International Scholars Journals

African Journal of Immunology Research ISSN 2756-3375 Vol. 11 (2), pp. 001-008, February, 2025. Available online at www.internationalscholarsjournals.org © International Scholars Journals

Full Length Research Paper

Impact of Highly Active Antiretroviral Therapy on Hematological Parameters of HIV-Positive Patients in North Eastern Nigeria

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Accepted 6 January, 2024

We evaluated the changes in blood profile of patients in a prospective 30 month observational follow up study involving 145 antiretroviral naive acquired immune deficiency syndrome (AIDS) participants. Participants were divided into two groups at one year of highly active antiretroviral therapy (HAART), antiviral success (viral load < 2.60 log_{10} copies/ml); and antiviral failure (viral load > 2.60 log_{10} copies/ml. The mean ± standard deviation (SD) viral load in the antiviral success group (119 patients) was 5.25 ± 0.53 and 5.09 ± 0.71 log_{10} copies/ml in antiviral failure group at baseline. Antiviral success cohort had significant reduction of viral load at 6 months, achieved viral suppression at one year and maintained undetectable viral load in the subsequent follow-up period. Antiviral failure participants on the other hand failed to achieve significant viral load suppression at six month and had fluctuation and persistence of viral load. In the antiviral success group, the mean ± SD CD4+ T-cell count increased significantly at 6 month of treatment (P ≤ 0.038 versus baseline), and in the subsequent follow-up period (P < 0.05). Detectable human immune deficiency virus-ribonucleic acid (HIV-RNA) viral load at six months was associated with unremarkable increase in CD4 count, and its persistence at 12 month with virological failure. This observation may imply that early poor immunological improvement may suggest virological failure. Initial unremarkable change in CD4 count parameters in response to HAART may predict early virological failure and efficacy of therapy in the absence of viral load in our environment.

Key words: Human immune deficiency virus (HIV), acquired immune deficiency syndrome (AIDS), highly active antiretroviral therapy (HAART), haemoglobin, white blood count, $CD4^+$ count

INTRODUCTION

Haematological abnormalities seen in human immune deficiency virus (HIV) infected individuals involve all lineages of blood cells and the abnormalities seem to be dependent on the level of virus replication, as these

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abnormalities are severe in late-stage acquired immune deficiency syndrome (AIDS) patients with high viraemia (Lee et al., 2001). Although the mechanism underlying these abnormalities is still obscure, HIV-1 infection of marrow stromal cells may result in cytopenia and derangement of blood profile (DHHS/Henry, 2000; Moses et al., 1996; Bahner et al., 1997). The incidence of anaemia, the most common haematological abnormality in HIV seropositive patients increases with the progression of the disease. Neutropenia is most commonly seen in the advanced stages of AIDS and often caused or exacerbated by concomitant myelosuppressive drugs. Adverse drug reactions from anti retroviral drugs or those used in management of opportunistic infections may result in neutropenia in patients with HIV/AIDS. Thrombocytopenia also occur in the setting of HIV/AIDS especially among those with low CD4 cell count and older age (Scadden et al., 1990; Spivak et al., 1989; Frickhofen et al., 1990).

Bone marrow abnormalities are found in all stages of HIV disease, and increase in frequency as the disease progresses. Several morphologic abnormalities of the bone marrow have been reported in AIDS patients (Creag-Kirk et al., 1988). Bone marrow examination may be useful for the definitive assessment of iron stores which can assist in the differentiation of iron-deficiency anaemia from anaemia of chronic disease.

Use of highly active antiretroviral therapy (HAART) has been associated with improvements in immune function, increase in haematopoietic progenitor cell growth and significant declines in HIV-1 RNA levels (Moses et al., 1996; Bahner et al., 1997). A decrease in serum erythropoietin levels (Spivak et al., 1989), auto-antibodies to erythropoietin or marrow suppression by opportunistic infections, tumours or various medications may also contribute to the haematological abnormalities commonly observed in HIV- infected persons (Frickhofen et al., 1990; Creag-Kirk et al., 1988; Seneviratne et al., 2001; Sipsas et al., 1999). HAART may ameliorate many of these effects in an indirect manner simply by rebuilding the immune system and decreasing the HIV viral burden (Semba et al., 2001; Mellors et al., 1995; Walker et al., 1998).

