Prevalence of Anemia and Immunological Markers in HIV-Infected Patients on Highly Active Antiretroviral Therapy in Northeastern Nigeria

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Abstract

Background: There are conflicting reports on the impact of highly active antiretroviral therapy (HAART) in resolving hematological complications. Whereas some studies have reported improvements in hemoglobin and other hematological parameters resulting in reduction in morbidity and mortality of HIV patients, others have reported no improvement in hematocrit values of HAART-treated HIV patients compared with HAART-naive patients.

Objective: This current study was designed to assess the impact of HAART in resolving immunological and hematological complications in HIV patients by comparatively analyzing the results (immunological and hematological) of HAART-naive patients and those on HAART in our environment.

Methods: A total of 500 patients participated, consisting of 315 HAART-naive (119 males and 196 females) patients and 185 HAART-experienced (67 males and 118 females) patients. Hemoglobin (Hb), CD4+ T-cell count, total white blood count (WBC), lymphocyte percentage, platelets, and plasma HIV RNA were determined.

Results: HAART-experienced patients were older than their HAART-naive counterparts. In HAART-naive patients, the incidence of anemia (packed cell volume [PCV] <30%) was 57.5%, leukopenia (WBC < 2.5), 6.1%, and thrombocytopenia < 150, 9.6%; it was, significantly higher compared with their counterparts on HAART (24.3%, 1.7%, and 1.2%, respectively). The use of HAART was not associated with severe anemia. Of HAART-naive patients, 57.5% had a CD4 count < 200 cells/µL in comparison with 20.4% of HAART-experienced patients (P < 0.001). The mean viral load log10 was significantly higher in HAART-naive than in HAART-experienced patients (P < 0.001). Total lymphocyte count < 1.0 was a significant predictor of <CD4 counts < 200 cells/µL in HAART-naive patients, but this relationship was not observed in HAART-experienced patients.

Conclusion: HAART has the capability of reducing the incidence of anemia, other deranged hematological and immunological parameters associated with disease progression, and death in HIV-infected patients. Total lymphocyte count fails to predict CD4 count < 200 cells/µL in our cohort; thus, its use in the management and monitoring of HIV-infected patients in our settings is not reliable.

Keywords: antiretroviral, lymphocyte, total leukocyte count, CD4, World Health Organization/Aids Clinical Trials Group
**Background**

Human immunodeficiency virus (HIV) infection has a variety of effects on hematopoiesis. Pancytopenia is part of its natural history.\(^1\)\(^-\)\(^4\) Cytopenia is a common complication of infection with human immunodeficiency virus type 1 (HIV-1), and, in the course of the disease, more than 70% of the patients develop anemia, frequently requiring transfusion.\(^5\)

Neutropenia, lymphopenia, and thrombocytopenia may occur indicating that more than one hematopoietic lineage may be impaired. Dysfunction of the bone marrow has been suggested as a possible mechanism; the degree of cytopenia often reflects the severity of the disease.\(^6\)

HIV-1 infection of marrow stromal cells is sufficient to result in anemia and other cytopaenias.\(^7\)\(^-\)\(^9\) A decrease in serum erythropoietin levels,\(^10\) autoantibodies to erythropoietin, or marrow suppression by opportunistic infections, tumors or various medications,\(^11\)\(^-\)\(^14\) may also contribute to the cytopenia commonly observed in HIV-infected persons. Highly active antiretroviral therapy (HAART) may ameliorate many of these effects in an indirect manner simply by decreasing the HIV viral burden\(^15\)\(^-\)\(^17\) and stimulating hematopoietic progenitor cell growth.\(^18\)

Although HAART use in HIV infection has generally been accepted as the gold standard in the management of HIV patients,\(^19\) some antiretroviral drugs (ie, nucleoside analogue reverse transcriptase inhibitors, especially zidovudine) may cause anemia or worsen existing anemia, and, for this reason, zidovudine is usually excluded from the antiretroviral regimen of severely anaemic patients.\(^20\)

