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ORIGINAL ARTICLE

Impact of Highly Active Antiretroviral Therapy on Chronic Hepatitis B Serological Markers among Senegalese HIV Co-infected Children

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ABSTRACT

Background: Coinfection with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) causes complex interactions. The aim of this study was to evaluate the seroprevalence and HBV evolution among HIV coinfecting children receiving highly active antiretroviral therapy (HAART).

Methods: A descriptive cross-sectional study was carried out among 252 HIV infected children enrolled in the Hôpital d'enfants Albert Royer, Dakar, Senegal, from April 2013 to March 2015. Clinical characteristics, immuno-virological status, alanine aminotransferase (ALT) levels, and HBV serological marker were taken from the patients' medical records.

Results: Overall, 7 children were HBsAg positive with a determinate prevalence rate of 2.8%. Median age at HIV diagnosis was 3.5 years (1.3-14.4 years). According to World Health Organization (WHO) staging, 40.1% of children were stage 4 and 25.8% were stage 3. Of the 7 HIV/HBV-co-infected children, 6 (86%) received lamivudine alone at initiation of treatment, and only one child received tenofovir associated with emtricitabine. Overall median HAART duration treatment including lamivudine alone or tenofovir+lamivudine (or emtricitabine) was 7.7 years (3.3-11.3). Only the two children (29%) receiving lamivudine during follow-up had high HBV DNA load despite having good immuno-virological status. Suppression of HBV DNA replication was achieved in 5 (71.4%) of 7 children.

Conclusion and Global Health Implication: HIV/HBV coinfection prevalence was low in our study. HBsAg and HBeAg loss were low while suppression of HBV DNA replication was still higher on tenofovir. Screening and monitoring HBV infection among all HIV infected children are required to direct treatment in order to improve children HBV/HIV coinfecting outcome.

Key words: HBV infection • HIV infection • Children • antiretroviral therapy • Serological markers • Serprvalence • Immunology • Virology • Senegal

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I. Introduction

1.1. Background of the Study

The global prevalence of hepatitis B virus (HBV) infection in people infected with human immunodeficiency virus (HIV) is 7.4% and about 1% of people infected with HBV (2.7 million people) are also infected with HIV.¹ In sub-Saharan Africa (SSA), HBV, and HIV infections are major global health problems, with over two-third of the total of 34 million people with HIV, and at least 8% of the population, chronically hepatitis B infected.² Overall, between 40% to 60% of seropositive people are likely to be HBV infected and the prevalence estimation of chronic hepatitis B defined as persistence of hepatitis B surface antigen (HBsAg) for > 6 months among HIV infected is higher, between 15% to 20% reaching up to 34% of all the seropositive people, with higher rates in West African and Southern African cohorts.^{2,3} These viruses share common ways of transmission in infants and children as a result of mother-to-child transmission due to inadequate diagnosis of the mother and, hence, absence of prophylaxis of blood-borne viruses in pregnancy and the postpartum period.⁴ Coinfection with HIV and HBV viruses causes complex interactions. The impact of HBV on HIV natural history is less certain, although it is believed that HBV infection increases susceptibility to ART-related liver toxicity, impairs CD4 recovery, accelerates immunologic progression, and increases the morbidity and mortality of HIV-infected patients.^{5,6} The natural history of HBV infection is modified by HIV infection. The course of chronic HBV is more aggressive, which can result in higher rates of chronic HBV, reduction of HBsAg seroconversion, higher levels of HBV replication and often reactivation (HBeAg, and HBV DNA detection), accelerated cirrhosis, and increased likelihood of developing hepatocellular carcinoma, and decreased treatment response compared with persons without HIV coinfection.⁴ Among HIV-infected patients, several different HBV serological patterns may be encountered because of the patient's immunosuppression and increased risk of exposure to HBV.⁷ In Senegal, a country with a high chronic hepatitis B endemicity, 85% of people have been exposed to HBV, the prevalence of chronic hepatitis decreased from 17% to 11% between 1999

to 2015. The global prevalence of HIV infection remains stable with 0.5% in the general population.⁸ In Senegal, data are scarce in the pediatric HIV-HBV co-infected children.

1.2. Objectives of the Study

The objective of this study was to investigate the prevalence of HBV infection in children with HIV infection, and to describe the HBV serological markers and HBV DNA among HIV-infected children and adolescent receiving highly active antiviral therapy (HAART). We hypothesized that there would be a significant association between HAART and evolution of chronic hepatitis B serological markers.