In view of the paucity of data on the effect of HAART on blood profile of HIV-infected individuals in African literature, the present study prospectively analysed the effects of HAART on changes in viral load, $CD4^+$ count, haemoglobin, white blood count and platelets.

MATERIALS AND METHODS

Study area

The study was conducted in the Department of Medicine, University of Maiduguri Teaching Hospital, Borno State. This is a 500 bedded hospital designated as a Centre of Excellence for infectious diseases and provides primary, secondary and tertiary services for the North Eastern part of Nigeria. It also caters for the neighbouring countries such as Cameroon, Niger and Chad Republics.

A total of 145 AIDS patients who were HAART eligible based on Centre for Disease Control and prevention classification system for HIV-1 infection (Segal et al., 2011) were recruited into the study between May and December, 2007. The participants were extracted from a cohort of 960 patients studied for West African College of Physician (FWACP) fellowship dissertation (Flow chart 1). The following cases were defined as having AIDS: HIV-1-positive adults with a $CD4^+$ count < 200cells/µl or the clinical condition listed in the AIDS surveillance case definition (Centers for Disease Control and prevention, 1993). Using a structured, pre-evaluated questionnaire, information was obtained on demographic characteristics, clinical manifestation, medication used, blood transfusion, sexual and drug use behaviours. Patients with haematological diseases or other chronic condition affecting metabolism were excluded. HAART experienced prior to the study were excluded. All participants included had adherence of ≥ 80%. Adherence was defined through a self-reported evaluation by the patient and registered as percentage by the physician. An evaluation higher than 80% was classified as "adherent", whereas lower than 80% was considered as "non-adherent" and were excluded.

Patients were divided into two groups: antiviral success (where viral load was < 2.60 $\log_{10}$ copies/ml after treatment); and antiviral failure (where viral load was > 2.60 $\log_{10}$ copies/ml after treatment). Permission was obtained from the University of Maiduguri Teaching Hospital (UMTH) Ethical Committee. Written informed consent (signed or thumb printed) was obtained from patients.

Blood samples analysis

Samples for CD4+ T-cell count was collected between 9:00 and 10:00 am and assayed within 6 h of collection of whole blood, using standardized flow cytometric Cyflow machine (manufactured by Cytec, Partec, Germany, 2005). Haemoglobin and WBC was analysed using Haematology analyzer (manufactured by Sysmex®, Corporation Kobe, Japan) while plasma HIV RNA levels was measured using freshly frozen specimen separated within 6 h of phlebotomy, utilizing the Amplicor HIV-1 Monitor Test, version 1.5, manufactured by Roche® Germany, with a minimum cut off value of 200 copies per ml. Using the outlined standard testing techniques, data on the determined parameters was collected on initial visit, 6, 12, 18, 24 and 30 months after HAART.

Statistical analyses

Data were analysed using the Statistical package for social sciences (SPSS®) statistical package, version 15.0 (SPSS Inc., Chicago, IL, USA) for Windows®. Normal distributions were analysed using the Kolmogorov-Smirnov test, and the results of analysis of variance and rank sum tests of multiple sets of data were analysed by the Pearson's χ^2-test and P value < 0.05 was considered to be statistically significant.

RESULTS

A total of 145 HAART naive adult AIDS participants were consecutively recruited into the study. The study popula-

Flow chart 1. Chart showing the number of participants recruited into the study.

Number of participants enrolled into the study = 960	
Number of participants with < 80% adherence(chart documented) = 715	Number of participants with ≥ 80% adherence (chart documented) = 145
Participants that achieved that virological success at 12 months = 119	Participants that achieved that virological success at 12 months = 26

Table 1. Sociodemographic characteristics of participants, stratified by antiviral outcome.