The most troublesome and common toxicities of zidovudine are, notably, anemia and neutropenia.\(^20\) There are conflicting reports on the impact of HAART in resolving hematological complications. Whereas some studies have reported improvements in hematocrit and hemoglobin values resulting in reduction in morbidity and mortality of HIV patients,\(^19\)\(^,\)\(^21\) another study has reported no improvement in hematocrit values of HAART-treated HIV patients compared with HAART-naive patients.\(^22\) This current study was designed to assess the impact of HAART in resolving immunological and hematological complications in HIV patients by comparatively analyzing the results (immunological and hematological) of HAART-naive patients and those on HAART in our environment.

**Methods**

**Study area and design**

This cross-sectional study was carried out in the Department of Medicine, University of Maiduguri Teaching Hospital, Borno State, from September 2007 through March 2008. This is a 500 bed 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 neighboring countries such as the Republics of Cameroon, Niger, and Chad. Permission was obtained from the University of Maiduguri Teaching Hospital (UMTH) Ethical Committee. Written informed consent (signed or thumb print) was obtained from patients.

**Study population and procedure**

A total of 536-HIV positive patients were consecutively recruited into the study. Using a structured, pre-evaluated questionnaire, information was obtained on demographic characteristics, clinical manifestations, medication used, blood transfusions, and sexual and drug use behavior. The study population consisted of HAART-naive patients and patients who had been on HAART for \(\geq 12\) months. Criteria for HAART initiation for patients on therapy was based on the Centers for Disease Control and Prevention (CDC) criteria.\(^23\) HAART use was defined as receipt of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI). The HAART regimen was verified from patient’s clinical records. Pregnant patients and patients on medications that could affect the hematological system (antibiotics, vitamin supplements, or tuberculosis treatment) at the time of sampling were excluded from the study.

**Blood sample analysis**

The HIV serological reactivity was determined by enzyme-linked immunoassay (ELISA) and confirmed by western blot analysis. Samples for CD4+ T-cell count were collected between 9:00 AM and 10:00 AM and assayed within 6 hours of collection of whole blood using standardized flow cytometric Cyflow machine (Cytex Development Inc, Partec, Germany). Hemoglobin (Hb), total white blood count (WBC), lymphocyte percentage, and plateletes were analyzed using a hematology analyzer (Sysmex® Corporation, Kobe, Japan). Plasma HIV RNA levels were measured.
using freshly frozen specimens separated within 6 hours of phlebotomy utilizing the Amplicor HIV-1 Monitor Test, version 1.5 (Roche®, Germany), with a minimum cutoff value of 200 copies per mL.

**Statistical Analysis**
The software program SPSS version 15 (SPSS Inc, Chicago, IL) was used. Results are presented as means ± SEM. Unpaired t tests were used to compare the means of all continuous variables. Categorical data were analyzed using Fisher exact test or Chi-square test for trend. Linear regression was used to test for the degree of association between test parameters. A P value of <0.05 was considered to be statistically significant.

**Demographic and social characteristics of the study population**
Of the 536 participants that were consecutively recruited into the study, 36 had incomplete or missing records and were excluded from the analysis. Records of 500 subjects were complete, comprising 315 (63%) HAART-naive and 185 (37%) HAART-experienced participants, with median ages of 27.09 ± 16.92 (range, 17–70 years) and 34.43 ± 15.06 (range, 18–67 years), respectively (P < 0.001). Of the 315 HAART-naive participants, 119 (37.8%) were male, and 196 (62.2%), female, with median ages 32.28 ± 17.91 (range, 17–67) years and 24.72 ± 14.89 (range, 17–70) years, respectively (P < 0.001). Of the 185 HAART-experienced participants, 67 (36.2%) were male, while 118 (63.8%) were female, with median ages 38.77 ± 14.81 (range, 20–67) years and 34.08 ± 12.45 (range 18–66) years (P < 0.001), respectively. The age profile as depicted in Table 1 indicates that the majority of the of the participants were <50 years, with the highest proportion (32.1%) from 30 to 39 years of age in HAART-naive participants, while 40% of HAART-experienced participants were from 40 to 49 years of age. Heterosexual transmission was the presumed risk factor in almost all the study participants. Categorization of the participants based on educational attainment shows that a quarter of the participant had

