Management of HIV-1 Infection With a Combination of Nevirapine, Stavudine, and Lamivudine

A Preliminary Report on the Nigerian Antiretroviral Program

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Objective: To evaluate treatment outcome in the first 12 months among HIV-positive patients managed with a combination of nevirapine + stavudine + lamivudine under the current national antiretroviral (ARV) program in Nigeria.

Design: This was a prospective observational, cohort study on 50 ARV-naive patients who met the inclusion criteria for the program and had given informed consent. All patients were in stage 2 or stage 3 periods of infection based on World Health Organization clinical classification. The patients were treated with the generic brands of ARVs and treatment consisted of oral nevirapine (Nevimal, Cipla, Mumbai, India), 200 mg daily, lamivudine (Lamivir, Cipla), 150 mg twice daily, and stavudine (Stavir, Cipla), 40 mg twice daily. Prior to initiation of treatment, the clinical history and baseline data for each patient were documented. The levels of plasma HIV-1 RNA, $CD4^+$ cell counts, frequency of opportunistic infections, and estimated body mass index were recorded at baseline and subsequently at intervals during treatment. Data obtained at the various sampling times for each parameter were compared against their baseline values.

Results: Data on the plasma HIV-1 RNA levels indicated that between baseline and week 24, the median viral load of the patients decreased by 1.79 $\log_{10}$ copies/mL. Equally between baseline and week 48 the median $CD4^+$ cell counts increased by 186×10^6 cells/L, the frequency of opportunistic infections decreased by 82%, the median body mass index increased by 4.8 kg/m^2, and 36% experienced side effects, which were minor and transient. The most prevalent side effect recorded was skin rash associated with nevirapine. Good adherence to this triple regimen was recorded in >85% of the patients.

Conclusions: The overall results within the 12-month treatment period indicated an effective suppression of viral replication, the reconstitution of the immune system, and improvement of the physical well-being of the study population. Though there may be differences in global distribution of the infecting HIV-1 subtypes, the clinical and biologic results of this study compared favorably to those documented in cohorts treated with branded and generic ARV drugs in some developed and developing countries. The cumulative data in this study further confirmed that the correct use of generic brands of ARVs is a feasible option in HIV care and support programs in resource-poor countries.

Key Words: HIV, ARV program, Nigeria

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Reports in contemporary literature have confirmed the efficacy of antiretroviral (ARV) drugs in the clinical management of patients infected with HIV.[1–3] Treatment with a combination of 2 nucleoside reverse transcriptase inhibitors (NRTIs) and a more potent nonnucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI) constitutes the highly active antiretroviral therapy (HAART) regimen, which is presently being adopted as the gold standard in the clinical management of HIV infections.[4,5]

Indeed, it has been documented that HAART has remarkably sustained both the suppression of viral replication and the enhancement of immune restoration in infected patients.[6–9] Thus where available and correctly used, HAART has significantly reduced morbidity and mortality rates in infected patients. The reported benefits of HAART have encouraged its use in the clinical management of people living with HIV in several developed and a few developing countries.[4,7]

In January 2002, the Federal Government of Nigeria initiated a national ARV treatment program as part of an expanded response to care and support for people living with HIV/AIDS. Under this program, 10,000 adults and 5000 children are to be treated with a 3-drug (ARV) combination regimen. The program commenced in February 2002 in 25 treatment centers across the 6 geopolitical zones of the country. Presently, >9000 adults are being treated with a combination of the generic brands of 2 NRTIs (lamivudine + stavudine) and one NNRTI (nevirapine). The program is being highly subsidized by the government to make the drugs cheap and affordable, at a cost of $10 for the monthly treatment of a patient. The

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Nigerian program is the largest ongoing ART program in sub-Saharan Africa and one of the very few using generic ARVs.

It has been reported that within 6 months of treatment, an effective HAART achieves a significant suppression of viral replication and progressive reconstitution of the immune system of the patient.[4,6] Under the Nigerian national program, 50 ARV-naive patients undergoing treatment in one of the 25 treatment centers had received ARV treatment continuously for 12 months and had been monitored clinically and biologically for this period. This study focused on evaluating treatment outcome among these 50 patients. Data generated from the patients were analyzed and the results obtained are documented in this paper as a preliminary report on the Nigerian ART program.

