

Viral Hepatitis Co-infection Impact on Response to Antiretroviral Therapy and HIV Disease Progression: Virologic and Immunological Indices Outlook

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Abstract: *Introduction:* Due to the availability of anti-retroviral treatment (ART), infected individuals with HIV in Sub-Saharan Africa live longer with reduced mortality and morbidity. But there's rising cases of co-infection with viral hepatitis, reliable data on Hepatitis V virus (HBV) or Hepatitis C (HCV) co-infection prevalence among HIV infected adults in North Central Nigeria. *Methods:* A descriptive cross sectional study was carried out among 289 seropositive drug experienced HIV patients attending Federal Medical centre Keffi in Nasarawa State from December 2019 to march, 2020. The enrolled participants 18 years were tested for anti-HCV and HBsAg. Serological markers profile for Hepatitis B virus was performed on HBV positive samples. HBV DNA viral load and CD4+ T cells count were determined using BD faces analyser and CORBAS Tag-MAN Ampli-prep analyser (USA) respectively. *Results:* The HBV/HCV coinfection prevalence among seropositive HIV drug experience patient was 5.1%. the prevalence of HBV-HIV and HCV- HIV coinfection were 9.5 and 9.3% respectively. Active viral carriers of HBsAg were associated with HBV-HIV co-infected individuals was 8.6% and the HBsAg is associated with severe immune-suppression and decrease in CD4+ T cells and increase in viral load. Dependent risk factors for HCV-HBV-HIV infection are: CD4+ T cells OR; 0.4 (0.1-1.5), age 18-30years 2.1 (1.6-2.1), multiple sex partners 0.7 (0.1-2.3). Participants aged 18-30 years [OR=2.1 (1.6-2.1); p=0.046], male gender [OR=0.9 (0.3-1.4); p=0.034], CD4+ T cell count [OR=0.4 (0.1-1.5); p=0.045], History of Blood transfusion [OR=0.8 (0.2-4.0); p=0.012] and being married [OR=0.6 (0.2-4.3); p=0.039] were independent risk factors of HIV-HBV-HCV co-infections. *Conclusion:* Increase in viral load, severe immune suppression and decrease in CD4+ T Cells was predominant highlights in HBV, HCV coinfection amount HIV patients, increase HBV, HCV screening should be encouraged among seropositive HIV infected individuals.

Keywords: Suppression, Virological, Immunological, Mortality, Morbidity

1. Introduction

The human immunodeficiency virus (HIV) has continues to become a global public health problem with 39.7 million of people living with HIV globally in 2020 [1]. In Sub-Saharan Africa region, it's estimated that over 70% of new infection occurs annually with increase in morbidity and

mortality [2]. Over the years, HAART has been used to reduce HIV related morbidity and mortality [3]. with great transformation of HIV infection from been fatal to a manageable chronic disease [3]. In resource limited countries, rapid scale-up of anti-retroviral therapy (ART) for HIV (AIDS) and it has been successful [4]. In Nigeria, significant progress has been in terms of HIV prevention and control with programs been implemented that has reduced related

HIV complications. And Burden [5]. This program includes scale-up of ART treatment with optimal access. Nigeria also helped the “test & treat” approach a 2016 WHO consolidated guideline on the use of anti-retroviral drugs for the management for HIV infection. There has been usable decline. In the annual new infection in Nigeria as a result of scale-up of HIV care related services. Despite rapid scale up of HIV related service delivery in Sub-Sahara Africa and other resource constrain countries, there has been increase in HIV drugs resistances which has become a challenge in many national ART roll-out programs [6], it has become pertinent to have a robust treatment monitoring response approach [7].

