

Original Article

Effect of Lamivudine (Epivir), Nevirapine (Vivumine) and Stavudine (Stavir) on CD4⁺ Count of HIV Patients Attending University of Benin Teaching Hospital (UBTH), Benin City, Edo State, Nigeria

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ABSTRACT

Background: Anti-retroviral drugs are broadly used to alleviate the sufferings of HIV patients in Sub-Saharan countries. Few studies have been carried out to assess the effects of these drugs on the immunological parameters of patients in the above-mentioned region.

Objective: To assess the effect of the Lamivudine, Nevirapine and Stavudine combination on the CD4⁺ count of HIV patients attending the University of Benin Teaching Hospital, Benin City, Nigeria.

Method: An assessment of CD4⁺ counts of 37 HIV patients from different socio-economic groups on tri-therapy, notably Lamivudine-Nevirapine-Stavudine combinations, attending the University of Benin Teaching Hospital, was carried out before therapy, three months and six months after administration of the drugs using Dynabeads[®] T4 -T8 Quantification Protocol (DYNAL BIOTECH ASA: NORWAY).

Results: Out of the 37 studied subjects, 32 (86.48%) patients showed a marked increase in their CD4⁺ counts at three and six months, four (12.5%) subjects showed a continuous decrease in CD4⁺ level up to six months after therapy, while one (3.12%) patient had a decrease in CD4⁺ after three months and a sudden rise at six months. The mean CD4⁺ cell count increased from 255 at base line to 284 at week 12, and to 346 at week 24. Traders were the most affected by HIV virus followed by people in the group referred to as "others", civil servants, and students with prevalence rates of 43.24%, 24.32%, 18.91%, 13.51% respectively. Statistically, there was a significant difference between HIV-1, HIV-2 and HIV-1 and 2 which had a prevalence rate of 89.19%, 8.10% and 2.70% respectively ($p < 0.05$).

Conclusion: The importance of early diagnosis, continuous evaluation and sound clinical management of HIV is strongly emphasized.

KEYWORDS: CD4, combination, Edo State, lamivudine, nevirapine, stavudine

INTRODUCTION

As the world enters the third decade of the AIDS epidemic, the evidence of its impact is undeniable. Wherever the epidemic has spread unchecked, it is robbing countries of the resources and capacities on which human security and development depend. In some regions, HIV/AIDS, in combination with other crises, is driving ever-larger parts of nations towards destitution. By far the worst affected region, sub-Saharan Africa is now home to 29.4 million people living with HIV/AIDS. Approximately 3.5 million new infections occurred there in 2002, while the epidemic claimed the lives of an estimated 2.4 million Africans in the past year. Ten million young people (aged 15-24) and almost three million

children under 15 are living with HIV. Only a tiny fraction of the millions of Africans in need of anti-retroviral treatment are receiving it. Many millions are not receiving medicines required to treat opportunistic infections, either. These figures reflect the world's continuing failure, despite the progress in recent years, to mount a response that matches the scale and severity of the global HIV/AIDS epidemic^[1]. The past five years have witnessed significant strides in the ambulatory management of persons with HIV infection throughout the course of their disease. Greatly improved understanding of viral pathogenesis and the development of resistance are tightly linked to the rationale of utilizing potent, combination anti-retroviral therapy. Falling prices of highly active

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Table 1

Age and sex distribution of HIV serotypes among patients

Ages	HIV-1		HIV-2		HIV 1 and 2	
	Male n (%+ve)	Female n (%+ve)	Male n (%+ve)	Female n (%+ve)	Male n (%+ve)	Female n (%+ve)
10-20	0 (0.0)	3 (5.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
21-30	3 (21.4)	9 (47.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
31-40	5 (36.7)	4 (21.0)	0 (0.0)	2 (100.0)	0 (0.0)	0 (0.0)
41-50	5 (36.7)	2 (10.5)	1 (100.0)	0 (0.0)	1 (100.0)	0 (0.0)
> 50	1 (5.8)	1 (5.1)	0 (0)	0 (0.0)	0 (0.0)	0 (0.0)
Total	14(100.0)	19 (100.0)	1 (100.0)	2 (100.0)	1 (100.0)	0 (0.0)

Key: n = number, +ve = positive

anti-retroviral therapy (HAART) are enabling physicians in the developing countries to offer triple anti-retroviral drug regimens to greater numbers of their patients who desperately need the life saving medication. However, widely accepted guidelines to monitor anti-retroviral therapy using frequent CD4⁺ count testing and HIV Plasma Viral Load (PVL) can cost more than US\$ 1000 per year^[2]. CD4 count testing is quite complex, requiring machinery and expensive reagents^[3]. As a result, physicians are faced with the challenge of managing anti-retroviral therapy largely by following the clinical response, without the benefit of regular laboratory support.

