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Original Research Article

Virologic outcome among HIV-1 infected adults on second-line antiretroviral therapy in Jos, Nigeria

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Abstract

More people living with HIV (PLHIV) are now accessing free antiretroviral therapy (ART) through public health programmes in resource-limited settings. Currently, third-line (3L) ART for patients failing second-line (2L) ART in most of these programmes is not readily available. Yet, data on effectiveness of 2LART are limited. To adequately address and prepare for the need for 3L, critical assessments of the outcomes of second-line ART are needed. This was a retrospective cohort study of patients accessing 2L ART at the Jos University Teaching Hospital (JUTH), Jos adult HIV clinic from 2004 to 2018. We determined the proportion of patients failing 2L ART, evaluated time to virologic failure, time to lost to follow up and time to death using Kaplan-Meier estimates. Virologic failure (VF) was defined as 2 consecutive viral load result >1000copies/ml when the patient had been on ART for at least 6 months and undetectable viral load as < 400 copies/ml. A total of 285 patients were included in the study, with a mean age of 45±9.5 years. Females were 194 (68.1%). All patients were on boosted protease inhibitor, the predominant ART for use as 2L regimen was Lopinavir boosted with ritonavir in combination with Tenofovir, Lamivudine and Zidovudine (43.9%). The baseline median viral load was 54481 (IQR 6950-161640) copies/ml. The proportion of patients with virologic failure was 33(11.6%) at 48 weeks. The proportion of patients with detectable viral load was 66.0%, 30.2%, 30.5% and 27.9% at 12weeks, 24weeks, 48weeks and 72 weeks, respectively. The mean time to virologic failure, loss to follow up and death on second-line ART was 7.473± 0.269 (CI 6.946-8.000) years, 7.228±0.250 (CI 6.783-7.717) years, and 9.697±0.091 (CI 9.519-9.874) years respectively. In conclusion, 2L ART virologic failure rates in our cohort are comparatively low to other LMIC but fall short of target 95-95-95. There is an urgent need for wide availability of 3L ART.

Keywords: Antiretroviral treatment; Virologic outcome; HIV-1; Second-line treatment.

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1. Introduction

The epidemic of HIV has affected virtually all parts of the world, with an estimated 38 million people worldwide living with HIV [1]. Unfortunately, sub-Sahara Africa (SSA) where Nigeria is situated carries 64% of the global HIV epidemic burden. Nigeria is the most populous country in SSA, and so it has a high absolute number of PLHIV despite a relatively low HIV prevalence of 1.4% [2] In addition, Nigeria has the highest new HIV infection rate and the second highest epidemic (1.9 million people) worldwide. [2]

Among adults aged 15-49 years, Akwa Ibom State in the South-south zone has the highest HIV prevalence (4.8%) followed by Benue State (4.3%) in the North-central zone and Jigawa and Katsina States had the lowest prevalence at 0.3% [2] Approximately 160,000 people died from AIDS-related illnesses in Nigeria in 2016.[1]

Providing ART for PLHIV substantially reduces morbidity and mortality and increases their life expectancy; it does not only benefit those living with HIV, but it dramatically reduces the chances of onwards HIV transmission to others. [4-10]

The Nigerian National Guidelines for HIV prevention, treatment and care 2016was the guideline in use which was an adoption of the World Health Organization (WHO) recommendation of using a combination of two nucleoside/nucleotide reverse transcriptase inhibitors (NRTI) with a Non-nucleoside reverse transcriptase inhibitor (NNRTI) as 1L. Sometimes 1L regimen may fail due to development of resistance or other factors such as drug interactions, poor adherence, and adverse drug reaction. Second line regimen (2L), which is a combination of 2 nucleoside/nucleotide reverse transcriptase inhibitors with ritonavir boosted protease inhibitors (PI/r), may fail due to similar reasons as those causing failure 1L treatments.[11,12] Worldwide about 26million people are on ART, that is more than halve of all PLHIV. In Nigeria about 780,000 are on cART as of 2016. [1,13] The proportion of patients on 2Lin resource-limited settings is estimated to be between 1-5%. [14-16]

