Immunological profile in persons under antiretroviral therapy in a rural Nigerian hospital

Baba Maiyaki Musa,[1] Usman Gebi,[2] Mary-Ann Etiebet,[2] Helen Omuh,[2] Patrick Ekedegwa,[3] Patrick Dakum,[2] William Blattner[4]

[1]Rasta Nurah General Hospital, Eastern province, Saudi Arabia; [2]Institute of Human Virology, Abuja, Nigeria; [3]General Hospital Otukpo, Benue State, Nigeria; [4]Institute of Human Virology, University of Maryland School of Medicine, USA

Abstract

Human immunodeficiency virus (HIV) contributes significantly to morbidity and mortality in sub-Saharan Africa, with Nigeria having the third highest burden of HIV infection globally; efforts are made to increases access to HIV/AIDS care and treatment. This has currently reached rural areas with limited manpower and laboratory evaluation capacity. This review is necessitated by the paucity of interim report on treatment profile in Nigerian rural areas. We report on the immunological profile of patients on antiretroviral therapy (ART) in Otukpo General Hospital, a rural Nigerian hospital. This is a retrospective cohort study of patients receiving ART treatment and care, on April 2009, when 2347 patients were under ART therapy. Out of these, 96 patients were selected by simple random sampling from hospital register, with their data abstracted from standardized Ministry of Health registers and facility documents kept at the hospital, and analyzed for descriptive and biometric measures. Ninty-six patients (29% males) with a median age of 35 years, median baseline CD4 lymphocyte count 221 cells/mL, median one year CD4 lymphocyte count of 356 cells/mL and median one year CD4 lymphocyte increment of 124 cells/mL were studied. There is no statistically significant difference in baseline CD4 lymphocyte count when data is disaggregated by type of drug regimen (AZT, D4T and TDF). Fourty-four percent, 23% and 33% of patients were on TDF, D4T & AZT based regimen, respectively (P=0.66). Increment of >100 cells/mL was seen in 64.58% of the reviewed patients. There was a higher CD4 lymphocyte count increment in patients on TDF & D4T compared with those in AZT based regimens (ANOVA; P<0.0003). Multivariate linear regression model showed one year CD4 lymphocyte count, one year increment in CD4 lymphocyte count, WBC count, and absolute neutrophil count to be significant correlates of baseline CD4 lymphocyte count (P<0.0001). Equally, multivariate logistic regression found age, platelet count and CD4 lymphocyte count at 12 months showed to be significant predictors of CD4 lymphocyte increment above 100 cells/µL (P<0.0001). Despite advanced disease presentation and a very large-scale program, high quality HIV/AIDS care was achieved as indicated by good short-term, immunologic outcomes, while TDF & D4T induce higher immunological recovery compared with AZT. This report suggests that quality HIV care and treatment can be effective despite the challenges of a resource-limited setting.

Introduction

Human immunodeficiency virus (HIV) contributes significantly to morbidity and mortality in sub-Saharan Africa, with Nigeria having one of the highest burdens of HIV infection globally. This has lead to a rapid scale up in the provision of anti retroviral medication to eligible patients throughout the country, which in recent times have reached rural areas.

Although there is substantial variation in the size and rate of CD4 lymphocyte T cell count recovery among patients receiving antiretroviral therapy (ART), there are only few studies describing the pattern of immunological response to ART in rural settings.

This study intends to highlight interim immunological outcome in ART treatment program from a Nigerian rural area.

Materials and Methods

This is a retrospective cohort study of adult patients receiving ART and care, in Otukpo General Hospital, Benue State, Nigeria. Eligibility for inclusion in the study was based on being hitherto ART naïve adult patient, enrolled on ART with minimum of two CD4 lymphocyte count results available (at initiation and at 12 months post commencement of therapy); documentation of clinical evaluation on at least two visits and documentation of basal hematological profile. All patients were on first-line ART regimen, which comprised of nucleoside reverse transcriptase inhibitor (NRTI9, zidovudine (AZT), stavudine (D4T), or nucleoside reverse transcriptase inhibitor Tenofovir disoproxil fumarate (DTF) with lamivudine (3TC) or emtricitabine (FTC) plus a non-nucleoside reverse transcriptase inhibitor (efavirenz or nevirapine). All studied patients were on one of AZT/3TC/NVP, D4T/3TC/NVP and TDF/FTC/EFV regimen. Exclusion criteria were age less than 15 years and prior history of ART exposure.

