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Research Article

Prevalence and Predictors of Virological Failure among Adults HIV Patients Receiving First Line ART in Northwestern Tanzania: A Cross Sectional Study

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Abstract

Background: Prevalence of immunological failure has been shown to be high in some African countries. Few studies however have assessed the magnitude of virological failure in Tanzania. This study aimed at determining virological failure and its associated factors in north western Tanzania.

Methods: A cross sectional study was conducted among HIV-infected patients who were receiving first line ART at Bugando medical centre. Virological loads were measured and socio-demographic and clinical information were collected for analysis. Patients with a single viral load of > 10,000 copies/ml were coded as having virological failure as per WHO definition and poor adherence level was defined as any adherence level of < 95%. Data analysis was done using STATA 11 to determine the proportion of patients with virological failure and its associated factors.

Results: In total 274 patients were enrolled and, 43 (15.7%) met the criteria of virological failure. The odds of having virological failure were independently associated with baseline CD4 counts of < 200 cells/µl (AOR = 8.6 (1.7 - 42.1), p = 0.008), poor adherence (AOR = 15.4 (6.6 - 36.1), p < 0.0001) and Nevirapine based regimen (AOR = 4.1 (1.6 - 10.4), p = 0.003).

Conclusion: Virological failure is prevalent among HIV patients on first line ART. Test and treat, adherence counseling and regular virological monitoring could optimize the virological outcome of HIV patients receiving first line ART in Tanzania and similar setting.

Keywords: *HIV/AIDS; First Line Antiretroviral Therapy; Virological Treatment Failure; Northwestern Tanzania*

Introduction

With the use of antiretroviral therapy (ART), morbidity and mortality due to HIV have been reduced significantly; in many cases, making HIV a chronic manageable disease [1]. The development of treatment failure however has been associated with increased morbidity and mortality [2,3]. Despite the scaling up of ART use in resource limited settings; optimal treatment monitoring remains a big challenge in this locale [4,5]. Virological monitoring which is the gold standard remains unavailable in most of the settings. Guidelines on HIV treatment therefore recommend the use of clinical and immunological monitoring in settings where viral load is not readily available [6].

Studies in sub-Saharan Africa have demonstrated a relatively high prevalence of immunological failure [7,8]. However, the accuracy of immunological criteria in detecting treatment failure has been found to be low [9-12]. Immunological criteria have been found to have low specificity and positive predictive value and therefore lead to a lot of misclassifications [13]. In most of the sub-Saharan African countries, routine viral load monitoring remains unavailable.

Predictors of HIV treatment outcomes in clinic cohorts have not been widely studied. Most of the known predictors of virological failure are based on analysis from clinical trial data. These may not be applicable to the more heterogeneous clinic cohorts. Adherence to treatment has been identified as the most important predictor of virological success [14,15]. Other predictors of virological failure include younger age, high baseline viral load; low CD4 count and missed clinic visits [16,17].

In Tanzania, overall HIV prevalence in the general population stands at 5.1% [18]. In 2014, it was estimated that there were 1,400,000 people living with HIV in the country [19]. HIV prevalence is higher among women (6.2%) than among men (3.8%). HIV prevalence is higher in urban areas for both women and men than in rural areas. Tanzania began to provide care and treatment services in October 2004. Between the year 2010 and 2013, the country contributed to 5% of the total number of people newly accessing HIV treatment globally

[20]. Routinely, treatment monitoring is done using clinical and immunological criteria. Viral load monitoring is not readily available. Very few studies have assessed virological failure and its predictors in Tanzania. This study aimed at determining the prevalence and predictors of virological failure in a clinic cohort in Northwestern Tanzania.