The adoption of the target 90-90-90 by UNAIDS in 2014 to eliminate HIV epidemic by 2020 has led to significant progress and acceleration of the AIDS response. AIDS-related deaths have reduced by 42% and new HIV infections by 47% globally between 2010 and 2020. Globally 84% of people who have HIV knew their status, 73% are on cART and 66% of those on cART are virally suppressed. The picture is disappointing in West and Central Africa where only 42% know their status, 83% are on ART and 73% of them are virally suppressed.[1]

Nigeria has a worse picture with only74% of PLHIV who knew their status and with just 89% of all PLHIV receiving treatment in 2020. Among, people on ART, less than a quarter are virally suppressed.[1,17]

The population of people who do not know they have HIV and those on ART that are not virally suppressed constitute a large population that are potential a source for sustaining the HIV epidemic which will slow down progress towards achieving the goal of ending the HIV epidemic by 2020. Patients that are on ART who are not virally suppressed could have resistance to antiretroviral drugs (ARV), or other factors which include poor adherence to the ARV, malnutrition/mal-absorption of drugs, poor potency or improper dosing and drug-drug interactions.[11]

High efficacy of 2L regimen has been documented in randomized trials [18]. However, data from low- and middle-income countries (LMIC) have demonstrated high rates of virological failure (VF) among patients on 2L regimens, predominantly driven by suboptimal adherence and prolonged exposure to previous failing regimens[19, -22]. These rates of VF tend to increase the longer the patient is on 2L regimen.[23]

For patients failing 2L therapy, treatment options are largely unavailable in most developing countries, including Nigeria. Current WHO guidelines provide some guidance for treatment in the case of 2L failure, but these are prefaced with the caveat that many low and middle-income countries have financial constraints that will limit the adoption of 3L options. Thus, there is a need to determine the virologic outcome in HIV patients on 2L ART in our environment, and determine the factors responsible for 2L ART failure.

2. Methods

2.1 Study area

The study was conducted at the outpatient HIV Clinic in of the Jos University Teaching Hospital (JUTH), Jos Plateau State. The centre commenced ART services in 1997, and in 2001 became one of the Governments of Nigeria (GON) ART sites. The centre has been receiving PEPFAR support since 2004; initially through the Harvard PEPFAR, and now through APIN public health initiatives (APIN). To date the centre has cumulatively enrolled over 27,000 patients.

2.2 Study population

This study included all patients on 2L ART for at least 6 months[24] who must also have viral load record at 24 weeks and 48weeks after commencement of 2L ART. Those with incomplete or missing records that cannot fit into analysis were excluded from the study. There were 6, 279 patients on 1L ART and 1,014 patients who were switched to 2L in the Clinic as at the time of the study. Data from 387 patients on 2L ART had VL at 24 weeks and a further 102 where excluded because there was no viral load result at 48 weeks. A total of 285 (74.0%) met the inclusion criteria

2.3 Study design

The study was a retrospective cohort analysis of all patients who were switched to 2L ART at JUTH Adult HIV Clinic. Secondary data was utilized for the study, collected in a longitudinal manner and stored in the clinic's database (FileMaker Pro, v10; FileMaker, Inc, Santa Clara, California, USA). All study participants provided informed consent for use of their data and/or samples for research. ART initiation and monitoring followed the Nigerian National HIV Guidelines recommendations, including both HIV-1 viral loads monitoring. The COBAS Amplicor HIV-1 monitor test kit version 1.5 (Roche, Indianapolis, Indiana) using the standard method (lower limit of detection, 400 copies/mL) was initially used, but later the COBAS AmpliPrep/TaqMan HIV-1, version 2.0 (automated) method (lower limit of detection, 20 copies/mL) was used as the earlier machine was phased out. For, this study Virologic failure (VF) was defined as a detectable HIV

