Original article

Long term highly active antiretroviral therapy outcomes in HIV infected Nigerians and those co-infected with hepatitis B and C

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ABSTRACT

Aims: HIV co-infected with hepatitis B and/or C virus is common largely due to shared routes of transmission. Paucity of data exists for long term treatment outcomes of HIV infected patients, and those co-infected with hepatitis B and C (HBV, HCV) despite the high burden in Nigeria. The aim of study was to describe treatment outcomes of long-term HIV, and assess the effect of hepatitis B and C co-infection on long-term response to antiretroviral therapy (ART) in HIV infected Nigerians. Methods: A cohort study of HIV infected adults consecutively initiating ART between July 2004 and December 2007, followed up for 7 years (2011-2014). HBV and HCV infection were diagnosed by hepatitis B surface antigen (HBsAg), and antibody detection (HCVAb). HIV viral load and CD4 were monitored 3-monthly, after initiating ART. Treatment outcome comparisons were made between HIV mono-infected and HIV co-infected with hepatitis B, hepatitis C and both. Results: A total of 2,801 adults were included (median age: 35.5 years; 64.2% female), of whom 197 (7.03%) were co-infected with HBV and 53 (1.89%) with HCV. During the 7-year follow up, 369 (13.17%) individuals were lost-to-follow-up. Immune reconstitution measured by CD4 recovery was lower in both HBV and HCV co-infection, but was not statistically significant ($p \leqslant 0.05$). Median baseline HIV viral load was 4.63 log copies/ml for all groups which decreased to undetected at a median time of 6 months, and remained so for the study duration. Conclusion: Significant clinical, but no immunological and virological difference was found in ART treatment outcomes between HIV patients and those co-infected with HBV and HCV, after 7 years of follow-up. In other words, hepatitis B and C co-infection does not affect treatment if eligible patients are placed on ART regimes that are potent against HIV.

Introduction

There are approximately 37.9 million people worldwide living with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) in 2019 [1]. An estimated 1.8 million individuals worldwide became newly infected with HIV – about 5,000 new infections per day. HIV is still a dreaded disease affecting millions worldwide [2]. With decades of the evolution of antiretroviral drugs given to patients, the impact on long term use of such is largely unknown. To further complex the issue, co-infection with the blood borne hepatitis viruses, hepatitis B (HBV) and C (HCV) further highlights a necessary look into how such cohorts will fare over a long term of treatment.

Highly active antiretroviral therapy (HAART) has increased the life expectancy of HIV-infected individuals who maintain long-term suppression of HIV replication and restore their CD4 counts [3–5]. Factors such as the initial HAART regimen, baseline HIV

RNA, adherence, and side effects influence the success of achieving long-term HIV RNA suppression; however, it is unclear whether HBV or HCV co-infection affects long-term response to HAART. Chronic hepatitis B (CH-B) occurs in 5–10% of HIV-infected individuals and its long-term influences on HIV RNA suppression, CD4 recovery, and mortality while on HAART are not fully characterized. Duda et al [6] conducted a baseline study for on-going monitoring of the evolution of care delivery over time; evaluating HIV treatment outcomes in relation to site capacity for comprehensive care. Despite the importance of ensuring optimal outcomes, few studies have addressed the capacity of HIV programmes to deliver comprehensive care. This study sought to describe such capacity using a developing country example.

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2. Materials and Methods

2.1 Study Design and Population

This was a case controlled retrospective study, carried out at the Centre for Human Virology and Genomics (CHVG) of the Nigerian Institute of Medical Research (NIMR), Lagos. The Federal Government of Nigeria initiated an antiretroviral drug access programme in 2002, and NIMR was selected as one of the 25 centres. NIMR currently provides comprehensive HIV care, treatment and support for over 16,000 individuals. Majority (75%) of them are from Lagos and Ogun States, while the rest are from the neighboring states.

CHVG is a national reference laboratory for HIV established in 2001, and it was one of the first National centers that the US government's President's Emergency Plan for AIDS Relief (PEPFAR) fund benefited from. CHVG implements quality management system and is certified by the International Organization for Standardization (ISO) 9001:2008. It has been accredited to ISO 15189:2012 by the South African National Accreditation System and was recently listed by WHO as a pre-qualification laboratory.