| Table 1. Demographic and social characteristics of the study population. |
|-----------------------------|-----------------------------|-----------------------------|
| **Age (years)** | **HAART naive** n = 315 (63%) | **On HAART** n = 185 (37%) |
| 10–19 | 20 (6.3) | 3 (1.6) |
| 20–29 | 84 (26.7) | 26 (14.1) |
| 30–39 | 101 (32.1) | 57 (30.8) |
| 40–49 | 63 (20) | 74 (40) |
| 50–59 | 21 (6.7) | 16 (8.7) |
| 60–69 | 16 (5.1) | 5 (2.7) |
| 70–79 | 10 (3.2) | 4 (2.2) |
| **Median ± SD** | 27.09 ± 16.92 (17–70) | 34.43 ± 15.06 (18–67) | 0.000 |
| **Sex** | | |
| Male: no (%) | 119 (37.8) | 67 (36.2) |
| Mean ± SD (min-max) | 32.28 ± 17.91 (17–67) | 38.77 ± 14.81 (20–67) |
| Female: no (%) | 196 (62.2) | 118 (63.8) |
| Mean ± SD (min-max) | 24.72 ± 14.89 (17–70) | 34.08 ± 12.45 (18–66) |
| **Risk factor** | | |
| Heterosexual | 298 (94.6) | 180 (97.3) |
| Blood transfusion | 3 (0.95) | 0 |
| Iv drug use | 0 | 0 |
| MSM | 0 | 0 |
| Unknown | 14 (4.4) | 5 (2.7) |
| **Educational status** | | |
| No formal education | 67 (21.3) | 33 (17.8) |
| Quranic education | 18 (5.7) | 10 (5.4) |
| Primary education | 54 (17.1) | 31 (16.8) |
| Secondary education | 119 (37.8) | 73 (39.5) |
| Tertiary education | 57 (18.1) | 38 (20.5) |
no western education; the majority of the educated had secondary education. Almost half of HAART naïve and one-third of HAART experienced were married, quarter of the studied participants were single in both group, while HAART experienced had more divorced participants as presented in Figure 1. Demographic and social characteristics of the study participants evaluated in this study are presented in Table 1.

Hematological profile, viral load, and cytopenic tendency stratified by HAART use

