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Research Article

HIGH LEVEL OF OCCULT HEPATITIS B VIRUS INFECTION IN TREATMENT-NAÏVE HIV INFECTED PATIENTS IN COTONOU, BENIN

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Abstract- Human Immunodeficiency Virus (HIV) and Hepatitis B virus (HBV) infections share the same routes of transmission and are both endemic in sub-Saharan Africa. Proper management of these infections require reliable diagnosis of co-infected patients. We aimed to assess the magnitude of HBV infection in treatment-naïve HIV infected patients in Cotonou.

This cross-sectional study was conducted from July 2014 to January 2015 on consecutively recruited treatment-naïve HIV infected patients attending the National Reference Center for Research and Management of HIV infection. Blood was collected from each patient for detecting HBs antigen (HBs Ag) by ELISA, HIV viral load, HBV viral load and CD4 counts.

In total, 133 patients were included with a mean age of 38.3 years and a male to female ratio of 1.0:2.0. HBs Ag was positive in 15 (11.3%) of the patients while HBV viral load was detected in 52 (39.1%). The rate of occult hepatitis B (OBI) e.g. negative HBs Ag but positive HBV viral load was 27.8%. Patients with OBI were more likely to have low HBV viral load ($p < 0.001$) than those without OBI.

In conclusion, the prevalence of OBI is high among treatment-naïve HIV infected patients in Cotonou. Universal access to molecular tests is needed in the country to detect HBV infection in these patients.

Keywords- HBV, HIV, Occult hepatitis, Benin.

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Introduction

In 2015, the World Health Organization (WHO) estimated that about 34 million people were infected with the human immunodeficiency virus (HIV) worldwide [1]. Sub-Saharan Africa is the most affected area with 70% of all persons infected [1]. Similarly, hepatitis B virus (HBV) infection is also a global public health problem. About 257 million people live with HBV, particularly in sub-Saharan Africa[2]. Thus, the prevalence of HIV / HBV co-infection is high in this region, favored by the fact that both virus share the same routes of transmission [3, 4].

Patients with HBV and HIV co-infection are about four times at risk of developing cirrhosis than those without HIV infection; furthermore HIV facilitates faster progression of liver disease to hepatocellular carcinoma [4, 5]. Therefore, diagnosing HBV infection in all HIV infected patients is crucial for appropriate management of patients since only few antiretroviral drugs are active against the two virus [6].

Tools available for diagnosing HBV infection are either serology or molecular tests. In developing countries such as Benin, information available on HBV infection in HIV infected patients are generally limited to serology tests that lack sensitivity compared with molecular tests[7, 8].

In this study, we used both serology and molecular tests to determine the magnitude of HBV infection in treatment-naïve HIV infected patients in Cotonou Benin Republic, West Africa).

Materials and Methods

Setting: Benin is a country with a size of 114,763 square kilometers and an estimated population of 10.9 million [9]. HIV prevalence rate among adults is 1.1%[10]. National data for HBV infection is not available although, a study in selected pregnant women in the northern part of the country reported a prevalence rate of 15.5% [11]. Cotonou is the biggest city in the country where the National Reference Center for Research and Management of HIV infection is located.

Subjects: This cross-sectional study was conducted from July 2014 to January 2015. All treatment-naïve HIV infected adults (18 years and above) attending the National Reference Center for Research and Management of HIV infection were recruited into the study.

Samples: Venous blood was collected from each subject into two tubes. Ethylenediaminetetraacetic acid (EDTA) tubes were used to collect blood for whole blood analysis (CD4 count) and plasma separation (viral load measurement) while plain tubes were used for serum separation (serology).

Tests: All tests were performed and interpreted according to manufacturer's instructions. Internal quality controls were performed for each run of tests. HBs Antigen (HBsAg) was detected using Monolisa® HBs Ag Ultra (Biorad, France) while HIV screening was performed using rapid immuno-chromatography-based tests: Alere Determine HIV-1/2® (Alere Medical, Japan) for screening while samples that were reactive were confirmed by Immuno Comb HIV 1&2 BiSpot® (Orgenics, France).HIV viral load was measured by NucliSens® v2.0 assay (Biomerieux, France) after RNA extraction of total nucleic acid with miniMAG® extractor (Biomerieux, France).HBV viral load measurement was carried out using Cobas TaqMan® 48 (Roche Diagnostics, USA) after high pure extraction. CD4 count was done using Partec CyFlow® Counter (Partec GmbH, Germany).