The study population consisted of HIV positive confirmed adults, who had visited the Clinical Sciences Department (CSD) and CHVG of NIMR for medical consultation and laboratory tests respectively, from July 2004 to December 2007 and followed up for 7 years.

2.2 Ethical Considerations

Informed consent was obtained in writing from all patients in accordance with the WMA Declaration of Helsinki and in accordance with the ICH guideline for Good Clinical Practice (6th revision, 2008). The medical ethics committee for research in humans also called the Institutional Review Board of NIMR approved the protocol of this study.

2.3 Clinical and Pharmacy visits

Patients had regular (3 monthly) visits to the CSD for measurement of vital signs and consultation with doctors. Reports on any clinical presentations while on ARVs, adverse effects and other health complaints were noted. That completed, patients were issued requests for both laboratory visit and drug re-fills from the pharmacy section of the clinic.

2.4 Laboratory Analyses

Phlebotomy: Venous blood (8 mls) was obtained by means of vacutainer from each patient, and put into potassium ethylene diamine tetra acetate (K+EDTA) anticoagulant. Patients were bled for HIV viral load, CD4, and also clinical chemistry, hematology (not reported in this study). All samples (except CD4 and hematology samples which were analyzed same day) were centrifuged at room temperature at 3500 rpm for 10 min within 24 h of collection. The plasma was then separated and stored at -70 °C until analyzed.

Serology: HIV was confirmed by Enzyme Linked Immunosorbent Assay (ELISA) method (GenscreenTM ULTRA HIV Ag-Ab, Bio-Rad, Marnes-la-Coquette, France), while HBV infection was diagnosed by hepatitis B surface antigen (HBsAg) detection, with Monolisa HBsAg Ultra3; BioRad Hercules, CA, USA. HCV diagnosis was carried out with the principle of antibody detection (HCVAb) using Dia.Pro Diagnostic Bioprobes, srl, Milan, Italy.

HIV viral load (VL) test: HIV VL was estimated at 3-month intervals, using the COBAS Ampliprep/COBAS TaqMan HIV-1 Test, v.2.0 test kits (Roche Diagnostics, Branchburg, USA) on the COBAS

AmpliPrep, TaqMan48 and 96 analyzers. One milliliter of blood plasma was pipette into sample tubes and utilized by the instrument. On the instrument the process is divided into three major steps, which are all automated and include: specimen preparation, reverse transcription, and simultaneous PCR amplification and detection of target RNA. The assay takes about five and a half hours. The limit of detection/dynamic range of the assay is 20 -100,000,000 IU/ml.

CD4 Count: CD4 count assay was analyzed at baseline and 3-month intervals using the CY-S-3022 CyFlow® Counter instrument and reagents (Sysmex Partec GmbH, Gorlitz, Germany). Briefly, EDTA whole-blood sample (20 µl) was mixed with antibody conjugated to a fluorochrome in a 1:1 ratio. After a fixed incubation time, the buffer was added and the mixture analyzed on the flow cytometer. The light source excites the fluorescent dye linked with the stained cell and the emitted light is detected, while blood sample is running through the instrument. The concentration of detected cell population is calculated by the integrated software (Fryland et al., 2006).

2.5 Data abstraction and statistical analysis

Data were abstracted from records of adult patients greater than 18 years, which had laboratory results, clinical information, and drug intake combinations. Data abstracted were from the CSD and CHVG medical databases, FileMaker Pro, version 10. Abstracted data were analyzed using Microsoft Excel 2010 and SPSS (de-linked and cleaned before analysis). They were sorted into four categories of interest; HIV-1 mono-infected, HIV-HBV co-infected, HIV-HCV co-infected and HIV-HBV-HCV tri-infected groups. Parameters collected include; age, sex, height, weight, treatment regime combination, first line/second line, HIV viral load, CD4, serology status of HIV and hepatitis B and C, and clinical condition. Summary statistics including mean, median, frequencies, percentages and rates were computed. SPSS, version 20 was used to test assumptions.

