HIV-HBV prevalence and Liver Function Profiles in HAART experienced patients at two referral hospitals in Harare, Zimbabwe

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ABSTRACT

HIV-HBV coinfection is common in areas of high HIV endemicity. We screened for HBV and did liver function tests in 111 HIV infected patients. In the study 79(71.12%) were female. The age range was 19 to 62 years and the median age was 42 years. Prevalence of HIV-HBV was 5.4(6/111).There was no association between gender and HIV-HBV co-infection (p=0.527663). The CD cell count was below 200 cells/µl in 37.8% of all the patients. 84.7%of the patients were once exposed to HBV and only 2.7 were vaccinated against HBV. The median CD4 cell count was 274.0 cells/µl.

Key words: HIV-HBV co-infection prevalence, HAART active, HBV exposure, HBV vaccination, CD4+ cell count and ALT.

1 INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) has resulted in marked reduction of Acquired Immune Deficiency Syndrome (AIDS) related mortalities and morbidities (1;2).

Despite increase in life expectancy of HAART active patients, liver diseases such as liver cirrhosis, liver fibrosis and hepatocellular carcinoma (HCC) associated with viral hepatitis are major causes of non-AIDS related mortality representing 10-15% of deaths in HIV infected patients(3;4).

Hepatitis B virus (HBV) and HIV share transmission routes and two most important blood-borne pathogens in terms of prevalence, morbidity and mortality in co-infection in Sub-Saharan Africa (SSA), where both viruses are highly endemic(5). Of the 34 million people living with HIV, 22.5 million live in SSA. Additionally, approximately 65% to 98% of populations in SSA have been exposed to HBV, 8% to 20% being chronic carriers (6) outlying the 4% to 6% lifetime exposure rates and 0.2% to 0.5% carrier rates in low endemicity regions. Consequently, widespread co-infections are possible, with 16% to 98% of HIV positive individuals in SSA being carriers of HBV or showing exposure to HBV (7).

Progression of chronic HBV to cirrhosis, end-stage liver disease (ESLD) ,and HCC is quicker in HIV-HBV co-infected individuals than HBV mono-infected people(8). HIV- HBV co-infection has negative impacts on HIV outcomes including risk of chronic HBV ,higher HBV deoxyribonucleic acid (DNA),milder necroinflamation, increased progression to cirrhosis, decreased efficacy to anti-HBV therapy and increased progression to HCC(9). HIV individuals are 6 times more likely to develop chronic HBV than HIV negative counterparts and are likely to lose previously developed protective hepatitis B surface antibody (HBsAb) thus develop acute HBV infection (10). Prior to the introduction of HAART, many HIV-HBV co-infected individuals were prone to death due to clinical complications associated with HIV compared to HBV (7) (11).Therefore it is important to constantly screen HBV in HAART active population.

The individual prevalence of HIV and HBV in SSA is fairly documented. However, there are limited studies

describing the prevalence of HIV-HBV co-infection. Literature shows large discrepancies in HIV-HBV prevalence across SSA ranging from 4.6% in Nigeria to 12% in Malawi(12). South Africa has been reported to have HIV-HBV prevalence ranging from 5-17% (13;14). This leaves Zimbabwe lagging as it only reported HBsAg seroprevalence ranging from 7.6% and 15 % in HIV individuals initiating HAART and HAART naive respectively (13). HBV screening in the HIV population is not routine in Zimbabwe (15; 16).

The liver is a major organ of the human body mainly functions in bile production, storage of (iron, vitamins and trace elements), detoxification and conversion of waste products for excretion by kidneys. HBV infected people are prone to liver ailments. Furthermore, the hepatotoxic effect of HAART causes liver damage. Approximately 10% of HIV infected individuals develop liver ailments due to the hepatotoxic effect of HAART (17).The major culprit in HAART is nevirapine. Nevirapine forms first line of treatment in Zimbabwe and is received by 60.5 % of HAART active patients as part of a triple combination with tenofovir and lamivudine (18;19). Considerable attention has been focused in administering HAART and effective management of patients.