One of the early observations of immune system impairment in HIV infection was a reduction in the number of CD4⁺ T cells. Uninfected individuals have approximately 1100 CD4⁺ T cells/ml of whole blood; in AIDS patients, the numbers drop drastically, often reaching a level below 200/ml^[4].

Many anti-retroviral combinations containing lamivudine have been found to be effective at suppressing HIV viral load and increasing CD4⁺ cell counts, and in some studies, delaying clinical progression of HIV disease. While the resistance mutation selected by lamivudine may restore sensitivity to zidovudine in the short-term^[5], over time, resistance to the two-drug combination frequently emerges. For this reason, three-drug combinations are recommended.

Nevirapine has been studied in several combination regimens for the treatment of HIV infection, but little long-term data exists from studies comparing nevirapine-containing regimens with regimens of established potency, and such studies have been relatively small. Initial therapy with nevirapine + stavudine + didanosine compared favorably with the combination of efavirenz with the same two nucleoside analogues at six months of therapy^[6]. Also at six months, another study of initial treatment found that the combination of nevirapine + zidovudine + lamivudine (as Combivir) compared favorably with a regimen of the protease inhibitor nelfinavir + Combivir^[7].

Table 2

Distribution of HIV positive patients by occupational status

Serotypes	Traders	Students	Civil servants	Others	Total
	n (%)	n (%)	n (%)	n (%)	n (%)
HIV-1	14 (85.5)	5 (100.0)	6 (85.7)	8 (88.8)	33 (89.1)
HIV-2	1 (6.2)	0 (0.0)	1 (14.2)	1 (11.1)	3 (8.1)
HIV 1 & 2	1 (6.2)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.7)
Total	16 (43.2)	5 (13.5)	7 (18.9)	9 (24.3)	37 (100.0)

Anti-retroviral combinations containing stavudine have been found to be effective at suppressing HIV viral load and increasing CD4⁺ cell counts. In general, three-drug combinations have been found to have a more sustained effect than two-drug combinations. As Anti-retroviral drugs have to be taken for a long period, the probability of developing resistance is very high. Using multiple drugs that attack HIV at different stages or in different ways maximizes effectiveness and reduces the chance of developing drug resistance. However, increasing the number of drugs for treatment increases cost, an important consideration in resource constrained communities^[8].

MATERIALS AND METHODS

Study subjects

The subjects used in this study are HIV/AIDS patients attending University of Benin Teaching Hospital (UBTH) Edo State, Nigeria. Patients with liver and kidney disorders, leukaemia and also, infants, pregnant or lactating mothers were excluded from this study.

Laboratory Analysis

CD4⁺ T-Lymphocyte count was assessed on heparinized whole blood using Dynabeads[®] T4-T8 Quantification Protocol (Dynal Biotech ASA: Norway). Analysis was carried out within four hours of blood collection.

RESULTS

A total of 37 HIV patients were studied, out of which 16 (43.2%) were male and 21 (56.7%) were female. Out of these 37 patients, thirty-three (89.1%) had HIV-1 comprising of 14 (42.4%) male and 19 (57.6%) female. Three (8.1%) patients had HIV-2 and one (2.7%) patient was positive for HIV-1 and 2 (Table 1).

Table 2 shows the different socioeconomic groups in this study. Traders recorded the highest infection rate of 43.2% (16). Out of these, 14 (85.5%) were HIV-1 positive while one (6.2%) had HIV-2 and one (6.2%) had both HIV-1 and 2 infections.

