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Original Article **Open Access**

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

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Abstract:

Background: HIV co-infection with hepatitis B (HBV) and/or hepatitis C virus (HCV) is common, largely due to shared routes of transmission, but paucity of data exists for long term treatment outcomes of HIV infected patients, and those co-infected with HBV and HCV despite the high burden in Nigeria. The aim of study was to describe the long-term treatment outcomes in HIV infected Nigerians and to assess the effect of HBV and HCV co-infections on long-term response to antiretroviral therapy (ART).
Methodology: This was a retrospective study of HIV infected adults (> 18 years old) consecutively initiating ART between July 2004 and December 2007, who were followed up for 7 years (2011 and 2014). HBV and HCV infections were diagnosed by detection of serum hepatitis B surface antigen (HBsAg) and HCV antibody (HCVAb) respectively. HIV viral load and CD4 count were monitored 3-monthly after initiating ART, and treatment outcomes based on these were compared between patients with HIV mono-infection, HIV/HBV, HIV/HCV and HIV/HBV/HCV co-infections. Clinical and laboratory data of the patients were abstracted from the medical databases, FileMaker Pro, v 10, entered into Microsoft Excel, and analyzed using SPSS version 20.0.
Results: A total of 2,800 adults were evaluated (median age of 35.5 years; 64.2% female), of whom 197 (7.0%) were co-infected with HBV, 53 (1.9%) with HCV, and 15 (0.5%) with HBV and HCV. During the 7-year period, 369 (13.2%) patients were lost to follow up. Immune reconstitution, measured by CD4 recovery, was lower in both HBV and HCV co-infections compared to HIV mono-infection, but this was not statistically significant (p>0.05). Median baseline HIV viral load was 4.63 log copies/ml for all groups, which decreased to undetectable level at a median time of 6 months and remained so for the study duration.
Conclusion: This study revealed a higher virologic failure among HIV/HCV co-infected group compared to other groups. No immunological difference in ART treatment outcomes between HIV mono-infected and those co-infected with HBV and HCV after 7-year follow-up. Gradual rise in CD4 was found to be an immunological evidence of the body's recovery from HIV, buttressed by the drop in viral load over the 7-year period.

Keywords: ART, HIV, HBV, HCV co-infection, long term outcomes

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Résultats à long terme du traitement antirétroviral hautement actif chez les Nigérians infectés par le VIH et ceux co-infectés par les virus des hépatites B et C

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Abstrait:

Contexte: La co-infection par le VIH avec l'hépatite B (VHB) et/ou le virus de l'hépatite C (VHC) est courante, en grande partie en raison des voies de transmission partagées, mais il existe peu de données sur les résultats du traitement à long terme des patients infectés par le VIH, et ceux co -infectés par le VHB et le VHC malgré le fardeau élevé au Nigéria. Le but de l'étude était de décrire les résultats du traitement à long terme chez les Nigérians infectés par le VIH et d'évaluer l'effet des co-infections par le VHB et le VHC sur la réponse à long terme au traitement antirétroviral (TAR).
Méthodologie: Il s'agissait d'une étude rétrospective sur des adultes infectés par le VIH (>18 ans) ayant commencé un traitement antirétroviral consécutivement entre juillet 2004 et décembre 2007, suivis pendant 7 ans (2011 et 2014). Les infections par le VHB et le VHC ont été diagnostiquées par détection de l'antigène de surface sérique de l'hépatite B (AgHBs) et des anticorps anti-VHC (HCVAb) respectivement. La charge virale du VIH et la numération des CD4 ont été surveillées tous les trois mois après le début du TAR, et les résultats du traitement basés sur ceux-ci ont été comparés entre les patients atteints de mono-infection VIH, VIH/VHB, VIH/VHC et VIH/VHB/VHC. Les données cliniques et de laboratoire des patients ont été extraites des bases de données médicales, FileMaker Pro, v 10, saisies dans Microsoft Excel et analysées à l'aide de SPSS version 20.0.
Résultats: Un total de 2800 adultes ont été évalués (âge médian de 35,5 ans; 64,2% de femmes), dont 197 (7,0%) étaient co-infectés par le VHB, 53 (1,9%) par le VHC et 15 (0,5%) par le VHB et VHC. Au cours de la période de 7 ans, 369 (13,2%) patients ont été perdus de vue. La reconstitution immunitaire, mesurée par la récupération des CD4, était plus faible dans les co-infections par le VHB et le VHC que dans la mono-infection par le VIH, mais cela n'était pas statistiquement significatif (p>0,05). La charge virale VIH de base médiane était de 4,63 log copies / ml pour tous les groupes, ce qui a diminué à un niveau indétectable à une période médiane de 6 mois et le reste pendant toute la durée de l'étude.
Conclusion: Cette étude a révélé un échec virologique plus élevé parmi le groupe co-infecté par le VIH / VHC par rapport aux autres groupes. Aucune différence immunologique dans les résultats du traitement TAR entre le VIH mono-infecté et ceux co-infectés par le VHB et le VHC après un suivi de 7 ans. L'augmentation progressive des CD4 s'est avérée être une preuve immunologique de la guérison du corps du VIH, étayée par la baisse de la charge virale au cours de la période de 7 ans.

