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Hepatitis B Virus Co-Infection: Yet Another Reason for Early Initiation of Treatment in HIV Infected Individuals[*]

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ABSTRACT

Background: Hepatitis B virus (HBV) co-infection with HIV is becoming a major challenge due to shared routes of transmission. The burden is apparent in regions with widespread use of antiretroviral treatment, which led to the enhanced emergence of liver-related diseases and mortality. Though there are conflicting results about the effect of chronic HBV infection on response to highly active antiretroviral therapy (HAART) (CD4$^+$ cell count and HIV viral load, HIV RNA copies/ml), HAART is known to cause immune mediated HBV specific liver damage after it reconstitutes cell-mediated immunity. The relationship of different HAART regimes with immune recovery is an area of research interest. **Objective:** It is in order to determine the changes in immune recovery during HBV infection in the setting of HAART among HIV positive individuals attending care and treatment services. **Methods:** Two cohorts of co-infected patients were analyzed from data of one to seven months retrospectively. The first group (n = 380) was antiretroviral drug naive and the second cohort (n = 380) was on HAART for the entire period. The study was conducted in one referral hospital and six health centers. Data were gathered from 760 patients using their intake form, their follow-up form and their medical records supplemented by data from a structured questionnaire. HBV infection was determined by using HBsAg rapid and confirmatory tests and CD4 cells were enumerated by using laboratory registers and patient cards. Bivariate and multivariate logistic regressions were done by using SPSS Version 18 and Epi info Version 3.5. **Results:** Poor immune recovery due to HBV infection was improved after initiation of HAART. Before the initiation of HAART, the mean CD4 cell count of HBV infected individuals was lower than that of non-HBV infected ones, 234/mm^3 and 384/mm^3, respectively (p < 0.05). Individuals co-infected with HBV had experienced delayed recovery of immune cells (CD4 cell count). However, after, on average, more than two years of therapy, the association is reversed. In addition to HBV infection, CD4 cell count of patients on chronic HIV care/pre-ART was decreased by older age, living in rural areas and previous opportunistic infections. **Conclusion:** HBV infection has different outcomes between pre-ART and ART-initiated individuals. In the former cohort, HBV infection causes significant delays in immune recovery which is reversed after initiation of anti-HIV treatment. HBV co-infection has a significant and immediate negative effect on CD4 cell counts and immune recovery before HAART but such effects slowly subside after initiation of the treatment. As a result, HBV infection is another issue to consider for swift initiating of HAART for HIV infected individuals in long-term care.

Keywords: HAART; CD4 Cell Count; HBsAg; HBV/HIV Co-Infection; Immune Recovery

1. Introduction

Since the introduction of highly active antiretroviral treatment (HAART) for treatment of HIV, morbidity and mortality have decreased greatly in HIV-infected individuals. However, the management of other non-HIV associated chronic diseases in HIV patients has become increasingly important. In this regard, Hepatitis B virus (HBV) co-infection with HIV is still a major challenge [1,2].

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HBV is the leading cause of chronic liver disease and liver-related death worldwide, with the majority of these cases occurring in areas of Africa and Asia where HBV prevalence is high with population prevalence sometimes over 8%. Around the world, 90% of HIV-infected persons have biological signs of prior HBV infection and 5% - 15% suffer from chronic infection [3]. As a consequence, 2 - 4 million of the 34 million people living with HIV globally also have chronic HBV infection [4]. Conditions associated with hepatitis B and C infections are currently among the leading causes of hospital admission of HIV infected individuals, and recent studies have shown increasing rates of liver disease and related death among those with HIV [5].

Infections with HIV and HBV are often shared because of similar routes of transmission (sexual intercourse, blood transfusion) [3]. Many countries with a high HBV disease burden are also affected by a high HIV burden, leading to frequent HIV/HBV co-infection [6]. The impact of HIV and HBV co-infection is especially apparent in regions with widespread use of HAART. Studies have showed that in HIV-HBV co-infected patients, HBV increases HIV replication, ART related hepatotoxicity and delays immune recovery (CD4$^+$ cell count) [7].

