A decade of Anti-Retroviral Therapy in Nigeria: Efficacy of First Line Regimens in Treatment-Naive HIV/AIDS Patients.

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ABSTRACT

Background: The proportion of persons who become infected with resistant strains of HIV may be increasing. We assessed the efficacy of first line anti-retroviral (ARV) regimens since they were first introduced in Nigeria.

Methods: A descriptive prospective cohort study comparing baseline body mass index (BMI), CD+4 counts and viral load (VL) with those obtained at 6th month of highly active antiretroviral therapy (HAART) in 300 HIV infected treatment-naive patients. Data were analysed with Epi-Info version 3.3 software and a probability value < 0.05 was considered significant.

Results: The mean BMI at baseline of 22.9±4.6 kg/m^2 increased to 24.6±4.4 kg/m^2 at 6th month of HAART. Therefore, the absolute increase in mean BMI was 1.7kg/m^2 and was statistically significant p<0.05. The median CD4+ counts at baseline and at the end of the study shows counts of 127 cells/µl and 236 cells/µl respectively. This corresponds to a median increase of 109 cells/µl but was not statistically significant p=>0.05. When immunological response was measured as an increase from baseline of at least 50cells/µl, the proportion of patients with CD4+ count increase = 50cells/µl at the sixth month of HAART was 68%. The baseline median viral load was $\log_{10}$ 4.90, $\log_{10}$(IQR 3.41-6.41) but became less than $\log_{10}$ 2.60, $\log_{10}$(IQR 2.60-5.26) at 6th month of HAART. Hence, a median viral load reduction of at least $\log_{10}$2.30 p<0.05 was achieved.

Conclusion: This study supports the belief that using limited ARV regimens can result in acceptable treatment outcomes many years after they were first introduced.

Key Words: HIV, antiretroviral drugs, efficacy, Nigeria

INTRODUCTION

According to the estimate from the Joint United Nations Programme on HIV/AIDS (UNAIDS), about 33.3 million people were living with HIV/AIDS worldwide with an estimated 22.5 million in Sub-Saharan Africa by the end of 2009[1]. Nigeria reported her first HIV/AIDS case in 1986[2] and current estimates put Nigeria's HIV/AIDS prevalence at 3.6% in 2007 with over 300,000 new infections occurring in 2008[1]. In absolute numbers, nearly 3 million people live with HIV/AIDS in Nigeria. Early in the evolution of HIV/AIDS epidemic in Nigeria, anti-retroviral therapy (ART) was minimal and often initiated with single or dual agents. In 1999 however, the national AIDS treatment programme geared towards expanding access to antiretroviral drugs was instituted[3] and was followed by rapid scale-up in the subsequent years. Currently, nearly 30% of about 860,000 HIV/AIDS patients requiring treatment in Nigeria are receiving highly active antiretroviral therapy (HAART) according to the WHO 2006 criteria for initiating ART; a significant, though inadequate, increase when compared with ART coverage of 5% about ten years ago[1,4].

As ART becomes widespread in a given area, one might expect an increase in the proportion of patients who become infected with drug resistant strains. The extent to which resistant HIV will be transmitted depends on many factors, but the most important is ART use (ART coverage in an area, duration of ART use and number of patients on failing regimen)[5,6]. While most resistance to antiretrovirals (ARVs) will be acquired, resistance against antiretroviral drugs in previously untreated HIV-positive patients (primary drug resistance) is of growing relevance. It is characterized by reduced drug susceptibility in phenotypic testing or the presence of resistance-associated mutations in genotypic testing in subjects who were never exposed to antiretroviral compounds. The reason for this phenomenon is infection with resistant virus strains,[7] as described for sexual,[8] vertical,[9] and parenteral[10] path of transmission. For instance, ten years following the ART scale-up in Kampala, a repeated survey showed that 8.6% of newly HIV infected patients had mutations associated with resistant strains and likely represented an increase from a previous survey[11]. Consequently, clinical and laboratory measures of ART efficacy could be inferior in treatment-naive patients following widespread use of ART after a significant period of time.

In this study, we evaluated the efficacy of the commonly used first line ARVs in treatment-naive HIV infected patients following widespread use of ARVs. Our primary measures were body mass index (BMI), CD4+ cell counts and viral loads (VL) at baseline and six months of HAART.

