Prevalence and predictors of Immunological failure among HIV-infected adults on HAART in Northwestern Tanzania: A cross sectional study

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Abstract

Background: Guidelines for the treatment of HIV recommend the use of immunological and clinical criteria for treatment monitoring in resource limited settings. Data on the magnitude of immunological treatment failure in sub-Saharan Africa is scarce. This study aimed at assessing the magnitude and factors associated with immunological failure among HIV infected patients on HAART.

Methods: A cross sectional study was conducted at Bugando Medical centre HIV care and treatment centre between February-July 2011, involving HIV-infected patients on first line ART for at least one year. Patients with concurrent infections and critically ill were excluded. A designed questionnaire was used to collect socio-demographic and clinical data of patients. Continuous variables were summarized by median and interquartile ranges (IQRs) and categorical variables were summarized by frequency and percentage. Logistic regression was used to find the predictors of immunological failure.

Results: 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 were female (65.7%); the baseline CD4 count was 139.5 cells/ul (IQR 60-210). Most

of the study participants (47.8%) presented with WHO clinical stage 3 at the time of enrollment to the clinic. Out of the 274 study participants, 57% fulfilled the criteria for immunological failure. WHO clinical stage 3 or 4 at ART initiation ($p<0.001$), low level of reported adherence ($p=0.001$) and longer duration on ART ($p<0.001$) were predictors of immunological failure in this cohort.

Conclusion: Immunological treatment failure was very high in this cohort of HIV-infected patients on first line ART. WHO clinical stage 3 or 4 at enrollment, low level of adherence and longer duration on ART were predictors of immunological failure.

Keywords: HIV/AIDS, adult, antiretroviral therapy, CD4 lymphocyte count, treatment monitoring, treatment failure, risk factors, Tanzania

Introduction

With the use of antiretroviral therapy, mortality due to HIV has declined significantly, making HIV a chronic manageable disease (1). However, reports show that treatment outcomes in a more heterogeneous clinic settings are unacceptably poor when compared to populations involved in clinical trials (2). Treatment failure, regardless of the underlying cause is usually associated with increased mortality and morbidity (3).

In Tanzania, HIV care and treatment centres were established in the year 2004. As of 2012, the country had approximately 1.4 million HIV-infected adults; out of whom 28% were enrolled to care (4). Currently the country has more than 260,000 HIV patients on treatment, which represents about 65% of those in need (4). The mortality has been reported to have been significantly reduced as a result. However, optimal treatment monitoring remains a big challenge. Viral load monitoring which is a gold standard remains unavailable in Tanzania; immunological monitoring, which is recommended by guidelines as an alternative together with clinical monitoring, is also suboptimal. There are also reports of suboptimal adherence levels to treatment (5).

In resource limited settings where viral load monitoring is not routinely available, guidelines recommend immunological and clinical criteria for the diagnosis of treatment failure (6). This is the practice in Tanzania based on the existing policy. Literature is scant on the issue of immunological monitoring in Tanzania. There is scarcity of reliable data on the rates and predictors of immunological failure as well. The aim of this study was to investigate the magnitude and predictors of immunological failure among HIV infected adults receiving first line ART attending care and treatment clinic in northwestern Tanzania.

Methods

Study design

This was a cross sectional study conducted at Bugando Medical Centre (BMC) care and treatment clinic between February–July, 2011.

Study population

The study involved HIV-infected adults (age ≥18 years), receiving first line ART for a minimum of 1-year. Patients with concurrent infection(s) and those who were critically ill were excluded from the study.

Study setting

This study was conducted at Bugando care and treatment centre (CTC) in Mwanza, Tanzania. Bugando is a tertiary level teaching hospital for the Lake Zone of Tanzania. The hospital serves around 13 million people from six regions located in the Lake Zone, which include Mwanza, Kagera, Shinyanga, Tabora, Mara and Kigoma. The hospital runs both inpatient and outpatient treatment activities, with an approximate bed capacity of 900. CTC activity is a core part of outpatient activities, which started in 2004, and currently it serves

more than 10,000 patients, of whom approximately 5000 are on ARTs. Most of the patients (two-thirds) are receiving first line ART.