The mean hemoglobin of $11.89 \pm 1.61$ (95% confidence interval [CI], 11.64–12.13) in HAART-experienced participants was significantly higher than the mean hemoglobin of $9.76 \pm 2.82$ (95% CI, 9.45–10.07) in HAART-naive participants ($P < 0.001$). Using packed cell volume (PCV) <30% to define anemia, 57.5% (180/313) of HAART-naive participants were 3 times at risk of anemia compared with 24.3% (41/169) or HAART-experienced participants ($P < 0.001$). The mean WBC and the incidence of leukopenia were higher among HAART—naive participants ($P < 0.001$). The mean total leukocyte count (TLC) of $2.05 \pm 1.34$ (95% CI, 1.86–2.24) in HAART-experienced participants was significantly higher than the mean TLC of $1.61 \pm 1.02$ (95% CI, 1.50–1.72) in HAART-naive participants ($P < 0.001$), consequently HAART-naive participants had 4 times the risk of developing leukopenia (TLC < 2500 µL$^{-1}$) than HAART-experienced participants ($P < 0.001$). The mean lymphocyte % of 46.11 ± 12.70 (95% CI, 44.27–47.90) and incidence of lymphopenia (<40%) of 98.3% were significantly higher in HAART-experienced participants than 31.85 ± 12.37 (95% CI, 30.43–33.28) and 73.2% in HAART-naive participants ($P < 0.001$). The mean neutrophil % of $54.98 \pm 15.72$ (95% CI, 53.22–56.73) in HAART-naive participants was higher than $38.35 \pm 10.49$ (95% CI, 36.82–39.87) in HAART-experienced participants ($P < 0.001$), conversely neutropenia defined as neutrophil % (% < 60%) showed HAART-experienced preponderance ($P < 0.001$). Although there was no difference in mean platelets counts, the risk of thrombocytopenia ($<150 \times 10^3$/µL) was 8 times higher in HAART-naive participants ($P < 0.001$). The mean CD4 count of $347.73 \pm 183.85$ (95% CI, 320.77–374.70) was significantly higher in HAART-experienced than $238.98 \pm 216.57$ (95% CI, 214.93–263.03) in HAART-naive participants ($P < 0.001$), the risk of immunological AIDS (<200 cell/µL) was 3 times in HAART naive than HAART experienced ($P < 0.001$). The mean viral load log10 was significantly lower in HAART experienced ($3.17 \pm 1.04$ copies/mL) than $5.58 \pm 2.23$ copies/mL in HAART-naive participants ($P < 0.001$). The haematological profile, viral load and cytopenic tendency of the participants stratified by HAART use is as presented in Table 2. The incidence of cytopenia in the study population is as shown in Figure 2.

World Health Organization Clinical Trials Group, anemia toxicity, stratified CD4 count by CDC and TLC grades

Classification of the study population according to the World Health Organization/AIDS Clinical Trials

![Figure 1. Distribution of the participant based on marital status.](image-url)
Prevalence of anemia and immunological markers in HIV patients

Group (WHO/ACTG) anemia toxicity grades as presented in Table 3 gave a 60.1% and 36.1% calculated incidence of anemia (Hb < 10.5 g/dL) in HAART-naive and HAART-experienced participants respectively ($\chi^2 = 17.54$, $P < 0.001$). The odds of developing grade 1 anemia in HAART-naive and HAART-experienced participants were similar ($P = 0.18$); however, HAART-naive participants were 2 times at risk of developing grade 2 anemia ($P < 0.001$). Grade 3 and 4 anemia were not seen in HAART-experienced patients.

The Centers for Disease Control and Prevention (CDC) criteria were used to classify the study population into three categories based on CD4 counts: stage 1 (CD4 > 500 cells/µL), stage 2 (CD4 between 200 and 499 cells/µL) and stage 3 (CD4 < 200 cells/µL). The risk of having CD4 count < 200 cells/µL was thrice in HAART-naive participants than those on

**Table 2. Hematological profile, viral load, and cytopenic tendency of the study population.**

| Characteristics | HAART naive | On HAART | $P$-value |
|-----------------|-------------|----------|-----------|
| Participants stratified by HAART use | | | |
| Sample size (n) | 315 | 185 | | |
| HB (g/dL) | 9.76 ± 2.82 (95% CI 9.45–10.07) | 11.89 ± 1.61 (95% CI 11.64–11.13) | 0.000 |
| PCV < 30% | | | |
| TWBC ($\times 10^3$µL$^{-1}$) | 5.94 ± 2.91 (95% CI 5.61–6.26) | 5.05 ± 1.58 (95% CI 4.81–5.29) | 0.029 |
| TLC ($\times 10^3$µL$^{-1}$) | 1.61 ± 1.02 (95% CI 1.50–1.72) | 2.05 ± 1.34 (95% CI 1.86–2.24) | 0.000 |
| LC (%) | 31.85 ± 12.37 (95% CI 30.43–33.28) | 46.11 ± 12.70 (95% CI 44.27–47.90) | 0.000 |
| NC (%) | 54.98 ± 15.72 (95% CI 53.22–56.73) | 38.35 ± 10.49 (95% CI 36.82–39.87) | 0.000 |
| PLT ($\times 10^3$µL$^{-1}$) | 297.61 ± 127.19 (95% CI 283.46–311.75) | 291.86 ± 95.91 (95% CI 277.07–306.65) | 0.000 |
| CD4 count (cells/µL) | 238.98 ± 216.57 (95% CI 214.93–263.03) | 347.73 ± 183.85 (95% CI 320.77–374.70) | 0.000 |
| Viral load log10 | 5.58 ± 2.23 (95% CI 1.21–2.56) | 3.17 ± 1.04 (95% CI 0.76–1.03) | 0.000 |