Materials and Methods

Study design and setting

This was a cross sectional study conducted between February and July 2011 among HIV-infected adults receiving first line ART with a follow up period of at least 1 year. This study was conducted at Bugando care and treatment centre (CTC) in Mwanza, Tanzania. Bugando is a tertiary and teaching hospital for the Lake Zone of Tanzania. The hospital serves around 16 million people from 6 regions of the Lake Zone, which are Mwanza, Kagera, Shinyanga, Tabora, Mara and Kigoma. The hospital runs both inpatient and outpatient treatment activities, with an approximate bed capacity of 900. CTC activities is one of the core part of outpatient activities, which started in 2004, and currently it serves more than ten thousand patients, of whom about 5000 are on ART. More than two thirds of these patients are on first line regimens and the rest are on the second line regime. The patients' clinic visits are usually on monthly basis. On follow up patients are clinically evaluated and then ART refill is done. TB symptom screening and other OI is done routinely; body weighing every visit is also done and CD4 estimations are done routinely every 6 months. Drug refill is done monthly at refill points, missed pills are recorded as number of days missed per week and ART is provided at the clinic free of charge.

Study participants

The study involved all HIV-infected patients aged 18 years and above enrolled for HIV care and treatment services who were still receiving first line ART and they were on ART for at least one year. Patients who were critically ill, with concurrent infections, and those on second line were excluded from the study.

Sample size and patients' enrolment

A minimum sample size of 260 patients was estimated using Kish and Leslie formula for cross sectional study assuming 13% of adult HIV positive patients on first line ART will have virological failure [11]. The adult HIV patients on first line ART with a minimum ART use of 1 year (12-months) were identified from daily CTC listing at Bugando on routine basis and they were invited by researchers to participate in this study. Patients fulfilling the inclusion criteria and who provided written consent were serially enrolled until the sample size was reached.

Sample collection and processing

For each patient enrolled into the study, about 1.5ml of blood was collected in an Ethylenediaminetetraacetic acid (EDTA) bottle for viral load. This sample was centrifuged in the intensive care unit (ICU) side lab to obtain plasma which was again transferred into cryovials and sent to BMC main lab for viral load measurements using COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, v2.0 series (Roche Molecular systems Inc, Germany) according to manufacturer's guidelines. The test has the capacity to quantitate HIV-1 RNA over the range of 20 - 10,000,000 copies/mL.

Data collection and statistical analysis

A structured questionnaire was used to collect information regarding, demographic data, date of diagnosis of HIV, date of ART initiation and regime, compliance level which was assessed using patient response and pill counting, body mass index (BMI), tuberculosis (TB) status, co morbidities, co medications, CD4 counts, VL, and other routine laboratory. The data was entered, verified and a cleaned, using Microsoft excel spread and the data analysis was done using STATA version 11 (College Station, Texas). Continuous variables were summarized by medians and interquartile ranges (IQRs) and categorical variables were summarized by frequency and percentage. The virological failure as study endpoint was defined a measurement of a single viral load of > 10,000 copies/ml as per WHO definition [2]. Poor adherence was defined as any adherence level of < 95% as described previous [21]. Logistic regression was used to find the predictors of virological failure. The variables with a p value of < 1.0 from the univariate analysis were included in multivariate analysis. Factors were considered to be significant associated with virological failure if the p value was < 0.05 on multivariate mode.

Ethical statement

The permission to conduct this study was obtained from the department of Internal Medicine and Bugando research and ethical committee. Written informed consent was obtained from all participants, and the study involved only those patients who consented. All patients with virological failure were switched to second line as per existing national guideline. Patients' identifiers were not included in analysis to further maintain confidentiality.

Results

General characteristics of study participants

A total of 274 participants were enrolled for this study. The median duration on ART was 26 months (IQR 12 - 45). Majority of the participants 178 (65.7%) were female; the baseline CD4 count was 139.5 [60 - 210] cells/µl. Most of the study participants 197 (71.9%) presented with WHO clinical stage 3 or 4 at the time of enrollment to the clinic (Table 1) and for the most part of the participants, 108 (39.4%) were on TDF+FTC+EFV ART regimen as summarized in figure 1.

