Journal of
AIDS & Clinical Research
ISSN: 2155-6113

Reginald et al. J AIDS Clinic Res 2011, S2
DOI: 10.4172/2155-6113.S2-002

Research Article Open Access

Hematological and Metabolic Toxicities of Current Antiretroviral Regimens in Ahmadu Bello University Teaching Hospital Shika Zaria, Northern Nigeria

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Abstract

The introduction of the highly active antiretroviral therapy (HAART) in 1996 has drastically reduced the morbidity and mortality associated with the HIV infection. Although short term toxicities of the antiretroviral drugs are being reported, there's dearth of data on their long term complications, particularly in sub-Saharan Africa. This study was designed to identify hematological and metabolic toxicities in HAART-experienced patients in our facility from January 2000 to December 2009. Patients on HAART for ≥ 2 weeks, and have at least one abnormal laboratory result (hemoglobin < 10.0 g/dl, white blood count < 4,500/ mm^3, absolute neutrophil cell count < 1,400/ mm^3, platelets < 150,000/mm^3, alanine transaminase > 40 iu/L, creatinine > 130 mmol/L, fasting blood sugar > 6.7mmol/L, fasting cholesterol > 2.5mmol/L, fasting triglyceride > 0.5mmol/L) on follow-up evaluations were studied. Of 3641 patients, 357 (9.8%) comprising 231 females (64.7 %) and 126 males (35.3%) with respective mean ages of 36.16 ± 9.06 years and 42.56 ± 9.36years had hematological and metabolic toxicities, due mainly to zidovudine/lamivudine/nevirapine (51.8 %), stavudine/lamivudine/nevirapine (16.5%), and truvada/nevirapine (10.4%). Common laboratory toxicities were elevated alanine transaminase enzyme (39.8%), leucopenia/neutropenia (38.0%), elevated creatinine level (12.3%), and low hemoglobin (11.5%), although the most severe toxicity was grade 4 anemia. Risk factors for these toxicities were: young age, female gender, pre- and on- ART CD4+ > 250 cells/μL. In conclusion, the current first line antiretroviral regimens produced various forms of hematological and metabolic toxicities, except glucose or lipid abnormalities.

Keywords: HAART; Antiretroviral regimens; Laboratory toxicities; Zaria; Nigeria

Background

The advent of the highly active antiretroviral therapy (HAART) in 1996, and subsequent scaling up of antiretroviral therapy (ART) in many sub-Saharan African countries through funding sources such as government programs, the Global Fund to prevent AIDS, tuberculosis and malaria, and United States President's Emergency Plan for AIDS Relief (PEPFAR), has substantially improved the prognosis of many HIV/AIDS patients who have access to the antiretroviral (ARV) drugs [1-5]. These ARV drugs consist of cheap, generic fixed-dose (and non-fixed-dose) combinations of 2 nucleoside transcriptase inhibitors (NRTIs), plus one non-nucleoside reverse transcriptase inhibitor (NNRTI); or one nucleotide reverse transcriptase inhibitor (NtRTI) plus one NRTI plus one NNRTI. The combinations are: NRTIs {stavudine (d4T) or zidovudine (AZT) plus lamivudine (3TC)} and NNRTI {nevirapine (NVP) or efavirenz (EFV)}; or NtRTI {tenofovir disoproxil fumarate (TDF)} plus NRTI {3TC or emtricitabine (FTC)} plus NNRTI {NVP or EFV} [6,7]. A survey conducted in 2006 in 23 resource limited countries (17 of which were in sub-Saharan Africa), found that these nucleoside/ nucleotide, and nonnucleoside reverse transcriptase inhibitors were the backbone of first line HAART in these countries [8,9], inspite of reported incidences of toxicities [10]. The high incidence of d4T and/or NVP-related toxicities in African cohorts was a major reason for either modifying ART, discontinuing treatment or lost to follow up [10-12]. In order to reduce these toxicities, the World Health Organization (WHO) in 2006 recommended the use of 30 mg of d4T in all patients, irrespective of body weight (instead of 40 mg for patients > 60 kg body weight) or the use of AZT or TDF as alternatives to d4T [13]. The WHO also recommended that NVP should be avoided in females and males whose baseline CD4+ cell counts were above 250/μl and 400/μl respectively [14]. Although ART-related toxicities are of topical clinical challenges in Africa, few long term follow-up data are available to clinicians and others working in HIV medicine. Such information is necessary as a guide to the development of new treatment strategies and improvement of patient care. It was therefore the objective of this study to determine the hematologic and metabolic toxicities of current first and second line antiretroviral regimens in HAART-experienced adult patients at our facility from January 2000 to December 2009.