Abbreviations: TWBC, Total white blood count; LYM%, Lymphocyte percent; Neut%, Neutrophil percent; TLC, Total leukocyte count; PLT, Platelets numbers.

**Figure 2. Incidence of cytopenia in the study population.**
HAART ($P < 0.001$), and the chances of having a CD4 count between 200 and 499 cells/µL was 2 times higher in patients on HAART than those who were HAART naive ($P = 0.001$). No significant difference was observed in the proportion of participants with CD4 counts $\geq 500$ cells/µL when HAART-naive participants were compared with HAART-experienced participants ($P = 0.025$). There was no difference in the proportion of participants with TLC $< 1.010^3$/µL in both groups, HAART-naive participants had a significantly higher proportion of participants with TLC 1.0 to 2.0 ($P = 0.001$), while HAART-experienced participants displayed twice the preponderance ($P < 0.001$).

CD4 count categories stratified by World Health Organization AIDS Clinical Trials Group grades and Centers for Disease Control and Prevention criteria

Analysis of the three categories of CD4 counts, WHO/ACTG anemia toxicity and defined TLC grades are as depicted in Table 4. Based on the analysis of the three categories of CD4 counts and TLC in HAART-naive participants, when TLC was $<1000$ µL$^{-1}$, there was a gradual increase in the proportion of patients within the three CD4 categories, from 1.7% in stage 1, 6.8% in stage 2, and to a peak percentage of 91.5% in stage 3 ($P < 0.001$). With a TLC between 1000 and 2000 µL$^{-1}$, a steady increase was maintained across all the three stages. A similar proportion of patients within the CD4 stages 1 and 3 was observed with a higher proportion of 48.3% in stage 2 when the TLC was $>2000$ µL$^{-1}$.

Taking grades of anemia into account, a steady increase in the proportion of participants was observed from stage 1 through stage 3 across all grades.

In patients on HAART, when the TLC was $<1000$ µL$^{-1}$, 1000 to 2000 µL$^{-1}$, and $>2000$ µL$^{-1}$, patients within category 2 had the highest proportion of participants than category 1 and 3 across all grades. The pattern of incidences of grades 1 and 2 was not consistent, and grades 3 and 4 were absent in HAART-experienced participants.