Liver function tests (LFTs) give information about the state of a patient's liver by measuring different proteins and enzymes produced by liver cells or released when liver cells are damaged(20).Common tests include alanine aminotransaminase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gammaglutamyl transferase (GGT), serum bilirubin and prothrombin time albumin. LFTs reflect different functions of the liver, such as anions excretion (bilirubin), hepatocellular integrity (transaminases) and protein synthesis (albumin) (21).

LFTs help in monitoring patient response to drugs and determination of liver injury development and severity. In resource

limited regions, LFTs are mostly carried out before ART initiation (22). This study aimed to determine the prevalence of HIV-HBV co-infection in HAART active individuals in Harare, Zimbabwe and to assess their liver function profiles.

2.0 MATERIALS AND METHODS

2.1 Study sites and period

This was a cross sectional analytical study to determine HIV-HBV co-infection in adults treated with HAART, their HBV serological profiles and LFTs profiles were assessed. Socio-demographic and clinical information was collected. This study was conducted from February 2015 to January 2016 at two Opportunistic Infection (OI) clinics at Parirenyatwa

Group of Hospitals (PGH) and Harare Central Hospital (HCH) in Harare. These hospitals located are the largest teaching and referral hospitals in the country. Samples were analysed at the Chemical Pathology Research Laboratory (CPRL) at PGH. Patients visit the clinics for routine medical follow up and medication refills. During these visits, patients are routinely monitored for CD4+ cell count .Viral load testing is conducted selectively to verify suspected treatment failure.

These sites were ideal for this study because of the diversity of patients who are enrolled at the clinic and large number of patients on HAART. Furthermore, the CPRL provided an excellent set up in terms of laboratory facilities which were needed in this study.

2.2 Sample collection and processing

Blood samples were collected by venopuncture. Ten millilitres of blood was collected, put into 2 plain tubes labelled with an assigned patient unique identifier corresponding to patient code on questionnaire. Blood was left to clot, centrifuged at 3000 rpm for 5 minutes and serum aliquoted into cryotubes. One cryotube was used for HBV serology and the other one for LFT analysis. Samples for LFT analysis were frozen at -80 ^{0}C for at least six weeks before analysis.HBV serological tests were performed on the day of sample arrival.

To screen for HBV disease, the NOVA one step HBV multi-panel test kit produced by Atlas Link, Inc (Technology Co., Ltd, Beijing, China) was used. The kit

is based on principle of immunoassay combined with conjugated colloid gold technology to detect the five markers

associated with Hepatitis B infection which includes HBsAg, HBsAb, HBeAg, HBeAb, and HBcAb. The activity and concentration of ALT, AST, GGT and total bilirubin (TBil) were determined using the Beckman Coulter AU680 Chemistry analyser (Beckman Coulter, Inc., Mishima, Japan) following the manufacturer's instructions.

2.3 Statistical methods

Data was analysed using the Stata version 13(manufactured by statacorp, Texas, USA). The mean comparison for LFTs and CD4+ counts was using the mean comparison t-test. A p-value of <0.05 was regarded as significant.

2.4 Ethical consideration and patients' enrolment

Ethical approval was granted by Institutional Review Board of the College of Health Sciences Joint Research Ethics Committee (JREC) and Medical Research Council of Zimbabwe (MRCZ). Patients were enrolled on a voluntary basis following detailed informed consent explaining all the aspects of the study. Confidentiality of participants' information was strictly maintained and participants' rights were respected. Laboratory test findings were delivered to the patients and treating practitioner for appropriate patient management.

2.5 Sample size calculation

Expected prevalence (P) of HIV-HBV among HAART active individuals was based on previous studies among patients initiating HAART and assumed to be 7.6%. The precision (d) or acceptable margin of error of the prevalence estimated was set at 0.05. The minimum required sample size at analysis stage was 107.

3.0 RESULTS

3.1 General description of results

Of the 111 participants 79(71.12%) were female. The age range was 19 to 62 years and median age was 42 years. Prevalence of HIV-HBV was 5.4(6/111).There was no association between gender and HIV-HBV co-infection (p=0.527663). The CD cell count was below 200 cells/µl in 37.8% of the subjects. The median CD4+ cell count

was 274.0 cells/µl.