Sample size and sampling

Sample size was estimated using Kish and Leslie formula. A minimum sample size of 220 patients was calculated assuming 50% of adult HIV patients had immunological failure. Patients fulfilling the inclusion criteria were serially enrolled until sample size was reached.

Data collection and laboratory analysis

HIV-infected patients aged 18 and above 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 were invited to participate in this study. These patients are usually followed up monthly or every two months depending on their clinical status. CD4 measurements are usually performed every 3-6-months. Patients who consented to participate in the study were enrolled. A structured questionnaire was used to collect information regarding demographic data, date of HIV diagnosis, date of ART initiation and regime, compliance level (which was assessed using patient response method), BMI, TB status, co morbidities, co medications, CD4, VL, ART serum levels, and other routine laboratory results. For each patient enrolled into the study, 1.5ml of blood was collected in an EDTA bottle for viral load. The study endpoint was development of immunological failure during follow up.

Definition of immunological failure

For this study, immunological failure was defined as per the WHO 2010 guideline. Immunological failure is defined as a fall of follow-up CD4 cell count to baseline (or below), or CD4 levels persisting below 100 cells/mm3, or 50% fall from on-treatment peak value; in the absence of concurrent infection(s) (7).

Statistical analysis

The data was entered, verified and cleaned, using Microsoft Excel and the data analysis was done using STATA version 14 (College Station, Texas). Results were expressed using medians and interquartile ranges (IQRs. Logistic regression was used to find predictors of immunological failure. The variables with a p value of <0.2 were included in multivariate analysis. The p value of <0.05 was considered to be significant.

Ethical statement

The permission to conduct this study and publish the findings was obtained from Catholic University of Health and Allied Sciences (CUHAS/BMC joint research and ethical committee). The involved only those patients who consented to participation. All patients with immunological failure were switched to second line ARV treatment. All the findings were made available in patients' medical records and to the attending clinicians.

Results

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). The majority of the participants were female (65.7%); the baseline CD4 count was 139.5 cells/ul (IQR 60-210) (table 1). Most of the study participants (47.8%) presented with WHO clinical stage 3 at the time of enrollment to the clinic (table 1).

Table 1: Baseline demographic and clinical characteristics of HIV-infected adults on first line ART attending CTC at BMC (n=274)

Variable	Number(%) or median (IQR)
Age (years)	39 (33-45)
Gender	109 (69.9)
Female	178 (66)
Males	93 (34)
WHO stage	
Stage 1	11 (4.0)
Stage 2	66 (24)
Stage 3	131 (48)
Stage 4	66 (24)
BMI (kg/m^2)	21.9 (19.7-24.0)
Baseline CD4 (cells/ul)	139.5 (60-210)
ARV regimes	
Stavudine based	34 (12)
Zidovudine based	129 (47)
Tenofovir based	111 (41)
Duration of ART (months)	26 (12-45)
TB co-infection	
Yes	118 (43)
No	156 (57)
Adherence level	
≥95%	266 (97.1)
<95%	8 (2.9)

Immunological failure

Out of the 274 study participants, 156 (57%) experienced immunological failure after using ART for at least 1-year. Of those experiencing immunological treatment failure, 23 (8.4%) participants had CD4 counts below pre-treatment levels, 104 (38.0%) had ≥50% drop from on-treatment peak and 29 (10.6%) had persistent CD4 <100 cells/mm^3.

Predictors of immunological failure

Using the WHO definitions of immunological failure, in adjusted analyses, immunological failure was associated with WHO clinical stage 3 or 4 at the time of enrollment (OR 0.35 [IQR 0.21-0.58], P<0.001), longer duration on ART (OR=1.07 [IQR 1.04-1.09], P <0.001) and low level of reported adherence to ART (OR=1.73 [IQR 1.26-2.37], P=0.001) (table 2).