RNA greater than 1000copies/ml at 2 different occasions after 6months. Clinic counselors provided adherence counselling before 1L ART initiation and at the time of VF prior to switch. Adherence counselling was continuous at each contact with the facility. Adherence level of 95% and above was regarded as optimal and below is suboptimal.[25]

2.4 Sample size calculation

The sample size was determined using Open Epi epidemiological calculator (Epi info 7.2). The method for cohort studies by Fleiss with correction of continuity was used with the following assumptions: Two-sided significance level (1-alpha) of 95; power (1-beta, % chance of detecting a difference) of 80%; ratio of sample size Unexposed/exposed 1; Percentage of outcome in unexposed 25%; Risk ratio 1.8, odds ratio 2.5; Percentage of outcome in exposed 45.5%.[26]A minimum sample size of 188 was calculated.

2.5 Sampling technique

A total sampling technique was applied. All complete records of patients that presented for treatment in the Adult ART clinic from 2004 to 2018 who met the inclusion criteria were included in the study.

2.6 Data collection technique

The data for this study included patient information that are routinely collected at pre-assessment, starting ART, ART switch and subsequent follow-up visits on standardized forms, and also at pharmacy drug pick up data. Trained data clerks enter the information in the forms into an electronic data platform using FILEMAKER PRO software (FileMaker Inc, Santa Ana, CA, USA). The data extracted from the electronic data base included socio-demographic characteristics, WHO staging, CD4 Viral load, first line treatment regimen, duration on therapy and percentage adherence. The data was cleaned and then coded for statistical analysis. To estimate adherence, a medication possession ratio was calculated by dividing the number of days that a patient submitted refill prescriptions by days since regimen initiation. Patients are routinely scheduled for clinic visits every 28 days or 56days (depending on how long and how virally suppressed they are). At each visit, the patients were given a 30-day or 60-day supply of medication and patients accrue 2 or 4 extra days of pills at each refill. Any missed refill visit resulted in a reminder phone call or a tracking visit to the patient.

2.7 Data analysis

Quantitative variables such as age of the study subjects are expressed as mean± standard deviation (SD), and viral load were expressed as median (interquartile range-IQR); Mann Whitney-U test was used to determine the variation in median viral load at baseline and at 72 weeks. Qualitative variables such as sex, marital status, educational level were presented using frequency tables, and expressed as percentages and Chi-square test was used to determine the associations between the socio-demographic characteristics and the virologic outcome. Kaplan-Meier curves were generated to estimate the mean time of VF, loss to follow up and survival at each time point. In generating the curves, VF was define as the latest VL greater than 1000 copies/ml otherwise VF was determined as viral load greater than 1000 copies/ml on two consecutive tests (24 weeks and 48 weeks). Undetectable viral RNA is defined as RNA copies less than 400 copies/ml which was the lower limit of detection of the assay. Patients who failed treatment after 48 weeks of ART would be compared with those who did not. All other variables were considered as independent variables such as age, sex, occupation.

The association between each independent variable and the outcome (VF) was examined using the Chi squared or Fisher's exact test for cells less than 5 for categorical variables, while the Wilcoxon-Mann-Whitney test was used for comparison of two medians. Univariate analysis was used to examine the association between the independent variables and outcome with the results expressed as odds ratios with their 95% CIs. Variables that were associated with treatment failure in the univariate analyses at $p<0.05$ would be fit into multivariate analysis using risk ratio and 95% CI as both point and interval estimate of the measure of effect of independent predictors of treatment failure. Stata software version 13.0 (Stata Corporation, College Station, Texas, USA) was used for analysis and a p-value of <0.05 would be considered statistically significant.

2.8 Ethical consideration

All patients included in the study provided written informed consent for their data to be used. The HIV clinic principal investigator and APIN granted permission for use of the secondary data for this study.

3. Results

3.1 Characteristics of the study population

Data from 387 patients on 2L cART were extracted from APIN/JUTH database between June 2004 and August 2018. A total of 285 (74.0%) met the inclusion criteria and were included in this analysis.