3. Results

Demographics of Study population: A total of 2,801 patients were enrolled within the study period. The median age of the study participants was 35.5 (IQR 25 - 49) years. The majority of the study population was HIV mono-infected with 2,535 (90.5%) patients, followed by the HIV-HBV co-infected 197 (7.0%); HIV-HCV co-infected 53 (1.9%), while the HIV-HBV-HCV triple infected were only 15 (0.5%). The demographics collected included marital status, education, occupation and risk factors. Majority (61.6%) were married, 41.1% had at least a secondary school education, while 63.8% had income generating jobs. Demographics of the populations are shown in Table 1.

CD4: Median CD4 of the 4 categories of patients at each laboratory visit were determined and plotted on a chart. Three monthly CD4 values of the HIV monoinfected, HIV-HBV co-infected, HIV-HCV co-infected and the HIV-HBV-HCV triple infected could be seen increasing from baseline (month 0) to the 84th month (Figure 1). Median CD4 for baseline were 221, 184, 222 and 135 cells/µL for the HIV monoinfected, HIV-HBV co-infected, HIV-HCV co-infected and HIV-HBV-HCV triple infected groups respectively. At the end of the study (84th month) mean CD4 values had increased to 583, 528, 531 and 549 cells/µL for the HIV mono-infected, HIV-HBV co-infected, HIV-HCV co-infected and HIV-HBV-HCV triple infected groups respectively.

HIV-1 viral load: The median HIV-1 viral load of the 4 categories of patients at each laboratory visit were determined and plotted on a chart. Three monthly viral load values of the HIV monoinfected, HIV-HBV coinfected, HIV-HCV co-infected and the HIV-HBV-HCV triple

infected reduced from baseline (month 0) to the 84th month (Figure 2). Median HIV-1 viral load for baseline were 252,285 (5.4 log), 286,534 (5.4 log), 206,363 (5.3 log) and 84,480 (4.9 log) RNA copies/mL for the HIV monoinfected, HIV-HBV coinfected, HIV-HCV co-infected and HIV-HBV-HCV triple infected groups respectively. At the end of the study (84th month) viral load values had dropped to not detected (0 RNA copies/ml) for the HIV monoinfected, HIV-HBV co-infected, HIV-HCV co-infected and HIV-HBV-HCV triple infected groups respectively. The viral load values show a gradual drop of viral titer lingering to the 24th month before 'not detected' is achieved.

Clinical Assessment: Based on appointments, regular quarterly visits were made to NIMR HIV clinic by the patients. The majority (88%) of HIV mono-infected patients were clinically stable (no medical complaints) during the period of assessment. Those with virologic failure were 0.9%. A total of 55 (2.16%) persons developed pulmonary tuberculosis. In addition, HIV-HBV, HIV-HCV and HIV-HBV-HCV groups all recorded clinical stability at 88%, 84.9% and 80% respectively, as shown in table 2 below. During the 7-year follow up period, 369 (13.17%) individuals were lost-to-follow-up or may have died. Mortality was 29.4% higher for HBV co-infected compared to mono-infected patients (p≤ 0.05). After the seventh year of ART, the independent mortality risk was a 4.5-fold increase in hepatitis B and C co-infection (p≤ 0.05). Immune reconstitution (CD4 recovery) was lower in both HBV and HCV co-infection, but was not statistically significant (p≤ 0.05). Median baseline HIV viral load of 4.63 RNA log copies/ml for all groups reduced to undetected at a median time of 6 months, and remained so for the study duration.

Table 1: Demographics of the study HIV, HIV-HBV, HIV-HCV and HIV-HBV-HCV patients on long term ART therapy