Characteristics	Overall (n = 145)	Antiviral success group (n = 119)	Antiviral failure group (n = 26)	p-value
Age, years	35.68±8.40	36.42±9.25	34.86±7.37	0.189
Female, sex (%)	98 (67.6)	81(68.1)	17 (66.4)	0.960
Risk factor				
Heterosexual	123	103 (85.7)	20 (76.9)	0.414
Homosexual	0	0	0	
IV drug use	0	0	0	
Blood transfusion	3	3(2.5)	0	
Unknown	19	13(10.9)	06 (23.1)	0.177
Educational status				
No formal education	38	22(18.5)	16 (61.5)	0.000*
Primary education	50	39(32.8)	02 (7.7)	0.020*
Secondary education	34	21(17.7)	05 (19.2)	0.999
Tertiary education	23	18(15.1)	03 (11.5)	0.869
Marital status				
Married	77	76(63.8)	21 (80.7)	0.153
Single	39	22(18.5)	05 (19.3)	0.999
Divorced	22	16(13.5)	00	
Separated	07	05 (4.2)	00	
CD4 count	165.17±132.54	171.04±108.80	152.19±112.85	0.376
Viral load $\log_{10}$	5.46±0.87	5.25±0.53	5.09±0.71	0.762

tion were divided into two treatment groups at the end of the study; the antiviral HAART success and failure. Participants that had no formal education were more likely to fail HAART therapy. Conversely, those that had at least primary education showed antiviral success preponderance. Marital status had no effect on the antiviral outcome, the socio-demographic characteristics of participants, stratified by antiviral outcome, is as depicted in Table 1. All the participants had received up to 30 months of uninterrupted HAART. Seven patients were lost to follow up, with three mortalities (2 males and a female) within 3 months of recruitment, the other 4 requested for transfer to Health facility closer to their homes.

The CD4+ Tcells/µl and haemoglobin concentration increased significantly from the 6th month (in comparision to baseline $P < 0.05$), their levels remained significantly high throughout the study. Conversely, there was no significant change in the levels of platelets and WBC at any point throughout the study (Table 2).

The mean ± standard deviation (SD) viral load in the antiviral success group (119 patients) was 5.25 ± 0.53 $\log_{10}$ copies/ml at baseline. This decreased to an undetectable level after 12 months of treatment and remained relatively stable in the subsequent follow-up period. The mean ± SD of viral loads in the 26 antiviral failure cases was 5.09 ± 0.71, it fluctuated and was detectable at 30 months of treatment at a mean ± SD

Table 2. Changes in blood profile 145 AIDS after 30 months of HAART.

Treatment duration (months)	$CD4^+$ T-cell (cells/µl)	Haemoglobin (g/dl)	WBC (cells/µl)	Plateletes (platelets/µl)
0 (Baseline)	167.67±109.38	10.27±2.08	5.32±2.36	300.57±106.12
6	260.46±142.46*	11.23±1.80*	4.89±1.74	302.78±113.56
12	341.19±173.85*	11.78±1.58*	4.98±1.60	297.23±99.91
18	371.86±205.02*	12.02±1.68*	4.76±1.34	309.88±98.47
24	410.97±244.72*	11.95±1.73*	5.00±1.54	295.38±91.49
30	481.48±481.01*	11.95±1.61*	4.80±1.23	279.25±73.80

Data presented as mean ± SD. WBC: white blood cell count.*P < 0.05 compared with baseline; least-squares difference of one way analysis of variance.

Table 3. Viral load (VL) in patients with Acquired Immuno Deficiency Syndrome during 30 months of highly active anti-retroviral therapy (HAART).

Treatment duration (month)	Antiviral success Group (n = 119) VL log_{10} (copies/ml)	Statistical significance[a]	Antiviral failure Group (n = 26) VL log_{10} (copies/ml)	Statistical significance[a]	Statistical significance[b]
0 (Baseline)	5.25±0.53		5.09±0.71		0.040*
6	3.96±0.98	0.000*	3.41±0.95	0.152	0.897
12	2.30	-	4.78±0.77	0.688	-
18	2.30	-	4.51±0.82	0.477	-
24	2.30	-	4.43±0.64	0.608	-
30	2.30	-	4.40±0.48	0.056	-

Data presented as log_{10} mean ± SD. [a]Statistical significance versus baseline; least-squares difference of one way analysis of variance. [b]Statistical significance of antiviral failure group versus antiviral success group; least-squares difference of one way analysis of variance.*Statistically significant.