METHODS

This was a prospective cohort study that was carried out at the Jos University Teaching Hospital (JUTH) to determine the efficacy of first line HAART in treatment-naïve HIV infected patients. Clinical response was measured as increase in body mass index (BMI); Immunologic response was measured as increase in median CD4+ and proportion of patients with CD4+ increases =50cells/µl from baseline while the virologic control was measured as log decrease in median viral load and proportion of patients with

undetectable viral load after commencement of HAART. The study was conducted between November, 2006 and April, 2007.

Three hundred consecutive treatment-naïve patients who met inclusion criteria where studied. Patients included were 18 years and above, had confirmed HIV infection by Western Blot and were eligible for ART according to 2005 Nigerian guideline[12]. We excluded patients already on ART and those less than 18 years of age.

The study was approved by the Research and Ethics Committee of JUTH, Jos. All the participants signed an appropriate informed consent form before enlisting for the study

The patients were followed up over a period of six months on tablets of Lamivudine(3TC) 150mg twice daily, Stavudine(d4T) 40mg twice daily, Nevirapine(NVP) 200mg daily for two weeks then twice daily if no Nevirapine side effect was observed. This was the commonest first line HAART regimen. Patients less than 60kg body weight were given Stavudine 30mg twice daily. Any other HAART regimens were noted. Patients were counselled on adherence and drug pick-ups were checked in the pharmacy computerized data-base. Complicating diseases were recorded together with therapeutic interventions.

Laboratory investigations were done according to the national guidelines.[12] CD4+ lymphocytes were counted using Flow cytometry with CD4 Easy Count kit-CY-R-1004 while Viral Load was determined using Polymerase Chain Reaction(PCR) technology with Amplicor HIV-1 Monitor® Test, Version 1.5 (Lower limit of detection <400 copies/µl).

Those positive for hepatitis B surface antigen or hepatitis C antibody were assumed to have hepatitis infection.

The Epi-Info Version 3.3 2004 statistical software was used for statistical analysis. Results were presented as median for skewed variables and means ± standard deviation (SD), and tables. The Chi-square(X^2) test was used to test proportions of categorical variables and a p value of < 0.05 was considered significant.

RESULTS

A total of 300 patients were enrolled into the study but 292(97.3%) patients completed the study. Five patients discontinued due to hepatotoxicity (two were concurrently on anti-tuberculosis therapy), two patients because of severe muco-cutaneous reactions and one patient was lost to follow-up.

The characteristics of the study population is shown in table 1.The patients were predominantly middle aged(37.8±6.8 years) females(64.7%) and mostly on 3TC, d4T, NVP(84%) with 96% treatment adherence. There were 48% of patients with assumed hepatitis infection and another 15% with tuberculosis (TB).

The results of our clinical and laboratory measures of ART efficacy are shown in table II.

The mean BMI at baseline was 22.9±4.6 kg/m^2. At six months on HAART, mean BMI was 24.6±4.4 kg/m^2. Therefore, the mean increase in BMI from the beginning of HAART to six months was 1.7kg/m^2 and was statistically significant $p<0.05$.

The median CD4+ counts at baseline and at the end of the study shows counts of 127 cells/µl and 236 cells/µl respectively. This corresponds to a median increase of 109 cells/µl but there was no statistically significant difference in median CD4+ at 6 months of HAART compared with baseline median CD4+ p=>0.05. When immunological response was measured as an increase from baseline of at least 50cells/µl, the proportion of patients with CD4+ count increase = 50cells/µl at the sixth month of HAART was 68%. The comparison of median CD4+ cells of patients with TB to their counterparts without TB at baseline and at 6 months did not show statistically significant difference in median CD4+ counts. For instance, median CD4+ count at baseline was 114 cells/µl in those with TB and 125 cells/µl in those without TB (p=0.13), and 220 cells/µl in those with TB and 231 in those without TB (p=0.20) at sixth month of HAART.