Mots clés: TAR, VIH, VHB, co-infection par le VHC, résultats à long terme

Introduction:

There are approximately 37.9 million people worldwide living with human immunodeficiency virus and acquired immunodeficiency syndrome (HIV/AIDS) in 2019 (1). An estimated 1.8 million individuals worldwide became newly infected with HIV and about 5000 new infections per day. HIV remains a dreaded disease that is affecting millions worldwide (2). With decades of evolution of antiretroviral therapy (ART), the impacts of long-term use of ART drugs is largely unknown. To further complicate the issue, co-infections with blood borne hepatitis viruses such as hepatitis B (HBV) and C (HCV) highlights a necessary look into how such cohorts will fare over a long-term 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 the 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. However, in spite of 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 in a developing country, Nigeria, as a model.

Materials and method:

Study setting, design and population

This was a retrospective comparison 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 neighboring States. The demographics collected included marital status, education, occupation and risk factors.

CHVG is a national reference laboratory for HIV established in 2001, and it was one of

the first national centers that benefited from the US Government President's Emergency Plan for AIDS Relief (PEPFAR) fund. CHVG implements quality management system certified by the International Organization for Standardization (ISO) 9001:2008. The CHVG laboratory was accredited to ISO 15189:2012 by the South African National Accreditation System (SANAS) in 2018 within the scope of molecular diagnostics, chemistry and serology, and was recently listed by WHO as a pre-qualification laboratory.

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

Ethical considerations

Informed consent was obtained in writing from all patients in accordance with the World Medical Assembly (WMA) Declaration of Helsinki, and in accordance with the International Council for Harmonisation (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 study protocol.

Clinical and pharmacy follow up visits

Based on clinic appointments, regular quarterly visits were made to NIMR HIV clinic by the patients in order to have consultations with the medical doctors in charge. Reports on any clinical presentations while on ARVs, adverse effects and other health complaints were noted. Once completed, patients were issued requests for both laboratory visits and drug re-fills from the pharmacy section of the clinic.

Laboratory analyses

Venous blood samples (~8 ml) for estimations of HIV viral load, CD4 count, clinical chemistry, and haematology (not reported in this study) were obtained by means of vacutainer from each patient, and put into potassium ethylene diamine tetra acetate (K^+ EDTA) bottles. All samples (except for the CD4 count and haematology) were centrifuged at room temperature at 3500 rpm for 10 min within 24 hours of collection. The plasma was then separated and stored at -70°C until analyzed.

HIV was confirmed by Enzyme Linked Immunosorbent Assay (ELISA) method (Gen screen™ Ultra HIV Ag-Ab, Bio-Rad, Marnes-la-Coquette, France), while HBV infection was diagnosed by detection of hepatitis B surface antigen (HBsAg) with Monolisa HBsAg Ultra3 (BioRad Hercules, CA, USA). HCV diagnosis was made by antibody (HCVAb) detection using Dia Pro Diagnostic Bioprobes, srl, (Milan, Italy).

HIV viral load (VL) was estimated at 3-month intervals by reverse transcription-PCR assay 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 pipetted into sample tubes of the instrument, and the process divided into three major steps (all automated); 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. The median HIV-1 viral load of the 4 categories of patients at each laboratory visit were determined and plotted on a chart.

The 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 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 a blood sample is running through the instrument. The concentration of detected cell population was calculated by the integrated software. The median CD4 counts of the 4 categories of patients at each laboratory visit were determined and plotted on a chart.

Data abstraction and statistical analysis

Data were abstracted from records of adult patients (>18 years) who had laboratory results, clinical information, and drug intake combinations from the CSD and CHVG medical databases, FileMaker Pro, version 10. The patients 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. Data collected from each patient included age, gender, marital status, education, occupation, height, weight, risk factors, treatment regime combination, first line/second line, HIV viral load, CD4 count, serology status of HIV, hepatitis B and C, and clinical conditions.