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Received Sptember 13, 2011; **Accepted** October 20, 2011; **Published** October 23, 2011

Citation: Reginald OO, Mohammed MH, Olayinka AT, Sani GB, Tobi-Ajayi E, et al. (2011) Hematological and Metabolic Toxicities of Current Antiretroviral Regimens in Ahmadu Bello University Teaching Hospital Shika Zaria, Northern Nigeria. J AIDS Clinic Res S2:002. doi:10.4172/2155-6113.S2-002.

Materials and Methods

Study site

The ABUTH HIV PROGRAM started in January 2000 under the Nigerian National ARV Program with the mandate to provide the following services: HIV counseling and testing (HCT), HIV care and support, ART, and prevention of mother to child transmission of HIV (PMTCT) at subsidized rates. In 2006 the Program was incorporated into the HARVARDPEPFAR HIV Program with subsequent expansion of the original mandate of comprehensive care and support for HIV-infected patients, HAART, prophylaxis for opportunistic infections (OIs), laboratory and clinical monitoring, all for free. From 2000 to 2006, d4T and AZT- based regimens were the only drugs prescribed in the following combinations: d4T/3T/NVP; d4T + 3TC + EFV; AZ/3TC/NVP; AZT/3TC + EFV; while in January 2007, ritonavir-boosted lopinavir (aluvia tablets) and truvada-based regimens in the following combinations: [truvada (TDF/FTC) + NVP; TDF/FTC + EFV], were introduced. However, in compliance with the revised WHO recommendations of 2006 [13], d4T was withdrawn from the Program in June 2008.

Patient population

The patients were drawn from the 7 Northwestern states of Kaduna, Katsina, Zamfara, Sokoto, Kebbi, Kano and Jigawa , and adjoining North central states of Niger, Nassarawa and Kogi, including the Federal Capital, Abuja. All HIV-infected patients were offered support and care, and only patients with AIDS-defining illnesses and/or CD4+ counts <350 cells/μL were offered HAART according to the Nigerian Guidelines on Antiretroviral Treatment [14].

Patient clinic visits

At the first visit patients were educated and counseled on various aspects of HIV viz: Western blot confirmation; clinical staging; ARV medication adherence, toxicity and failure recognition; drug-drug/food interactions; social interactions among HIV-infected persons and between HIV infected and non-HIV infected individuals. The patients were screened for tuberculosis and other OIs, and phlebotomy for Western blot confirmation, baseline plasma viral load (pVL) and CD4+ cell count, hepatitis B and C serology, blood chemistry, hematology, and liver enzymes was done, after which a second appointment was given. During the second visit (2-4 weeks intervals), eligible patients were started on any of the first line regimens, based on various criteria [14-16]. All patients started on NVP-based HAART were scheduled to return 2 weeks after initiation for review, and dose escalation, unless contraindicated. Subsequent visits were divided into medication refill/drug pick-up, scheduled and unscheduled.

Medication refill visits (every 4 weeks) were for the purpose of receiving routine HAART and other supplementary medications by patients who are in stable conditions. Scheduled visits (12 weeks intervals) were for medical and medication adherence evaluations, and laboratory tests {pVL, CD4+ cell count, blood chemistry, hematology, and liver enzymes, although pVL was done every 24 weeks if previous pVL was undetectable}. During unscheduled visits, patients with complaints, related or unrelated to HIV infection and/or treatment such as drug toxicities, immunological, virological and clinical failures were identified and treated. Patients with virologic failures were switched to second line regimen, while for patients with toxicities, the offending drug(s) were discontinued, and substituted with safer alternatives. For example, efavirenz was substituted with nevirapine in NVP-induced hepatotoxicity; patients with AZT or d4T- induced toxicities were switched over to truvada.