A study on extra-chromosomal HBV-DNA in peripheral mononuclear cells has found that this type of HBV-DNA is more prevalent among AIDS patients than that among asymptomatic HIV carriers. Another *in vitro* study has demonstrated that HBV-X protein (HBx) super-induces ongoing HIV replication and HIV-1 long-terminal repeat (LTR) transcription. These findings suggest that HBV could alter the course of HIV infection, inducing faster progression to AIDS [8]. HIV in turn increases HBV carriage rates, increased replication, hepatitis flares, progression to chronic HBV infection and end stage liver disease (cirrhosis and hepatocellular carcinoma). It also increases the number and frequency of reactivation episodes. [9]. Cirrhosis due to HBV is more common in co-infected patients than those mono infected by HBV despite low ALT levels [10,11]. The annual risk of developing cirrhosis during HBV infection appears to be much higher in those co-infected with HIV. This may be especially true in those with low CD4 counts [12]. Data of such HBV-HIV interaction in different settings and geographical areas are limited.

There are conflicting results about the effect of chronic hepatitis B on the response to HAART (CD4$^+$ cell count and HIV viral load, HIV RNA copies/ml). A cohort study in Italy has showed increasing divergence of mean CD4 lymphocyte counts up to 36 weeks after HAART initiation between patients with and without chronic hepatitis B as compared to those with chronic hepatitis B having a lesser CD4 increase (P = 0.03) [13]. In a cohort study in Denmark HBV infection sero-status is observed to have no effect on the response to HAART in terms of HIV viral load suppression and CD4$^+$ cell count [3]. Similar findings were documented in Nigeria where HIV RNA suppression and absolute CD4 rise were found to be similar between HBsAg positive and negative patients started on HAART [14].

HAART in turn was associated with immune mediated HBV specific liver damage after HAART-reconstituted cell-mediated immunity [9,15]. As the potential of chronic hepatitis B to blunt immune recovery after initiation of HAART is an area of special relevance to low-income settings in Africa and Asia, which comprises the countries with high HBV endemicity, more studies are needed to characterise the effect of chronic hepatitis B co-infection on CD4 lymphocyte recovery during antiretroviral therapy. If reduced immune recovery is found to occur more frequently in co-infected populations, current WHO guidelines for antiretroviral monitoring may be sub-optimal [6].

Despite these mounting challenges, HIV/HBV co-infection in the setting of HAART and immune recovery is not explored at large in Ethiopia. So the intention of the current study is to determine whether there is a need for early screening and treatment for HBV among HIV patients as well as its ultimate effect on immune recovery before and after initiation of HAART.

2. Materials and Methods

2.1. Patient Selection

Two cohorts of patients were chosen retrospectively from a database of patients followed in the ART units of Debre Berhan Hospital and six health centers (Shewarobit, Debresina, Mendida, Deneba, Enewary and DebreBerhansix Health Centers, North Shoa Zone, Amhara, Ethiopia). These patients are previously identified as HIV infected individuals. A total of 760 patients, all of them above the age of 15 years, were included in the study. Blood specimens were collected during the course of routine clinical follow up, other clinical and socio-demographic data were obtained from patient interviews and follow up chart, and Debre Berhan University Institutional Ethical Review Committee approved the research. Oral consent was obtained from each participant after the purpose, confidentiality, protection and anonymity of the research was explained.

The cohorts are defined as;

HAART naive—380 HIV infected individuals that did not initiate HAART throughout the study period (*three months*).

HAART initiated—380 HIV infected individuals that were on HAART at the baseline and for the entire duration of the study which lasts for three months.

Exclusion criteria: HIV patients under the age of 15 years and with less than three months of follow up were excluded from analysis.

2.2. HBV Infection Determination

Serological testes for determining HBV infection were done by detecting the presence of HBsAg presence in patients serum with SD HBsAg rapid test kit (SD Company, Korea), and positive results were confirmed with HBV confirmatory reagent AxSYM HBsAg (Abbott AXSYM System, ABBOTT Diagnostic division, Germany) according to the manufacturer's manual.

2.3. CD4 Cell Count

CD4 cell count of patients was done with FACS counter as cells/mm^3 (BD FACSCount™ System, (BD Biosciences, 2350 Qume Drive, San Jose, CA, United states of America) The mean CD4 cell count of patients was calculated as the average numbers of CD4 cell count of an individual for the period in follow up calculated by adding all CD4 counts in patients follow up chart and divided by the number of counts.

2.4. Statistical Analysis

Data was entered, cleaned using EPI INFO software and analyzed using SPSS 18. Both descriptive and analytical statistical procedures were employed. Univariate, Bivariate and multivariate logistic regressions with relative risk (RR) along with the 95% confidence interval were used to ascertain the association between covariates and dependent variables. Fisher exact tests, analysis of variance, correlation and relative risk (RR) were used to assess the relationship between HIV/AIDS patient's characteristics and immune recovery (CD4 cell count).