As of April 2009, 2347 patients were on ART; out of these, a convenient sample of 96 patients was chosen through simple random sampling. Random number table was used with numbers chosen based on serial numbers on Hospital register. Selections were serially made until designated sample size was achieved. Data was abstracted from standardized Ministry of Health registers and facility documents kept at the hospital, and analyzed for descriptive and biometric measures.

Data were analyzed using Stata version 11.0 (College Station, Texas, USA). Differences in categorical variables were assessed using Pearson's χ^2-test. Differences in means were assessed with ANOVA analysis, with Bonferroni test used to evaluate single paired comparison. All statistical tests were two-sided at α=0.05. Correlates were determined using multivariate linear regression, while predictors were determined using multivariate logistic regression analysis.

Results

Ninety-six patients (29% males) where studied with a median age of 35 years, 95% CI [35-37]. Majority of the patients are in the age range 15-40 years, with 4.2% below 18 years and 33.3% above 40 years. The median baseline CD4 lymphocyte count was 221cells/mL, 95% CI [189.00-238.65] with no gender differ-

Correspondence: Baba Maiyaki Musa,
Rasta Nurah General Hospital, Eastern province, Saudi Arabia.
E-mail: babamaiyaki2000@yahoo.co.uk

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ence, [Pr (|T| > |t|) = 0.1317]. Median one-year CD4 lymphocyte count was 356 cells/mL, 95% CI [330.99- 453.00, also with no gender difference: [Pr (|T| > |t|) = 0.0591] and median one year CD4 lymphocyte increment of 124 cells/mL, CI [110.00- 181.844] with no gender difference: [Pr (|T| > |t|) = 0.3445] (Table 1).

Median values for hemoglobin [Hb] was 6.1g/dL; median white blood cell [WBC] count was 6.1×10^9/L; median platelet count was 221×10^3 cells; median creatinine level was 90.7 µmol/L; median absolute neutrophil count was 2.15×10^9 cells/L (Table 1).

When disaggregated by type of NRTI drug regimen (AZT, D4T, TDF), there was no statistically significant difference in sex, absolute neutrophil count, hemoglobin platelet count and base line CD4 lymphocyte count. However there was statistically significant difference in age, WBC, creatinine and number of patients with CD4 lymphocytes count >100 cells/mL (P<0.05).

The sub-analysis also shows 64.58% of patients having CD4 lymphocyte count increment of >100 cells/mL, with 43.75% being on TDF, 22.91% on D4T and 33.33% on AZT based regimen (Table 2).

All studied patients were on TDF, D4T & AZT based regimen in the proportion (44%, 23% and 33%), respectively (P=0.66), with no statistically significant gender difference in type of drug usage (Figure 1 and Table 3).

Whereas there was no difference in one year CD4 lymphocyte count among the regimen types [Prob>χ^2=0.192], there was a higher CD4 lymphocyte count increment in patients on TDF & D4T compared with those in AZT (ANOVA; P<0.0003) (Figure 2 and Table 4).

Multivariate linear regression model shows correlation among baseline CD 4 count and one year CD4 lymphocyte count, one year increment in CD4 lymphocyte count, WBC count, and absolute neutrophil count (P< 0.0001) (Table 5).

Multivariate logistic regression model shows age, platelet count and CD4 lymphocyte count at 12 months to be significant predictors of CD4 lymphocyte increment above 100 cells/µL (P=0.03, 0.005 and 0.006, respectively) (Table 6).

Table 1. Median values.

Measures	Values
Median age	35 years
Median baseline CD4 lymphocyte count	221 cells/µL
Median one year CD4 lymphocyte count	356 cells/µL
Median one year CD4 lymphocyte count increment	124 cells/µL
Median baseline creatinine	90.7 µmol/L
Median baseline hemoglobin	6.1 g/dL
Median baseline white blood cell count	6.1×10^6 cells/mL
Median baseline absolute neutrophil count	2.15×10^6 cells
Median baseline platelet	221×10^3 cells
Age groups	
<18 years	4.2%
15-40 years	62.5%
>40 years	33.3%

Table 2. NRTI drug regimen variables.