Abstracted data were entered into Microsoft Excel 2010 (de-linked and cleaned before analysis) and analysed using the Statistical Package for Social Sciences (SPSS) version 20.0.

Results:

Demographics of study population:

A total of 2,800 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 were HIV mono-infected with 2,535 (90.5%) patients, followed by 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%). Majority (61.6%) were married, 41.1% had at least a secondary school education, while 63.8% had income generating jobs. The demographics of the study population and risk factors associated with HBV and HCV co-infections are shown in Table 1.

CD4 cell count:

Three monthly CD4 values of the HIV mono-infected, HIV/HBV and HIV/HCV co-infected, and the HIV/HBV/HCV triple infected patients increased from baseline (month 0) to the 84th month (Fig 1). The median ± SD CD4 values at the baseline were 221±34, 184±22, 222±28 and 135±24 cells/μL for the HIV mono-infected, HIV/HBV and HIV/HCV co-infected and HIV/HBV/HCV triple infected patients respectively. At the end of the study (84th month), the median ± SD CD4 T cell values had increased to 583±34, 528±32, 531±56 and 549±19 cells/μL for the HIV mono-infected, HIV/HBV and HIV/HCV co-infected, and HIV/HBV/HCV triple infected patients respectively.

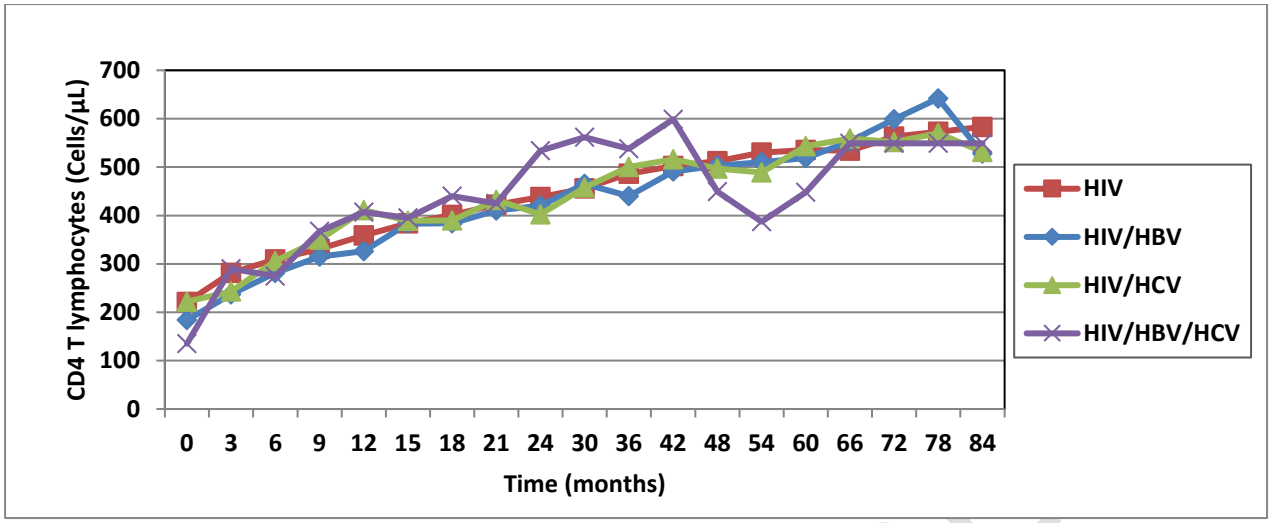
HIV-1 viral load:

Three monthly viral load values of the HIV mono-infected, HIV/HBV and HIV/HCV co-infected and the HIV/HBV/HCV triple infected patients reduced from baseline (month 0) to the 84th month (Fig 2). The median ± SD HIV-1 viral load at baseline were 252,285 ±3921 (5.4 log), 286,534 ±358 (5.4 log), 206,363 ±1772 (5.3 log) and 84,480 ±1879 (4.9 log) RNA copies/mL for the HIV mono-infected, HIV/HBV and HIV/HCV co-infected, and HIV/HBV/HCV triple infected patients respectively. At the end of the study period, viral load values had dropped to undetectable level (0 RNA copies/ml) for all the patient groups. The viral load values showed a gradual drop of viral titer lingering to the 24th month before 'not detected' was achieved. The median baseline HIV viral load of 4.63 RNA log copies/ml for all groups reduced to 'undetected' level at a median time of 6 months, and remained so for the study duration.