Laboratory methods

HIV antibody status was determined by use of an enzyme-linked immunosorbent assay [ELISA]-based testing algorithm (Murex HIV 1.2.0 and Ortho Antibody Capture ELISAs performed in parallel). Plasma HIV-1 RNA level s were quantified using the Amplicor HIV-1 monitor test, version 1.5 (Roche Diagnostic Systems, Branchburg, NJ), with a lower limit of detection of 200 copies/mL. CD4+ cell counts were determined within 4 hours of obtaining the blood sample using the FACSCalibur flow cytometer by Partec. Hematology analysis (hemoglobin, white blood cell count, absolute neutrophil count, platelet count) was done using automated analyzer Sysmex KX 21, while serum chemistry (urea, creatinine, alanine transaminase, glucose, bilirubin, cholesterol, triglyceride) were done using automated analyzer Hitachi 902.

Study design

We studied all adult patients who had normal baseline laboratory values, but developed at least one of the following abnormal laboratory values: hemoglobin <10.0 g/dl, white blood cell count < 4,500/ mm^3, absolute neutrophil cell count < 1,400/ mm^3, platelet counts < 150,000/ mm^3, serum alanine transaminase > 40 i.u/L, serum creatinine > 130 mmol/L, fasting blood sugar > 6.7mmol/L, fasting serum cholesterol > 2.5mmol/L, fasting serum triglyceride > 0.5mmol/L, after at least 2 or more weeks of HAART. HAART-experienced patients with abnormal baseline laboratory values were excluded. The laboratory toxicities were graded in severity from 1(mild) to 4 (severe) according to guidelines provided by Harvard School of Public Health [17].

Ethical clearance

The study was approved by the Institutional Research Ethical Review Board of ABUTH Shika. Oral and written consents were sought from participating subjects.

Data collection

Data were collected from both paper and electronic patient database, and were then entered into an electronic database of the Statistical Package for Social Sciences (SPSS) version 17 for analysis. Laboratory data on toxicities due to d4T-based regimens was collected up to December 2008 because of their withdrawal from the program earlier that year, while information on toxicities due to the second line regimen (AZT + truvada + ritonavir boosted lopinavir) was started in January 2007 when the regimen was introduced into the program.

Statistical analysis

We used descriptive statistics to calculate frequency distributions, means, median, standard deviations, range, percentages, and proportions. Quantitative variables at baseline and during HAART were compared using Student "t" test while qualitative variables were compared using chi-square. Bivariate correlate and multinomial logistic regression analyses were performed to determine associations between toxicity and gender, age group, baseline CD4+ levels > 250 cells/μL, on-ART CD4+ levels > 250 cells/μL, and baseline pVL. Statistical significance was set at 5% level of probability.

Results

Socio-demographics

Of the total of 3641 patients on ART, 2458 (67.5%) were females while 1183 (32.5%) were males. The age group 16-39 years formed 59.2% (2155) of the patient population, followed by the 40-59 years age group (1399, 38.4%). The proportion of females with toxicities were almost twice (231, 64.7%) those of males (126, 35.3%), (χ^2= 12.391, P=0.02). More than 70% of the patients had western education with about one-third of them attaining tertiary education (χ^2= 14.665, P= 0.00), although a sizeable proportion (794, 21.8%) were illiterate. Majority (47.2%, 1717) were unemployed, while 37% (1342) and 15% (582) were self-employed, and government employed respectively (Table 1).

Pattern of antiretroviral regimens use

Three thousand, four hundred and eighty-one (95.6%) of the patients were on the 6 first- line regimens, while remaining 160 (4.4%) were on the only second -line regimen (AZT + truvada + ritonavir boosted lopinavir). The patient distribution on the first line regimens were: 2025 (56%) on AZT/3TC/NVP; 1145 (31%) on d4T/3TC/NVP; 170 (5%) on truvada + NVP; 78 (2.1%) on AZT/3TC/EFV; 58 (1.6%) on truvada/EFV and lastly 5 (0.1%) on d4T+3TC+EFV respectively (Table 2).

Proportional distribution of toxicities among the antiretroviral regimens

Three hundred and fifty-seven (9.8%) of the patients had various forms of laboratory toxicities. As shown in table 2, AZT/3TC/NVP was responsible for toxicities in 185 (52%) of cases, followed by d4T/3TC/NVP in 59 (16%); truvada + NVP (37, 10%); AZT + truvada + lopinavir/r (31, 9%); AZT/3TC +EFV and truvada/ EFV (6% each), and lastly d4T +3TC + EFV (2, 1%). Although the 3 efavirenz-based regimens exhibited proportionately lower toxicities than the nevirapine-and protease inhibitor-based regimens, one of them (d4T+3TC+EFV) produced a toxic effect in 40% of patients on the regimen, which is about 8 times higher than those due to d4T/3TC/NVP. The other two regimens also had toxicity rates of 30-35%, in contrast to the 9% toxicity rate of the most prescribed regimen, AZT/3TC/NVP (Table 2).