Table 2: Logistic regression analysis for predictors of Immunological failure among HIV-infected patients on first line ART

	Unadjusted		Adjusted	
Variable	**OR [95% CI]**	**P value**	**OR [95% CI]**	**P value**
Age	1.04 [1.01- 1.06]	0.005		
Sex	1.69 [1.02- 2.80]	0.043		
Baseline BMI (kg/m^2)	1.08 [1.02- 1.14]			
Baseline CD4 (cells/ul)	0.999 [0.996- 1.0]	0.25		
WHO stage	0.22 [0.14- 0.34]	<0.001	0.35 [0.21- 0.58]	<0.001
Duration on ART (months)	1.09 [1.07- 1.12]	<0.001	1.07 [1.05- 1.10]	<0.001
Adherence	1.81 [1.44- 2.29]	<0.001	1.73 [1.26- 2.38]	0.001

Discussion

In this study, more than 50% of the patients on first line ART were experiencing immunological failure. This was unconfirmed immunological failure, without a confirmatory CD4 count. The analysis was limited to HIV-infected patients on ART for at least one year. Advanced HIV at diagnosis, longer duration on ART and low adherence level significantly predicted the risk of immunological failure.

The prevalence found in this study is higher compared to studies elsewhere. Other reports in sub-Saharan Africa report rates between 10-32%. A study done in Nigeria, using the same definitions of immunological failure, without confirmatory CD4 found a relatively higher prevalence of immunological failure (35%) (8). Another study in Ethiopia found a prevalence of 22% (9). When using unconfirmed criteria, the prevalence of immunological failure has been found to be very high. This is because CD4 count measurement is known to have large variability. Studies that used confirmatory CD4 have come up with relatively lower immunological failure. Studies using confirmatory CD4 found a prevalence of <15%. Differences in rates of immunological failure between studies using confirmed CD4 counts and those using unconfirmed CD4 counts have come up with large differences.

Clinic enrollment with WHO clinical stage 3 or 4 was associated with the risk of developing immunological failure in this study. This is similar to the findings in other studies. A study done in Ethiopia found that immunological failure was significantly associated with WHO clinical stage 3 or 4 (9). It was difficult to compare our findings with other studies in sub-Saharan Africa which used definitions for immunological failure other than the WHO definitions (10,11). Another factor associated with immunological failure in this study was poor adherence. Low level of adherence has been associated with immunological failure in other studies elsewhere (12). Poor adherence is usually associated with HIV clinical progression (13).

WHO immunological criteria have been shown to have a high negative predictive value in detecting treatment failure despite low sensitivity and positive predictive value (8,14). This makes it as a good test for ruling out treatment failure in patients on ART. However, because of the low sensitivity and positive predictive value, it is recommended that targeted viral load should be used in patients with immunological failure as a confirmatory test for treatment failure (6).

In this study, 38% of the participants were diagnosed with immunological criteria using the criteria for a ≥50% drop of CD4 from the on-treatment peak value. This finding is similar to a study done in Ethiopia which found that 58% of the patients with immunological failure had a drop of CD4 of ≥50% from the peak on-treatment value (9). This shows that most of the patients had experienced an initial increase in CD4 before it started to drop later on. Several studies have shown rapid CD4 gain in the first year following the initiation of ART (15,16).

This study is one of the few that address the issue of immunological failure in Tanzania, and identify some of its risk factors. However, this study had several limitations. It was based on a single clinic; thus the results may not necessarily be generalizable. The sample size was relatively small as well. A multicentre study or analysis of the national data should be done to better analyze the situation in Tanzania.

Conclusion

Immunological failure was prevalent in this cohort of HIV-infected patients. Treatment initiation with WHO clinical stage 3 or 4, longer duration on ART and low level of reported adherence were significantly associated with treatment failure. Targeted viral load monitoring should be made accessible in this setting to minimize unnecessary switches given the low positive predictive value of immunological criteria.

Conflict of interest

The authors have no conflict of interest to declare

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