ORIGINAL ARTICLE

A Prospective Cohort Study of Immunologic and Virologic Outcomes in Patients with HIV/AIDS and Hepatitis Virus Co-Infection in Jos, Nigeria

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Abstract

Background: *In this era of highly active antiretroviral therapy (HAART), hepatitis B and C virus (HBV and HCV) co-infection have emerged as significant co-morbid conditions. Local reports indicate that co-infection is not uncommon in Nigeria as in other sub-Saharan African countries.Whether treatment outcomes of HIV mono-infected patients differ from those with co-infection remains largely unknown. We hypothesised that co-infected patients will have lower CD4+ count recovery and viral load reduction following HAART.*

Methods: *A cohort study in antiretroviral therapy-naïve HIV-infected adults involving 150 cases (HIV and co-infection) and 150 controls (HIV infection only). Patients' care was according to the National guidelines and patients received first line therapy mostly comprising Lamivudine, Stavudine and Nevirapine. Medication adherence was monitored using pharmacy computerised system, and CD4+ cell counts and HIV viral load (VL) were compared at baseline, 3 and 6 months of therapy.*

Results: *There were 98(65.3%) and 96(64%) female cases and controls (p=0.79) respectively.The mean ages of cases and controls were 38±8.4 and 37±8.9 years (p=0.20) respectively.Cases comprised 73(48%) HBV, 70(47%) HCV and 7(5%) with both HBV and HCV infection.Medication adherence was >95% in both arms. Attrition rate was 2.7%(8); seven of them were co-infected. Five cases (3.3%) compared to zero controls developed clinical hepatitis. The proportions of patients with CD4+ count <200 cells/µl among cases and controls were 111(74%) and 109(72%), p=0.36 at baseline; 66(45.5%) and 64(42.7%), p=0.21 at 3 months; 60(42%) and 56(37.6%), p=0.40 at 6 months respectively. Significantly, more controls (60.7%) had CD4+ increases 50cells/µl at 3 months compared to 37(54.5%) HCV+ cases (p=0.03). No significant difference in CD4+ counts between controls and cases at 6 months. The baseline median VL for cases and controls were log_{10}4.95 and log_{10}4.83 (p=0.17) respectively. The proportions of cases and controls with undetectable VL at 3 and 6 months were 96(66.2%) and 97(65.5%); p=0.74, and 116(81.1%) and 97(79.3%); p=0.10 respectively.*

Conclusion: *Co-infection has limited impact on immunologic and virologic outcomes, but may be an important cause of hepatotoxicity.*

Key Words: *HIV/AIDS, Hepatitis virus Co-Infection, HAART*

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Introduction

Since the discovery of Acquired Immunodeficiency Syndrome (AIDS) in 1981[1] and isolation of the Human Immunodeficiency Virus (HIV) in 1984[2], the disease has become a pandemic. Currently, it is one of the most important diseases worldwide. According to the estimate from the Joint United Nations Programme on HIV/AIDS, about 33.4 million people were living with HIV/AIDS worldwide with an estimated 22.4 million in Sub-Saharan Africa by the end of December, 2008[3]. Sub-Saharan Africa is the home to 67% of the adults living with HIV/AIDS in the world and registered up to 72% of about 2 million HIV/AIDS deaths in 2008. The current global estimates put Nigeria as second in Sub-Saharan Africa and fourth globally with an estimated 3 million people living with HIV/AIDS. Although South-South Nigeria has the highest zonal averages, the individual states with the highest HIV prevalence are situated in the North Central zone.

As a result of shared routes of transmision[4], Hepatitis B Virus or Hepatitis C Virus co infection with HIV is not uncommon. Uneke et al[5] reported HBsAg prevalence of 25.9% in those with HIV infection and 14.3% in those without HIV infection among blood donors in Jos while Idoko et al[6] reported a prevalence of 10% for anti-HCV and 9% for both anti-HCV and HBsAg respectively in HIV infected patients in North Central Nigeria.