The proportional distribution of hematological and metabolic toxicities

Elevated serum alanine transaminase enzyme was the commonest abnormality seen in 103 (29%) patients, followed by absolute neutropenia (69, 19.3%); leucopenia (68, 19%); anemia (56, 16%); elevated serum creatinine level (53, 15%) and thrombocytopenia in 8 (2%) patients respectively (Figure 1).

The proportional distribution of hematological and metabolic toxicities of each antiretroviral regimen

All 7 regimens contributed to the elevation of serum alanine transaminase enzyme in the following proportions: all the 2 (100%) patients on d4T+3TC+EFV; 9 of 20 patients (45%) on truvada/ EFV; 12 of 31 patients (39%) on AZT+ truvada+ Lpv/r); 21 of 59 patients (35%) on d4T/3TC/NVP); 7 of 23 patients (30%) on AZT/3TC+EFV); 46 of

Social characteristics of patients	Number of patients on ART (N=3641, 100%)	Number of males on ART (N=1183, 32.5%)	Number of females on ART (N=2458, 67.5%)	Males with toxicities (N=126, 3.5%)	Females with toxicities (N=231, 6.3%)	Patients with toxicities (N=357, 9.8%)	Statistical level of significance χ2= 12.391 P=0.02
Age group							**χ2= 20.743 P=0.00**
15	2 (0.1)	0	2 (0.1)	0	0	0	
16-39	2155(59.2)	408(11.2)	1747(48.0)	51(1.4)	200 (5.5)	251(6.9)	
40-59	1399 (38.4)	721(19.8)	678 (18.6)	71 (2.0)	29 (0.8)	100 (2.8)	
≥ 60	85(2.33)	54 (1.5)	31(0.9)	4 (0.11)	2 (0.1)	6 (0.2)	
Mean age (years)	39.2 ± 6.6 (15-69)	40.1±4.2 (16-69)	32.3± 5.2 (15-60)	42.6 ± 9.4 (19-68)	36.2 ± 9.1 (17-59)		**t= -6.297, P= 0.00**
Educational status							**χ2= 14.665 P= 0.001**
None	794 (21.8)	161(4.4)	633(17.4)	20(0.5)	62 (1.7)	82 (2.2)	
Primary school	608 (16.7)	224 (6.2)	384 (10.5)	24 (0.6)	41 (1.1)	65 (1.7)	
Secondary school	1032 (28.3)	298 (8.1)	734 (20.2)	24 (0.6)	67 (1.9)	91 (2.5)	
Tertiary	1207 (33.1)	500 (13.7)	707 (19.4)	58 (1.6)	61 (1.7)	119 (3.3)	
Occupation							**χ2=36.282 P= 0.000**
None	1717 (47.2)	295 (8.1)	1422(39.1)	13 (0.3)	127 (3.5)	140 (3.8)	
Government employed	582 (15.9)	342 (9.4)	240(6.6)	52 (1.4)	50 (1.4)	102 (2.8)	
Self employed	1342(36.9)	546 (15.0)	796 (21.9)	61 (1.7)	54 (1.5)	115 (3.2)	

Table 1: Socio-Demographic characteristics of patients.

Antiretroviral Regimens (2000-2009)	Number of persons on each regimen	Proportion of persons on each regimen (%)	Number of persons with toxicity	Proportion of persons with toxicity (%)	Toxicity rate of each regimen (%)
Zidovudine/Lamivudine/Nevirapine	2025	55.6	185	51.8	9.1
Stavudine/Lamivudine/Nevirapine	1145	31.4	59	16.5	5.2
Truvada+ Nevirapine	170	4.7	37	10.4	21.8
*Zidovudine + truvada+ ritonavir boosted lopinavir	160	4.4	31	8.7	19.4
Zidovudine/Lamivudine+ Efavirenz	78	2.1	23	6.4	29.5
Truvada/Efavirenz	58	1.6	20	5.6	34.5
Stavudine+Lamivudine+Efavirenz	5	0.1	2	0.6	40.0
Total	3641	100.0	357	100	9.8

*Second line regimen

Table 2: The pattern of antiretroviral regimens use and proportional toxicities.