3.2 General characteristics

Females constituted 194(68.1%) of the study population, mean age of the patients was 45±9.5 years. The age group 41 to 50 constituted 107 (37.5%) of the population. Most of them were married 150 (53.9%), 116(41.7%) had tertiary education and 78(27.4%) were civil servants. The predominant mode of HIV acquisition was hetero-sexual sex 269 (97.7%). Females constituted the majority in the younger age groups (≤30, 31-40, and 41-50), but males are majority in the older age group of (51-60 and ≥60). Tertiary level of education was attained by both sexes in similar proportion but more females ended in primary education more than males (15(17%) Vs 39(20.5%).

Majority of the females were divorced 13 (6.9%) or single 46(24.2%) than the males 5(5.7%) divorced and 15(17.0%) single. Most males where civil servants (40.7% Vs 21.1%) compared to females who were mostly unemployed (29.9% Vs 3.3%) (Table 1). Percentage of patients with optimal Adherence to cART deceased from 85.6% on first line to 84.9% on second line therapy

3.3 Virologic outcome

The baseline VL was 54481 (IQR 6950-161640) copies/ml, Viral blip was experienced by 26(9.1%) and 19(6.7%) of our cohort at 24 week and 48weeks respectively. The proportion of patients with VF was 33(11.6%) at 48 weeks. (Figure 1)

The VL suppression (undetectable) was 34%, 69.8%, 69.5% and 72.1% at 12weeks, 24weeks, 48weeks and 72 weeks respectively. There was a rapid viral suppression from 12week to 24 weeks and subsequently marginal increases in viral suppression. At about 18week there was equilibrium between suppression and detection of viral load. (Figure 2)

3.4 Time to event analysis

For the period understudy, 61.1% were active on care, 24.6% were lost to follow up and 1.1% was dead (Table 2). The mean time to failure on 2L ART was 7.473± 0.269 95% CI (6.946-8.000) years (Figure 3). The mean time to loss to follow up on 2L ART was 7.228±0.250 95% CI (6.783-7.717) years.(Figure 4). The time to lose to follow up for treatment success was 9.140years and 6.290 years 95% CI (2.123-10.444) for treatment failure. (P<0.022) (Figure 5). The mean time to death on 2L ART is 9.697±0.091 95%CI (9.519-9.874) (Figure 6). There was no difference in time to death for patient having treatment failure or treatment success P< 0.168 (Figure 7).

Table 1: Sociodemographic Characteristics of Study population

Sociodemographics	Frequency (n = 285)	Percentage
Age Group (Years)		
≤ 30	10	3.5
31-40	88	30.9
41-50	107	37.5
51-60	58	20.4
≥ 61	22	7.7
Sex		
Male	91	31.9
Female	194	68.1
Occupation		
Civil servants	78	27.4
Artisans	33	11.6
Traders	49	17.2
Farmers	20	7.0
Unemployed	61	21.4
Student	26	9.1
Soldiers	1	0.4
Retiree	6	2.1
Others	11	3.9
Marital Status		
Married	150	53.95
Divorced	18	6.48
Single	61	21.94
Widowed	42	15.11
Separated	7	2.52
Total	278	100
Educational Status		
Primary	54	19.42
Secondary	88	31.66
Tertiary	116	41.73
None	20	7.19
Total	278	100
Risk Factor For Transmission		
Heterosexual	250(97.66)	97.66
MSM	1(0.39)	0.39
Transfusion	1(0.39)	0.39
Unknown	4(1.0)	1.56