Highly Active Antiretroviral Therapy (HAART) has become the standard treatment for patients with HIV/AIDS worldwide[7]. Effective HAART therapy leads to sustained suppression of viraemia and re-population of

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CD4+ T-lymphocytes which is associated with decreased risk of opportunistic infections, hospitalization and mortality[8-11]. However, with the increasing life expectancy of HIV infected persons treated with HAART, the contributions of Hepatitis B and C infection as causes of liver disease in the setting of immune dysregulation in people living with HIV/AIDS is assuming greater importance[12].

On the other hand, hepatitis virus can induce excessive immune activation which is increasingly being recognized as an important pathogenic factor for HIV disease progression. Although HBV has a marked hepatic tropism, it has been shown that this virus is also able to infect T-lymphocytes[13,14], suggesting that HIV and HBV may encounter each other at the cellular level in co-infected patients. The HBV genome encodes a 17-kDa protein, termed HBxAg, which induces HIV-1 replication[1519]. The HCV protein E2 may directly mediate excessive immune activation as it lowers the threshold for T cell activation[20] following stimulation. HCV infection may also interfere with the proximal points of the immune cascade, such as dendritic cell functions[21] which is key to the evolution and regulation of immune responses to HIV and HCV. The high incidence of auto-immune phenomena such as cryoglobulinemia and vasculitis occurring in hepatitis C also suggests immune dysregulation brought about by excessive immune activation.

An immune system already over-activated by HIV may not be able to keep up with this additional drainage of its reserves.

While it has been observed that the recovery of CD_4+ cells in response to HAART is blunted and progression to AIDS is hastened in those who are co-infected with hepatitis B or C compared with persons who are not[22,23], other studies failed to show similar findings[24,25]. The Swiss HIV Cohort Study (SHCS) enrolled 3655 HIV-infected subjects commencing HAART (37.2% of whom were also co-infected with HCV) and the relative risk of an AIDS defining illness or death was 1.7 in HCV positive persons compared with HCV negative persons[26]. Importantly, this effect was independent of HIV viral load during HAART, active continuation of intravenous drug abuse (which may be related to poor compliance with therapy), and the number of changes to HAART during follow-up, suggesting that compliance and hepato-toxicity issues did not confound the result of this study.

A preliminary report[27] on the Nigerian antiretroviral programme indicated that between baseline and six months, the median viral load was reduced by 1.7$\log_{10}$ copies/ml and the median CD4+ count was increased by 140 cells/µl. The primary objectives of this study were to determine the immunologic and virologic responses to HAART in HIV patients co-infected with HBV and/or HCV compared with controls at 3 and 6 months of therapy.

Materials and Methods

This is a prospective cohort study that was carried out at the HIV out-patient clinic (clinic II) and medical wards of the Jos university teaching hospital (JUTH), North Central Nigeria to determine the immunologic and virologic responses to HAART in patients infected only with HIV (controls) compared with those co-infected HBV and/or HCV (cases). Immunologic response was assessed as increase in median CD4+ and proportion of patients with CD4+ increases =50cells/µl while the virologic response was assessed as log decrease in median viral load and proportion of patients with undetectable viral load from baseline after commencement of HAART.

A sample size of 150 patients with HBsAg and/or HCV anti-body was used for the study following approval by the Research and Ethics Committee of JUTH. All the patients signed an appropriate informed consent form before enlisting in the study.

Patients included in the study satisfied the following inclusion criteria; Positive test for HIV infection by ELISA, Confirmation of HIV status by western blot, Positive HBsAg and/or anti-HCV antibody as cases, and eligible for Anti-retroviral therapy (ART) according to 2005 Nigerian guideline[28]

The exclusion criteria were; Patients already on Anti-retroviral therapy, Patients less than 18 years of age and decompensated liver disease.

One hundred and fifty consecutive cases and same number of controls that satisfied the inclusion criteria were recruited between November 2005 and April 2006. Each qualified patient had a comprehensive history taken and detailed clinical examination performed. The patients were followed up over a period of six months on tablets of Lamivudine, Stavudine and Nevirapine; this was the commonest first line HAART regimen. Patients were counseled on adherence and drug pick-ups were checked in the pharmacy computerized data-base. Complicating diseases were recorded together with therapeutic interventions. The same information was recorded for the 150 age and sex matched controls of HIV infected patients.