Variable	Number(%) or median (IQR)
Gender	109 (69.9)
Females	178 (65.7)
Males	96 (34.30)
Age (years)	39 [33 - 45]
Age group	
> 45 years	61 (22.26)
< 45 years	213 (77.74)
Baseline CD4	
< 200 cells/µl	196 (71.5)
≥ 200 cells/µl	78 (28.5)
WHO stage	
Stage 3 and 4	197(71.9)
Stage 1 and 2	77 (28.1)
BMI (kg/m^2)	21.9 [19.7 - 24.0]
BMI categories	
Under weight	38 (13.87)
Normal weight	130 (47.45)
Over weight	86 (31.39)
Obese weight	20 (7.30)
TB co-infection	
Yes	118 (43.1)
No	156 (56.9)
Duration of ART (months)	26 [12 - 45]
ART regimen base	
EFV base	179 (65.33)
NVP base	83 (30.29)
LPV base	12 (4.38)
Adherence level	
≥ 95%	217 (79.2)
< 95%	57 (20.8)

Table 1: *Baseline demographic and clinical characteristics of 274 adult HIV-infected patients on first line ART attending CTC at BMC*

ART: Antiretroviral Therapy: ABC: Abacavir; AZT: Zidovudine; CI: Confidence Interval; d4T: Stavudine; EFV: Efavirenz; FTC: Emtricitabine; LPV: Lopinavir; NVP: Nevirapine; TDF: Tenofovir.

Virological response and predictors of virological failure

Out of the 274 study participants, 43 (15.7%) were found to have a viral load of > 10000 copies/ml and when the threshold for virological failure was decreased to > 5000 copies/ml, the prevalence becomes 21.9% (n = 60). Viral suppression (viral load of <400 copies/ml) was found in 157 (57.3%) of the study participants (Figure 2). Several factors were tested for association with virological failure. The odds of having virological failure were independently associated with baseline CD4 counts < 200 cells/µl (AOR = 8.6 (1.7 -