Drug base variable	AZT	D4T	TDF	P
Sex				χ^2 0.661
Female	24	14	30	
Male	8	8	12	
Age, in years				
Mean & S.D.	41.50, 11.39	31.54, 5.56	36.61, 9.72	0.0013
WBC				
Mean & S.D	5.38, 1.80	7.49, 1.35	6.21, 1.68	0.0012
Absolute neutrophil count				
Mean & S.D	1.41, 1.52	2.22, 2.14	1.80, 1.47	0.2203
Hemoglobin g/dL				
Mean & S.D	11.63, 1.25	11.08, 2.09	11.71, 6.68	0.9074
Platelet count				
Mean & S.D	214.67, 62.99	267.78, 86.95	284.29, 140.46	0.0734
Creatinine				
Mean & S.D	214.67, 62.99	267.78, 86.95	284.28, 140.46	0.0004
Baseline CD4 lymphocyte count				
Mean & S.D	296.13 114.48	253.27 103.39	261.76, 234.01	0.6104
Difference in CD4 count				
<100 cells/mL	23	2	9	χ^2 0.0001
>100 cells/mL	9	20	33	

Table 3. Gender difference in type of drug.

Type of regimen	Sex		Total
	F	M	
AZT	24	8	32
D4T	14	8	22
TDF	30	12	42
Total	68	28	96

Person $\chi^2(2)$=0.8277; Pr=0.661.

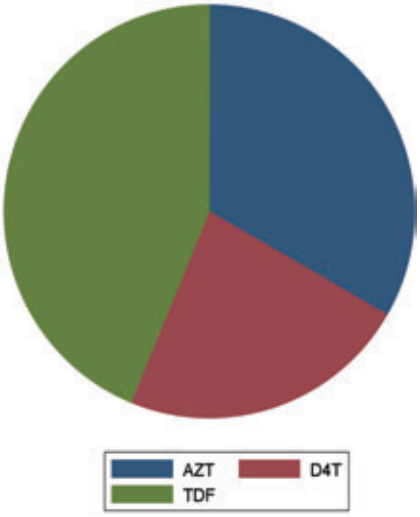

Figure 1. Drug type spreading.

Discussion

The HIV/AIDS epidemic predominantly affects people in the reproductive age group, with far reaching disastrous impact on socio-economic structures of societies.[1] This study has similarly found 64% of studied patient to be in the age group 15-40 years, in the locality of Otukpo, Benue State, Nigeria, a strategic agricultural area in Nigeria; the cost of HIV/AIDS will be significant in economic, social and human terms. This could have an effect on the standard of living in the area as has been witnessed in other areas, with similar epidemic patterns.[2-4]

In parts of Africa young women ages 15-24 are up to six times more likely to be HIV-positive than young men of the same age, with these proportion growing slowly.[5-7] This study has similarly found the affected patients to be predominantly women. This obviously will

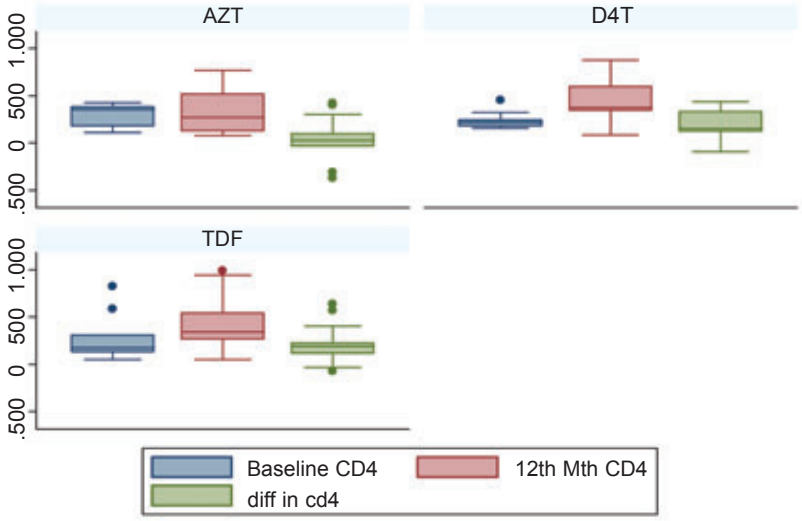

Figure 2. CD4 lymphocyte count analysis among regimen types.

Table 4. Bonferroni test analysis.