Hepatitis B surface antigen, Hepatitis C antibody, CD4+ count, HIV viral load, chemistry and haematology tests were done for all patients in the study and control groups at entry. The investigations were repeated at 3 monthly intervals for analysis. CD4+ lymphocytes were counted using Flow cytometry with CD4+ Easy Count kit-CY-R-1004 while Viral Load was determined using Polymerase Chain Reaction(PCR) technology with Amplicor HIV-1 Monitor® Test, Version 1.5. Lower limit of detection is <400 copies/ml and all viral load results were log-transformed. Other investigations were done when they are indicated.

The Epi-Info Version 3.3 2004 statistical software was used for statistical analysis. Results were presented as tables, bar chart, median for skewed variables and means ± standard deviation. The student t-test was used for comparison of means of paired variables while Chi-square(X^2) test was used to test proportions of categorical variables. A p value of < 0.05 was considered significant and values < 0.01, as highly significant in all statistical comparisons.

Results

A total of 300 patients were enrolled into the study, but 295(98.3%) and 292(97.3%) patients completed the third month and sixth month of the study period respectively. Seven cases compared to one control did not complete the study. Among the cases, five patients discontinued due to hepatotoxicity (two were concurrently on anti-tuberculosis therapy) and two(28.6%) because of severe muco-cutaneous reactions. One patient was lost to follow-up among the controls.

The age and sex distribution of cases and controls are shown in Figure 1. The mean (±SD) ages of the cases and controls were 38.3±8.4 (22-66) years and 37.3±8.9 (21-71) years respectively (p=0.20). There were 98(65.3%) females and 52(34.7%) males among the cases while females were 96(64%) and males, 54(36%) among the controls (p=0.79).