2. Methods

2.1. Study Setting

Full details of the rationale for the Maggsen ANRS Pediatric Cohort Study and methods are provided elsewhere.⁹ Briefly, the cohort included HIV-1-infected children aged two to < 16 years under active follow-up in two Senegalese HIV clinics from April 2013 to March 2015. Enrolled children were followed-up until March 2016. Children were seen every three months for a complete clinical assessment, and every six months for laboratory monitoring/fasting blood analyses. The present cross-sectional analysis uniquely included patients in the Albert Royer University Teaching Health Center (CHNEAR). This hospital is of the highest level with medical and surgical wards, and a large HIV infected children's care and research unit for our country. Most children of all ages presenting with severe diseases are referred to CHNEAR by secondary or peripheral health facilities as well as by other hospitals of the same standing category (level III).

2.2. Data Collection and Analysis

Personal and clinical data as well as preliminary information regarding biological parameters include hepatitis b surface antigen (HBsAg), CD4⁺ lymphocyte counts, alanine amino transferase (ALAT), and plasma HIV RNA levels were extracted from the cohort medical records. Serological markers of HBV-infection (HBsAg), hepatitis B e antigen (HBeAg), anti-hepatitis B surface (HBs) antibody, and quantitative analysis of HBV-DNA were performed.

Clinical cases were presented and described using descriptive analysis. Median are presented with their minimum and maximum. Statistical analyses were performed using R studio version 3.5.0.¹⁰ Prevalence of Hepatitis B co-infection was expressed as a proportion. Ethics clearance for the MAGGSEN ANRS cohort protocol was given by the Ethics and Regulatory Committee and the Ministry of Health in Senegal. All parents or surrogate caretakers provided written informed consent.

3. Results

3.1. Sociodemographic Characteristics

From April 2013 to March 2015, a total of 220 HIV-infected children and adolescent were enrolled in the cohort study and 32 additional eligible children were considered so that the present analysis included 252 participants. Among these, 108 (42.9%) were boys. Median age at diagnosis was 9.5 years (6.5-12.5). They consisted of 87 urban, 140 suburban and 25 rural residents. According to WHO disease staging, 40% of children were stage 4 and 26% were at stage 3. Overall, the prevalence rate of HBV-HIV co-infection was 2.8% (n= 7, 4 boys and 3 girls). Baseline characteristics of 7 HBV-HIV co-infected children are summarized in Table 1.

3.2. Biological and Chronic Hepatitis B Serological Markers at Last Follow Up

From the baseline CD4 count, median CD4 was 599 cell/mm³ (484-1393). Median ALT was 27UI/L (24-44). One out of three children who had HBeAg screening was positive at enrollment and two was negative. None had DNA HBV measurement at inclusion. Overall median HAART duration treatment including lamivudine alone or tenofovir+lamivudine (or emtricitabine) was 7.7 years (3.3-11.3). At any time of follow-up two children presented high ALT titer at 1.5 normal limits, which spontaneously normalized. Lab tests at last follow-up are summarized in Table 2. Five of the HBsAg positive subjects had detectable HBeAg a marker for HBV replication. Of them one was negative at inclusion. Five of 7 patients achieved undetectable load HBV titers at least once during follow-up after tenofovir-based treatment was initiated. Only two children receiving lamivudine at the

time of the study had HBV DNA replication with high viral load and positive to HBsAg and HBeAg. However, they had good immuno-virological status with CD4 levels above normal limits and DNA HIV undetectable. HBsAg loss occurred in 1 children (case 1) (14.3%). Of the two children HBeAg negative at inclusion (case 1 and case 3), second (case 3) became HBeAg positive. Suppressed HBV DNA replication was achieved in 5 of the 7 children who received tenofovir associated with lamivudine or emtricitabine. The 2 children received lamivudine alone were replicative with high HBV DNA load > 200.000IU/mL.