Source	SS	Analysis of variance df	MS	F	Prob>F
Between groups	521518.442	2	260759.221	8.75	0.003
Within groups	2770552.46	93	29790.8867		
Total	3292070.91	95	34653.378		

Barlett's test for equal variances $\chi^2(2)=3.6530$ Prob>$\chi^2=0.161$.

Comparison of diff in CD4 by type of regimen (Bonferroni).

Row mean-col mean	AZT	D4T
D4T	167.645 0.002	
TDF	149.329 0.001	-18.316 1.000

Table 5. Multivariare linear regression.

Source	SS	df	MS
Model	1207152.4	6	201192.067
Residual	172069.542	66	2607.11427
Total	1379221.95	72	19155.8604

Number of obs=73; F(6,66)=77.17; Prob>F=0.0000; $R^2=0.8752$; Adj $R^2=0.8639$; Root MSE= 51.06.

Baseline CD4	Coeff.	Std. Err.	t	P>|t|	[95% CI]	
Diff. in CD4	-0.6826205	.0503586	-13.56	0.000	-0.7831646	-0.5820763
WBC	-0.13.9389	4.098695	-3.40	0.001	-22.12221	-5.755589
Absol. neutr~t	18.12517	4.975141	3.64	0.001	8.191983	28.05836
Oneyr CD4	0.7754799	.0436665	17.76	0.000	.6882969	0.8626629
Age	0.4064612	.6574477	0.62	0.539	-0.9061755	1.719098
HB	1.70998	1.427488	1.20	0.235	-1.140092	4.560052
_Cons	44.05268	37.91478	1.16	0.249	-31.64661	119.752

have an effect on the stability of homes, rearing of children and often on economy, where women are active members of the economic circuit. Several young women become sexually involved with numerous male associates or clients in return for financial support.[8,9] Some African societies encourage marriage after demise of spouses; if this happens without proper precautions, it will have the effect of propagating the spread of HIV in a geometric manner.[10-12]

Several studies, from developing countries have found low base line CD4 lymphocyte count in HIV positive, ART naïve patients who are at the verge of commencing treatment and care.[13,14] These has been attributed to late presentation to point of care and is often associated with advance co-morbidities like tuberculosis and diarrheal diseases.[15] This study found the median baseline CD4 lymphocyte count to be 221 cells/mL, with no gender difference. Several studies have found CD4 lymphocyte count, especially counts of <200/mm^3, to be a major risk factor for both disease progression and failure to respond to antiretroviral therapy.[16]

As a result of the scale-up of antiretroviral treatment (ART) programs and substantial financial support worldwide, an increasing number of HIV-infected individuals in low-income and middle-income countries (LIMCs) now have access to ART. Despite this progress, important questions remain on the best use of ART and how patients should be maintained on a successful regimen. Physicians often choose a particular regimen base on perceived ease of administration, potential for good adherence, and relativity in frequency of adverse effect among others. Another factor is the proportionate availability of different types of ART within various financed treatment programs.[17,18] Drugs are frequently procured on a large scale in order to reduce cost, with the choice of agents largely driven by affordability rather than toxicity. In this study, TDF based regimen appears to be the most frequently prescribed nucleoside reverse transcriptase inhibitor (NRTI). TDF based regimen have the advantage of dosing simplicity, with concomitant effect on adherence. Its safety profile is also encouraging, considering the almost universal occurrence of major side effect, anemia and peripheral neuropathy among users of AZT and D4T, respectively.

A wide-range of clinical trial have not identified short-term differences (i.e. at week 48 or 96) in CD4 lymphocyte count between different antiretroviral regimens in patients starting AZT or D4T.[19-21] One exception to these treatments was a study that demonstrated a significantly higher increase in CD4 lymphocyte cell count in patients taking a stavudine/lamivudine nucleoside backbone with indinavir compared with zidovudine/lamivudine with indinavir.[22] Our review shows higher CD4 lymphocyte count

increment in group of patients on D4T compared with those on AZT. This may potentially be due to confounders like differences in adherence, which was not accessed in this study. Another issue is that our study is observational and not subjected to randomization; in this perspective, it has inherent limitations.