METHODS

Study Design

This was a prospective, observational cohort study carried out at the Clinical Research Center of the Nigerian Institute of Medical Research (NIMR), Lagos. The institute is a parastatal of the Federal Ministry of Health and it is one of the 25 treatment centers for the ongoing national ART program in the country.

Between February and April 2002, 50 HIV-infected, ARV-naive patients were enrolled at this center for the ART program. The patients were the first 50 subjects who were enrolled after meeting the inclusion criteria for the ART program and obtaining their informed consent. The inclusion criteria required that subjects be either male or female, must be aged ≥15 years, have laboratory evidence of HIV infection, have no history of ARV therapy, and have $CD4^+$ cell counts of between 200–350 $\times$ 10^6 cells/L. Asymptomatic and symptomatic patients with $CD4^+$ cell counts $<200 \times 10^6$ cell/μL were included. Patients on concurrent antituberculosis therapy (rifampicin) or with abnormal hepatic function tests were excluded. The 50 patients meeting these criteria who subsequently initiated ARV therapy at the center constituted the study population. Prior to initiation of treatment, the HIV serostatus of each patient was reconfirmed by screening with the Genie II HIV-1 & 2 rapid test kit (Biorad, Marnes Lar Coquette, France) and confirmed by the DIA PRO HIV 1 & 2 & 0 enzyme-linked immunosorbent assay kit (Diagnostic Bioprobes SRI, Milan, Italy).

A questionnaire was completed for each of the patients to record their clinical history and biodata. The patients were thereafter placed on a combination regimen of the 3 ARVs adopted for the national ART program. Prior to initiation of treatment, the body mass index, Karnofsky score, and types and frequencies of opportunistic infections were recorded for each patient. These parameters were subsequently evaluated at weeks 12, 24, 36, and 48 during treatment. Venous blood (10 mL) was aseptically obtained from each patient to estimate their CD4 cell counts and viral load levels. The grant support for this preliminary study made provision for only 3 viral load tests (baseline and weeks 12 and 24) and 4 CD4 cell counts for (baseline and weeks 12, 24, and 48) each of the patients within the 1-year treatment period. The $CD4^+$ cell counts were determined using the Dynabead Technique (Dynal A.S., Oslo, Norway) and results were expressed as 10^6 cells/L of blood. The viral load levels were estimated by the polymerase chain reaction–based Amplicor HIV-1 monitor system version 1.5 (Roche Diagnostic System, Branchburg, NJ) and the results were expressed as viral copies/mL of plasma. The lower limit of viral detection in this study was 400 viral copies/mL.

Clinical Management

Each of the 50 patients was placed on oral nevirapine (Nevimal, Cipla) 200 mg daily, lamivudine (Lamivir, Cipla) 150 mg twice daily, and stavudine (Stavir, Cipla) 40 mg twice daily. This regimen was continued for 2 weeks after which the dosage of nevirapine was increased to twice daily.

After the 50 patients had commenced the ARV therapy, they were placed on weekly clinical appointments for the first 4 weeks. Subsequently it was every 2 weeks for the next 8 weeks and monthly thereafter. At every visit, the patients were examined for opportunistic infections and clinical information was obtained on adherence, side effects, and tolerance. At initiation and during treatment, patients in whom opportunistic infections were diagnosed were placed on appropriate drugs for these infections. Adherence in this study was measured by interviewing patients on their frequency of drug intake, the number of drugs taken, or number of drugs still with them on each clinic visit. Based on cumulative data obtained, patients were classified into 3 broad groups, those who had consistently taken ≥95% of their drugs between clinic visits (high adherence), those who had taken 80%–94% of their drugs (good adherence), and those who had taken <80% of their drugs (poor adherence).[10] Occasional home visits were made to some of the patients to enhance psychosocial support as well as encourage adherence to the drug regimen. All major ethical considerations were put in place before and during the study. Informed written consent was obtained from all the patients after they were sufficiently counseled. Relevant confidentiality was maintained at initiation and during treatment.