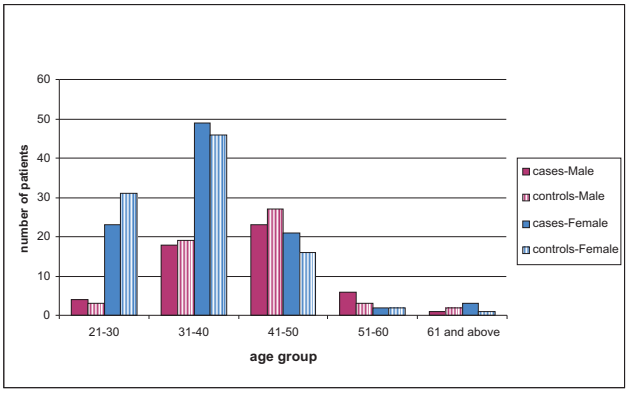

FIGURE 1 AGE AND SEX DISTRIBUTION OF CASES AND CONTROLS

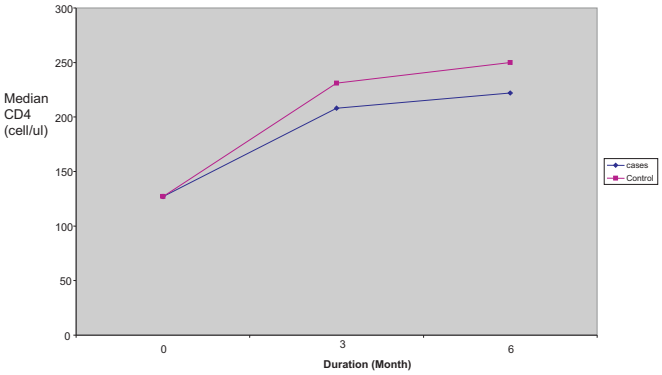

Figure 2. CHANGES IN MEDIAN CD4+ BETWEEN CASES AND CONTROLS

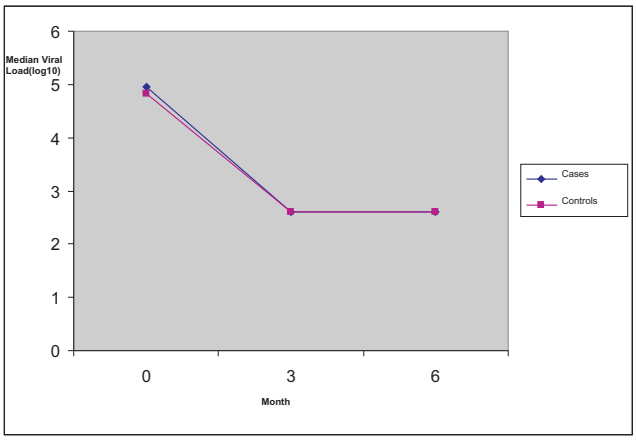

Figure 3. THE CHANGES IN MEDIAN VIRAL LOAD IN CASES AND CONTROLS

All patients in the case and control groups had HIV type 1 after testing for both HIV 1 and HIV 2. The cases had 73(48.0%) patients that were positive for HBsAg, 70(47.0%) for anti-HCV antibody and seven(5.0%) for both HBsAg and anti-HCV.

Among the cases, a total of 381 doses of ARVs were missed out of 26,100 doses estimated to be taken by three months (145 patients x 60 doses/month x 3 = 26,100). This accounted for 1.5% of the total doses, implying 98.5% adherence. The doses missed in the control group by the same period was 351(1.3%) out of a total of 27,000 estimated to be taken, implying adherence of 98.7%. (p=0.70). Similarly, adherence by the sixth month was 98.4% among the cases and 98.5% among the controls (p=0.86).

Immunologic Response to HAART

The changes in median CD4+ count in the cases and controls over the 6 month study period is shown in Figure 2 while the proportion of patients among cases and controls that achieved CD4+ count increase of 50 or more cells/µl from baseline at 3 months and 6 months of HAART is shown in Table 1.

Both cases and controls had median CD4+ count of 127cells/µl at baseline which rose to 208 cells/µl and

231 cells/µl at the third month of HAART respectively. This corresponds to a median increase of CD4+ cells of +81cells/µl for the cases and +104cells/µl for controls (p=0.22). At the sixth month of HAART, median CD4+ count among the cases was 222 cells/µl and 250 cells/µl among the controls. The median increase from baseline to six months was therefore +95cells/µl for cases and +123cells/µl for controls (p=0.26).

The proportion of patients with CD4+ count below the critical value of 200 cell/µl at baseline among the cases was 111(74%) and 109(72.7%) among the controls (p=0.36). The proportion of those with CD4+ counts below 200cells/µl among cases was 66(45.5%) compared with controls 64(42.7%) at 3 months of HAART (p=0.21), and also among cases 60(42.0%) and controls 56(37.6%) at the end of the study period (p=0.40).

However, when immunological response was measured as an increase from baseline of at least 50cells/µl, the proportion of patients with CD4+ count increase = 50cells/µl at the third month of HAART were 88(60.7%) for cases and 99(66%) for controls (p=0.01). At the end of the study period, 95(67.4%) cases and 101(67.8%) controls had increase of =50cells/µl (p=0.74). Furthermore, when the cases that achieved CD4+ increase of =50cells/µl at 3 months of HAART were sub-analyzed as those with HBsAg or anti-HCV and compared with controls, HBsAg positive cases were 48(68.6%); p=0.53 while anti-HCV positive patients were 37(54.5%); p=0.03. There was statistically significant difference in CD4+ increase of =50cells/µl between controls and anti-HCV positive, but not HBsAg positive patients. On the other hand, there was no statistically significant difference in CD4+ increase of =50cells/µl at 6 months of HAART between HBsAg positive patients 48(64.7%); p=0.14 and anti-HCV positive patients 44(64.7%); p=0.14 when compared with controls.

The comparison of median CD4+ cells of cases and controls with TB to their counterparts without TB at baseline, at 3 months and at 6 months did not show statistically significant difference in median CD4+ counts.

