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Original Article

Predictors of clinical failure in HIV/AIDS patients on antiretroviral therapy in a resource limited setting, Nigeria: A comparative study

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ABSTRACT

Background: The monitoring of HIV-infected individuals on ARV may be clinical or laboratory. Viral load testing is the backbone of accessing treatment failure but Nigeria is faced with the challenge of the high cost of viral load testing hence its less usage in most centres. The prospective study evaluated possible markers that could distinguish clinically failing and stable HIV/AIDS patients on ARV in resource-limited countries like Nigeria.

Material and methods: The 72 HIV-1 infected patients on ARV that consecutively attended ART clinic in December, 2010 at General Hospital, Ugep, Cross River State were reviewed for CD4 values, white blood cell count (WBC), total lymphocyte count (TLC), platelet count, haematocrit, mean corpuscular haemoglobin concentration (MCHC), potassium, creatinine, glucose, alanine aminotransferase (ALT), and aspartate aminotransferase (AST). The results were compared with standard references, between clinically failing and stable patients, and between clinically failing patients that switched drugs and those that maintained their drugs.

Results: Of the 72 patients, 19.4% had clinical failing conditions and there were more female than male patients. Of the clinically failing patients, 42.9% switched drugs in the course of treatment. TLC and CD4 values were significantly lower ($p < 0.05$ and $p < 0.02$ respectively) in clinically failing patients than clinically stable patients. Only ALT levels in clinically failing patients that maintained their drugs were significantly lower ($p < 0.01$) than in those clinically failing patients that switched drugs.

Conclusions: Apart from CD4 count, TLC is a reliable prognostic marker for disease progression in HIV/AIDS patients on ARV in our centres where viral load is not readily available. ALT levels may be used to determine HIV/AIDS failing patients that switched drugs.

1. Introduction

Nigeria belongs to the group of countries highly endemic for HIV infection with 3.6–3.9% national prevalence [1–3]. Epidemiological studies had established that estimated 3.3 million people were HIV infected in the country. The country has been estimated to have the 3rd highest HIV prevalence worldwide. The national sentinel survey of 2008 showed that out of 740,000 HIV infected adults that required antiretroviral therapy (ARV), 198,000 patients received treatment [1–3]. The most remarkable and alarming aspects of the antiretroviral treatment are the issues of patients' monitoring and treatment failure. The effectiveness of antiretroviral regimens has been proven based on the assessment of CD4+ T-lymphocyte and plasma HIV viral RNA levels [4]. Other markers like Beta 2 microglobulin (B2M), neopterin, p24 antigen are sometimes used to monitor the progress of HIV disease and the body's response to antiretroviral drugs. Unfortunately, these markers including viral load (VL) and CD4 count are scarcely available in our environment hence WHO clinical staging guides clinicians to assess response to antiretroviral treatment. Monitoring patients on therapy is critical. Routine evaluation of laboratory studies is imperative for early detection of treatment failure and drug toxicities. Most of researches on HIV/AIDS were carried out in the developed countries but limited data were available in the developing countries especially in the Sub-Saharan Africa on the issue of readily available biomarkers for HIV monitoring to support those claims. Some authorities affirmed that changes in haematological and immunological profiles may serve as reliable rapid assessment tools for HIV/AIDS research and diagnosis in resource-limited areas [5,6]. On the other hand, CD4 count, resistance and viral load tests are rarely available in resource poor settings due to high cost, inadequate infrastructure and insufficiency of trained personnel to administer

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tests whilst clinical monitoring alone is highly unsupportive [7,8]. Moreover, certain clinical conditions like immune reconstitution syndrome and adverse drug reactions may be confused with clinical failure. Further researches have been proposed to prospectively study the use of TLC and clinical staging (and also with additional markers) and make comparison with the use of clinical staging alone to influence clinical, immunological, and virological outcomes of HAART in resource limited settings [9,10].

To address these issues, a prospective assessment of clinical, immunological, haematological and biochemical changes in clinically stable, clinically failing and clinically failing HIV patients that switched ARV during the course of treatment was carried out in rural Nigeria to serve as a baseline data in our environment and to inform policy makers. The most routine tests in evaluating the HIV patients were used for the study to ensure continuity of care to this group.

2. Method

The study was conducted at the antiretroviral centre of the General Hospital, Ugep, Cross River state, Nigeria. The centre was jointly supported by the state government, Family Health International (FHI) and United States Government through United States Agency for International Development (USAID) under the Global HIV/AIDS Initiative Nigeria (GHAIN) project. The HIV prevalence in the state was 8.0%; accounting for the fourth highest in the country.

