Prevalence and Risk Factors of First Line Antiretroviral Therapy Failure Amongst Adult HIV Patients at a Nigerian Teaching Hospital: A 10 Year Retrospective Study.

Vivian Kwaghe[1], Isiaka Abdulrahman[2], Naanle Kumtong[2], Kufre Nkanga[2], Rapnap Lamda[2]

[1]Department of Internal Medicine, University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria
[2]HIV Treatment (PEPFAR) Clinic, University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria.

ABSTRACT

Background: The rapid scale up of antiretroviral therapy (ART) is associated with the development of drug resistance and subsequent ART treatment failure. The timing and accuracy of identifying treatment failure in resource-limited settings are fundamental but challenging. The aim of this study is to determine the prevalence of first-line ART failure, and to identify those risk factors that contribute to treatment failure. **Methods:** A retrospective study was conducted on 10335 adult People Living with HIV/AIDS (PLWHA) who had started first line ART between the period of January 2006 and December 2016 at the University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria. Standardized questionnaire containing information on socio-demographic characteristics, baseline clinical and laboratory parameters information was used in reviewing their medical records. Data was analyzed using SPSS version 20. **Results:** Out of the 10335 PLWHA recruited in the study, 9199 were on 1st line and 1136 failed first line and were switch to 2nd line over the period of the study. The majority of the participants were females, constituting 65.2% of the total population. The mean Age at Initiation of HAART was 37.4years.The prevalence of 1st line ART failure was 11%. Poor adherence, low baseline CD4 count, missed clinic appointments were found to be predictors of treatment failure. **Conclusion:** The prevalence of 1st line ART failure was 11%. The likelihood of 1st line ART failure occurring was most for patients who had poor adherence, low baseline CD4 count and those who had missed clinic appointments.

Keywords: HIV/AIDS, treatment failure, adherence.

INTRODUCTION

HIV has been a global challenge for the past three decades. About 78 million people have become infected with HIV since the start of the epidemic. According to the joint UNAIDS and WHO report of 2015, 36.7 million people worldwide are living with HIV; 70% of whom live in Sub Saharan Africa.[1] Nigeria has the second largest HIV epidemic in the world.[2] Although HIV prevalence among adults is remarkably small (3.1%) compared to other sub-Saharan African countries such as South Africa (19.2%) and Zambia (12.9%), the size of Nigeria's population means 3.5 million people were living with HIV in 2015.[3] As of December 2015, an estimated 17.0 million people globally were receiving antiretroviral therapy.[1]

The rapid scale-up of antiretroviral therapy (ART) in resource-limited settings over the past decade has resulted in substantial reductions in morbidity and mortality and increased life expectancy for people living with HIV/AIDS.[4-6] Despite the significant

Name & Address of Corresponding Author
Dr. Vivian Kwaghe,
Department of Internal Medicine,
University of Abuja Teaching Hospital,
Gwagwalada, Abuja,
Nigeria.

reduction in morbidity and mortality among the HIV-infected patients receiving combination ART, a considerable number of patients fail to achieve a sustained virological and immunological response to therapy.

The benefits of ART are however eroded when virological treatment failure develops. Patients who remain on a failing first- line ART regimen experience higher morbidity and mortality.[7,8] Such patients should therefore be switched to a potent second-line regimen.

Treatment failure can be defined as progression of disease after initiation of HAART. Failure can be assessed by clinical (the appearance of new opportunistic infections, ongoing weight loss, etc.), immunologic (a decline in CD4 count), or virologic (a viral rebound above a set threshold of 1000 copies/mL) criteria.[9]

Viral load monitoring has become the standard of care for monitoring the success of and diagnosing the failure of ART and has been explicitly recommended, when available, by the World Health Organization (WHO) since 2010.[10,11]

In settings in which there is no access to viral load testing, clinical monitoring alone or a combination of clinical and immunologic monitoring is used to assess response to ART and also to determine treatment failure.[12]

Patients who have failed the first-line ART are 46% more likely to fail the second-line ART and have a greater likelihood of experiencing drug resistance.[13] The development of drug-resistant virus strains can be another threat if the resistant virus is transmitted in the population early detection of treatment failure is therefore crucial to sustain the effectiveness of the first-line therapy.[14,17]

The documented factors associated with treatment failure include poor adherence, certain ART regimen combinations, primary infection with drug resistant strains of HIV, prior exposure to antiretroviral monotherapy, drug–drug interactions, drug side effects, drug toxicity, high baseline plasma viral load and low baseline CD4 count.[18-21]

The purpose of this study is to determine the prevalence of first-line ART failure and to identify those associated risk factors that contribute to treatment failure in HIV patients in a tertiary hospital in Nigeria. Identification of these risk factors will help the health professionals to suspect and diagnose treatment failure early, and switch early to a potent second line regimen; therefore preventing the accumulation of drug resistant mutations and drug toxicity. This in turn will lead to improvement in the quality of care, and reduction in morbidity and mortality among HIV patients.