Table I. Immunologic response in cases and controls at third and sixth month of haart

CD4 INCREASE	3 MONTHS		6MONTHS	
	CASES N (%)	CONTROLS N (%)	CASE N (%)	CONTROLS N (%)
PRESENT	88(60.7)	99(66)	96(67.1)	101(67.8)
ABSENT	57(39.3)	51(34)	47(32.9)	48(32.2)
TOTAL	145(100)	150(100)	143(100)	149(100)

X^2 = 6.05 **DF**= 1 **P**=0.01 **X^2**=0.11 **DF**=1 **P**=0.74

Virologic Response

The median viral load for the cases and controls are shown in Table II while the proportion of patients with undetectable viral load at 3 months and 6 months of HAART is shown in Table III. The trends in viral load from the beginning to the end of the study is shown in figure 3.

At baseline, the median viral load in for cases and controls were $\log_{10}$ 4.95, $\log_{10}$(IQR 4.01-6.45) and $\log_{10}$ 4.83, $\log_{10}$(IQR 3.87-6.37) respectively (p=0.17). By the third month of HAART, the median viral load had become less than $\log_{10}$2.60 (undetectable), $\log_{10}$(IQR 2.60-6.04) and less than $\log_{10}$2.60, $\log_{10}$(IQR 2.60-6.27) for cases and controls respectively (p=0.86). Similarly, at the end of the study period, median viral load was less than $\log_{10}$ 2.60, $\log_{10}$(IQR 2.60-5.47) and less than $\log_{10}$2.60, $\log_{10}$(IQR 2.60-5.14) for cases and controls respectively (p=0.25). In absolute numbers, the median viral load of 90,109 copies/ml for cases and 67,522 copies/ml for controls reduced to less than 400 copies/ml at three and six months of HAART. Hence, a median viral load reduction of at least $\log_{10}$2.35 was recorded for the cases and $\log_{10}$2.23 for controls at the third and sixth month of HAART. The median viral load was $\log_{10}$5.02 in HBsAg positive patients (p=0.38) and $\log_{10}$4.83 in anti-HCV positive patients (p=0.56) when compared to controls at baseline. The median viral load was $\log_{10}$2.60 in HBsAg and anti-HCV positive patients at 3 months when compared with controls (p=0.58), and $\log_{10}$2.60 in HBsAg and anti-HCV at 6 months when compared with controls (p=0.48).

There were 96(66.2%) and 97(65.5%) patients with undetectable viral load by the third month of HAART among the cases and controls respectively (p=0.74). The number of patients with undetectable viral load increased to 116(81.1%) and 119(79.3%) among the cases and controls respectively at the sixth month of HAART (p=0.10).

Table II. Changes in median viral loads of cases and controls

DURATION (months)	0		3		6	
STUDY GROUP	Cases	controls	Cases	controls	Cases	controls
MEDIAN VIRAL LOAD Log_{10}	4.95	4.83	<2.60	<2.60	<2.60	<2.60
RANGE Log_{10}	4.01-6.45	3.87-6.37	2.60-6.04	2.60-6.27	2.60-5.47	2.60-5.14
p-value	=0.17		=0.86		=0.25	

Table III. Proportion of patients with undetectable viral load at third and sixth month of haart

VIRAL LOAD GROUP	3 MONTHS CASES N (%)	3 MONTHS CONTROLS N (%)	6 MONTHS CASES N (%)	6 MONTHS CONTROLS N (%)
UNDETECTABLE	96(66.2)	97(64.7)	116(81.1)	119(79.3)
DETECTABLE	49(33.8)	53(35.3)	27 (18.9)	30(20.7)
TOTAL	145(100)	150(100)	143(100)	149(100)

X^2 = 0.11 DF= 1 P=0.74 X^2= 2.67 DF=1 P=0.10

Discussion

The immunologic and virologic responses in this study demonstrate that effective antiretroviral therapy can have profound improvements in outcomes for those with HIV co-infection with HBV or HCV similar to those with HIV mono-infection.