185 patients (25%) on AZT/3TC/NVP), and 6 of 37 patients (16%) on truvada+NVP respectively.

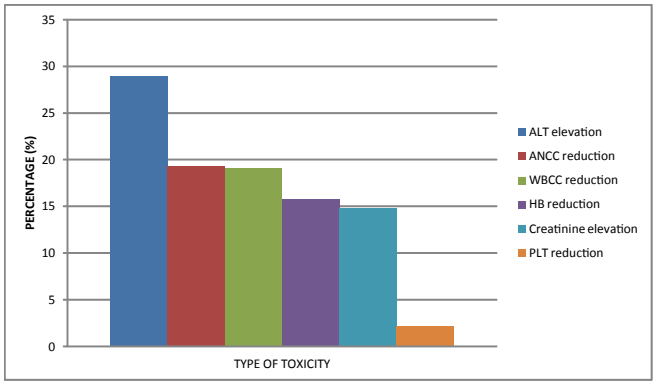
Of the 53 patients with elevated serum creatinine levels, 31of 37 patients (84%) were on truvada + NVP; 11 of 20 patients (55%) on truvada /EFV; and 11 of 31 patients (35%) on AZT+truvada+Lpv/r respectively. Out of 56 patients with anemia, 46 (82%) were on zidovudine-based regimens [AZT/3TC/NVP (35/185, 19%), AZT+ truvada+Lpv/r (8/31, 26%), AZT/3TC+EFV (3/23, 13%)]; while the other 10 (18%) were on stavudine-based regimens. Zidovudine-based regimens also produced higher proportions of leucopenia, and absolute neutropenia than stavudine-based regimens. This was demonstrated in figure 2.

Severity of hematologic and metabolic toxicities

The most severe toxicity was anemia (grade 4), followed by leucopenia, thrombocytopenia, and elevated serum creatinine (grade 2 each); and lastly elevated serum alanine transaminase enzyme, and absolute neutropenia (grade one each) (Table 3).

Risk factors associated with toxicities

Ages between 16 and 39 years, female gender, baseline CD4+cell counts > 250/μL, on-ART CD4+ cell counts > 250/μL, and ARV regimen, were the significant risk factors for ARV toxicities identified in this study, while male gender and baseline plasma viral load were not significantly correlated with risk factors for toxic reaction (Table 4).



ALT (alanine transaminase), ANCC (absolute neutrophil cell count), WBCC (white blood cell count), HB (hemoglobin), PLT (platelet)

Figure 1: Proportional distribution of hematological and metabolic toxicities.

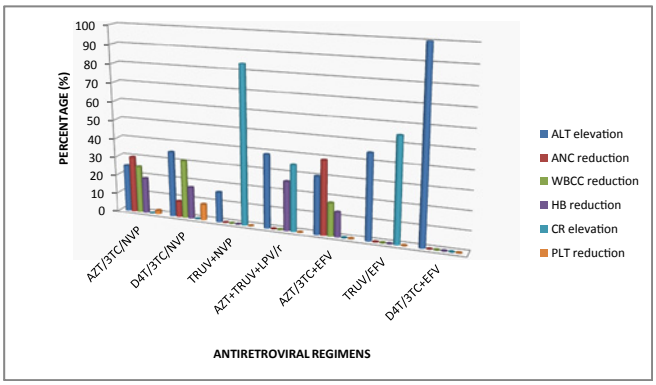


Figure 2: The proportional distribution of hematological and metabolic toxicities of each antiretroviral regimen.

Immunological and virological responses of affected patients to HAART

The patients' median CD4+ rose from a baseline of 120 cell count/μL to 250 cell count/μL, while the number with undetectable pVL rose from zero at baseline to 259 (72.5%) as shown in Table 5.

Discussion

Majority (67.5%, 2458) of our patients on HAART were females. Also, 59% (2155) were in the 16-39 years age group, and, although 61% (2239) of them received secondary education and beyond; about 22% (794) were illiterate, while 17% (794) stopped at the primary school level. Only 16% of the patients were government employees, as 47% (1717) and 37% (1342) were either unemployed or self employed. These socio-demographic indices are similar to those reported by several workers in many HIV treatment programs in sub-Saharan African countries in particular, and developing countries in general [18-20].