**Discussion**

Hematological abnormalities are among the most common complications of HIV, which involves all lineages of blood cells. Establishing the presence of abnormal hematological manifestations in HAART-naive HIV patients and those on HAART and performing a comparative analysis within the two study
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The incidence of cytopenia in this study was significantly higher in HAART-naive patients than in patients on HAART. Consistent with this report, since the introduction of HAART, several studies have examined the prevalence of anemia, indicating that the prevalence of severe anemia has declined while mild to moderate anemia remains relatively common with use of HAART. HIV-1 infection of marrow stromal cells is sufficient to result in anemia and other cytopenias. A decrease in serum erythropoietin levels, auto-antibodies to erythropoietin, or marrow suppression by opportunistic infections, tumors, or various medications may also contribute to the anemia commonly observed in HIV-infected persons. HAART may ameliorate many of these effects in an indirect manner simply by decreasing the HIV viral burden. A study has shown that HAART was associated with an increase in hematopoietic progenitor cell growth. Although the mean platelet count was similar in both HAART-naive and HAART-experienced participants, the relative risk of developing thrombocytopenia in HAART-naive populations was 8 times that of the HAART-experienced. This finding is in sharp contrast to studies conducted previously that reported a similar thrombocytopenic incidence in HAART-naive and HAART-experienced patients. Taking into account participants’ levels of immunosuppression based on CD4 counts, it was shown that the incidence of grades 1 to 4 anemia among HAART-naive participants with severe, moderate, and mild immunosuppression declined significantly with increased CD4 levels. Although the linear relationship between level of immunity and grades of anemia was lost in HAART-experienced patients, severe grades (3 and 4) were not present in patients on HAART as a result of declines in the prevalence of opportunistic infections and immune-reconstitution, consistent with other reports. The laboratory parameter most studied as a potential alternative to CD4 count is TLC. In places where CD4 count testing is not available, the WHO recommends considering treatment for WHO stage 2 disease if TLC is <1200 µL. The use of TLC is not recommended in asymptomatic patients. Evidence frequently cited to support the use of a TLC cutoff of 1200 µL for stage 2 disease includes a South African cohort study in which TLC < 1250 µL was found to be an equivalent predictor of disease progression compared to CD4 counts.
with CD4 count < 200 cells/mm³. Our study questions this cutoff because 27.6% of HAART-naive and 12.5% of HAART-experienced participants in this report had CD4 counts < 200 cells/µL. A previous study in Nigeria reported that a third of patients with CD4 counts < 200 cells/µL had TLC > 1200 µL⁻¹. This may imply that an acceptable reproducible cut has been elusive. Further, in an analysis of WHO stage 2 patients in an antiretroviral therapy (ART) program (n = 51 281), CD4 counts and TLC counts were significantly positively correlated. Using TLC < 1200 µL⁻¹ as a predictor of CD4 count < 200 cells/µL resulted in 31.5% sensitivity, 96.0% specificity, 95.9% positive predictive value, and 31.6% negative predictive value. Increasing the cutoff value to 1900 µL⁻¹ resulted in 67.0% sensitivity, 67.9% specificity, 86.3% positive predictive value, and 40.4% negative predictive value. Taken together, TLC < 1200 µL⁻¹ was a poor predictor of CD4 count < 200 cells/µL, and over half of patients with CD4 count < 200 cells/µL would have been inappropriately excluded by TLC-guided treatment with a cutoff of 1200 µL⁻¹. Thus, TLC is of limited usefulness for guiding initiation of ART: some patients with CD4 count < 200 cells/µL will not be started on ART because their TLC will be >1200 µL⁻¹. Some investigators have suggested that incorporating the hemoglobin level, and perhaps body mass index or platelet count, will improve the accuracy of TLC, but it remains to be seen if additional parameters such as these will provide more useful information on a consistent basis.

Conclusion
HAART has the capability of reducing the incidence of anemia, other deranged hematological and immunological parameters associated with disease progression, and death in HIV-infected patients. Total lymphocyte count fails to predict CD4 count < 200 cells/µL in our cohort; thus, its use in the management and monitoring of HIV-infected patients in our settings is not reliable. In agreement with WHO and other reports, females of reproductive age are at a greater risk of becoming HIV-infected than males, and this could perpetuate documented social complications associated with HIV infection. Continued efforts to educate the vulnerable regarding social lifestyle and possible risk factors associated with HIV cannot be over-emphasized.

Author Contributions
Conceived and designed the experiments: BD, IK, AH. Analysed the data: BD, IK, AH. Wrote the first draft of the manuscript: BD, IK, AH, AD, MAS. Contributed to the writing of the manuscript: BD, IK, AD, MAS. Agree with manuscript results and conclusions: BD, IK, AH, AD, MAS. Made critical revisions and approved final version: BD, IK, AH. All authors reviewed and approved of the final manuscript.

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