Logistic regression was carried out to determine adjusted effect of each factor on immune recovery. Variables with more than two categories were entered in to the model in the form of two "indicator" contrasts comparing each category to the first group as reference. A backward stepwise procedure based on the likelihood ratio was used to select the variables included in the final model. The significance for variable removal and entry was set to 0.10 and 0.05 respectively. The Hosmer and Lemeshow test was used to check the goodness-of-fit of the model. Only covariates that were statistically significant at the bivariate level were included in the multivariate binary logistic regression to control for confounding. Though many variables were included in the analysis, only covariates significantly associated with dependent variable were considered. Risk Ratio (RR) and 95% confidence intervals were derived from each variable coefficient in the final model. The significance of each coefficient was tested by the Wald test.

3. Results

3.1. Socio-Demographic and Clinical Characteristics of Study Population

A total of 760 HIV-positive adults, 50:50 Pre-ART and ART initiated, were included in the analysis of this study; the study participants composed of 61.6% females and 80% live in urban areas, half of these without a secure source of income. Half of them were without a secure source of income.

According to the current study, 182 (23.9%) had been treated for TB and one out of five HIV-infected individuals developed pulmonary tuberculosis. According to the medical history, 372 (48.9%) individuals developed opportunistic infections, 308 of whom are currently taking cotrimoxazole.

3.2. Clinical Characteristics of HIV Infected Individuals on Pre-ART and ART Follow-Up

The average enrolment of pre-ART cohort in chronic HIV care was ≤6 months (54.2%), 7 - 12 month (15.7%), 13 - 24 months (18.9%), and ≥24 months (11%) from whom 172 (46.6%), had CD4 cell count ≥ 350 cells/mm^3.

In the ART initiated cohort same number of patients was followed for, on average, 28 ± 17.4 months. Half of them had been on ART for ≥24 months (2 years), 17.6% of individuals started ART at a very low baseline CD4 cell count, <50 cells/mm^3 and only 40% started at the right time (baseline CD4 count of 101 - 200 cells/mm^3). In addition, adherence was based on self-report, functional status (working status), as well as type of regimen a patient is taking and whether there was a substitution was assessed.

3.3. Immune Recovery in the Pre-ART Cohort

According to the results of the current study, an infection with HBV did greatly decrease the CD4 cells of HIV co-infected individuals and further increase the progression of HIV infection. CD4 cell count records were found from 94% of the patients. Each CD4 cell count was the average value of all CD4 cell counts registered on the patient's follow up card for the whole duration the patient was enrolled in chronic HIV care. A CD4 cell count of ≤200 cells/mm^3 was positively associated with HBsAg seropositivity (P = 0.02) in which individuals co-infected with HBV had experienced delayed recovery of immune cells. In those individuals, the likelihood of a low CD4 cell count (≤200 cells/mm^3) was 2.55 times higher in those with a positive HBsAg test result (RR = 2.55, 95% CI: 1.49 - 4.38).

The mean CD4 cell count of HBsAg positive and negative Pre-ART individuals also showed that the mean CD4 cell count of HBsAg negative study subjects was

higher than that of HBsAg positive individuals, 384/mm^3 and 234/mm^3 respectively(P = 0.02, 95% CI: 229, 531) (**Figure 1**).

In addition to Hepatitis B virus infection, CD4 cell count of patients on chronic HIV care/pre-ART was decreased by older age, living in rural area and previous opportunistic infections (**Table 1**).

3.4. Immune Recovery in the ART Cohort

In contrast to the Pre-ART cohort, the relationship between HBV infection and immune recovery was reversed. In our research, it was found that after initiation of HAART, the effect of HBV infection on CD4 cells was halted. The CD4 count of individuals for the whole duration of initiated ART indicated that 151 (39.7%) had CD4 cell count ranging from 201 - 350 cells/mm^3. The true population mean was estimated to be 249 ± 8, (95% CI: 170, 326).