Majority of the patients were on fixed- dose, and sometimes, non fixed-dose, generic combinations of zidovudine/lamivudine/nevirapine (2025, 56%) and stavudine/lamivudine/nevirapine (1145, 31%) respectively. These 2 regimens are the backbone of first-line HAART in resource-limited countries, and inspite of the WHO recommendations regarding the use of stavudine, the drug is still widely prescribed in many of these poor countries [21]. However, in compliance to the revised WHO recommendations of 2006 [13], stavudine was withdrawn from our facility in June 2008.

The distribution of the current regimens among the 3641 patients showed that majority (3481, 96%) were on the 6 first-line drugs while the remaining 160 (4%) were on the only second-line drug available. For more than six years, none of the patients was on either tenofovir or boosted lopinavir tablets, as these drugs were not available in the Program until January 2007. In spite of this, we observed significant virologic and immunologic benefits, as evidenced by a two-fold increase of CD4 + cell counts/μL from median baseline of 120 (with a range of 4-348) to a median on- therapy value of 250 (range 15-1664), and increase in the number of patients with undetectable plasma viral load from zero at baseline to more than 70% on treatment, although 357 (9.8%) of the patients, mostly females of 16-39 years age group developed toxic reactions.

In spite of this, we can imply that the zidovudine or stavudine-based first-line regimens were effective. This assertion is supported by previous works on the sub-Saharan African region [21-23].

Because of the complex nature of HIV and AIDS, and the complexity associated with the interaction of the drugs with the virus, the causal relationship between therapy and toxicity is often difficult to determine definitively. As clinical experience with the ARV drugs continues to increase, the understanding of the pathophysiologic and biochemical mechanisms of their clinical toxicities will continue to evolve [24], particularly, the factors which predispose patients to ARV-associated toxicities. In this study, we were able to use both bivariate correlations and multinomial logistic regression analysis to determine that young age, female gender, pre- and on- ART CD4+ > 250 cells/μL were significant risk factors for the development of toxic reactions. All of these factors have been described by previous workers [25-28], except on- ART CD4+ > 250 cells/μL. However, toxic reactions during an immune reconstitution inflammatory syndrome, which, itself, is due to rapid rise of CD4+ lymphocytes soon after ART initiation can explain the significant role of this factor [29].

Variable values	Laboratory characteristics					
	Serum alanine transaminase (i.u/L)	Serum creatinine (mmol/L)	Hemoglobin (g/dL)	White cell count ($x10^9$ cells/L)	Absolute neutrophil count ($x10^9$ cells/L)	Platelet count ($10^3/mm^3$)
Normal reference value	12-40	120-1470	10-14g	4.5 -10.0	1.4 – 1.6	150-400
Median baseline value (range)	23 (6.7-43.0)	34 (10-130)	11.3 (10-15)	5.2 (2.9-8.1)	2.2 (1.3-3.3)	207 (148-490)
Median value with ART (range)	85.3 (40-444.2)	245.5 (120-1470)	6.3 (2.0-9.9)	3.4 (0.85-4.9)	1.0 (0.4-2.0)	80 (68.3-125)
P-value	0.00	0.00	0.02	0.00	0.04	0.00
Toxicity grade[reference value]	1 [50-103]	2 [170-390]	4 [<6.5]	2 [3.0-3.5]	1 [1.0-1.3]	2 [50-75]
Number of patients (%)	103 (28.9)	53 (14.8)	56 (15.7)	68 (19.1)	69 (19.3)	8 (2.2)

Table 3: Severity of hematologic and metabolic toxicities.

Variable	Pearson's correlation coefficient (r)	Odd ratio (OR) 95% Confidence Interval (CI)	P-value
Age group 16-39 years	0. 738	2.1 (0.80-3.51)	0.00
Female gender	0.954	1.6 (0.13- 1.89)	0.01
Male gender	-2.431	0.4 (0.16- 0.72)	0.62
Baseline CD4+ > 250cells/µl	0.626	1.7 (0.78 – 3.2)	0.02
On-ART CD4+ > 250cells/µl	0.591	1.2 (0.32- 3.1)	0.00
Baseline pVL	-0.979	1.00 (0.24- 1.57)	0.07
Regimen	0.682	1.8 (0.41- 2.15)	0.00

Table 4: Analysis of risk factors for toxic reactions.