The mean CD4⁺ cell count at base line was 255 cells/ml, 284 cells/ml at week 12, and 346 cells/ml

Table 3a

Evolution of CD4⁺ count of patients with CD4⁺ count less than 200 cells/ml at three and six months of drug administration

No. of CD4 ⁺ before treatment	0-200 cells/ml			
	0-25(%)	26-50(%)	51-75(%)	>75%
No. of CD4 ⁺ increased	0-25(%)	26-50(%)	51-75(%)	>75%
No. of patients with increased CD4 ⁺ at 3 months	7 (38.8)	6 (33.3)	1 (5.5)	0 (0.0)
No. of patients with increased CD4 ⁺ at 6 months	3 (16.6)	5 (27.7)	6 (28.2)	1 (8.3)
No. of patients with continuous decreased CD4 ⁺	4 (12.5)			

at week 24. Patients were categorized into four groups based on the number of CD4⁺ /ml of blood before therapy commenced. Out of 18 patients in group A with a CD4 of 0 - 200 cells/ml, seven (38.8%) had an increment of not more than 25 cells/ml, six (33.3%) had an increment of 26 - 50 cells/ml, one (5.5%) recorded an increment above 50 cells/ml after three months of therapy and four (12.5%) instead had a decrease in their CD4 count. After six months, three (16.6%) recorded an increment of 0 - 25 cells/ml, while five (27.7%) had an increment of 26 - 50 cells/ml, six had an increment ranging from 51 - 75 cells/ml, one (8.3%) had an increment above 75 cells/ml and three patients experienced a continuous decrease in their CD4⁺ count (Table 3a). Group B, comprised of patients with a CD4⁺ count of 201 - 400 cells /ml. Out of 12 patients in this group, six (50%) had an increment of 26 - 50 cells/ml after three months of drug administration, four (33.3%) recorded a rise of 51 - 75 cells/ml, one (8.3%) had an increase of less than 25 cells /ml and one (8.3%) patient observed no increment in his CD4⁺ count. After six months, six (50%) had an increment 51 - 75 cells/ml, four (33.3%) recorded a rise of 76 - 100 cells/ml, one patient observed an increase of less than 25 cells/ml while the last patient had an increment of 35 cells/ml (Table 3b). Group C comprised of patients whose CD4⁺ count range between 401 and 600 cells/ml. Out of a total of six patients in this group, two (33.3%) had a rise of 51 - 75 cells/ml, two (33.3%) patients recorded a rise of 76 - 100 cells/ml, while one (16.6%) and one (16.6%) patient experienced a rise below 25 and 50 cells/ml respectively after three months of therapy. At six months, four had a rise of 76 - 100 cells/ml and the last two had an increase between 25 and 75 cells/ml (Table 3c). Group D which consisted of only one patient with a CD4⁺ count above 600 cells/ml, after six months of drug administration, had a CD4⁺ increase of more than 100 cells/ml (Table 3d).

Table 3b

Evolution of CD4⁺ count of patients with CD4⁺ count between 201-400 cells/ml at three and six months of drug administration

No. of CD4 ⁺ before treatment	201-400 cells/ml			
	0-25(%)	26-50(%)	51-75(%)	>75%
No. of CD4 ⁺ increased	0-25(%)	26-50(%)	51-75(%)	>75%
No. of patients with increased CD4 ⁺ at 3 months	1 (8.3)	6 (50.0)	4 (33.3)	0 (0.0)
No. of patients with increased CD4 ⁺ at 6 months	1 (8.3)	1 (8.3)	6 (50.0)	4 (33.3)

DISCUSSION AND CONCLUSION

This study revealed that HIV-1 had the highest prevalence rate of 89.1% (33 /37) as compared to other types. This finding does not agree with that of Libra^[9], who reported that HIV-2 is more prevalent in West Africa. However, the geographical distribution of HIV-2 is not fully understood, but there is enough evidence to speculate about the origins and differentiation of this geographical pattern. Foci of infection probably developed in some African countries, such as Guinea-Bissau, Angola and Mozambique, in the 1970s. The decolonization of these countries led to the movement of people, and the virus, to historically associated countries such as Portugal, India and Brazil. In Ivory Coast, a focus was probably created due to the dismantling of the plantation economy, with all its demographic, cultural and social consequences. The virus was dispersed to countries close to the Guinea and Ivory Coast foci by the migration of workers and prostitutes. Thus, the disease has spread from the Atlantic coast of Africa, where it was endemic-sporadic, to other more distant African countries and out of Africa into Europe and North America^[10].

The HIV patients were grouped into four categories based on their occupational status namely: Students, Traders, Civil servants and others. A high prevalence rate was recorded among the traders who assumed the lead with a prevalence rate of 43.2%. This could be due to the fact that most commercial sex workers (CSW) fell into this category as most of them claimed to be traders when they reported to the hospital.