MATERIALS AND METHODS

This is a retrospective Cross-sectional Study that involved the review of the medical records of 10335 HIV patients who started ART between January 2006 and December 2016 at the University of Abuja Teaching Hospital, Gwagwalada, Abuja, Nigeria.

The HIV centre at the University of Abuja Teaching Hospital was established in March of 2005. It is one of the largest PEPFAR/USG-supported ART centres in the North Central zone of Nigeria. The hospital is a tertiary health institution that serves as a referral centre to neighboring states like Niger, Kaduna, Plateau, Nassarawa and Kogi states. It is a three hundred and fifty bedded capacity hospital.

A well-structured questionnaire was used to extract information from the patients' case notes. It contained patient information on socio-demographic characteristics, baseline clinical and laboratory parameters, treatment related information - first-line ART regimens, duration on first-line regimen, adherence history, and reasons for switch to 2nd line and 2nd line ART regimen etc.

Inclusion criteria
1. HIV/AIDS patients greater than or equal to 18 years of age who started ART between January 2006 and December 2016.
2. All Patients switched to Second-line HAART between January, 2006 and December 2016 with a CD4 and VRL results; prior to switch as contained in the National HIV/AIDS Treatment Guidelines, 2014.

3. The patient must have at least one follow-up visit in the last 6 months.

Exclusion Criteria
1. Patients less than 18 years of age.
2. Patients on PMTCT or on Post Exposure Prophylaxis.

The data was entered into Microsoft Excel, 2016 and analyzed using SPSS version 20. Bivariate analysis was done using Cross tabulation and a test of association carried out using binary logistic regression at a significant level of $p < 0.05$. The results were presented in tables using frequencies and percentages.

Ethical approval was obtained from the Medical and Ethics Research Committee of the University of Abuja Teaching Hospital. Patient information obtained from their medical records was kept confidential and anonymous.

RESULTS

Table 1: Distribution of patients by sex, missed appointment, current regimen line, and Adherence assessment level

Sex	Frequency	Percent
Female	6735	65.2
Male	3600	34.8
Total	10335	100
Missed appointment		
No	8952	86.6
yes	1383	13.4
Total	10335	100
Current Regimen Line		
1st Line	9199	89
2nd Line	1136	11
Total	10335	100
Adherence assessment		
<95%	391	3.8
>95%	9944	96.2
Total	10335	100
Baseline CD4 cell count		
≤ 200	6264	60.6
>200	4071	39.4
Total	10335	100

Table 2: shows the different variables among those who failed first line ART and switched to 2nd line and those who remained on first line.

Variables	1st Line art	2nd Line art	Total	p-value
Sex				
Female	6008(89.2)	727(10.8)	6735	
Male	3191(88.6)	409(11.4)	3600	0.77
Missed appointment				
No	8870(99.1)	82(0.9)	8952	
yes	323(23.8)	1054(76.2)	1383	0.0001
Adherence				
<95%	283(72.4)	108(27.6)	391	
≥ 95%	8916(89.7)	1028(10.3)	9944	0.00004
Baseline CD4				
≤ 200	5381(84.9)	883(14.1)	6264	
>200	3818(93.8)	253(6.2)	4071	0.00001

Table 3: logistic regression

	Unadjusted			Adjusted		
	OR	CI	P value	OR	CI	P value
Sex	1.07	0.867-1.32	0.77	1.06	0.858-1.309	0.79
Missed	0.003(No)	0.002-0.004	0.0001	0.002	0.001-0.003	0.0003
CD4	0.652(≤200)	0.559-0.76	0.00005	0.488	0.297-0.8	0.005
Adherence	2.302(<95%)	1.24-3.38	0.000	37.199	23.93-57.8	0.00006

From a total number of 10335 HIV patients enrolled during the study period, 6735 (65.2%) were females and 3600 (34.8%) were males. The mean age of the study population was 37.4 years. Most of the participants had completed primary school, 4.8% of them however had no formal education. The average monthly income was 138 USD.

Most patients presented with advance disease, the majority (60.6%) having CD4 cell counts of ≤200 Cells/mL at initiation of HAART.

During the study period, a total of 1136 (11%) of the participants developed virological failure (viral load ≥ 1000 copies/ml). The mean duration on first line ART before development of treatment failure was 140 weeks [Table 1].