Table 4. CD4+ T-cell count in patients with acquired immuno deficiency syndrome during 30 months of highly active antiretroviral therapy (HAART).

Treatment duration (month)	Antiviral success Group (n = 119) (cells/µl)	Statistical significance[a]	Antiviral failure Group (n = 26) (cells/µl)	Statistical significance[a]	Statistical significance[b]
0 (Baseline)	171.04±108.80	-	152.19±112.85	-	0.376
6	273.89±141.15	0.038*	201.27±135.45	0.900	0.000*
12	359.13±175.58	0.000*	259.12±141.57	0.205	0.000*
18	394.39±201.43	0.000*	268.77±192.73	0.132	0.000*
24	435.26±246.23	0.000*	299.77±207.59	0.230	0.000*
30	519.61±515.72	0.000*	306.96±196.92	0.140	0.000*

Data presented as mean ± SD. [a]Statistical significance versus baseline; least-squares difference of one way analysis of variance. [b]Statistical significance of antiviral failure group versus antiviral success group; least-squares difference of one way analysis of variance. *Statistically significant.

level of 4.40 ± 0.48 log_{10} copies/ml as shown in Table 3. In the antiviral success group, the mean ± SD CD4+ T-cell count increased significantly at 6 months of treatment (P ≤ 0.038 versus baseline), and then increased steadily and significantly in the subsequent follow-up period (P < 0.05). The increase in CD4+ T-count was not significant at any point in the antiviral failure group (Table 4). The change in mean ± SD WBC count was insignificant in

Table 5. White blood count (WBC) in patients with acquired Immuno deficiency syndrome during 30 months of highly active antiretroviral therapy (HAART).

Treatment duration (Months)	Antiviral success Group (n = 119) (cells/µl)	Statistical significance[a]	Antiviral failure Group (n = 29) (cells/µl)	Statistical Sigificance[a]	Statistical significance[b]
0 (Baseline)	5.49±2.45		4.56±1.73		
6	4.92±1.76	0.167	4.76±1.67	0.997	NS
12	5.04±1.65	0.426	4.68±1.38	1.000	NS
18	4.87±1.35	0.303	4.31±1.25	0.996	NS
24	4.97±1.24	0.833	4.45±1.61	1.000	NS
30	5.10±1.82	0.490	4.15±0.98	0.969	NS

Data presented as mean ± SD. [a]Statistical significance versus baseline; least-squares difference of one way analysis of variance. [b]Statistical significance of antiviral failure group versus antiviral success group; least-squares difference of one way analysis of variance. NS: not statistically significant between group differences (P > 0.05).