Prospective clinical trials have demonstrated the improvement in lipoatrophy when zidovudine or stavudine are substituted by tenofovir, as such this strategy has often been strongly recommended in antiretroviral therapy.[23] Other studies showed comparatively better immunological recovery when TDF is used compared with AZT or D4T.[24,25] Our study has shown better immunological recovery among those on TDF, compared with those on AZT. This result can partly be explained by possibility of a low pill regimen, motivating better compliance, preferential selection of patients to start TDF base regimen; and presumably, patients on AZT and D4T might have been *ab initio* infected with HIV strains carrying genomic resistance to these drugs. In the past, some patients in Nigeria had been on regimens based on D4T and AZT with less rigorous tracking of adherence. Furthermore, with TDF requiring 3 point mutation for complete resistance, it is reputed to be a more 'forgiving drug' compared to the other two drugs, thus the potential to better fair. TDF is a widely used drug in clinical practice due to its excellent combination of effectiveness, durability and tolerability, in addition to its ease of administration in a single daily dose; int his study, we had not assessed pattern of adherence, and however it is likely that it may play a key role in the outcome. We have equally not looked at incidence of renal impairment among the studied population.

As more patients start ART, in locations with limited resources, caregivers face the emerging challenge of achieving and maintaining immunological recovery with often less than ideal means of assessing progress of therapy. This has lead to the search for correlates of immunological status. Our study has shown that, one year CD4 lymphocyte count, one year increment in CD4 lymphocyte count, baseline WBC count, and absolute neutrophil count are significant correlates of baseline CD4 lymphocyte count. Some studies have not consistently associated baseline CD4 lymphocyte count with immunological recovery; however, most studies do find this association.[26-28]

Whereas, we have found age, platelet count, and CD4 lymphocyte count at 12 months to be significant predictors of CD4 lymphocyte increment above 100 cells/µL; different studies have described varying permutations of predictors. These factors include but are not restricted to level of adherence, baseline CD4 lymphocyte count, baseline viral load, hemoglobin, total lymphocyte count, WHO HIV disease stage, and Alanine transaminase (ALT) among others.[30-32]

Table 6. Multivariate logistic regression.

CD4 diff. cat.	Odd ratio	Std. Err.	|z|	P>|z|	[95% CI]	
WBC	0.9705083	0.3269259	-0.09	0.929	0.5014909	1.878172
Absol. neutr~t	0.4761149	0.2706727	-1.31	0.192	0.1562433	1.450849
Platelet	1.030436	0.0108929	2.84	0.005	1.009306	1.052008
One yr CD4	1.022787	0.0083326	2.77	0.006	1.006585	1.03925
Age	0.7489997	0.1017784	-2.13	0.033	0.5738726	0.9775698
HB	1.309255	0.2922285	1.21	0.227	.8453454	2.027749

Logistic regression; Log likelihood = 16.490353; Number of bos =61; LR $\chi^2(6)$= 48.79; Prob>χ^2=0.0000; Pseudo R^2=0.5967.

There are several important limitations to note in this study. First of all, our study is observational, and patients were not randomly allocated to different ART regimens; as such, any findings should be interpreted from this perspective. The differences in CD4 lymphocyte cell count increment could reflect other differences among patients other than the antiretroviral drugs they were taking, and which we either do not know or cannot account for. Such differences include the selection of patients chosen to start different ART regimens and changes in the population over time. Differences in adherence are unlikely to explain these findings as our basic assumption, is varying level of adherence is likely uniformly distributed among treatment groups. We have also demonstrated that there are no differences in baseline CD4 lymphocyte count among groups.

Overall, we have come to agree that there are different levels of immunological recovery among various treatment regimens; as such, guidance should be sought when initiating therapy based on evidence and best practices. This consideration has become more urgent considering challenges in the options of antiretroviral choices, in LIMCs, with attendant implication on cross-resistance, leading to increased morbidity and mortality. We also have to contend with the fact that second-line and salvage regimens have higher pill burden, complex nutritional requirements, more side effects and potential for spread of resistant virus.

This study paves the way for conducting a well planned prospective cohort study to address both immunological responses, adherence and adverse effect of the myriad of ART used in the Nigerian landscape.

Conclusions

Despite advanced disease presentation and a very large-scale program, high quality HIV/AIDS care was achieved as indicated by good short-term and immunologic outcomes. Furthermore, it is noted that TDF & D4T induce higher immunological recovery compared with AZT. This report suggests that quality HIV care and treatment can be effective, despite the challenges of a resource-limited setting.

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