Data analysis: Data were analyzed using EpiData 3.1.Chi-square test was used for comparison and p-value < 0.05 was considered significant.

Results

A total of 133 HIV-infected patients were enrolled in the study with a mean age of 38.3 years and a male to female ratio of 1.0:2.0. The mean CD4 count of patients was 168.2 cells/µL.In total, 6 (4.5%), 33 (24.8%) and 94 (70.7%) of the patients had HIV viral load of 1.6-3.0, 3.1 -5.0 and ≥ 5 Log_{10} copies/mL respectively. None of the patients had ≤1.5 Log_{10} copies/mL.

As shown by [Table-1], HBs Ag was positive by serology in 15 (11.3%) while HBV DNA was detected by PCR in 52 (39.1%) of the patients. None of them had positive HBs Ag without a positive PCR result while 37(27.8%) were positive by PCR but negative by serology. Thus, the rate of occult hepatitis B (OBI) e.g., negative HBs Ag but positive HBV DNA in the study population was 37/133 (27.8%).

Table-1 *Comparison between serology for detecting HBs Ag and PCR for detecting HBV DNA*

HBs Ag	PCR		Total
	Positive	Negative	
Positive	15	0	15
Negative	37	81	118
Total	**52**	**81**	**133**

As shown by [Fig-1], 23 (62.2%) of the patients with OBI had a positive HBV DNA but less than 1.5 Log_{10} copies/mL while 11 (29.7%) had HBV DNA between 1.6 and 3Log_{10} copies/mL, and the remaining 3 (8.1%) had HBV DNA >3 Log_{10} copies/mL.

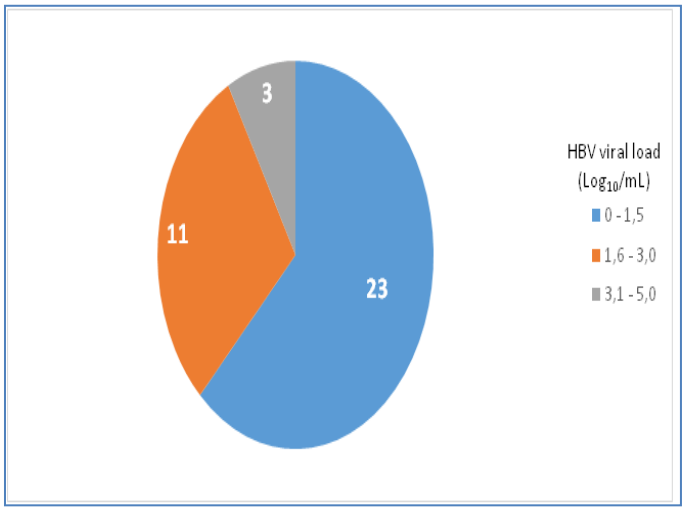

Fig-1 Distribution of HBV viral load in patients with OBI

Patients with OBI were more likely to have low HBV viral load than those without OBI (p < 0.001) but there was no statistical differences between patients with OBI and those without OBI on the levels of HIV viral load and CD4 counts [Table-2].

Table-2 *Comparison between patients with or without OBI*

	Occult hepatitis B infection		
	Yes	No	P
HBV viral load (Log_{10}/ mL)			
0 - 1.5	23	1	**p < 0.001**
1.6 - 3.0	11	2	
> 3	3	12	
HIV viral load (Log_{10}/ mL)			
0-3.0	2	0	**p = 0.57**
3.1 - 5.0	4	1	
> 5	31	14	
CD4 (cells/ µL)			
0 - 200	21	12	**p = 0.15**
200 - 350	12	1	
> 350	4	2	

Discussion

Due to the high prevalence of HBV/HIV co-infection in sub-Saharan Africa, its' burden needs to be assessed in each setting for proper programmatic management of both diseases. At individual level, diagnosing HBV infection in an HIV infected patient is crucial for choosing an appropriate antiretroviral therapy and treatment follow-up [6, 7].