Hepatocellular carcinoma arising from HBV and HCV accounts for 60% and 80% of global cirrhosis burden with 180million people infected with HIV and 400 million with HBV globally [8]. The HBV global prevalence in HIV infected individuals is 7.4% and 2.7 million people with HBV are infected with HIV [9]. In Sub-Sahara Africa, HCV/HBV co-infected with HIV are major global health burden, with two third of the population infected with HIV. Chronic cases of Hepatitis C and B have been observed in HIV patients with severe immune suppression and persistent HBV (Surface antigen) > 6 months in HIV patients is higher [10]. The impact of HBV-HCV. Co-infection in HIV infected individuals in less certain, its believed that HCV-HBV co-infections increases susceptible to liver toxicity as a result of ART uptake, increase viral load, decrease CD4+ T Cells with severe immune-suppression thereby leading to increase in morbidity and mortality rates. Several serological patterns of HBV and HCV emerged in HIV patients because of increased risk of exposure and immunosuppression [11].

During ART regimen uptake in HIV patient, several clinical manifestations have been observed individual co-infected with HBV < HCV. Leading to increase to liver toxicity related to ART [12]. HBV, HCV co-infection was among the eligibility criteria for the enrolment and implementation of the “treat all” policy required by all positive HIV patients on ART. This interplay has upheld the significance of timely screening of one virus on the presence of the other [13]. Significantly, HBV and HCV infection have been linked to wide range of clinical manifestation in HIV infected individual who are drug experienced with increase impaired immune response and ART related liver toxicity. Therefore, we aimed to determine the prevalence and impact of HBV and HCV coinfection on drug experienced HIV infected adults in North central Nigeria immunological and virological outcomes [14].

2. Methods

2.1. Study Design

We carried out a descriptive cross sectional study among 289 seropositive HIV -1 infected adults on treatment regimen accessing care services at Federal Medical Center keffi between December 2019 to March 2020. The enrolled

participants were > 18years who were tested for anti-HCV and HBsAg. Serological markers profile for Hepatitis B viral (HBsAg) was performed on HBV positive samples. The flow chart for screen of HCV and HBV among HIV infected adults is as stated in Figure 1. HIV RNA viral load was done on all the participants enrolled. We used a system random sampling technique to enroll participants.

2.2. Patients Data Collection Tools Procedure

We used key informant interview for a face to face interview and a structured questionnaire to collate sociodemographic data. We review medical records to determine duration since ART initiation, History of opportunistic infection, history of TB treatment, as eligibility criteria which forms basis for clinical data.

2.3. Clinical Operational Definition

At any point within in time within 6 months after HAART commencement, a Virological suppression level of <1000 copies Viral load (VL) was consider for HIV-RNA level in Nigeria, CD4+ cell count is defined base on CD4+ cell reference range as favorable (466 cell/mm³ for female and 400 cell/mm³ for male) and unfavorable (400 cells/mm³ for male and < 466 cell/mm³ for female).

2.4. Sample Collections and Preparation

A treatment phlebotomist was assigned to collect 5ml of blood sample using a K3 BD EDTA vacutainer disposal tube. The specimen was well labelled with patient ID and separated into two vials, one for HIV viral load testing and the former for CD4+ cells count. For viral load analysis, a whole blood sample tube was centrifuged for 10min at 1500RPM where plasma was separated and aliquot and store at -20.

2.5. Serology

Hepatitis B surface antigen. Testing for the hepatitis B surface antigen (HBsAg) was performed using the HBsAg enzyme linked immunosorbent assay (ELISA) (DIAsource Immunoassay SA, Louvain-la-Neuve, Belgium) according to the manufacturer's instructions. All non-reactive samples were recorded as negative. All reactive samples were tested a second time using the HBsAg confirmatory test according to the manufacturer's instructions. All samples reactive to both assays were recorded as positive while those that were non-reactive in the second test after being reactive in the first test were considered non concordant and were subjected to a sensitivity analysis before being included as either positive or negative (Figure 1). Hepatitis “e” antigen and IgM antibody to hepatitis B core antigen (HBc IgM). All samples reactive by ELISA for HBsAg were further tested for the presence of hepatitis “e” antigen (HBeAg) and IgM antibody to hepatitis B core antigen (HBc IgM) using ELISA kits (DIAsource Immunoassay SA, Louvain-la-Neuve, Belgium).