Table 1: Demographics of HIV patients on long term HAART and risk factors for HBV and HCV co-infections in Lagos, Nigeria

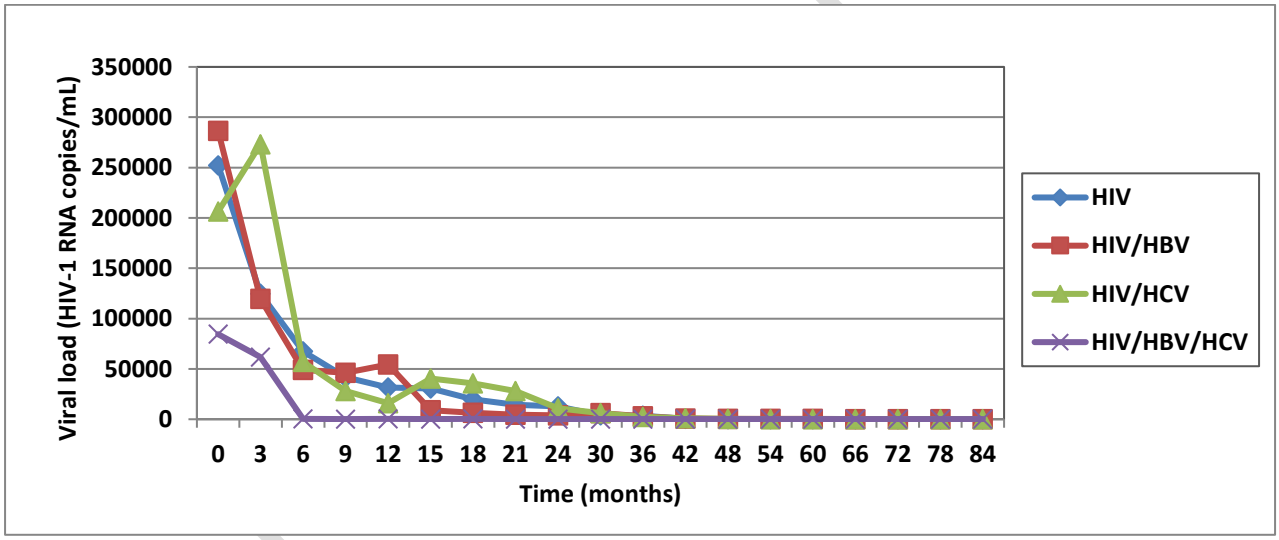
Characteristics	Total (%) (n=2800)	HIV (%) (n=2535)	HIV/HBV (%) (n=197)	HIV/HCV (%) (n=53)	HIV/HBV/HCV (%) (n=15)	*p* value
Marital status						
Married	1727 (61.6)	1577 (62.1)	109 (55.3)	32 (60.4)	8 (53.3)	0.34
Single	641 (22.8)	564 (22.2)	57 (28.9)	16 (30.2)	4 (26.7)	0.64
Widowed	284 (10.1)	259 (10.2)	19 (9.7)	5 (9.4)	1 (6.7)	0.55
Separated	84 (2.9)	72 (2.7)	10 (5.1)		2 (13.3)	0.78
Divorced	65 (2.3)	63 (2.4)	2 (1.0)			0.87
Education						
Tertiary	806 (28.8)	750 (29.5)	44 (22.3)	12 (25.0)	-	-
Secondary	1151 (41.1)	1031 (40.7)	88 (44.6)	25 (52.1)	7 (50.0)	-
Primary	534 (19.1)	468 (18.4)	49 (24.8)	10 (20.8)	7 (50.0)	-
None	115 (4.1)	107 (4.2)	-	-	-	-
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 generating	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 factors						
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)	-
MTCT	2 (0.07)	1 (0.04)	1 (0.5)	-	-	-
IVDU	1 (0.035)	1 (0.04)	-	-	-	-
Heterosexual/Transfusion	34 (1.2)	31 (1.2)	2 (1.0)	1 (1.9)	-	-
Heterosexual/MSM	1 (0.035)	1 (0.04)	-	-	-	-
Heterosexual/IVDU	1 (0.035)	1 (0.04)	-	-	-	-
Heterosexual/unknown	5 (0.2)	5 (0.2)	-	-	-	-

MSM = men who have sex with men; IVDU = intravenous drug user; MTCT = mother-to-child transmission



HIV = Human immunodeficiency virus; HBV = Hepatitis B virus; HCV = Hepatitis C virus

Fig 1: Profile of median CD4 cell count of the four categories of patients during the 7-year period



HIV = Human immunodeficiency virus; HBV = Hepatitis B virus; HCV = Hepatitis C virus
Gradual decline was observed in the four patient categories that leveled at the 24th month

Fig 2: Profile of median HIV viral load of the four categories of patients during the 7-year period

Clinical assessment:

Majority (88%, n=2231) of HIV mono-infected patients were clinically stable (with no medical complaints) during the period of assessment, 0.9% (n=24) developed virologic failure, and 55 (2.2%) 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). During the 7-year period, 335 (11.9%) patients were lost to follow-up or may have died. Immune reconstitution (CD4 recovery) was lower in both HIV/HBV and HIV/HCV co-infected patients, but this difference was not statistically significant (p>0.05).