3.2 HBsAg seroprevalence in HAART active patients

HBsAg was found in 5.4% of the patients (fig 3.1). Examination showed that people above the age 30(Table 3.1) were more likely to test positive for HBsAg than those below thirty (p=0.0105).

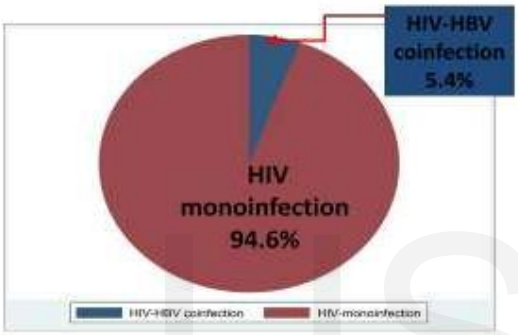


Fig 3.1: HBsAg in HAART active patients

Table 3.1: Distribution of HBsAg by age group

Age groups	Frequency	Percentage
Less than 20years.	0	0
20-29 years.	0	0
30-39 years.	2	33.333
40-49 years.	2	33.333
More than 50 years.	2	33.333
Total	6	100

3.3 HBV exposure, resolved infection (HBcAb) and vaccine response (HBsAb)

Fifteen of 111 participants (13%) were negative for all HBV serological markers. Three of the participants (2.7%) indicated immunity due to vaccination. The remaining 93 (83.7%) had at least one HBV maker (fig 3.2).

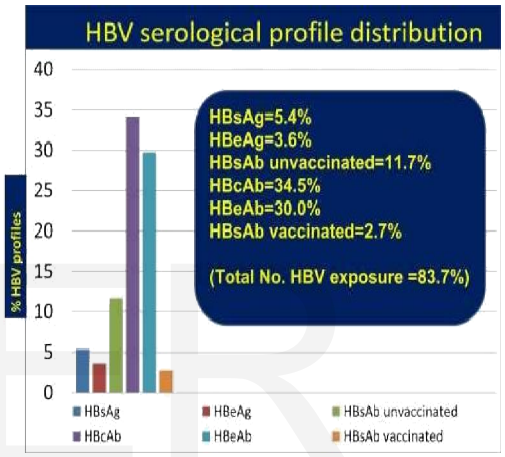


Fig3.2:HBVserological profile distribution

3.4 LFT elevation

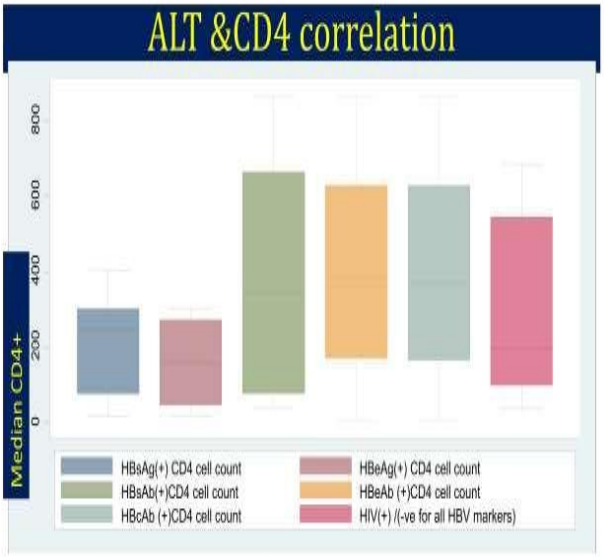
Mild to moderate LFTs were common in subjects who were HBsAg positive (p=0.003).Factors such as one's period on HAART and the use of herbal remedies were not significantly associated with elevation of liver damage markers. Severe LFTs were reported in 2 out of 6 (30%) HBsAg positive participants and HIV-monoinfected counterparts. The levels of GGT were a bit higher in both HBsAg positive and HIV-monoinfected individuals a mean value of

61.84545U/L (Table 3.2). **Table 3.2**: Demographic and clinical characteristics of the participants.