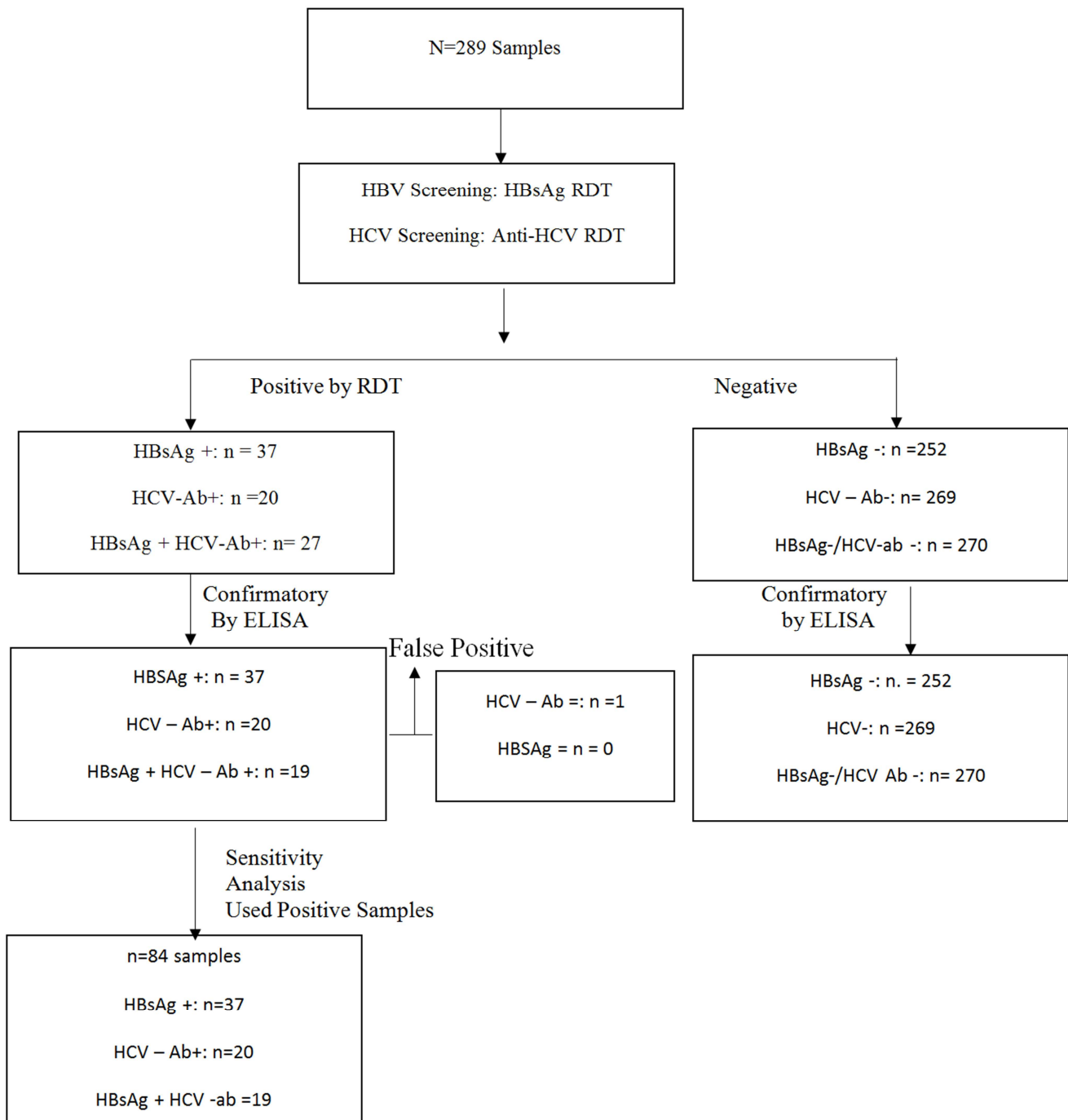


Figure 1. Viral algorithm for Hepatitis C virus (HCV) antibodies, Hepatitis B Surface antigen (HBsAg) from Seropositive HIV infected Samples n=289.