In those cohorts, the median CD4 cell count of patients was 249 cells/mm^3 ranging from 19 to 1068 cells/mm^3.
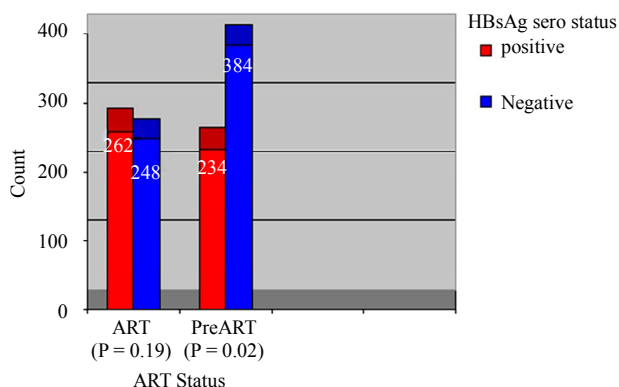

Figure 1. Mean CD4 cell count by HBsAg sero status of HIV infected individuals, North Shoa Zone, 2012.

The results indicated that individuals with a positive HBsAg test had relatively a higher mean CD4 cell count than those with negative HBsAg test result, 262 cells/mm^3 and 248 cells/mm^3 respectively. But the difference was not statistical significant (P > 0.05) (**Figure 1**). Besides HBV infection, CD4 recovery induced by HAART was boosted by high baseline CD4 count, ≥50 cells/ mm^3 (P = 0.00) and long duration of HAART, >2 years (P = 0.00). In the contrary any substitutions in the first line regimen (P = 0.02) and current usage of cotrimoxazole (P = 0.00, RR: 6.51, 95% CI 2.73, 15.55) halted CD4 cell recovery after initiation of HAART (**Table 2**).

The authors compared the prevalence of HBV-HIV co-infection among ART cohorts on different treatment regimens. The result indicated that though only 25 (6%) of the total 380 ART initiated study groups were taking TDF-3TC combined regimen, they accounted for 10% of HBsAg positive individuals, high proportion than any other regimen.

4. Discussion

By categorize HIV patients in two cohorts based on initiation of HAART, the current study identified important clinical difference with respect to Immune recovery when HIV patients are co infected with HBV. In the first cohort, Pre-HAART individuals, significant decrement of CD4 cell recovery was sought in HBV co infected subjects, Adjusted P = 0.02 [ARR: 5.97; 95% CI: (1.32, 27.04)] consistent with previous studies. A study reported in the international AIDS society conference that HBV infection independently reduce CD4 cell recovery [7-16]. In contrast two longitudinal studies from Britain did not show any impact of HBV co-infection on CD4 depletion, progression to full-blown AIDS, or AIDS induced mortality. However, these studies suffer from

Table 1. Multivariate logistic regression analysis of variables associated with immune recovery (CD4 cell count) in patients at Pre-ART cohort, North Shoa Zone, 2012.

Characteristics	Response	CD4 count among patients		Crude RR (95% CI)	Adjusted RR (95% CI)
		≤200 cells/mm^3	>200 cells/mm^3		
HBsAg sero-status	Positive	6	82	2.55 (1.49, 4.38)	5.97 (1.32, 27.04)[*]
	Negative	4	267		
Age	15 - 25	11	84		
	>25	77	188	2.52 (1.40, 4.52)	2.47 (1.14, 5.36)[*]
Residence	Urban	61	226		
	Rural	27	45	1.76 (1.22, 2.56)	2.58 (1.41, 4.73)[*]
History of previous opportunistic infection	Yes	43	63	2.28 (1.60, 3.24)	2.81 (1.64, 4.81)[*]
	No	45	208		

[*]*Significant at P value* < 0.05.

Table 2. Multivariate logistic regression analysis of variables associated with immune recovery (CD4 cell count) in patients at ART cohort, North Shoa Zone, 2012.

Characteristics	Response	CD4 count among patients		Crude RR (95% CI)	Adjusted RR (95% CI)
		≤200 cells/mm^3	>200 cells/mm^3		
HBsAg sero-status	Positive	6	82	0.71 (0.36, 1.41)	0.48 (0.16, 1.43)
	Negative	4	267		
Duration on ART	≤2 years	103	77		
	>2 years	54	146	0.48 (0.39, 0.60)	0.32 (0.19, 0.54)
Baseline CD4	<50	45	18		
	≥50	112	205	0.47 (0.38, 0.58)	0.14 (0.07, 0.29)
Are you currently taking Cotrimoxazole?	Yes	150	158	4.38 (2.25, 8.51)	6.51 (2.73, 15.55)
	No	8	64		
Substitution in the first line regimen	Yes	13	39	0.57 (0.35, 0.92)	0.41 (0.19, 0.88)
	No	145	183		

small sample size and lack of baseline CD4 cell count [15]. HBV could affect CD4 recovery either directly or by increasing HIV replication [7]. Such changes point out the importance of screening for HBV co-infection regardless of the individual's CD4 cell level and consider management options for co-infected cases. Additional parameters to consider include old age (Adjusted P = 0.02 [ARR: 2.47; 95% CI: (1.14, 5.3)]) and rural residence (Adjusted P = 0.00 [ARR: 2.58; 95% CI: (1.41, 4.73)]) both of which were found to independently halt immune recovery. The consequence of older age could be explained by a possible decrease in memory T-cells and lower naïve CD4 cell production in the course of time [17].