Table 2: Clinical assessment of the HIV patients with HBV and HBC co-infections on long term HAART during a 7-year follow-up in Lagos, Nigeria

Clinical assessment	HIV (%)	HIV/HBV (%)	HIV/HCV (%)	HIV/HBV/HCV (%)	*p* value
Stable	2231 (88)	175 (88.9)	45 (84.9)	12 (80)	0.763
Virologic failure	24 (0.9)	5 (2.5)	6 (11.3)	0	0.034
Pulmonary tuberculosis	55 (2.2)	7 (3.6)	2 (3.8)	0	0.048
Asymptomatic	4 (0.2)	0	0	0	-
Malaria	50 (1.9)	0	0	1 (6.7)	0.003
Urinary tract infection	11 (0.4)	0	0	0	-
Hypertension	19 (0.8)	1 (0.5)	0	0	0.098
Other complaints	120 (4.7)	5 (2.5)	0	2 (13.3)	0.323
Pruritis	11 (0.4)	3 (1.5)	0	0	0.569
Elevated ALT	10 (0.4)	1 (0.5)	0	0	0.762
Loss to follow up	296 (10.5)	27 (0.96)	9 (0.32)	3 (0.11)	0.006

ALT = Alanine Transaminase

Discussion:

Patient monitoring is an arduous task, involving skilled manpower, adequate resources, dedicated and disciplined health practitioners and other support staff. Even with all these in place, some patients would inevitably be lost. However, on the bright side, a far larger proportion is maintained in care, and stay healthy despite the burden of daily drug intake. The present study showed a larger proportion was virologically suppressed after 7 years of antiretroviral therapy. The instance of co-infections of either HBV or HCV or both did not influence viral load decline.

In this study, a large proportion were married (62.1% in the HIV-mono-infected, 55.3% in the HIV/HBV, 60.4% in the HIV/HCV and 53.3% in the HIV/HBV/HCV triple infected groups), followed by singles at 22.2%. In terms of education, about 40% had at least secondary school education across all the study categories, and a third of the population had tertiary education, while very few (4.2%) had no education at all. Majority (>63.8%) of the study population were persons with income generating occupation, while an average of 25% did not have paying jobs. In terms of risk factors, about 80% of the population reported being heterosexuals, 1.7% were homosexuals, 3.7% had had blood transfusion, and 10.9% had no known viral risk factors.

From the literature, it has been reported that once HAART intake is initiated, the natural progression of hepatitis B or C changes. Several authors have documented that HIV impacts the progression of HCV and increases the likelihood of subsequent liver damage (7,8). The main concerns regarding HAART treatment on co-infected persons are the effects a restored immune response have on the liver and delayed CD4 recovery (9). Clinically this study reports that a large percentage of patients are stable on HAART for the four groups. Sadly, virologic failure was observed more in the HIV/HCV co-infected group (11.3%) than the HIV/HBV (2.5%) and HIV (0.9%) mono-infected groups (p=0.034). This is comprehensible due to co-infection. Proponents of reduced monitoring of CD4 and viral load markers refer to a study in Uganda and Zimbabwe on children receiving first-line ART without viral load or CD4 monitoring who had 'not detected' values over 4 years (10), dispelling the need for constant viral load monitoring.

Our study corroborates a Latin American study which reported that despite advanced HIV disease and the use of antiretrovirals, a large fraction of early HAART initiators in the study cohort were alive and in care, with sustained virologic suppression and progressive immune recovery (11).

Conclusion:

Our study showed significant difference in virologic failure between the HIV/HCV co-infected patients than other patient groups, but no significant difference in the immunological features following ART treatment between HIV

mono-infected patients and those co-infected with HBV and HCV after 7 years of follow-up. The gradual rise in CD4 count was found to be an immunological evidence of the patient body's recovery from the damage inflicted by HIV. This was buttressed by drop in the viral load over the 7-year period.

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