Immunologic Response

In this study, immunologic response was significantly lower among the cases 88(60.7%) when compared with controls 99(66%) at the third month of HAART. When cases were separated into HBsAg and anti-HCV positive patients, the statistical difference was found only in the anti-HCV positive cases as just 54.5% of them achieved CD4+ increase of =50cells/µl from baseline at 3 months compared to 66% of controls. Greub et al[26] defined an immunologic response to treatment as an increase in the CD4+ cell count of at least 50 cells/µl from baseline and found that HCV co-infection was associated with a smaller CD4+ cell recovery in the Swiss Cohort Study. Zala et al[29] also reported that while 86% of HCV negative individuals had a CD4+ cell count increase of =75cells/µl at 48 weeks, only 64% of HCV positive individuals achieved this. Similarly, Klein et al[30] reported that co-infected individuals had a significantly reduced probability of achieving a CD4+ cell count increase of =50 cells/µl but found no statistically significant difference in mean CD4+ cell count 24 months after initiation of HAART with adjustment for baseline CD4+ cell count, viral load, previous nucleoside drug experience and duration of HIV infection. Law et al[24] found that the mean increases in CD4+ count of 100 cells/µl were significantly lower among HIV patients co-infected with HBV and HCV at weeks 4 and 8 following commencement of HAART, however by week 48 CD4+ cell increases were similar.

In contrast to the significant association between infection with HCV infection and reduced immunologic response at 3 months in this study, Sulkowski et al[31] in a United States-based study of 1995 patients reported no difference in CD4+ count rise and disease progression in those co-infected with HCV compared to HIV mono-infected patients. The disparity in findings may be related to the fact that 72% of his patients were not receiving HAART, 25% progressed to AIDS and 16% died. Therefore, the high mortality in their study may have prevented the observation of late and subtle changes in CD4+ counts.

The lack of consistency in results in several of the studies may stem from different definitions for what constitutes immunologic response, inconsistencies in the unit of measures and the fact that it can take 24 months of treatment for complete immunologic response to occur[33], beyond the time frame of many studies including this study. Also, confounders like intercurrent infection, psychological stress e.t.c responsible for decreases in CD4+ were not assessed. Furthermore, blunted response may mostly occur in those co-infected individuals with lower baseline CD4+ counts as is usually seen in Africa. For example, in Klien's[30] study where no difference in mean CD4+ cell count response was observed, the baseline CD4+ cell count was well above 200 cells/µl among co-infected and HIV mono-infected individuals. Lamivudine which is active against both HIV and HBV may blunt the full effect of HBV as reported in the CAESAR study[34] even though Law et al[24] reported no differential CD4+ cell response in HIV-HBV co-infected patients with and without lamivudine-containing antiretroviral therapy regimens. Lastly, positive HBsAg and anti-HCV serology do not translate to active infection and may justify similar treatment outcomes between cases and controls.

Virologic Response

The baseline median viral load was higher among the cases (log_{10}4.95) compared with controls (log_{10}4.83) p=0.17 while the viral load reductions were at least

log_{10}2.3 for cases and log_{10} 2.2 for controls at 3 and 6 months of HAART (p=0.86 at 3 months, p=0.25 at 6 months). Similar to this study, some reports from developing and developed countries on the efficacy of various antiretroviral regimens have documented reductions in viral load levels between log_{10}1.5 to log_{10}2.0 within 6 months[35,36]. These findings also agree with those of Grueb et al,[26] and Law et al[24] where median viral load reduction was log_{10}1.5 in patients with and without co-infection from week 4 up to 48 following initiation of HAART.

Although statistically non-significant, the higher baseline viral load among the cases (especially HBsAg positive) than controls may be attributed to the ability of HBV protein X to stimulate HIV viral replication as reported in several studies[16,17,37]. In this study also, there was no significant difference between the proportion of patients with undetectable viral load among the cases (66.2%) and controls (64.7%) at 3 months. Similarly, there was no significant difference in proportion of patients with undetectable viral load among cases (81.1%) and controls (79.3%) at the end of the study period.

Conclusion

HIV infection in the presence of positive HBsAg or anti-HCV has limited impact from the point of view of immunologic and virologic outcomes. This may indicate that the commonly available and cheap ARVs will be in use until better and affordable alternatives are available. Regardless, a management plan is advocated to prevent co-infection and ameliorate other challenges it presents in HIV/AIDS patients.

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