In HAART-initiated cohort, the effect is halted or insignificantly reversed. Individuals with a positive HBsAg test had relatively a higher mean CD4 cell count than those with negative HBsAg test result, 262 cells/mm^3 and 248 cells/mm^3 respectively. Though a slight increase in mean CD4 cell count was observed in HBsAg sero-positive individuals, the difference was not statistically significant (P > 0.05). The repression of the HBV effect on CD4 recovery after initiation of ART could be the result of boosting immunity and a consequent diminution of the HBV suppressive action. In the study of Chang and colleagues, HBV was found to have no effect on CD4 cell loss [18]. In Thailand, a cohort study showed that CD4 lymphocyte increases were similar regardless of hepatitis B status. A similar absolute CD4 cell rise between HBsAg positive and negative individuals who are started HAART was also found in Nigeria [6,15,16,19]. In this group high baseline CD4 cell level (>50 cells/mm^3) and long duration of therapy (more than 2 years) were found to boost patients CD4 cells, (P < 0.001). A unit increase

in baseline CD4 cell count will result in a 0.56 increase in each CD4 cell count after initiation of HAART (correlation coefficient, r = 0.56, P < 0.00). The type of primary regimen a patient start with did not have an effect on the expected immune recovery, a critical finding for clearing the confusion for putting regimen preferences based on their difference on effective increment of CD4 cells. Other studies reported similar findings [17,20] so physicians and patients should select the type of regimen based on the adverse effect and contraindication profile of treatment regimens but their difference in increasing CD4 cell counts.

In the current study, prevalence of HBV was also assessed in the two cohorts. Accordingly the prevalence of HBV co infection was two times higher in HAART initiated cohort, 5.3% versus 2.6%), a rate comparable with the prevalence in the general population and other studies done elsewhere. In a study done in Thailand, a chronic HBV prevalence of 8.7% was reported among patients receiving ART, consistent with the population prevalence of Thailand (5% - 10%) [6]. Though it is difficult to explain the higher rate of HBsAg positivity among ART initiated individuals, it may be explained by the fact that a nucleoside anti HBV drug like lamivudine requires a long term treatment to achieve HBsAg clearance or sero-conversion to anti-HBsAg. After short-term treatment, clearance could be achieved only in <5% of patients [21]. So if complete suppression was not achieved during treatment, then rather quickly resistance commences. It is reported that within the first year of treatment, 20% patients on lamivudine may develop mutation resulting in loss of activity on HBV [18]. In addition HIV could also reduce efficacy of anti-HBV therapy, including the risk of lamivudine resistance and decreased response to In-

terferon α [7]. In addition, we reported that type of first line regimen lacks association in contrary to the expected effect of Lamivudine on HBV clearance. In addition we have found that though only 25 (6%) of the total 380 ART initiated study groups were taking TDF-3TC combined regimen, they accounted for 10% of HBsAg positive individuals, high proportion than any other regimen. As we recalled otherwise this finding challenged importance of combination therapy containing tenofovir and lamivudine as part of combination antiretroviral treatment as it is superior in terms of HBV DNA suppression than was tenofovir or lamivudine administered alone. Since the mean duration of ART follow up was 28 months (more than 2 years), it was possible to explain such findings with emergence of mutant strains [7,15,18, 21,22]. But emergence of resistant mutation should be decided after a detectable HBV viral load measured as HBV DNA copies in serum or plasma.

5. Conclusion

This study analyzes the effect of HBV co-infection in HIV patients on immune recovery before and after initiation of HAART. We have shown that HBV co-infection has a significant and immediate negative effect on CD4 cell count and affiliated immune recovery before HAART but such effects subside after initiation of the anti-HIV treatment. As a result, HBV infection is another important issue to consider for rapidly initiating HAART among HIV-infected individuals in chronic care. Whether such drug resistance strains of HBV do exist, as also reported by other studies, as well as its effect on immune recovery, CD4 cell count requires further studies.

6. Acknowledgements

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