2.6. Hepatitis C antibodies

The presence of hepatitis antibodies is a strong marker of infection with HCV. HCV-Ab was detected using the Anti-HCV ELISA V 4.0 (DIAsource Immunoassay SA, Louvain-la-Neuve, Belgium), a fourth generation enzyme immunoassay kit, which uses recombinant HCV antigens (Core, NS3 and NS5 antigens). HCV-Ab reactive samples were confirmed with the same ELISA kit using the algorithm shown in Figure 1. For HCV, all samples reactive to both the screening and confirmatory assays were

recorded as positive while those that were non-reactive in the second test after being reactive in the first test were considered non-concordant and were subjected to a sensitivity analysis before being included as either positive or negative (Figure 1).

2.7. Plasma Viral Load Quantification

A (QIAGEN Gm6H, Hilden, Germany) Q1 Amp viral RNA Mini-Kit was used to extract Hiv-1 DNA following Standard operational procedure according manufactures instruction. The HIV RNA was quantify using Real-time

PCR (COBAS Amplipre/COBAS Taq-MAN Analyzer (Roche Diagnostic USA). A three (3) phase process was employed which include HIV-1 RNA isolation, formation of complementary deoxyribonucleic acid (cDNA) generation from reverse transcription of target RNA and amplification of targeted cDNA by Simo Haneous polymerase chain reaction. Specific probes of oval-labelled target florescence oligonucleotide were used for the quantification and detection, and amplification of target CDNA.

2.8. CD4+ T Lymphocytes Using Flow Cytometry

A BD Bioscience San Jose, CA USA flow cytometry system was used to enumerate CD4+ T Lymphocytes following standard operation procedure according to the manufacturers instruction. A reagent (Tro-count) containing CDA5, CDA, CD3 monoclonal antibodies labelled with (FITC, res.p, PE, PerCD) dyes are mixed with anticoagulated lysed red blood cells and whole blood using lysing solution A (BD Bioscience) multi-set BD software is used to enumerate absolute CD4+ cells count.

2.9. Ethical Consideration

This study was approved by the committee on Human Research and publication ethics of the Federal Medical Center, Keffi. A well written informed consent was obtained from all participants after the objectives and aims of the studies was explained.

2.10. Statistical Analysis

All data were cleared and checked for completeness in excel version 2019 before they were exported to Epi-info version 7.1 Descriptive analysis were done and presented as tables. We used binary logistics regression to identify associated factors with outcome variables. We also evaluated strength of association. Frequencies (percentages) were presented for categorical variables, while fishes and chi-squares were used to test for degree of association we employed odd ratios to determine predictive factors for HBV-HCV-HIV co-infection using other multivariate logistic regress at p value < 0.05 was considered statistically significant. All cleaned data and analysis were performed using version 7.04 of Graphical prism.

3. Results

A total of 289 seropositive HIV positive drug experience adults were successfully enrolled into the study after a well written informed consent was obtained, comprising of 109 (37.9%) male and 180 (62.3%) females. The overall mean

age of both gender was 32.9 years (18-50years). Majority are urban dwellers 189 (65.4%), single 100 (34.9%) and employed 192 (66.4%) as seen in table 1. The overall prevalence of (HCV/HBV) was 9.3% (27/289), HIV-HBV coinfection was 12.8 (20/289) female had higher prevalence rate in both HBV-HCV concurrent two-infection. In table 2, we outlined the baseline characteristics among the 289 cohort and stratify by gender of the 22 confirmed female with mean age 20 vs 35, p=0.002. The HCV didn't differ between males (337vs 32.6 cells/ μ l) and female (420vs 20.9 cells/ μ l), p=0.525) of the 37 confirmed HBsAg, 22 (12.2%) were positive while 15 (13.8) were male. We also tested for HBeAg positively as an indication for viral active replication out of the 37 HBsAg seropositivity 25 (13.9%) were positive for HBeAg-female while 10 (9.0%) of male were positive for HBeAg. There's a significant association in terms of risk factors for serological marks of HCV, HBV coinfection with gender (OR 0.4 (0.1-1.5), Age, 31.40 years (OR 95% CI: 1.4 (0.8-3.1), history of blood transfusion (ADR 95% CI: 0.8 (0.2-4.0), number of multiple Sex partner (OR 95% CI: 0.7 (0.1-2.3) and CD4+ T cells count < 250 (OR 95% 0.4 (0.1-1.5) as seen in table 3. The overall CD4+ T cell counts median as seen table 4 for HBV-HIV, HIV-HCV, and HIV-HCV-HBV are (190 vs 239 vs 230 cells/ μ l) with a median of HBsAg+ (200.0 (110.8-390.0), HBeAg status (130.0 (105.6-298.5), HCV Ab Status (200.6 (130.6-300.5), HBsAg-HCV-Ab Status (190.6 (131.6-320.5) respectively. Study participants with HBeAg active infection have lower CD+4 T cells counts (130 cells/ μ l) compare to cohort that are HCV-HBV co-infected.