Analysis of Data

Data were generated for each patient at baseline and at weeks 12, 24, 36, and 48 during treatment. The clinical and laboratory data recorded included viral load levels, $CD4^+$ cell counts, proportion of patients with opportunistic infections, body mass index, and Karnofsky performance scores. All the data were collated and analyzed statistically using Epi-Info version 6.04 (Centers for Disease Control, Atlanta, GA) and Stata version 6.0 (College Station, TX). The median and interquartile range were estimated for viral load, $CD4^+$ cell count, and body mass index at baseline and at each subsequent sample time. Changes from baseline with respect to viral load, $CD4^+$ cell count, body mass index, and Karnofsky score were analyzed using the Wilcoxon matched-pairs signed-ranks test. For statistical purposes, viral load observations below the limit of detection (<400 copies/mL) were assigned a value of 200 (the midpoint between zero and the lower limit of detection) as an estimate of the true value.

RESULTS

Prior to initiation of treatment, the clinical and biologic baseline characteristics of the 50 patients were recorded and data obtained are shown in Table 1.

Analysis of data obtained for all the patients at subsequent observation points showed that the median viral load of the patients decreased from 3.65 $\log_{10}$ copies/mL (interquartile range [IQR], 2.62–4.84) at baseline to 2.30 $\log_{10}$ copies/mL (IQR, 2.30–2.30) at week 24 ($P = 0.0000$), reflecting a median decrease of 1.23 $\log_{10}$ copies/mL (IRQ, 0.161–2.32) (Fig. 1). Omitting the 11 patients whose viral load values were below detection at baseline and remained below detection at week 12 and week 24, the median viral load dropped significantly from a baseline value of 4.13 $\log_{10}$ copies/mL (IQR, 3.35–5.04) to 2.30 $\log_{10}$ copies/mL (IQR, 2.30–2.30) by week 24 ($P = 0.0000$), with a median decrease of 1.79 $\log_{10}$ copies/mL (IQR, 1.05–2.54).

Using the subset that omitted patients whose viral load values were below detection at baseline and both subsequent observation points to evaluate treatment outcome, the percentage of patients with viral load values below detectable levels increased from 2.6% at baseline to 84.8% by week 24 (Fig. 2). Treatment outcome was also evaluated in terms of intention-to-treat analysis (losses to follow-up, missing data, and viral load values above the limit of detection were interpreted as treatment failures): including only patients with a possibility of detectable viral load decrease by week 24, the percentage of patients below the lower limit of detection rose from 2.6% at baseline to 71.8% by week 24.

The $CD4^+$ cell counts of the patients showed remarkable increase at all monitoring points after initiation of treatment. The median $CD4^+$ cell counts of the patients increased from 260×10^6 cells/L (IQR, 160–290) at baseline to 360×10^6 cells/L (IQR, 300–440) at week 12, 370×10^6 cells/L (IQR, 310–480) at week 24, and 445×10^6 cells/L (IQR, 370–542) at week 48. The increase in $CD4^+$ cell count was statistically significant at week 12 ($P = 0.000$), week 24 ($P = 0.0436$), and week 48 ($P = 0.0000$) compared with baseline. The median changes from

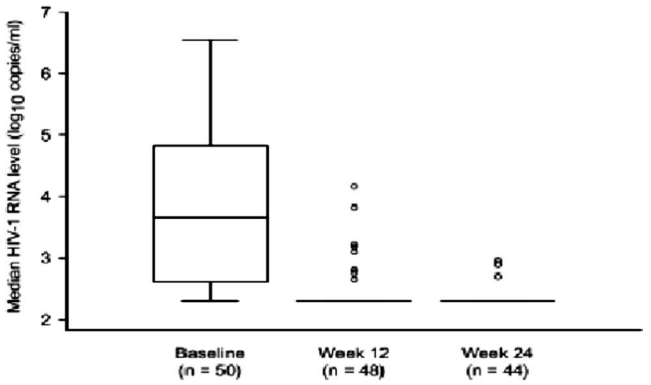

FIGURE 1. Changes in plasma HIV-1 RNA level of patients during treatment. The center line of the box marks the median; the box represents the interquartile range; whiskers extend to the upper and lower adjacent values; points beyond the adjacent values are plotted individually.