Out of the 2440 registered adult HIV cases in the centre, about 1020 were presently on ARV treatment. The criteria for initiating patients on HAART at the centre were in accordance with the National Guidelines for antiretroviral treatment, i.e. HIV patients with CD4 T-cells $\leq$350 cells/μL irrespective of clinical staging and all WHO clinical stages III and IV irrespective of CD4 counts. Triple therapy containing two Nucleoside Reverse Transcriptase Inhibitors (2NRTIs) and one Non Nucleoside Reverse Transcriptase Inhibitor (1NNRTI) formed the backbone of treatment at the study centre. A boosted protease inhibitor (1PI/r) plus two nucleoside analogues (2NRTIs) combination were recommended for second line therapy.

A representative sample of 72 consecutive HIV patients on HAART managed at the ART clinic of the General Hospital, Ugep, Cross River State in December 2010 constituted the study population. At presentation, the patients were staged according to WHO staging system and assessed for clinical failure. Socio-demographic data as well as treatment details were obtained from case notes of the patients. The following exclusion criteria were used: HIV infected adults who were less than 6 months on HAART, HIV infected patients who were less than 15 years old, patients on HIV post exposure prophylaxis (PEP), HIV patients who were not eligible for HAART but on opportunistic infection prophylaxis, HIV patients receiving HAART and on medications for co-morbid conditions like hepatitis infection, diabetes mellitus, hypertension and tuberculosis, HIV infected pregnant women on PMTCT (prevention of mother-to-child transmission) and HIV patients on HAART with poor adherence to treatment.

As used in this study, clinical failure was described as the occurrence or recurrence of opportunistic infections or malignancies that signified clinical disease progression or the onset or recurrence of either WHO stage III or IV defining conditions in the HIV patients on antiretroviral drug therapy after at least 6 months of good adherence and after immune reconstitution syndrome was excluded. Drug switching was indicated in patients with drug toxicities such as severe haematological toxicities, allergic reactions and treatment failure. For cases with haematological toxicities and allergic reactions, the offending drugs were substituted with alternative drugs in the same class whilst treatments failing patients were changed to second-line regimen.

10 ml of venous blood was drawn for laboratory testing requested for routine evaluation at 8:00 a.m. every morning after overnight fast. All laboratory measurements were obtained by the trained ART laboratory scientists at the facility under standardized conditions. The concentration values of serum potassium, glucose, creatinine, ALT and AST were determined with the Reflotron+ automated clinical chemistry analyser of Roche Diagnostics GmbH utilizing the enzymatic colorimetric principle. Total lymphocyte counts, absolute platelet values and haematocrit levels were determined via full blood count on ethyldimethylacetic acid (EDTA) blood using a QBC autoread+ counter. The CD4 T-lymphocyte counts were determined with Becton Dickinson FACS counter.

Data were analysed using the SPSS version 17 software program. All datasets were categorized into two medication groups (patients that switched drugs and those that maintained their drugs), and two HIV clinical status groups (clinically stable and clinically failing). For each group, continuous variables were described by the mean, and categorical variables were described by frequencies and percentages. Student's *t*-test and Chi-square test were used to compare the groups for continuous and categorical variables respectively. p values ≤ 0.05 were considered statistically significant.

The study approval was obtained from the local ethical committee of the hospital on the agreement that patient anonymity must be maintained, and that every finding would be treated with utmost confidentiality and for the purpose of this research only in compliance with the Helsinki declaration. The patients studied took part voluntarily, after giving written informed consent.

3. Results

Of these cases, 14 (19.4%) had clinical failing conditions whilst 58 (80.6%) were clinically stable. There were more female than male patients in both groups with male: female of 1:2.6 for clinically stable patients and 1:3.7 for clinically failing patients. Heterosexual transmission was identified as the major risk factor for HIV infection. Table 1 shows that clinically stable patients were older (41.11 ± 9.45 years versus 36.39 ± 6.83 years) than the clinically failing patients ($p < 0.025$). The age ranged from 25 to 69 years for

Table 1
Patients' characteristics.

Parameters	Clinically stable	Clinically failing	p- value
Sex			
Male	16 (27.6)	3 (21.5)	<0.750
Female	42 (72.4)	11 (78.5)	
N (%)	58 (100)	14 (100)	
Mean age ± SD (years)	41.1 ± 9.5	36.4 ± 6.8	<0.025*
Duration on antiretroviral treatment (months)	19.46 ± 15.90	16.0 ± 12.90	>0.100
Marital status			
Single	7 (18.4)	1 (9.1)	>0.500
Married	23 (60.5)	7 (63.6)	
Widowed	7 (18.4)	2 (18.2)	
Divorced	1 (2.6)	1 (9.1)	
N (%)	38 (100)	11 (100)	
Level of education			
None	8 (22.2)	0 (0.0)	>0.100
Primary	15 (41.7)	5 (45.5)	
Secondary	13 (36.1)	6 (54.5)	
N (%)	36 (100)	11 (100)	
Job status			
Unemployed	17 (42.5)	6 (54.5)	>0.25
Employed	23 (57.5)	5 (45.5)	
N (%)	40 (100)	11 (100)	

* Statistically significant.