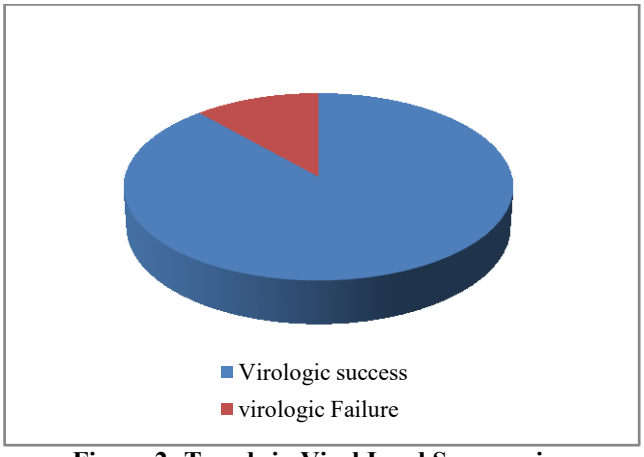


Figure 2: Trends in Viral Load Suppression

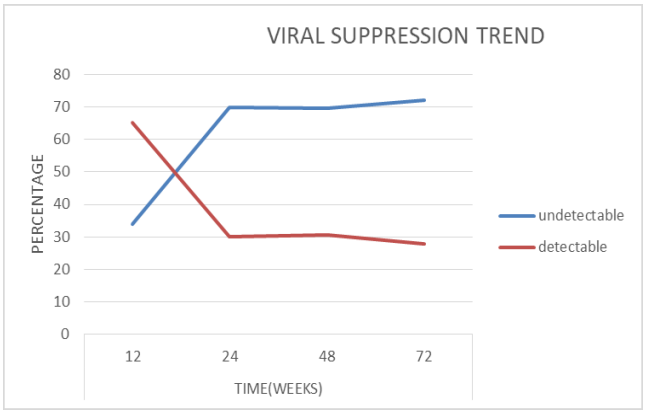


Figure 1: Pie Chart showing Virologic Outcome at 48 weeks

χ^2=41.912, P<0.0001

Table 2: Patient clinic status on second-line ART and Treatment outcome

	Frequency n (%)	Treatment Outcome		
		Success n (%)	Failure n (%)	p-value
Active	174(61.1)	157(90.23)	17(9.77)	0.099
Died	3(1.1)	2(66.67)	1(33.33)	
Transferred out	38(13.3)	36(94.74)	2(5.26)	
Loss to follow up	70(24.6)	57(81.43)	13(18.57)	

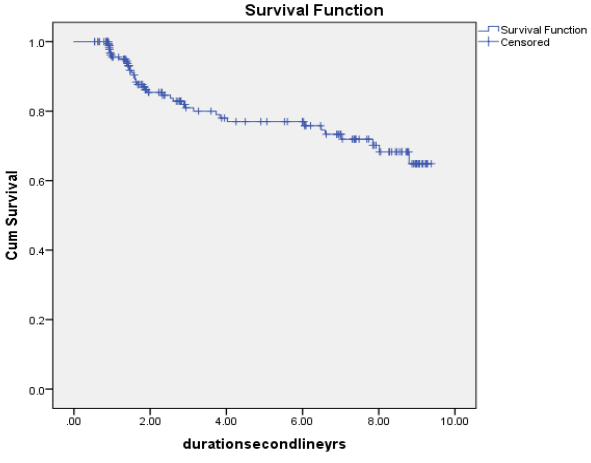
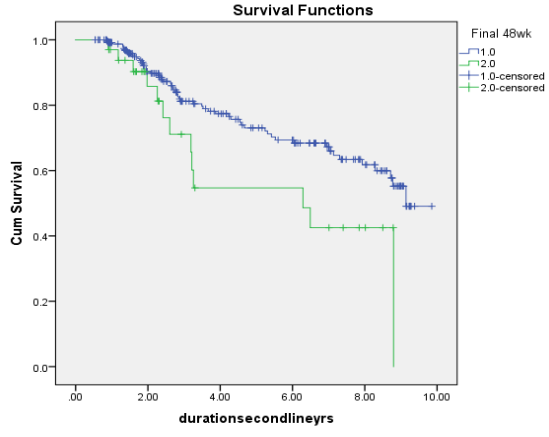


Figure 3: Kaplan Maier plot for Time to Virologic Failure for the study population



P<0.022 Log rank test

Figure 5: Kaplan Meier Plot for Time to Loss to follow-up of Treatment failure and Treatment Success

KEY: Blue; Treatment success, Green; Treatment failure.