	Total	HIV N (%)	HIV-HBV N (%)	HIV-HCV N (%)	HIV-HBV-HCV N (%)
	2801	2535	197	53	15
Marital status					
Married	1725 (61.6)	1576 (62.1)	109 (55.3)	32 (60.4)	8 (53.3)
Single	640 (22.8)	563 (22.2)	57 (28.9)	16 (30.2)	4 (26.7)
Widowed	283 (10.1)	258 (10.2)	19 (9.7)	5 (9.4)	1 (6.7)
Separated	82 (2.9)	70 (2.7)	10 (5.1)	-	2 (13.3)
Divorced	64 (2.3)	62 (2.4)	2 (1.0)	-	-
Education					
Tertiary	806 (28.8)	750 (29.5)	44 (22.3)	12 (25)	-
Secondary	1151 (41.1)	1031 (40.7)	88 (44.6)	25 (52.1)	7 (50)
Primary	534 (19.1)	468 (18.4)	49 (24.8)	10 (20.8)	7 (50)
None	115 (4.1)	107 (4.2)	7 (3.5)	1 (2.1)	-
Not indicated	174 (6.8)	174 (6.8)	-	-	-
Occupation					
Income generating	1828 (65.2)	1619 (63.8)	156 (79.2)	39 (73.6)	14 (93.3)
Non income gen.	816 (29.1)	762 (30.0)	40 (20.3)	13 (24.5)	1 (6.7)
Not indicated	156 (5.6)	154 (6.1)	1 (0.5)	1 (1.9)	-
Risk Factor					
Heterosexual	2210 (78.9)	1996 (78.7)	161 (81.7)	40 (75.4)	13 (86.7)
MSM	45 (1.6)	43 (1.7)	1 (0.5)	1 (1.9)	-
Transfusion	106 (3.8)	94 (3.7)	8 (4.0)	4 (7.5)	-
Unknown	310 (11.1)	277 (10.9)	24 (12.2)	7 (13.2)	2 (13.3)
PMTCT	2 (0.0007)	1 (0.04)	1 (0.5)	-	-
IVDU	1 (0.04)	1 (0.04)	-	-	-
Heterosexual/Transfusion	34 (1.2)	31 (1.2)	2 (1.0)	1 (1.9)	-
Heterosexual/MSM	1 (0.00035)	1 (0.04)	-	-	-
Heterosexual/IVDU	1 (0.00035)	1 (0.04)	-	-	-
Heterosexual/unknown	5 (0.18)	5 (0.2)	-	-	-

Table 2: Clinical assessment of the three groups of patients on HAART during 7-year follow-up

Clinical Assessment	HIV No. (%)	HIV-HBV (%)	HIV-HCV (%)	HIV-HBV-HCV (%)
Stable	2231 (88)	175 (88)	45 (84.9)	12 (80)
Virologic Failure	24 (0.9)	5 (2.53)	6 (11.32)	0
Pulmonary Tuberculosis	55 (2.16)	7 (3.55)	2 (3.77)	0
Asymptomatic	4 (0.15)	0	0	0
Malaria	50 (1.97)	0	0	1 (6.67)
Urinary Tract Infection	11 (0.43)	0	0	0
Hypertension	19 (0.75)	1 (0.50)	0	0
Other Complaints	120 (4.73)	5 (2.53)	0	2 (13.33)
Pruritis	11 (0.43)	3 (1.52)	0	0
Elevated ALT	10 (0.39)	1 (0.50)	0	0

Figure 1: Profile of median CD4 cell count increase during the 7-year period. Four groups of patients are shown.
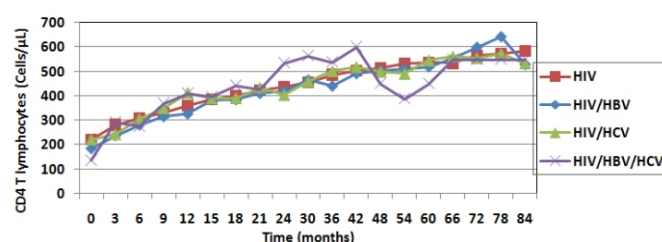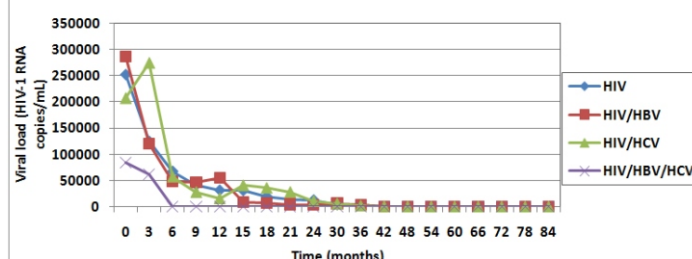

Figure 2: Profile of median HIV viral load decline during 7 years of antiretroviral (ARV) drug therapy. The four different groups of patients are indicated. Gradual decline is observed that leveled at the 24th month.

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