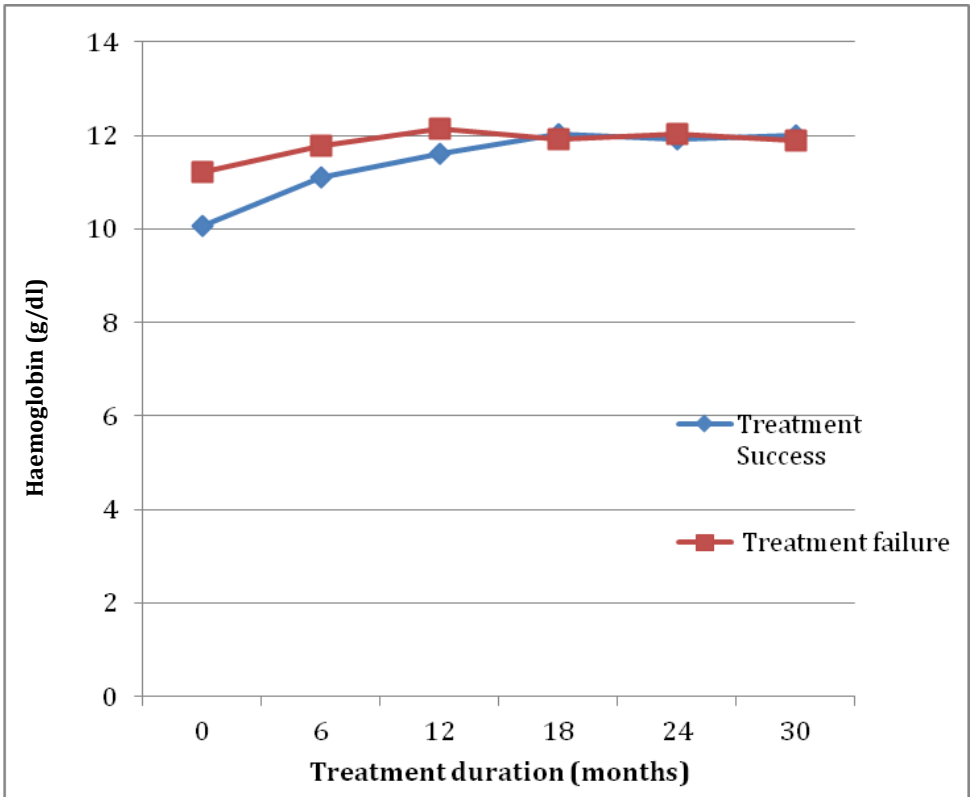

Figure 1. Haemoglobin concentration over time in AIDS patients during 30 months of highly active antiretroviral treatment, haemoglobin levels in the treatment success group were similar to treatment failure group (*P* > 0.05) (data presented as mean ± SD).

over the 30 months study in both antiviral HAART success and failure group, neither was any significant difference between these two groups observed (Table 5). Before the initiation of HAART, mean ± SD haemoglobin concentrations (g/dl) of 10.06 ± 2.09 in HAART success group was similar to 11.23 ± 11.23 in HAART failure. The mean ± SD haemoglobin increased to 12.01 ± 1.62, with a change of 1.95 ± 0.47 in the success group, the corresponding increase in HAART failure group was 11.88 ± 1.58, with a change of 0.65 ± 0.26 after 30 months of HAART (Figure 1). There were no significant differences in platelet count in either group from baseline to study

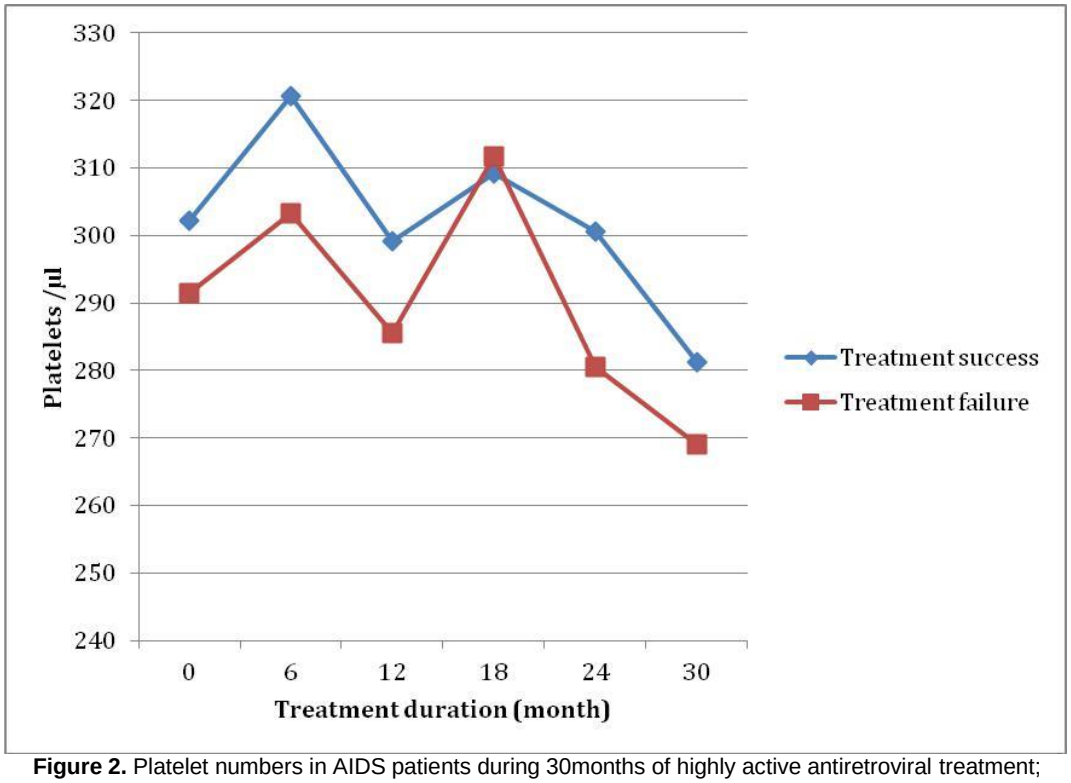

Figure 2. Platelet numbers in AIDS patients during 30months of highly active antiretroviral treatment; no statistically significant differences in platelet count versus baseline in either group (data presented as mean ± SD).