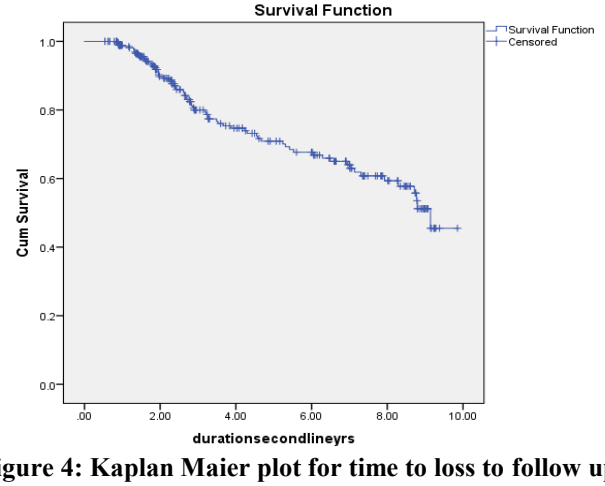


Figure 4: Kaplan Maier plot for time to loss to follow up for the study population

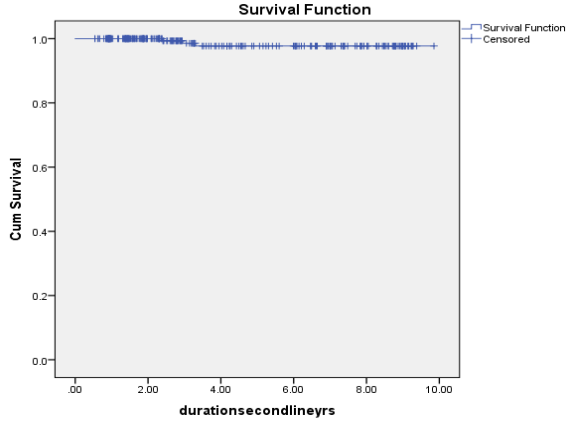


Figure 6: Kaplan Maier plot for Time to death for the study population

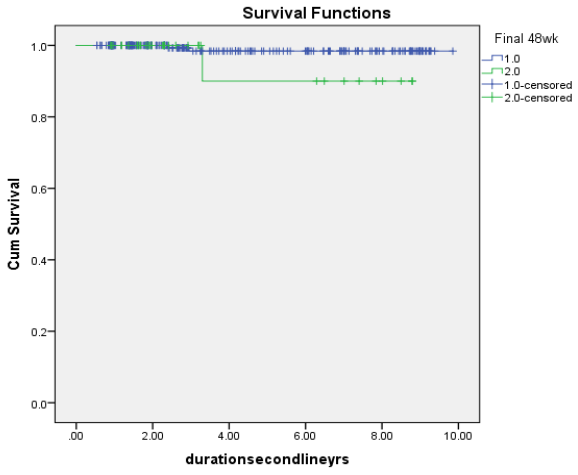


Figure 7: Kaplan Maier plot for Time to death for treatment failure and Treatment success

P<0.168 Log rank test; KEY: Blue; Treatment success, Green; Treatment failure.

4. Discussion

Antiretroviral Therapy (ART) has changed the prognosis of HIV infection from an ultimately fatal infection to a chronic illness. Sustained virologic suppression is the ultimate goal of ART with the attendant benefits to the individual patient and the community. A growing number of PLHIV are expected to be on 2L ART in low- and middle-income countries (LMICs)[25], and the rates of failure may differ from place to place. This study found that virologic suppression was rapid between 34% at 12 weeks and 69.8% at 24 weeks of ART and in-between at about 18 weeks equilibrium between suppression and viral detection was achieved and subsequently suppression rates increased marginally up to 72 weeks (69.5% to 72.1%)

In a Nigerian prospective cohort on 2L ART outcome at 6 to 9 months, 88.3% on treatment (OT) had an undetectable VL. At 12 months, 90.57% (OT) had UDVL at >12 to 24 months and at >24 months, 91.3% (OT) had undetectable VL. These rates of suppression are higher than what was obtained in this study, which is a retrospective study and may be more comparable to real clinic situations than a controlled prospective study. In another cohort study conducted in South Africa, Fox *et al*. reported a 77% viral suppression rate at 1 year on 2L ART. Also, Murphy *et al*. reported the rate of VF during the first 24 months of 2L ART using a cut off of less than 50copies/ml as 26%, 25%, 21%, and 25%, at 6, 12, 18 and 24 months respectively in a retrospective cohort in South Africa[26]. Although the study used a lower threshold, the rate of suppression is still better than what our study found; this may be attributable to the patient's better adherence and other clinic conditions.