TABLE 1. Baseline Demographic, Clinical and Biological Characteristics of the 50 Patients

	Baseline Values (%)
Demography	
Sex [n (%)]	
Male	22 (44)
Female	28 (56)
Age (y)	
Median	34.5
IQR	30–60
Biological	
$CD4^+$ cell count $\times 10^6$/L	
<200 [n (%)]	20 (40)
200–350 [n (%)]	26 (52)
Median	260
IQR	160–290
Plasma HIV-1 RNA (copies/mL)	
Median ($\log_{10}$)	3.65
IQR	2.62–4.84
Clinical	
Stage of infection (WHO classification) [n (%)]	
Stage 1	—
Stage 2	36 (72)
Stage 3	14 (28)
Stage 4	—
Karnofsky score [n (%)]	
<70	—
70	8 (16)
80	16 (32)
90	24 (48)
100	2 (4)
Body mass index (kg/m^2)	
Median	21.64
IQR	19.8–23.2
Presented with opportunistic infections (%)	38
Treatment regimen [n (%)]	
3TC + d4T + NVP	50 (100)

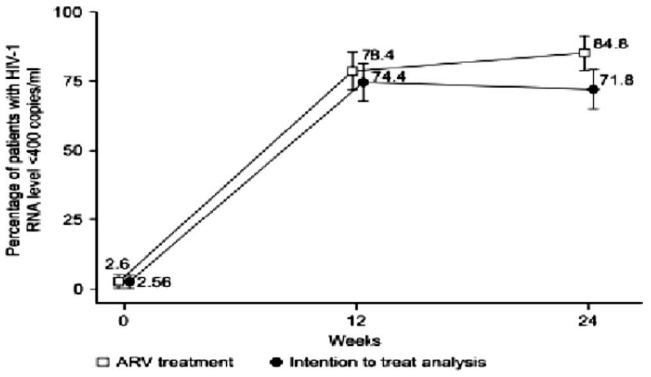

FIGURE 2. Percentage of patients with HIV-1 RNA levels below the lower limit of detection (<400 copies/mL) in the ARV treatment group and in the intention to treat analysis with standard error bars. Points are slightly offset on the x-axis to aid visibility.

baseline were +100 × 10^6 cells/L at week 12, +110 × 10^6 cells at week 24, and +186 × 10^6 at week 48.

It was also documented that the ability of the patients to carry out normal activities increased remarkably during treatment. The Karnofsky performance scores increased from 52% of patients with scores above 90% at baseline to 73%, 88%, and 96% at weeks 12, 24, and 48, respectively. Equally, the median body mass index of the patients increased significantly from 21.6 kg/m^2 (IQR, 19.8–23.2) at baseline to 22.3 kg/m^2 (IQR, 20.5–23.8) at week 12 ($P = 0.0007$), 22.7 kg/m^2 (IQR, 20.7–25.4) at week 24 ($P = 0.0000$), 26.1 kg/m^2 at week 36 ($P = 0.0000$), and 27.4 kg/m^2 at week 48.

At baseline, 38% of the patients presented with single or multiple opportunistic infections, with respiratory tract infections being the most prevalent. However, as treatment progressed, the proportion of the patients who presented with opportunistic infections decreased to 23.9% at week 12, 19.7% at week 24, and 6.8% at week 48. The data reflected 37, 49, and 82% decreases in the frequency of opportunistic infections among the patients at weeks 12, 24, and 48, respectively.

The combination therapy was well tolerated as 26 (52%) of the patients experienced no adverse side effects while 18 (36%) experienced periodic mild (grade 1) to moderate (grade 2) adverse effects based on the World Health Organization toxicity scale within 48 weeks of treatment. These side effects were often transient and not serious enough to discontinue treatment. Within the first 12 weeks, 2 (4%) of the patients developed active pulmonary tuberculosis; they were withdrawn from the ARV treatment and placed on antituberculosis regimens. Also within the first 12 weeks, 2 (4%) of the patients died.

The deaths were not drug related as both were quite ill at the time of initiation of treatment with low Karnofsky scores, matched with relatively high viral load levels and low $CD4^+$ cell counts. The recorded causes of death in these patients were anemia, heart failure, and septicemic shock. Between weeks 12 and 24, 2 (4%) of the patients failed to report back to the clinic. One of the patients was relocated out of Lagos while the other could not be traced in the recorded contact address. Also between weeks 36 and 48, another patient relocated out of Lagos. Prior to these, however, the 3 patients were responding adequately to treatment.