end point (Figure 2).

DISCUSSION

The decision to start HAART in patients with HIV involves making a judgment about when the benefits of therapy outweigh the harms; HAART should be commenced early enough to avoid any clinical consequences of immune suppression and maximise immune reconstitution, but late enough to minimise harms such as drug adverse effects, drug pressure risking development of resistance, and burdens such as the cost of medication (Cohen, 2000; Zachariah et al., 2006). Haematological abnorma-lities (anaemia, leucopoenia and thrombocytopenia) are common manifestations of advanced HIV-1 infection that could potentially limit the use of some components of antiretroviral therapy (ART) regimens (Zachariah et al., 2006; Levine et al., 2006).

The CD4+ cell count is central to the decision to initiate HAART in standard clinical practice along with clinical indices and HIV RNA viral load measurement (Anonymous, 2003). CD4 count and viral load tests are rarely available in resource poor settings for reasons of, high cost, inadequate infrastructure, and insufficient numbers of trained personnel to administer tests, among others (Colebunders et al., 2006). Even where the duo is available, CD4 count may fail to increase despite sustained virological suppression (discordant Immuno-virologic response), thus limiting the use of CD4+ cell count in monitoring response to HAART (Bisson et al., 2006; Taiwo and Murphy, 2008). Conversely, rapid changes in CD4+ T-cell count and function appear to have a temporal correlation with clinical immune reconstitution inflammatory syndrome (IRIS) events in conditions such as mycobacterial and cryptococcal infections; and some observational data using blood have suggested that IRIS occurs more frequently in individuals with faster and more marked elevations in blood CD4+ cell count after commencing HAART.

Clear evidence to support this hypothesis, especially at local sites of inflammation, however, is lacking. In Cytomegalovirus (CMV) uveitis, cryptococcal meningitis and tuberculosis, studies suggests that IRIS is more common when there is extensive disease presence (Breen et al., 2004; Shelburne et al., 2005; Karavellas et al., 2001; Jenny-Avital and Abadi, 2002). The underlying pathological mechanisms driving these events are unclear, although the available data highlight the impor-tance of CD8 T-cell responses, perharps with a Th2 bias,

as shown by increased plasma level of soluble CD30 (Stone et al., 2002; Hsieh et al., 2001). A plausible explaination of this would be that abundant microbial antigen, whether alive or dead, promotes a greater immune response when it encounters suddenly increased numbers of functionally active antigen specific cells. This may suggest that IRIS might be expected to be less frequent if HAART is delayed until such time as significant antigen clearance has occurred, following specific antimicrobial therapies (Shelburne et al., 2005; Stone et al., 2002; Hsieh et al., 2001). On the other hand, whereas several AIDS-defining infections associated with severe immunodeficiency, including pneumocystis jiroveci pneumonia (PCP), mycobacterium avium com-plex, and CMV retinitis, decreased significantly in the HAART era as did AIDS-defining malignancies such as kaposi sarcoma (KS) and primary central nervous system lymphoma (PCNSL).

Unfortunately, AIDS-related lymphoma (ARL) of intermediate and high-grade peripheral B-cell phenotype has not changed as significantly, with some studies reporting no change or even an increase in incidence, irrespective of the CD4+ cell counts (Skiest and Crosby, 2003; International Collaboration on HIV and cancer, 2000; Kirk et al., 2001; Matthews et al., 2000; Gerrald et al., 2002; Vaccher et al., 2003). The WHO recognised this problem in its guidelines for scaling up antiretroviral use in resource poor settings. It has recommended the use of TLC in addition to WHO clinical staging criteria in an alternative algorithm. The WHO has suggested that in the absence of information or the ability to count CD4+ T-cells, a TLC of 1200 cells/µl is typically equivalent to a CD4+ T-cell count of 200 cells/µl (WHO, 2003).