Characteristics	Period of study			
Immunological response of patients	**At baseline**	**With ART**	t	**P-value**
Median CD4+ cell count /µL (range)	120 (4-348)	250 (15-1664)	-8721	0.01
Virological response of patients	**At baseline**	**With ART**	**χ2**	P-value
Number of patients with detectable plasma viral load (%)	357 (100)	98 (27.5)	10.276	0.024
Number of patients with undetectable plasma viral load	0	259 (72.5)		
Total	357(100)	357 (100)		

Table 5: Immunological and virological responses of HIV-infected patients with toxicities.

The pattern of ARV associated toxicities showed that AZT-based regimens accounted for 62% of all toxicities, and about 82% of anemia, followed by d4T-based regimens with 32% of all toxicities, and 18% of anemia respectively. Tenofovir-based regimens (truvada) came third with 6% of all toxicities. Although the prevalence of anemia and other morbidities in HIV-infected patients were noted to generally decline with HAART, anemia and bone marrow suppression continue to be a problem in many patients on AZT and sometimes d4T [30-32]. Anemia was the most severe manifestation of thymidine nucleoside induced bone marrow suppression, although it occurred in fewer (56, 16%) patients than leucopenia or absolute neutropenia in 68 (19%) and 69 (19%) patients respectively.

Alanine transaminase enzyme elevation which occurred in 103 (29%) patients was the only metabolic abnormality observed in this study as there were no abnormalities of serum glucose or lipids among our patients. The liver enzyme elevation was the commonest toxicity, possibly because all the first line ARV regimens contain the nonnucleoside reverse transcriptase inhibitors (NVP or EFV), which are hepatic microsomal P450 cytochrome oxidase inducers with strong tendency to cause hepatitis. Also, the two protease inhibitors (PIs) - ritonavir and lopinavir in the second-line regimen have strong tendencies to cause hepatitis or hepatic enzyme abnormalities. This observations support the assertion that most ARV drugs can cause some degree of hepatic toxicity; the NTRIs probably through mitochondrial disruption; the NNRTIs as part of hypersensitivity reaction; and the (PIs) through an unknown mechanism [24].

Grade 2 elevation of serum creatinine levels was seen in 53 (14.8%) of our patients, all due to truvada- based regimens. Despite demonstrated renal safety in several clinical trials, and case reports, our result supports several observational data which suggest that TDF may be associated with nephrotoxicity. Rates of tenofovir nephrotoxicity in retrospective cohort studies have been reported in general at approximately 2%, with results showing that TDF recipients were about three times more likely than abacavir (ABC) users to develop higher-than-normal levels of serum creatinine [33]. TDF has been postulated to cause kidney damage through tubular mitochondrial disruption, as does the nucleotide analogue adefovir. However, in the absence of other risk factors for kidney disease, it does appear that this damage is reversible when TDF is withdrawn [34,35].

The limitations of this study are the lack of treatment randomization, and our inability to perform analysis of serum lactate concentrations.

In conclusion, this prospective cohort study suggests that although the current AZT, d4T and NVP-based-regimens showed evidence of virologic and immunologic benefits for the patients, they produced leucopenia, neutropenia, anemia, thrombocytopenia, elevations of serum alanine transaminase enzyme, and creatinine levels. Unlike many earlier studies, abnormalities of glucose and lipid metabolism were not detected in our patients. Young age, female gender, and regimen type, pre- and on -therapy CD4+ levels above 250 cells per microlitre were strong risk factors for toxicities.

Acknowledgements

We thank all the patients and staff of ABUTH HIV Treatment and Care Centre, who participated in the study. We thank especially the DATA staff of Nasara HIV Treatment Centre, APINHarvard HIV Program, Center for Global Health Northwestern University Chicago, Illinios USA, Center of Excellence for Life sciences and Translational Pharmacology/Bioinformatics, NYS UB University at Buffalo USA for proving technical support for this study.

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This article was originally published in a special issue, **Pharmacology of Antiretroviral Agents: HIV** handled by Editor(s). Dr. Di Wu, The Children's Hospital of Philadelphia, USA