Characteristic	Mean and standard deviation (sd)	Range
Age	42.0±0.93 years	(19-62)
AST	33.78±1.705 U/L	(14-133)
ALT	28.28±1.882 U/L	(9-119)
GGT	61.84545± 6.33652U/L	(9-394)
T-Bil	13.864± 2.916848U/L	(2-285)

ALT and CD4+ cell count comparison between HIV-HBV co-infected and HIV monoinfected individuals.

111 participants were grouped into six serogroups, HBsAg positive 6 (5.4%), HBeAg positive 4 (3.6%), HBsAb 16(14.4%), HBcAb 38 (34.2) %, HBeAb 33(30%) and negative for all HBV serological markers 13 (12%).HBsAg positive individuals had mild to moderate ALT level compared to positive HBeAg individuals(Fig 3.3). HBeAg positive participants had lower median CD4+ cell counts below 200cells/µl while HBcAb positive patients was above 200cells/µl and had median ALT within the normal range (**Fig:3.3**).



Group	A	B	C	D	E	F
n	6	4	16	39	33	13
ALT	22 (13-69)	25 (17-69)	22 (11-69)	21 (11-114)	21 (11-114)	21 (10-45)

Fig 3.3: Box and whisker plot of CD4+ cell counts of the six serological groups (A to E) ‘‘n’’indicates the number of participants in each group. ALT concentration for each group is indicated in the table below the plot as ‘‘Median (Interquartile Range)’.

3.6 Correlation between CD4+ cell count and ALT levels in HIV-HBV co-infected subjects.

There was positive correlation of 0.1534 between ALT levels and CD4+ cell count in HIV-HBV positive patients.

4.0 Discussion

HIV-HBV co-infection was 5.4%. Old age at presentation was a potential predictor of co-infection of HIV and HBV. Mild to moderate liver profiles (>40 to 124) was common in half of the co-infected individuals.

4.1 HIV-HBV co-infection

It is not surprising that 5.4% of subjects infected with HIV were positive for HBsAg. This is in line with the global trends that place Zimbabwe in the high prevalence region for HBV. SSA where Zimbabwe lies has an HBsAg seroprevalence that is above 5% and this is considered as high prevalence. Zimbabwe also has high prevalence of HIV with 15% of the population affected. However, the hepatitis B prevalence of 5.4% is lower compared to statistics from the NBSZ which routinely tests for HBV in blood donors and is the largest database in Zimbabwe for this type information.

Furthermore, the 5.4 % prevalence stands out against the 7.6 to 15% prevalence range found in earlier studies. The differences observed could be mainly attributed to the choice of participants and the time frame of the studies. The studies were done in HAART naive patients and those initiating HAART. Some of the earlier studies done were carried out in the era before ART became freely accessible to eligible patients. The easy accessibility of HAART which most contain lamivudine and tenofovir could have inadvertently resulted in treatment of HBV in co-infected patients and consequently reducing the HBV burden in circulation in the community in whom this study was conducted. It should be taken into consideration that chronicity of HBsAg depends on the immune system and also the age at which one got infected with the virus, information which was not availed in the previous studies. In this study, we did not look at serological markers that could indicate the timing of HBV infection, though the immunity of the patient was assessed based on CD4 cell count. Nevertheless, the immunity of the participants did not significantly affect the chances of being infected with HBV (p=0.675). Assessing the participants for the presence of antibodies against HBV would help to group patients that tested negative for HBsAg as previously exposed. Determination of chronicity was not done in this study.

Age (above 30years) was also associated with being HBV positive (p=0.012). Previous studies have reported that HBsAg is common in elder patients. This was probably due to the depreciation of the immune system as one gets old and hence the inability to clear the virus. On the other

hand, these patients might have contracted HBV during their early ages, but due to the limitation of resources we could not verify whether it was acute or chronic infection and also the patients were not aware of their HBV status.