TLC is calculated by multiplying the total WBC by the lymphocyte percentage (Taiwo and Murphy, 2008). The lymphocyte percentage of total WBC, which is necessary to calculate the TLC, is most accurate if determined within a few hours of phlebotomy (Taiwo and Murphy, 2008; Breen et al., 2004; Shelburne et al., 2005; Karavellas et al., 2001; Jenny-Avital and Abadi, 2002; Stone et al., 2002; Hsieh et al., 2001; Skiest and Crosby, 2003; International Collaboration on HIV and cancer, 2000; Kirk et al., 2001; Matthews et al., 2000; Gerrald et al., 2002; Vaccher et al., 2003; WHO, 2003; Akinola et al., 2004). Many haematology workstations in resource-limited settings are unable to meet this stringent criterion, and there are unavoidable excursions in ambient temperature that accelerate the degradation of laboratory samples. As such, TLC calculations are prone to error (Levine et al., 2004; Anonymous, 2003; Colebunders et al., 2006).

Another factor that can unravel potential correlation between TLC and CD4+ T-cell count is that TLC captures both B and T-cell subsets. Accordingly, a person with low CD4+ T-cell could have relatively high TLC if high amounts of B-cells are expressed due to immune hyperactivation from exposure to the wide variety of circulating antigens in sub-Saharan Africa (Taiwo and Murphy, 2008; Chen et al., 2007)..

Severe anaemia is very common in HIV infected patients, with 40% of HIV infected patients developing various degrees of anaemia in the advanced stage of disease (Sullivan et al., 1998; Bolge etb al., 2007; Sloand, 2005; Fangman and Scadden, 2005). This study is in agreement with previous studies that observed that anaemia is not related to disease progression or low CD4+ T-cell count (< 200 cells/µl), although anaemia can be significantly improved by HAART (Bolge etb al., 2007; Fangman and Scadden, 2005).

Previous studies have shown that TLC counts, an haemoglobin concentration in peripheral blood, decline significantly in HIV-infected patients before the onset of AIDS, particularly in the presence of opportunistic infections (Sloand, 2005; Moylett and Shearer, 2002). Thus, TLC and haemoglobin concentrations may be used in resource-limited settings as an indicator for the initiation of HAART. The Government of Nigeria with the support of implementing partners such as President's Emergency Plan for AIDS Relief (PEPFAR) Project provides free antiviral drugs, but routine detection of HIV RNA and CD4+ T-cells is neither available nor affordable in most clinical units, rendering necessary the urgent provision of additional monitoring indicators. Blood pro-files of patients with AIDS receiving HAART were followed up for 30 months in the infectious diseases unit at the University of Maiduguri Teaching Hospital, Maiduguri to search for additional monitoring indicators. It was found that CD4+ T-cell count and haemoglobin concentration increased shortly after HAART was initiated.

The present study found that haemoglobin concentration improved with HAART, and remained stable in both antiviral success and antiviral failure group. However, the increase in CD4 count was only observed in antiviral success group, this suggests that the haemoglobin concentration is not related to the efficacy of HAART. There was no significant change in WBC, regardless of the success or failure of HAART regimen. WBC is known to be influenced by other factors such as opportunistic infections (Moylett and Shearer, 2002; Yang et al., 2008). The findings of the present study suggest, therefore, that WBC is not suitable for determining when to begin or monitor the efficacy of HAART. The absence of change in platelet count in relation to increased CD4+ T-cell count in response to HAART in this study confirms the findings of others (Lau et al., 2005).

The use of CD4 count to monitor the long-term efficacy of therapy in the absence of viral load may still remain the consistent option in our environment. Haemoglobin concentration, white blood cell count and platelets are not

related to disease progression in HIV patients on HAART in this study.

ACKNOWLEDGEMENT

We wish to thank Dr Holly Rawizza, MD, APIN/Havard PEPFAR, 1635 Tremont Street, Boston, MA for immense support.

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