The overall CD4+ T-cell count median for HBV-HCV infected HIV cohort in the study was 190.0 cells/ μ l (range, 131.6-320.5 cells/ μ l) as summarized in Table 4. Study cohort who are HIV-HBV-HBeAg co-infected had had statistically significant lower CD4+ T-cell count (213.0 cells/ μ l) compared to HIV mono-infected participants (130.0 cells/ μ l) (p<0.0001) and also compared to HIV-HCV-HBV co-infected patients (190.0 cells/ μ l) (p=0.067). The HIV-1 viral load mean was 4.87log₁₀ copies/mL and was significantly higher among participants with HIV-HBV or HIV-HCV co-infection compared to HIV-HCV-HBV co-infection (11.67 vs 8.77 vs 8.98 log₁₀ copies/mL respectively) (p=0.011) as well as participants with HIV mono-infection (5.39 vs 4.82 log₁₀ copies/mL respectively) (p<0.0001) (Table 4). Table 4 shows HIV-HBV infected patients immunological and virological parameters with HIV-HBV co-infected patients with positive HBeAg had statistically significant lower CD4+ T-cell count (130.0 cells/ μ l vs 200.0 cells/ μ l; p-value=0.007[‡]) and higher viral load (9.6 copies/ mL vs 8.98 copies/mL; p-value=0.007) compared to the negative HBeAg counterparts.

Table 1. Sociodemographic Characteristics of Hepatitis B and C Con-infection among 289 Seropositive HIV Patient accessing care at Federal Medical Center, Keffi, North Central Nigeria.

Characteristics	Total number examine (n=289)	HBV-HIV Seropositivity n=37	HCV-HIV Seropositivity n=20	HIV-HBV-HCV Seropositivity n=27
		Positive n (%)	Positive n (%)	
Age (years)				
18 – 30	140	20 (14.3)	6 (4.2)	7 (5.0)

Characteristics	Total number examine (n=289)	HBV-HIV Seropositivity n=37	HCV-HIV Seropositivity n=20	HIV-HBV-HCV Seropositivity n=27
		Positive n (%)	Positive n (%)	
31 – 40	60	10 (16.7)	4 (6.7)	5 (8.3)
40 – 50	46	5 (10.9)	7 (15.2)	8 (17.4)
>50	43	2 (4.6)	3 (6.7)	7 (16.3)
Gender				
Male	109	15 (13.8)	9 (8.2)	12 (11.0)
Female	180	22 (12.2)	11 (6.1)	15 (8.3)
Marital Status				
Married	90	10 (11.1)	13 (14.4)	15 (16.7)
Single	100	15 (15)	4 (4.0)	5 (5.0)
Widow/Divorced	99	12 (12.1)	3 (3.03)	7 (7.1)
Residency				
Urban	189	30 (15.9)	18 (9.5)	20 (10.5)
Rural	100	7	2 (2.0)	7 (7.0)
Employability				
Employed	192	12 (6.25)	4 (2.1)	10 (5.2)
Unemployed	87	25 (25.7)	16 (16.5)	17 (17.5)
Level of Education				
Primary	60	12 (20)	4 (6.7)	5 (8.3)
Secondary	90	5 (5.6)	5 (5.6)	6 (6.7)
Tertiary	49	10 (20.4)	6 (12.2)	7 (14.3)
No formal Education	90	10 (11.1)	5 (5.6)	9 (10.0)

Table 2. Baseline Characteristics of HCV and HBV marker in relation to gender among Sero-positive 289 HIV infected adult accessing care at Federal Medical Center, Keffi, North Central Nigeria.