Knowledge regarding the prevalence of HIV-HBV co-infection in our setting where the roll of HAART program is still in progress is extremely important. This is because such information can be used as important tool in guiding policy marker into making HBV testing a routine test for all HIV infected patients whether HAART active or HAART naive. HBV testing in HIV infected patients has become a routine practice in developed nations including United States of America and the majority of European countries (15). Aspects in favour of routine HBV testing in HIV infected patients include the need to optimise choice of drugs that facilitate the clearance of HIV and HBV at the same time getting rid of those drugs that aggravate hepatotoxicity in HIV-HBV infected individuals.

4.2 HBV exposure, resolved infection (HBcAb) and vaccine response (HBsAb)

Fifteen (13%) of the 111 participants lacked all HBV markers, ruling out exposure and/ or infection and with no HBsAb. These patients were susceptible to acquiring HBV infection. In this group of 111 HAART active Zimbabwean adult patients, 93 participants had at least one HBV marker, giving an overall exposure of 83.7%. In addition, only 3 (2.7%) of the total recruited patients were vaccinated against HBV. This means in Zimbabwe vaccination against HBV is not optimal and there is need to introduce HBV vaccination in HIV infected patients since there are at great risk of contracting HBV due to the shared routes of transmission of the two viruses. HIV positive persons have 3 to 6 fold higher risk of becoming chronic carriers if they become infected with HBV compared to HIV negative controls, and this provides additional rationale for using HBV vaccine in HIV-infected patients. The advisory Committee on Immunization Practice (ACIP) of the United States (US)

Centre for Disease Control (CDC) recommends that all HIV infected individuals be vaccinated against HBV. Standard vaccination series are given at 0, 1, and 6 months. Although accelerated vaccine schedules currently are not recommended for HIV-infected individuals, a seroconversion rate of >60% at 12 months was demonstrated with a rapid vaccination schedule of 0, 1, and 2 months with double-dose 40 µg HBV vaccine. That may be an attractive schedule for some providers and vaccine recipients. Given the lower antibody response rates in HIV-infected individuals, HBV surface antibody titers should be checked 1 month after the vaccine series is completed to ensure seroconversion. In addition, there is also need to optimize HBV vaccination in HIV negative population.

4.3 LFT elevation

Liver function profiles, albeit, not severe was common in all the participants that tested positive for HBsAg. The liver enzymes were also elevated in HIV-monoinfected participants. Mild liver enzymes as measured by ALT, AST and GGT was common in all HBsAg positive patients (p=0.03).Two HBsAg positive patients had deranged GGT (>100).GGT elevation in these patients was probably due to multi-drug therapy.

Severe LFT elevation was not common and was not unexpected as some of the participants studied had poor immunity 37.8% having a CD4 cell count less than 200cells/µl. HBV on itself is not directly cytopathic. Poor immunity leads to failure of the body to launch inflammatory response against HBV and this failure of the immune system spares the body from adverse hepatotoxicity that would manifest as severe liver enzyme and T-Bil derangement had the immune system been stronger. It is therefore not surprising that LFTs were not severely elevated in majority of the participants who were HIV-HBV co-infected.

4.4 correlation between CD4 cell count and ALT levels in HIV-HBV co-infected subjects.

There was positive correlation between ALT levels and CD4 cell counts in

HBsAg positive participants. Their median CD4 cell count was approximately 200cells/µl and their ALT levels were within the normal range and this is because HBV does not cause hepatic damage unless the host immune system is intact. This can also be an addition in explaining why most of the participants had their LFTs in the normal range.

5.0 Conclusion

HIV-HBV co-infection is common among patients attending HCH and PGH OI clinics. Severe elevalation of LFTs, unlike mild to moderate LFT elevation is not common among HIV-HBV co-infected and also HIV mono-infected HAART active patients. As a result of a relatively high prevalence of HIV-HBV co-infection, it would be advisable to routinely test all HIV patients for HBV co-infection in order to optimise HAART. From this study it was also found that vaccination against HBV is not optimal in Zimbabwe.

6.0 Acknowledge

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7.0 Conflict of interest

The author declares no conflict of interests.

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