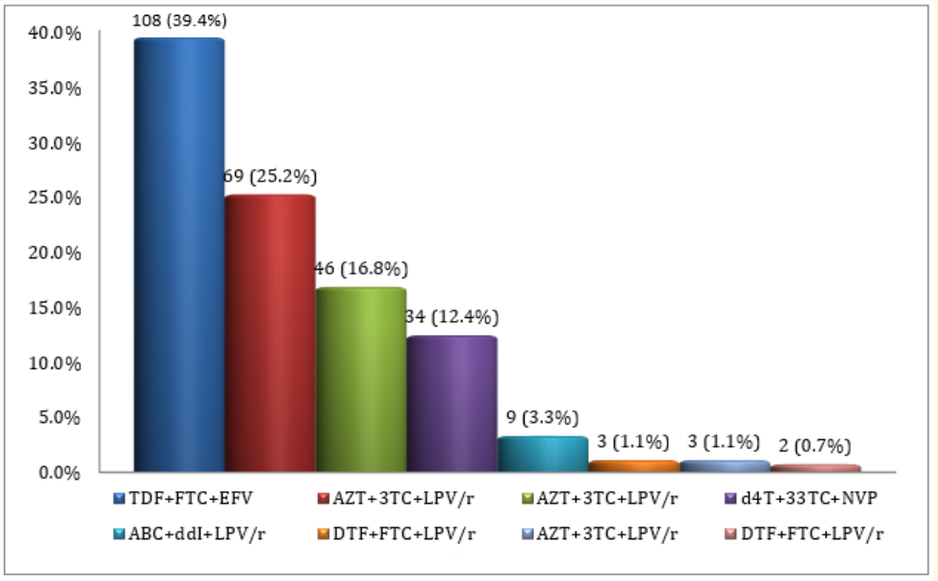

Figure 1: *Distribution of combined ART regimen among 274 participants.*

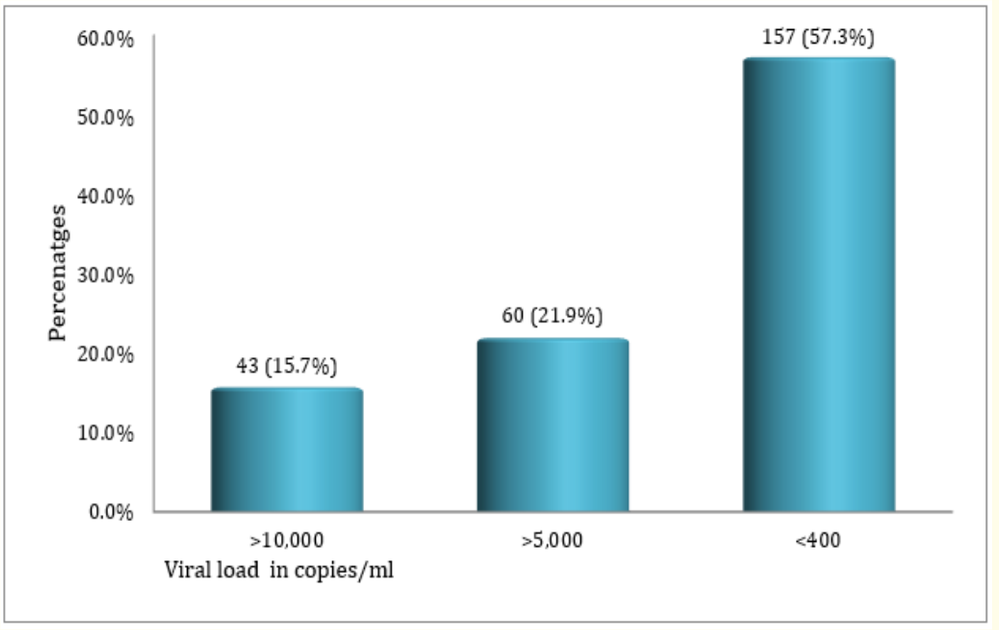

Figure 2: *Distribution of viral load among 274 participants.*

Discussion

In this study, the prevalence of virological failure by WHO defined criteria was relatively high in this cohort of HIV-infected adults. Low baseline CD4 count, reported low adherence level and Nevirapine based regimen were significantly associated with virological failure in this study. The predictors remained true regardless of the definition of virological failure used.

The prevalence of virological failure found in this study is similar to another study done in Nigeria reporting a prevalence rate of 13.7% as per WHO defined virological failure to be [11]. Using a virological cutoff point of 400 copies/ml a higher prevalence rate of 32% of virological failure was reported earlier in Tanzania (ADAR study) [22]. However, the prevalence in the index study is higher than reports

Variable	Unadjusted OR	P-value	Adjusted OR	P-value
Age				
< 45 years (ref)				
≥ 45 years	0.8 (0.3 - 1.8)	0.531	0.9 (0.3 - 2.6)	0.869
Sex				
Female (ref)				
Male	1.1 (0.6 - 2.2)	0.745	1.0 (0.5 - 2.5)	0.09
WHO stage				
Stage 3 and 4 (ref)				
Stage 1 and 2	0.5 (0.2 - 1.1)	0.072	1.2 (0.5 - 3.2)	0.684
Baseline CD4				
≥ 200 cells/µl (ref)				
< 200 cells/µl	10.1 (2.4 - 42)	0.002	8.6 (1.7 - 42.1)	0.008
ART regimen				
EFV based (ref)				
LPV based	0.5 (0.1 - 3.8)	0.843	0.1 (0.0 - 1.2)	0.005
NVP based	4.7 (2.3 - 9.2)	0.000	4.1 (1.6 - 10.4)	0.003
Adherence level				
> 95% (ref)				
< 95%	15.0 (7.1 - 31.8)	0.000	15.4 (6.6 - 36.1)	< 0.001

Table 2: *The univariate and multivariate analysis for factors associated with virological failure among 274 adults HIV positive patients on first line ART*

ART: Antiretroviral Therapy: CI: Confidence Interval; EFV: Efavirenz: LPV: Lopinavir; NVP: Nevirapine.

other East African countries. For instance in Uganda defining virological failure as viral load of > 10,000 copies/ml the prevalence was 7.1% [12] while in Kenya where a virological failure was defined as > 5,000 copies/ml the prevalence reported was 6% [23]. The study in Uganda was a prospective cohort study as opposed to our cross-sectional study. This could have resulted in closer medical attention and monitoring of participants explaining the low prevalence obtained.