Further analysis of the cumulative data on adherence indicated that 8 (18%) of the patients had high adherence to drug intake, 30 (68%) had good adherence, and 6 (14%) had poor adherence. The corresponding biologic data showed that the median viral load at 24 weeks, compared with baseline, decreased by 1.5 log, 1.3 log, and 0.6 log among patients with high, good, and poor adherence, respectively. Also the median CD4 cell counts increased by 170, 160, and 50 among the 3 groups of patients, respectively.

DISCUSSION

The ultimate virologic goal of ARV therapy is to reduce the viral load of the patient to below the limit of detection within 3–4 months of initiation of treatment.[4] The adopted virologic endpoint to assess the efficacy of any ARV regimen is the achievement of a minimum decline from baseline viral load of 1.5 log to 2 log by the end of the first month of treatment. Several reports from the developed and developing countries on the efficacy of various ARV regimens with or without PIs have documented reduction of viral load levels by between 1.5 log to 2.0 log within 6 months.[4,11–13] Observations in this study were in line with these earlier reports as a decline from baseline median viral load of 1.79 log was recorded by week 24 of treatment among the patients. This significant decline in the median viral load strongly indicated the efficacy of the treatment regimen. Other reports using the same combination of ARVs in some developing countries have documented similar findings.[14,15]

Furthermore, optimal response to effective ARV therapy is indicated by a median rise in CD4 cell count of 100–200 × 10^6 cells/L within the first year of treatment.[4] Reports of ARV treatment using various combination regimens in the developed and developing countries have documented varying levels of increase in CD4 cell counts in the treated patients.[16–18] In this study, an increase of 186 × 10^6 cells in the median CD4 cell counts of the patients was recorded at week 48 compared with baseline levels. The documented increase was well within the acceptable range for an effective ARV treatment. The achievement of this biologic endpoint was therefore indicative of the efficacy of the drug regimen in the restoration of the immune system.

This observed restoration of the immune system was accompanied by clinical improvements in the body weight and the ability for physical activity of most of the patients. The progressive reduction in the frequency of opportunistic infections also signified some improvement in the overall health status of the patients. Data in this study also indicated that the drugs were safe and well tolerated by the patients. This observation further confirmed the reports of earlier studies using the same combination of generic drugs in other developing countries.[14,15]

The level of adherence has been reported to significantly influence the outcome of treatment in the patients on ARVs. While good adherence results in effective reduction in viral levels and restoration of the immune system in the patients, nonadherence often leads to treatment failure.[10–18] Adherence to ARVs has been reported to be relatively lower among patients in the developing than the developed countries.[19] In this study, >85% of the patients had adequate adherence to drug intake. The recorded virologic and immunologic response to treatment was also comparatively higher in patients with good adherence than in those with poor adherence. In line with what had been reported with branded and generic ARVs, the findings in this study further showed that adequate level of adherence is critical to a successful ARV treatment. The deaths recorded in the study were not drug related and the 4% mortality rate recorded was within the range that has been reported in other ART programs in both the developed and developing countries.[20,21]

An ARV regimen is judged not to be effective if it fails to achieve sufficient suppression of viral replication, if it cannot stimulate satisfactory increases in $CD4^+$ cell counts, and if clinical progression of disease with opportunistic infections occurs despite treatment.[4] On the contrary, the cumulative data generated in this study strongly indicated that the treatment

regimen administered adequately achieved the suppression of viral replication, increased $CD4^+$ cell counts, reduced the frequency of opportunistic infections, and increased overall gain in body weight among the patients within the 12 months of treatment.

These observations compared favorably with reports of the efficacy of branded and generic ARV regimens in developed and developing countries.[9,13–15,22–25] The Nigerian program is ongoing and subsequent monitoring of relevant parameters including adherence will be carried out at regular intervals on the patients to further assess treatment outcome. This is important as some previous reports have documented a rebound in viral replication and decrease in $CD4^+$ cell counts as treatment progressed beyond 6–12 months.[4,20] These have been attributed to decreased adherence to drug intake and emergence of drug-resistant strains. Studies on the levels of primary ARV resistance among the study population are ongoing.

The study therefore documented the efficacy of the combination of generic formulations of nevirapine + stavudine + lamivudine in the clinical management of HIV infections in a developing country, making it clear that the proper use of affordable, generic ARVs is a feasible option for the clinical management of HIV infections in resource-poor countries.

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