Treatment failure was found to be 11.3% at 48 weeks when 2 consecutive VL results above 1000 copies/ml were used. This rate is lower than that documented In a meta-analysis of retrospective 2L outcomes in LMICs which showed the cumulative pooled proportion of adult patients failing therapy to be 21.8%, 23.1%, 26.7% and 38.0% at 6, 12, 24 and 36 months, respectively [25]. More than halve of the studies included in the pooled analysis used VL greater than 400copies /ml and only about halve had 2 consecutive measures. In another study in the USA, virologic failure was 17% at 6months for patients with viral load greater than 400copies /ml and 12% for those with viral load less than 400 copies/ml at commencement of 2L ART.[25]

It is important to note that the variability in definition for undetectable VL and VF makes comparison difficult across studies. This could be related to the newer and more sensitive viral load assays and also the occurrence of viral blips may have informed the cut off for virological failure above 1000 copies/ml on two measurements [26] in WHO guidelines and Nigerian national guideline for ART.

Viral blip was experienced by 26 (9.1%) and 19 (6.7%) of our cohort at 24 week and 48weeks respectively, although this may be attributed to variability in the testing process, temporary changes in drug concentration, or transient bursts of immune activation. Blips are not necessarily associated with emergence of drug resistance or worse adherence than those with consistently undetectable VL, or lower drug levels before, during, and after viral load blips.[27-29]

However, multiple blips, or those that start occurring with increasing frequency, may be an early sign of impending treatment failure. Persistent Low Level Viraemia between 50-199 copies/ml has also been shown to be associated with VF among ART-experienced patients under ART. [30]

Even with the best available therapy and optimal adherence, viral blips can occur. For this reason, guidelines advise that VL should be checked at least twice to see if the increase is an ongoing trend before deciding whether to change treatment.[31,32]

Further studies may be required to evaluate the significance of viral blips as regards transmission of HIV if the 95-95-95 target of ending the HIV epidemic is realistic as the emphasis of the last 95 target is to have 95% of patients on ART with undetectable viral load.[33] Patients now live longer on ART if they achieve sustained virologic suppression. The median time to virologic failure in this study was longer compared to that observed in the Swedish. Infcare database study, which was 4.5 years [34]. Differences in the definition of VF, cohort characteristics, and statistical design may have contributed. The study used a cut off of 200copies/ ml at 6months and two consecutive VL >50copies/ml and also most of the patients were switched due to other reasons than VF, and 8% in the Swedish cohort had NNRTI-DRM to 1L ART this goes further to buttress on the reasons for switch to 2LART. A study in Brazil also showed that the most frequent cause of switch to 2L was drug toxicities rather than VF and the

median time to VF was 40months[35]. Although this study did not have information on genotypic resistance testing, treatment failure was the main reason for switch to 2L ART. In determining the outcome variable as at the latest viral load result for the Kaplan Maier estimates, it was not possible to repeatedly use two consecutive HIV RNA measurements as in the definition of VF. Instead, we used a single VL result >1000copies/ml as VF, this could have led to some misclassification of patients as failures when in fact this would not have been confirmed. In addition, in real clinic situations, physicians may have only one measurement available and that implies that decisions to switch regimens may be based on only one measurement, meaning that patients might be unnecessarily subjected to treatment modifications. Studies have shown that individuals on 1LART virologic failure experienced re-suppression without switching [36]. To explore these speculations, additional studies are needed. The median VL in this study was below 100000 copies/ml. It has been documented that higher values are independent predictors of treatment failure and time to virologic suppression [37,38]. This may also be the reason for the long duration to VF in this cohort.

