differs from the results of a meta-analysis conducted in Sub Sahara Africa where the second line ART failure was associated with advance HIV disease [10]. This effect could have been hidden by the small sample size in this study

Baseline CD4 count greater than 200 cells/UL was strongly associated with higher odds of virologic failure, even after adjustment (AOR: 5.06, 95% CI: 1.54-16.61, p = 0.007). This is contrary to the findings of a meta-analysis conducted in SSA which revealed that low baseline CD4 counts (OR: 2.80; 95% CI: 1.83-4.29) were strongly associated with second line treatment failure [14]. Although CD4 provides information on the overall immune function of a person living with HIV, this result is adding to the body of knowledge that a poor CD4 count may rarely be used as an indication for treatment modification in PLHIV. This could also indicate that individuals with higher immune recovery before switching to second-line therapy may require more monitoring or targeted interventions.

Adherence to second-line ART emerged as a critical factor, with fair adherence significantly increasing the odds of virologic failure

compared to good adherence (COR: 14.9, 95% CI: 4.39-50.33, p = 0.001; AOR: 19.21, 95% CI: 5-75.37, p = 0.001). This is in line with findings of other studies where suboptimal adherence to therapy (OR: 1.92; 95% CI: 1.28-2.86) was strongly associated with increased second line failure rates [14]. Even though there was no statistically significant difference in virologic failure between patients with poor adherence and those with good adherence (COR: 1.14, 95% CI: 0.28-4.68, p = 0.853; AOR: 1.17, 95% CI: 0.26-5.32, p = 0.834), the strong association with fair adherence is evidence that sub optimal adherence is a critical risk factor for second line virologic failure. The association between poor adherence and virologic failure is likely to have been hidden in this study by the small sample size.

The delay in time to switch from first-line ART after the first detection of high viral load did not show a significant impact on virologic outcomes. Although patients who delayed switching for more than 12 months had increased odds of virologic failure (COR: 1.94, 95% CI: 0.63-6.02, p = 0.25), this result was not statistically significant. This could imply that, longer duration on a failing first line regimen could reduce the chances of viral load suppression on second line. A delay in recognizing treatment failure can result in the accumulation of resistance mutations that jeopardize next-line options and efficacy leading to a greater risk in mortality and may increase the transmission of resistant HIV.

Limitations

One of the major limitations of this study is that, the sample size was small as a result of missing data on some very important variables. Also, it was limited to secondary data extraction and this limited the measurement of some important variables

Conclusion

Virologic failure of second line ART is high in the NW region of Cameroon (16.5%) and significant predictors were baseline CD4 >200 copies/ml (AOR: 5.06, 95% CI: 1.54-16.61, p = 0.007) and suboptimal adherence AOR: 19.21, 95% CI: 5-75.37, p = 0.001). Even though Age at switch did not significantly predict virologic failure, the bivariate analysis revealed that people switching ART at 18-30 years age group were more likely to be virologically unsuppressed than older patients. Also, the delay time to switch from first high viral load on the first line ART was high and possibly reducing the chances of virologic suppression on second line ART. Patients who are virologically unsuppressed on first line ART should be provided with adherence support and timely interventions so that they can be switched to appropriate second line regiments on time to maximize the efficacy of second line ART. Also, specific attention should be given to patients switching ART at less than 30 years age group. Future research is recommended to throw more light on the relationship between baseline CD4, the model of ART dispensation and virologic failure of second line ART.

Recommendations

1. Strengthen adherence support interventions for patients on second-line ART, with special attention to younger adults (aged 18–30), as they are more likely to experience virologic failure.

2. Reinforce timely switching protocols to ensure that patients with confirmed high viral load on first-line ART are switched to second-line ART within 6 months, preferably earlier than 12 months, to reduce the risk of treatment failure and drug resistance accumulation.

3. Develop and implement targeted youth-friendly services for ART adherence and retention as a means to enhance adherence amongst youths.

4. Although not statistically significant in this study, the slightly higher failure rates among those receiving ART in the community setting suggest a need to strengthen supervision and adherence monitoring for community ART distribution models.

5. Conduct further research to throw more light on the relationship between baseline CD4, the model of ART dispensation and virologic failure of second line ART.

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Authors Contributions

NG, the principal investigator and corresponding author, designed the study, executed it, analyzed the data and wrote the first draft of the manuscript. EN and CA discussed the design and reviewed the manuscript. IN, MV and EM reviewed the manuscript. All authors read and approved the final manuscript.

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Disclaimer

The views expressed here are those of the author.

Competing Interests

We declare no conflicts of interest

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