4. Discussion

4.1. Discussion

This study found that chronic HBV seroprevalence among HIV infected children is low with less HBsAg and HBeAg loss and higher suppression of DNA HBV viral replication. This prevalence falls within the range of 1.2 % to 6.02% reported in the literature.^{11,12,13} In Senegal, this study on pediatric HIV infection has remained the first one so far to our knowledge. This prevalence in HIV infected children is similar to those reported in children born to mothers HBV infected (3%).¹⁴ Moreover, it is much lower than the earlier HBsAg prevalence rates reported in Ivory Coast (12.1%) and Burkina Faso (28.2%) HIV infected children.^{15,16} This low prevalence in HIV infected children is surprising because HBV prevalence is higher in Senegalese general population (11%) and all children received first dose of HBV immunization at 6 week of age.⁸ Furthermore, most of transmission occurring during perinatal/neonatal period with a higher risk to develop chronic infection (80 to 90%).^{8,17,18} Frequent HBeAg positive with high HBV DNA levels in HIV-infected have been reported in prior studies.^{15,19,20} In the literature, severe immune suppression, defined by higher mean HIV RNA and lower CD4%, was associated with higher detectable HBV DNA levels in children. These children were more likely to be HBsAg positive suggesting that children with more active HIV disease have less immune control of HBV.¹⁸ This high rate of HBV persistence and viral HBV replication is classically reported secondary to formation of stable episomal cccDNA, and integrated HBV. Furthermore, in HBV

Table 1: Baseline characteristics of children in the study

Patients	Case 1		Case 2		Case 3		Case 4		Case 5		Case 6		Case 7	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Sex														
Age at time of the study (years)	15.7	18.7	8.3	18.7	13.3	18.7	13.3	4.4	9.1	4.4	9.1	4.4	9.1	8.7
Age at HIV testing (years)	14.4	8.11	2.6	8.11	8.4	1.3	8.4	1.3	1.7	1.3	1.7	1.7	3.5	3.5
Residence	urban	rural	rural	rural	urban	urban	urban	urban	rural	urban	rural	urban	urban	urban
WHO staging	4	4	4	4	3	2	3	2	4	2	4	4	1	1
HBeAg	negative	negative	unknown	negative	positive	unknown	positive	unknown	unknown	unknown	unknown	unknown	unknown	unknown
HBeAb	negative	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown	unknown
ALT (IU/L)	28	24	27	24	24	26	24	26	35	26	35	35	44	44
CD4 count (cells/ μ L)	526	487	1352	487	484	1334	484	1334	1393	1334	1393	1393	599	599
HIV-1 RNA viral load	undetectable	undetectable	75700	undetectable	226000	undetectable	undetectable	undetectable	undetectable	undetectable	undetectable	undetectable	undetectable	undetectable
Age at ART initiation (years)	14.7	8.11	2.6	8.11	9.5	1.3	9.5	1.3	2.1	1.3	2.1	2.1	3.4	3.4
ART regimen at initiation	TDF+FTC+EFA	AZT+3TC+NVP	AZT+3TC+NVP	AZT+3TC+EFA	ABC+3TC+EFA	AZT+3TC+NVP	ABC+3TC+EFA	AZT+3TC+NVP	AZT+3TC+NVP	AZT+3TC+NVP	AZT+3TC+NVP	AZT+3TC+NVP	AZT+3TC+NVP	AZT+3TC+NVP
Age at ART switch (years)	No switch	16.7	18.7	16.7	16.11	No switch	16.11	No switch	4.3	No switch	4.3	4.3	5.5	5.5
Current ART regimen	TDF+FTC+EFA	TDF+FTC+EFV	TDF+3TC+LPV/R	TDF+FTC+EFV	TDF+FTC+EFV	AZT+3TC+NVP	TDF+FTC+EFV	AZT+3TC+NVP	ABC+3TC+LPV	AZT+3TC+NVP	ABC+3TC+LPV	ABC+3TC+LPV	TDF+FTC+EFV	TDF+FTC+EFV

WHO: World Health Organization, HBeAg: Hepatitis B e-antigen, HBeAb: Hepatitis B e-antibodies, ALT: alanine aminotransferase, ART: antiretroviral therapy, TDF: tenofovir disoproxil fumarate, FTC: emtricitabine, EFA: efavirenz, 3TC: lamivudine, ABC: abacavir, NVP: nevirapine.