Similar to many other studies, low baseline CD4 count and low levels of adherence were significantly associated with treatment failure in this study [7,17,24]. Adherence to ART has been shown to be the most significant predictor to virological success in other studies [14,15]. Non-adherence has been shown to be associated with virological failure [25]. It has also been found to be associated with failure to achieve virological suppression [26]. Non-adherence was also associated with poor virological response in the ADAR study done in Tanzania [22].

Low baseline CD4 has been associated with incomplete immune recovery in some reports [24]. Initiation of ART at higher baseline CD4 is associated with improved immune recovery, more survival benefit and prolonged virological suppression [27,28]. Low baseline CD4 count is associated with poor virological response [29], while high baseline CD4 is associated with sustained virological suppression [30]. The fact that majority of HIV positive individuals are still diagnosed at an advanced disease stage in Tanzania [31], it could imply higher risk of treatment failure later.

In our study, patients prescribed Nevirapine based regimen were more likely to experience virological failure than others. This finding is consistent with other studies that found that patients using Nevirapine based regimen were at higher risk of virological failure [32,33]. Time to treatment failure was shorter in clients on Nevirapine based regimen than in Efavirenz based regimen in one cohort study [34]. One systematic review found Efavirenz was significantly less likely to lead to virological failure than Nevirapine [35]. Previous studies done in Tanzania had demonstrated high prevalence of NNRTI primary resistance mutations [36,37].

Although the socio-demographic factors have been associated with treatment outcomes in other studies, in our study these were not significantly associated with virological failure. However, younger age had a tendency towards developing virological failure. This could be explained by the adherence levels; younger patients have been shown to have low adherence levels compared to older patients in several reports [38,39]. Longer duration on ART was also found to increase the risk of developing virological failure, although this was not statistically significant.

In Tanzania, treatment monitoring is routinely done using clinical and immunological criteria; viral load monitoring is still not readily available. Few studies that have been done had found relatively a high prevalence of virological failure in both children and adults [40,41]. Evidence shows that clinical and immunological criteria have low predictive value for virological failure [12,23]. The findings of this study highlights the need of using routine viral load monitoring in Tanzania to avoid misclassifications which usually lead to either delayed switches or unnecessary switches to second line [13].

This study had several limitations. It was based in a single clinic; the findings therefore may not be generalizable to the general population or other settings. Baseline data was obtained from patients' files (secondary data), these are usually incomplete; some important variables were missing. There was also limited number of socio-demographic factors that were explored or were available in this study. Individual differences in time of ART among study participants are another limitation for this observational study. It was not a randomized controlled trial, and patients initiated ART therapy at any time. However, only patients on ART for at least one year were enrolled for the study.

Conclusion

Virological failure was prevalent in this cohort of HIV infected patients on first line ART. Low baseline CD4 cell count, poor adherence and NVP based regimen were significantly associated with virological failure. Early HIV diagnosis and ART initiation coupled with intensive adherence counseling are important in improving treatment outcomes among HIV-infected patients initiating ART.

Conflicts of Interests

The authors declare no conflict of interest.

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Authors' Contributions

DWG: Designed the study, DWG, BCM, SBK: Collected and analyzed the data, DWG, BCM, and SBK: Did literature search and wrote the manuscript. EK, JRM: Critically reviewed the manuscript for its intellectual content. All authors read and approved the final manuscript.

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