Viral Infection type	Baseline characteristic		P-value
	Female n=180	Male n=109	
HBsAg			
Positive	22 (12.2)	15 (13.8)	0.002
Negative	158 (87.7)	94 (86.2)	
HBeAg			
Positive	25 (13.9)	10 (9.17)	0.456
Negative	155 (86.1)	99 (90.8)	
HCV Ab			
Positive	11 (6.1)	9 (8.2)	0.568
Negative	169 (93.9)	100 (100)	
HBsAg-HCV Ab			
HBeAg -, HCV Ab-	147 (81.9)	85 (77.98)	0.5678
HBsAg+, HCV Ab+	33 (18.3)	24 (15.1)	

HBsAg: Hepatitis B Surface antigen HBeAg: Hepatitis B envelope antigen HCV-Ab: Antibodies to Hepatitis C P-value

Table 3. Associated Risk Factor of HBV, HCV Co-infection among HIV infected adults accessing care at Federal Medical Center, Keffi, Nasarawa State.

Risk Factors	Hepatitis B Surface antigen n= (%)		Hepatitis C antibodies, n (%)		Hepatitis B/C Co-infection	
	HBsAg (+)	OR (95% CI)	HCV ab (+)	OR (95% CI)	HBV/HCV (+)	OR (95% CI)
Age (years)						
18 – 30	20 (14.3)	1	6 (4.2)	1	7 (5.0)	1
31 – 40	10 (16.7)	0.79 (0.36-2.0)	4 (6.7)	1.67 (0.3-9.2)	5 (8.3)	2.1 (1.6-2.1)
40 – 50	5 (10.9)	0.72 (0.33-2.9)	7 (15.2)	0.50 (0.2-4.0)	8 (17.4)	1.4 (0.8-3.1)
<50	2 (4.6)	0.54 (0.20-2.9)	3 (6.7)	1.6 (0.18-10.2)	7 (16.3)	0.8 (1.0-2.3)
Gender						
Female	15 (13.8)	1	9 (8.2)	1	12 (11.0)	1
Male	22 (12.2)	3.41 (2.05-5.0)	11 (6.1)	0.30 (0.10-4.3)	15 (8.3)	0.9 (0.3-1.4)
CD+ T Cell Count (cells/μl)						
<250	22 (22.2)	1	11 (6.1)	1	15 (8.3)	1
≥250	15 (13.8)	3.21 (2.0-5.0)	9 (8.2)	0.48 (0.15-6.3)	12 (11.0)	0.4 (0.1-1.5)
History of Blood Transfusion						
Yes	30 (15.9)	1	18 (9.5)	1	20 (10.5)	1
No	7	2.1 (1.8-4.0)	2 (2.0)	2.17 (0.80-8.7)	7 (7.0)	0.8 (0.2-4.0)
Sexual Partners						
One	25	1	16 (16.5)	1	10 (5.2)	1
Multiple	12	1.2 (1.1-3.0)	4 (2.1)	0.30 (0.20-6.1)	17 (17.2)	0.7 (0.1-2.3)
Marital Status						
Single	10 (11.1)	1				
Married	15 (15.0)	2.1 (2.0-3.9)	13 (14.4)	1	15 (16.7)	1

Risk Factors	Hepatitis B Surface antigen n= (%)		Hepatitis C antibodies, n (%)		Hepatitis B/C Co-infection	
	HBsAg (+)	OR (95% CI)	HCV ab (+)	OR (95% CI)	HBV/HCV (+)	OR (95% CI)
Divorce	12 (12.1)	1.7 (1.2-4.1)	4 (4.0)	1.4 (1.3-4.0)	5 (5.0)	0.4 (0.1-1.1)
Widowed			3 (3.3)	1.2 (1.0-4.5)	7 (7.1)	0.6 (0.2-4.3)

Table 4. Immunological and virological parameters of HBV-HCV co-infected with 289 HIV drug experience HIV seropositive patients attending FMC Keffi, Nasarawa State, North Central Nigeria.