At baseline, the median viral load and range expressed in $\log_{10}$copies/ml was $\log_{10}$ 4.90, $\log_{10}$(IQR 3.41-6.41). At the end of the study period, median viral load was less than $\log_{10}$ 2.60, $\log_{10}$(IQR 2.60-5.26). In conventional figures, the baseline median viral load of 90,010 copies/ml reduced to less than 400 copies/ml at six months of HAART. Hence, a median viral load reduction of at least $\log_{10}$2.30 was recorded at sixth month of HAART. While all patients had detectable viral load at baseline, 80% had undetectable viral load at the

Table I. Patients socio-demographic and clinical characteristics

Sex	**(%)**
male	**35.3**
female	**64.7**
CDC stage	**(%)**
A	**37**
B	**51**
C	**22**
HIV transmission	**(%)**
Heterosexual	**93**
Other	**7**
Tuberculosis (TB) co-Infection(%)	**15.3**
Hepatitis coinfection(%)	
[a]HBsAg	**25.3**
[b]HCV anti-body	**23**
a & b	**2.3**
ART regimen	**(%)**
3TC + d4T + NVP	**83.6**
3TC + d4T + EFV	**15.7**
3TC + ABC + AZT	**0.7**
ART adherence(%)	**96**

Table II. Changes in efficacy measures at six months of HAART

	Baseline n=300	Six Months n=293	p-value
Mean BMI(kg/m^2)	22.9	24.6	4.4 <0.05
	-413)	236(61-650)	>0.05
	-------	68	<0.05
VL(log_{10})	4.92	2.60	<0.05
VL undetectable(%)	--------	80	<0.05

end of the study.

DISCUSSION

Effective HAART therapy leads to sustained suppression of viraemia and re-population of CD4+ T-lymphocytes which is associated with decreased risk of opportunistic infections, hospitalization and mortality[13-16].

The results of this study showed that first line ARV regimens are still efficacious in treatment-naive HIV/AIDS patients years after scale-up and widespread use of ARVs. A preliminary report[17] on the Nigerian antiretroviral programme indicated that between baseline and six months, the median viral load was reduced by 1.7log10 copies/ml and the median CD4+ count was increased by 140 cells/μl while median body mass index increased by 1.2kg/m^2, and are in support of our findings.

The efficacy of first line ARV regimens in this study was shown by increase in BMI of 1.7kg/m^2 at the end of the study period which is comparable to BMI increase of 1.2kg/m^2 at 6 months reported by Idigbe et al[17] who studied 50 patients preparatory to ART programme scale-up in Nigeria; they were on a regimen most patients (83.6%) in this study received. The increase in BMI noted in our patients could be accounted for by the reduced frequencies of opportunistic infections and better nutritional tolerance following effective HAART as previously described[15,18].

In this study, the median CD4+ count of 236 cells/μl at the sixth month of HAART was not significantly higher than baseline median CD4+ count of 127 cells/μl p=>0.05. While our finding is still comparable to that of Idigbe et al[17], the non-significant increase of 109 cells/μl could be attributed to the rather short duration of this study; since it may take two years to fully assess the extent of immunologic recovery[19], a time frame beyond the scope of this study. In terms of proportion of patients who achieved CD4+ increase = 50cells/μl, 68% of our patients had CD4+ counts = 50cells/μl above their baseline values at the end of the study. This CD4+ cell recovery might prove clinically relevant because an increase of 50 CD4+cells/□L during the first 6 months of starting potent antiretroviral therapy is associated with a 68% decrease in any AIDS-related opportunistic illness[20]. In this study, co-Infection with TB and hepatitis viruses did not significantly impair immunologic recovery. This may have been because patients were already on anti-TB for variable durations at enrolment, and active hepatitis infection could not be established based on HBsAg and HCV antibody positivity.

Plasma viral load assay is a critical component for evaluating ART efficacy. The median viral load reduction was at least log_{10}2.30, and 80% of our patients had undetectable viral load at the end of the study. Broadly, our result is consistent with that of Phillips et al[21] in which 85 to 90% of patients had undetectable viral load depending on their baseline CD4+ and VL counts using <500 viral copies/μl as lower limit of detection over a 32 week period. Our finding, however, contrasts that of Garcia et al[22] in which about 80% had undetectable VL within 12 weeks of initiating HAART. This observation could have been due to differences in sample size and the ART regimen with our study.

Our study has important limitations and the findings thereof should be put in context. For example, we did not perform ARV resistance assay on those patients who failed to achieve adequate CD4+ count increases and virologic suppression. In addition, our measures of efficacy, especially CD4+ counts and VL were assessed only twice and are therefore unable to isolate any transient changes from true lack of treatment efficacy.

In conclusion, our study demonstrates that first line ARVs are still efficacious and supports the notion that a public health approach using limited ART regimens can result in acceptable treatment outcomes even many years after they were first introduced. Nevertheless, vigilance against degradation of efficacy, which may be inevitable over time, is needed to avert this danger.

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