However, patients failing 2L ART in this cohort have a significantly shorter duration of 2.31 years to fail. This is important as risk factors that could contribute to early failure like primary resistance to 2L, opportunistic infections, drug side effects and poor adherence among others must be investigated and addressed before and during 2L ART.

Lost to follow up (LTFU) impact negatively on the benefit of ART to the individual and community at large, about a quarter of the patients where LTFU, this is lower when compared to what was seen in Ethiopia [39]. Patients who were LTFU may have died or defaulted treatment and may return to care later. The median duration to LTFU in this cohort was about 7.0 years. This period coincided with decentralization of ART services to ensure wider availability, and some patients may have enrolled into care in other centres without proper referral.

But, however, patient failing second line ART have significant shorter duration to lost to follow up, these are patients that are likely to have low CD4 count and opportunistic infections and may have died without a report in the clinic a such they are recorded as lost to follow up.

Documented mortality among the patients was 1.1% which is much lower compared to what was seen in other African countries. This may likely be due to gross under-reporting of mortality in the clinic and those patients may have been captured as LTFU. A prospective study will capture such events better. The median duration to death on 2L was about 9 years and the median time to LTFU was 7years this may suggest that death usually occurs after lost to follow up, this may be subjected to further studies. Most studies in low-income countries showed that mortality is high early after commencement of ART. [40, 41] This is usually attributed to severe immunosuppression and opportunistic infections.

Although no risk factor was statistically significant in predicting VF in this cohort, this could likely be as a result of the nature of secondary data used for the study. Patients that have complete data and where included in the study are likely to be adherent on their treatment and may not exhibit significant difference and also missing data for some variables such as sex, age, co-morbidities, opportunistic infections could have contributed significantly in this regard. But it is noteworthy that drugs can only work in patients who take them, consequently adherence is cardinal to a successful ART. Optimal adherence was observed in 85.6% of the patients during their period on first line ART. It has been shown that failure to address patients' poor adherence behaviour at first-line virological failure, as indicated by sub-therapeutic drug concentrations with/without major DRMs, placed them at high risk of failing second-line ART. Optimal adherence decreased marginally during 2L cART to 84.9% this was however not statistically significant with treatment failure, this may be attributable to the high genetic barrier of boasted protease inhibitor that may require several mutations before VF[42]. Most of the patients are on Tenofovir containing second-line ART which has been shown to be less associated with treatment failure than other regimens.[43]

Other risk factors that have been documented to be associated with VF are age between 30 to 45 years, hereto-sexual transmission, infected with HIV for less than 6 years, patients with an initial VL of >100,000 copies/ml, low CD4 cell counts at second-line therapy initiation, use of suboptimal second-line regimens, a negative change in weight during the study period, a CD4 count <100 cells/mm^3 at switch, and patients categorised as WHO clinical stage IV at switch and Tuberculosis treatment were predictors of treatment failure in other studies. Other important factors identified as predictors of virological failure on second line cART in Tanzania include age less than 30years, being on first-line therapy for less than 3years and CD4 count of less than 200cell/ml[44].

Tuberculosis treatment is an important predictor in our environment because of its endemicity, the presence of Tuberculosis goes with immune activation, and its treatment interactions with protease inhibitors and the difficult access to rifabutin could all worsen outcomes.[45] These predictors are important for formulation of strategies which may include continued adherence intensification and targeted resistance testing before switching to 2L ARTART that could improve the outcome of this subgroup of at-risk patients identified by these predictors. A prospective study could better identify these risk factors.

5. Conclusion

The proportion of patients failing 2L ART in this cohort was comparatively low to other LMIC but fall short of target 95-95-95. There an urgent need for wide availability of third line ART for those failing 2L.

6. Limitations of the study

Missing data on some important variables such as viral load, age, sex, morbidities, could have impacted on the outcome of the study since the data was collected in the past. Therefore, the data that was included in the study are those with the complete dependent outcome variable.

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