It was also observed that more females (56.7%) were infected with the virus than males. This could be attributed to the fact that the conventional sex which is the vaginal intercourse, is riskier for women for a couple of reasons; one, because semen contains the highest concentration of the virus than any body fluid (except blood) and also because the ejaculation happens inside the vagina, which is porous and may allow the passage of HIV into the bloodstream^[11].

Females between the ages of 11 - 20 (20.3%) years were more infected than males (9.43%) of the

Table 3c

Evolution of CD4⁺ count of patients with CD4⁺ count between 401 and 600 cells/ml at three and six months of drug administration

No. of CD4 ⁺ before treatment	401-600 cells/ml			
No. of CD4 ⁺ increased	0-25 (%)	26-50 (%)	51-75 (%)	>75 (%)
No. of patients with increased CD4 ⁺ at 3 months	1 (16.6)	1 (16.6)	2 (33.3)	2 (33.3)
No. of patients with increased CD4 ⁺ at 6 Months	0 (0.0)	1 (16.6)	1 (16.6)	4 (66.6)

same age group, whereas males (50.9%) between 31 - 40 years of age were more infected than females (23.43%) of the same age group. This could be attributed to the fact that girls indulge in sexual practices earlier than their male counterparts and with an older male for monetary or material gratification.

Patients under investigation experienced little or no major side effects necessitating a change of drugs within the six month of study; patients who developed liver and kidney disorders, necessitating a change of regimen were excluded.

Out of the 37 subjects qualified for the study, 32 (86.48%) patients showed a marked increase in their CD4⁺ counts at three and six months. The mean CD4⁺ cell count increased from 255 at base line to 284 at week 12, and to 346 at week 24. This increase in the CD4⁺ count could be attributed the effectiveness of the drugs combination. Of the four (10.8%) patients with a continuous decrease in their CD4⁺ count up to the sixth month of therapy, three (75%) had HIV-1, 1(12.5%) was HIV-1 and 2 positive while the only patient with a decrease at three month and a sudden increase at six month of therapy was HIV-2 infected. These observations could indicate the emergence of some resistant strains in the sub- Saharan region. Gullick *et al*^[12] reported an increase in CD4⁺ count of HIV patients ranging from 100-200 cells/ml of whole blood in a trial combining lamivudine, indinavir and zidovudine over a period of 16 weeks. In this study, this result was achieved after 24 weeks; this observation could be a result of different HIV variants existing in different regions against which Highly Active Anti-Retroviral Therapy (HAART) acts differently. In the same vein, the drug combinations could also be responsible for delaying or impairing the patient's response. Barbur *et al*^[13] in a study using a combination of two drugs, namely, ritonavir and saquinavir reported an increase of 79 - cells/ml despite four months of triple therapy failure (two nucleoside analogue and one protease inhibitor).

Agbonlahor *et al*^[14] also reported an appreciable increase on the mean CD4⁺ count of HIV patients on

Table 3d

Evolution of CD4⁺ count of patients with CD4⁺ count greater than 600 cells/ml at 3 and 6 months of drug administration.

No. of CD4 ⁺ before treatment >600cells/ml				
No. of CD4 ⁺ increased	0-25(%)	26-50(%)	51-75(%)	>75(%)
No. of patients with increased CD4 ⁺ at 3 months	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)
No. of patients with increased CD4 ⁺ at 6 months	0 (0.0)	0 (0.0)	0 (0.0)	1 (100.0)

Mean CD4⁺, At base line: 255 cells/ml, At 3 months: 284 cells/ml, At 6 months: 346 cells/ml

a combination of four herbal extracts (*Ficus asperifolia* + *Ficus exasperata* + *Ficus sur* + *Sida corymbosa*), however, the mechanism of action of these extracts is yet to be understood and little or no side effects were observed. According to UNAIDS^[1] estimates, there are currently 40 million people living with HIV world wide, with 29.4 million of these in sub-Saharan Africa. With such staggering numbers of people already infected, strategies to deal with the epidemic incorporate the treatment of infected individuals alongside preventing new infections. Combination of at least three ARVS also known as highly active anti-retroviral therapy (HAART), is presently considered the treatment standard for people living with HIV/AIDS. The current recommendation is the use of a combination of different classes of ARVS: two nucleosides with a protease inhibitor or a non-nucleoside^[15].

In the absence of an effective therapy or vaccine against HIV, prevention and control of the spread of HIV infection will depend on the ability to change the sexual behavior of the populace through health education.

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