Table 2: Laboratory tests at last follow up clinical visit

Patients	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
CD4 count (cells/ μ L)	526	727	860	135	1384	997	559
HIV-1 RNA viral load (copies/mL)	74	91	undetectable	239482	undetectable	undetectable	undetectable
HbsAg	negative	positive	positive	positive	positive	positive	positive
HBeAg	negative	negative	positive	positive	positive	positive	positive
DNA-HBV (IU/ml)	negative	negative	negative	negative	118298224	4246530	negative
ALT	25	12	22	25	26	68	26

infection, HBsAg is produced in large quantities and is generally considered to inhibit adaptive immunity and effective production of HBsAb, which is required for long term HBV control.^{21,22} Among HIV-infected patients, several different HBV serological patterns may be encountered because of the patient's immunosuppression and increased risk of exposure to HBV. For example, presence of isolated antibody to hepatitis B core antigen (anti-HBc) and persistent chronic HBs antigenemia have been observed more often in HIV-infected patients because of impaired host immunity against HBV.⁷ In study conducted in Ivory Coast, 26% of the sample tested showed an unusual pattern of HBeAg/anti-HBeAg positive/HBV DNA positive, indicating that development of anti-HBeAg did not result in control of viral replication.²³ The WHO guideline recommends HAART containing at least two drugs effective against HBV for all HIV-HBV co-infected patients irrespective of disease stage or CD4 count.²⁴ In HBV/HIV-coinfected adults, adolescents and children aged of 12 years or more, the nucleos(t)ide analogues (NAs) which have a high barrier to drug resistance (tenofovir or entecavir) are recommended.²⁵ Due to the high prevalence of HBV-lamivudine resistance, HBV screening prior to initiation of ART is recommended to direct the selection of an appropriate optimal ART regimen for coinfecting children.¹⁵ In Senegal, current ART guidelines recommend zidovudine+lamivudine+nevirapine or efavirenz for children younger than 12 years, and tenofovir+lamivudine or emtricitabine+efavirenz for others older than 12 years old. While there are emerging data to suggest that antiretroviral regimens that contain drugs active against HBV infection (e.g., tenofovir, emtricitabine, and lamivudine) may modify the natural history of HBV disease in HIV-

infected individuals by slowing disease progression and, in some patients, leading to seroconversion, additional long-term follow-up is needed to evaluate the effect of dual treatment.²¹ However, Tenofovir-containing first-line HAART, which has potent anti-HBV activity, is preferred for HIV-HBV coinfection because, it has been successful in achieving sustained HBV suppression in both treatment-naive and lamivudine-resistant HIV-HBV-co-infected individuals.²⁶ Early and effective tenofovir based ART, reduce risk of death among coinfecting children underling the need for implementing universal HBV testing and prompt ART treatment. In this study, HBsAg and HBeAg loss and suppression HBV DNA replication were comparable with other results. In a systematic review and meta-analysis, Tenofovir was reported to have achieved high rates of suppression HBV DNA replication (85.6%) at three years of treatment, and HBeAg loss (86.6% and 75.0%) for HBeAg positive and negative patients respectively.²⁷ In a prospective study in China, lamivudine monotherapy-based cART was efficient for HBV treatment when baseline HBV DNA <20,000 IU/mL with HBV DNA suppression rate at 96.8%, slightly lower than tenofovir (98.0%). However, when DNA HBV was >20,000 IU/mL, tenofovir+lamivudine were associated with higher suppression rates (72.5%) than LAMIVUDINE alone (34.5%).²⁸ Additionally, the small sample of children in our study did not allow us to analyze possible associations between the evolution of serological markers and the clinical and laboratory variables described. Although, tenofovir is associated with viral replication DNA HBV suppression.

4.2. Limitations

This study has some limitations. It was a cross-sectional study and conducted in just one hospital in

Dakar with a limited number of co-infected children. Data were sparse from the first visit to follow-up visits making it difficult to draw many conclusions about the effects of therapy delivered to the children. For further studies among chronic hepatitis b co-infected children, we recommend close monitoring of children's immuno-virological status, liver enzyme and serological hepatitis b markers.

5. Conclusion and Global Health Implications

This study has demonstrated that overall seroprevalence of hepatitis b in HIV infected Senegalese children was low. HBsAg and HBeAg loss was low while suppression of HBV DNA replication was higher for children who received TENOFOVIR without liver toxicity was low demonstrating a positive evolution. There is therefore the need to ensure universal monitoring of HBV in HIV infected children as part of the national HIV program toward countrywide which would improve their quality of life.

Compliance with Ethical Standards

Conflicts of Interest: The authors declare that they have no conflicts of interest. **Financial Disclosure:** The authors declare that they have no financial disclosure.

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Key Messages

- Prevalence of HIV/HBV co-infection is low among Senegalese children
- Screening and monitoring of HBV in HIV infected should be done systematically for choose HBV-active HIV ART [3TC and/or TDF]
- Close monitoring should be performed in HIV/ HBV co-infected children.

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