Most of the participants (96.2%) had good adherence (adherence > 95%) to their ART. Comparing adherence between those that failed first line and those that did no fail, 90.5% of those that failed first line had good adherence compared to 96.9% of those that did not fail first line (p-value=0.00004). There was no difference in adherence between females (96.3%) and males (96.1%) [p-value=0.53].

Also, the mean baseline CD4 cell count of those who failed first line (46.6 cells/ml) was lower than that of those who remained on first line (124.8cells/ml) and this difference was statistically significant (p-value=0.00001). [Table 2].

A total of 1383 (13.4%) participants had records of having missed their clinic appointments at one point in time or the other. Among those with missed appointments, 76.2% failed first line and had to be switched to second line, compared to 23.8% of those who did not fail their first line ART regimen (p-value=0.0001).

Logistic regression model was used to access for risk factors for first line treatment. These include baseline CD4 ≤ 200 (adjusted odds ratio= 0.488, confidence interval=0.297-0.8, p-value=0.005), missed appointments (adjusted odds ratio=0.002, confidence interval=0.001-0.003, p-value=0.0003) and poor adherence (adjusted odds ratio=37.199, confidence interval=23.93-57.8, p-value=0.00006). [Table 3].

DISCUSSION

The treatment of HIV/AIDS with HAART over the last three decades has recorded a remarkable improvement in the quality of life of PLWHA as it reduces morbidity and mortality. However, these benefits of ART are eroded when virological treatment failure develops. Patients who remain on a failing first-line ART regimen experience higher morbidity and mortality.[7,8] Such patients should therefore be switched to a potent second-line regimen. Viral load testing is the goal standard for the diagnosis of treatment failure.

The aim of this study was to determine the prevalence of first-line ART failure and identify those risk factors that contribute to treatment failure. The prevalence of treatment failure in this study was 11%. This finding is comparable to that of Brhane et al in Northwest Ethiopia who reported a prevalence of 10.7% and Reynolds et al in Uganda who reported a prevalence of 9.9%.[22,23]

Poor adherence to ART has been shown to be a major risk factor for the development of treatment failure. In the Adult AIDS Clinical Trials Group protocol 370, Ickovics et al. reported that HIV/AIDS patients whose degree of adherence was less than 95% were 3-5 times more likely to have treatment failure compared to those with adherence levels of 95% or higher.[24] Similarly, Kwobah et al. identified that non adherence was associated with almost three times the odds of treatment failure.[25] Our study supports these findings in that those with poor adherence (<95%) are most likely to fail compared to those with good adherence (>95%). We showed that good adherence was found in 90.5% of those who failed first line ART, compared to 96.9% of those who did not fail first line ART (p-value=0.00004). In the logistic regression model, poor adherence was associated with first line treatment failure (p-value=0.00006). Reasons for poor adherence in our study population include forgetfulness, pill burden, lack of transport fare to the facility to pick up their ART. Some patients even abandon their ART after visiting spiritual healers who ask them to stop ART medications as a show of their faith.

In many developing Countries where facilities for viral load testing are not available, CD4 decline are used as surrogate marker for treatment failure. Analysis of the predictors in our study found that low CD4 count at ART initiation is a significant predictor for failure (p=0.005), which corroborates with several other studies.[26-28] The reason for this is not far fetch; a low baseline CD4 count causes more opportunistic infections leading to disease progression and more chances of associated ill health and lower compliance due to intolerance. The majority (84.9%) of our patients had baseline CD4cell counts ≤ 200 cells/ml. This is the trend in many parts of the Country and indeed Sub Saharan Africa where most patients present late to hospitals with advanced HIV infection and low CD4 counts.

We also identified missed clinic appointments as a predictor of first line ART failure. Among those that failed first line ART, 76.0% had missed clinic appointments, compared to only 0.9% of those who did not fail first line (p=0.0001). In the logistic regression analysis, missed clinic appointments is a predictor of treatment failure (p=0.0003). This is not surprising as patients who miss their clinic appointments are most likely to have poor adherence and may even run out of supply of ARV's. The major reason for missed appointments among our patients is lack of transport fare to the facility.

CONCLUSION

ART treatment failure is associated with increase morbidity and mortality among people living with HIV/AIDS. The prevalence of 1st line ART failure in this study was 11%. Unfortunately many HIV treatment facilities in Sub Saharan Africa do not have access to viral load testing, which is the goal standard for diagnosing ART treatment failure. In this study we showed that the likelihood of 1st line ART failure occurring was most for patients who had poor adherence, low baseline CD4 count and missed clinic appointments.

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