Parameter	HBsAg status			HBeAg status		
	HBsAg+			HBeAg+		
	Mean	Median (IQR)	P value	Mean	Median (IQR)	P value
Log (HIV Viral Load)	8.98	7.73 (5.8–9.8)	0.022†	9.6	6.84 (5.8–10.8)	0.031†
CD4+ T lymphocyte count (cells/μl)	239.5	200.0 (110.8–390.0)	0.007‡	260.5	130.0 (105.6–298.5)	0.018‡

Table 4. Continued.

Parameter	HCV Ab Status			HBsAg-HCV-Ab Status		
	HCV Ab+			HBsAg+-HCV-Ab+		
	Mean	Median (IQR)	P value	Mean	Median (IQR)	P value
Log (HIV Viral Load)	8.77	4.62 (3.8–5.6)	0.042†	11.67	5.73 (4.9–12.7)	0.073†
CD4+ T lymphocyte count (cells/μl)	275.5	240.6 (130.6–300.5)	0.009‡	185.5	190.6 (131.6–320.5)	0.067‡

†Mann-Whitney U test was used to compare non-parametric variables

‡Independent sample t-test for parametric variables (log [HIV viral load]).

p < 0.05 was considered statistically significant

4. Discussion

With the introduction of ART program in the management of HIV infection, morbidity and mortality rate has declined, but that could be complicated because of other opportunistic infections co-infection with viral Hepatitis B and C in Sub-Sahara Africa where resources are constraint and access to viral load estimation is difficult. This viral co-infection in HIV infected individuals has been associated with increased immune suppression and increase elevated liver enzymes and ART related liver toxicity [15]. Our study reveals overall prevalence rate of HIV-HBV, HIV-HCV, and HIV- HBV- HCV trio-infection at, 9.3%, 12.8% and 6.9% respectively. Our results were in agreement with a meta-analysis study that was carried in Sub-Sahara Africa on viral hepatitis B and C co-infection in HIV patients to be 0% to as 28% with higher prevalence rate reported in West-African countries [16]. Our study conducted in Ghana, where a prevalence rate of 13.0%, and 3.6% respectively was observed in HBV – HC co-infection among HIV patients. Lower prevalence rate was reported in Ethiopia than in Sub-Sahara Africa [17]. Our study in table 2 which is consistent with a study in Ghana that showed a higher HBeAg of 55.6% contrary to the Nigeria study of 70%. In Ethiopia, Manyazewa et al, reported a very low 0.8% *HBeAg) rate among HIV infected adults from a meta-analysis study, as observed, HBeAg status across both developed and developing countries [18].

5. Conclusion

Our study reveals sub-optimal virological level of suppression that requires strong commitment by all USAIDS

program in achieving the 90% target of USAIDS 90-90-90 BY 2020. Low immunological status was observed at age (>40years) with CD4 cell counts of < 250 cells/μl which are associated with Virological suppressions. Age enrollment was negatively associated with immunological outcome at age 18-30years. Urban residency and CD4+ baseline of <200 cells/μl was positively associated. We recommend enrollment on HAART at higher CD4 cell count levels in order to achieve the USAIDS plan of 90-90-90.

Limitations

The Data analyzed in this study is for a sub-population, and may influence the generalizability of this results, compared in a larger population.

Authors Contribution

R. A. J and A. Y. J conceptualized and designed the study, A. I A and JRA analyzed the data, D. T and AC revised the manuscript for intellectual and scientific content, and developed the results and discussion section. A. I. A, A. Y. J and R. A. J reviewed and revised the manuscript. All Authors read & agreed to publish the version of the manuscript

Conflict of Interes

The author declared that there is no Conflict of Interest.

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