In this study, using molecular tests, the prevalence of HBV infection in treatment-naïve HIV infected patients in Cotonou was 39.1%. The prevalence found in this study is high compared with findings from other studies within the sub-region [12, 13, 14]. Differences in prevalence rates depend on the HBV infection prevalence in general population and also on the sensitivity of the PCR technique used.

The prevalence rate of 27.8% for OBI obtained in this study was higher than the 15.1% and 21.3% reported in Khartoum, Sudan and Abidjan, Côte d'Ivoire respectively [15, 16]. Occult hepatitis B infection rate is also dependent on the population studied, the sensitivity of the molecular as well as the serology tests used. Among HIV patients however, several studies conducted worldwide have reported prevalence of OBI ranging from 0% to more than 88% [7, 8]. High OBI rate observed could be due to false positive HBV viral load results. This is unlikely to have occurred in our study since all tests were performed and interpreted in accordance with the manufacturer's instructions and all internal quality controls gave expected results.

From our study, patients with OBI were more likely to have low HBV viral load. This finding may be due to the lack of sensitivity of serology tests compared with molecular tests that amplify the DNA before detecting it [7, 8]. For detecting HBs Ag, ELISA, which is known to be the gold standard, was the serology test used. Other tests such as rapid immuno-chromatography-based, which are very common in low-resource countries might lead to a higher OBI rate since these tests lack sensitivity compared with ELISA [17].

The fact that OBI rate in HIV infected patients is high may be linked to a complex relationship between infections with both virus and immunity. However, we found no relationship between OBI and HIV viral load and CD4 counts. Nevertheless, the level of HBV replication in these patients is low. The clinical significance of this low replication needs further studies.

Access to molecular tests have been a bottleneck for managing some infections such as HIV infection in developing countries. In fact, these tests are either expensive or required sophisticated equipment, highly qualified personnel and specific infrastructure. Recently, more affordable and simple to implement technology such as GeneXpert has been developed, allowing universal access of molecular diagnosis of tuberculosis in developing countries with high burden of the disease [18, 19]. Universal access to molecular diagnosis and follow-up is thus possible for HIV and HBV infections.

This study has some limitations.

1. Firstly, though all patients included in the study were treatment-naïve HIV infected, they were mostly immunocompromised since the mean CD4 counts was 168 cells/ µL. In fact, we found no relationship between OBI and CD4 counts but could not exclude that the rate might be different in

less immunocompromised patients.

2. Secondly, in OBI positive patients, it was not possible to differentiate those who were at the initial phase of HBV infection. These patients were not truly OBI positive since serology might become later positive if the test was repeated after few weeks. The number of such patients is probably low in our study since the mean CD4 counts of HIV infected populations studied was low, suggesting that HIV infection in those patients is not recent. They may have probably been infected with HBV either at birth or during infancy (as commonly found in this region) or at the same time with HIV and may not be at the initial phase of HBV infection.

In conclusion, the prevalence of OBI is high among treatment-naïve HIV infected patients in Cotonou. Serology tests lack sensitivity to diagnose HBV infection in these patients and molecular tests should be used instead, stressing the need for universal access to these tests in HBV high endemic countries.

Abbreviations: OBI (Occult hepatitis B infection)

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Author contributions:

- Affolabi Dissou: Conception and design of the study, analysis and interpretation of data, drafting the paper, revising the paper
- Frederic Sogbo, Desiree Metodakou, Barnabe Lafia, Jeanne Orekan: Performing laboratory tests, revising the paper
- Raïmi Kpossou, Faridath Massou, Aderemi Kehinde, Marcel Zannou: Analysis and interpretation of data, revising the paper

Ethical considerations: The study was approved by the National Ethics Committee of Benin and written informed consent was obtained from all participants.

Conflict of Interest: None

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