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HIV–HBV coinfection among South African patients receiving antiretroviral therapy

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Abstract

There are approximately 33 million individuals with HIV infection worldwide. The majority of infections are in southern Africa where hepatitis B is also known to be endemic. As access to life-saving antiretroviral therapy (ART) increases, the possibility for hepatitis B treatment resistance increases because most ART regimens contain lamivudine. Patients coinfecting with HBV are therefore receiving monotherapy for HBV infection, leading to possible HBV-resistant mutants and the concurrent public health effect thereof. Additional information is needed on the prevalence of HIV–HBV coinfection and treatment response to ART. We present a summary of the information available from South Africa to date.

Introduction

The recent CDC workshop, *Drug-resistant and Vaccine-escape Hepatitis B Virus Mutants: Emergence and Surveillance*, highlighted the importance of mutant viruses and the challenges they bring in the treatment of hepatitis B. The significant complication of HIV coinfection along with chronic hepatitis B in resource-limited countries, where both infections are frequent, is concerning. As many of these countries continue to initiate life-saving antiretroviral therapy (ART) for HIV, this environment could become the breeding ground for the development of resistant HBV. Most ART programmes in these countries use lamivudine as part of the nucleoside reverse transcriptase inhibitor (NRTI) backbone for highly active antiretroviral therapy (HAART), thus treating HBV with monotherapy in the HIV–HBV-coinfecting patient. Other effective therapies (such as tenofovir) for treating HIV–HBV-coinfecting patients are often not available in government programmes of resource-limited countries. There are few data at present on the prevalence and clinical course of HIV–HBV-coinfecting patients receiving ART in resource-limited countries. South Africa, unfortunately, is home to one of the highest prevalence rates of HIV in the world, with a significant HBV coinfection rate. South Africa does, however, have a well-

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established medical and research infrastructure and provides an opportunity to study HIV–HBV coinfection and, potentially, provide better care for these patients.

HBV in southern Africa

HBV infection has long been recognized as being endemic in southern Africa, including Botswana, South Africa, Zambia and Zimbabwe, particularly among Black Africans [1,2]. HBV transmission in South Africa appears to be horizontal, that is child-to-child spread with infection beginning in childhood, as opposed to East Asia where vertical mother-to-infant spread is very common [1,2]. Other presumptive routes of spread include sexual contact and ritual scarification.

Even within southern Africa, there appears to be considerable variation with regard to the prevalence of HBV infection depending on the geographical location. In the mid 1980s, Botha *et al.* [1] conducted a serosurvey of HBV infection among children in Ovamboland in northern Namibia. In this relatively densely populated area of Namibia, among children over the age of 1 year, they found that the prevalence of hepatitis B surface antigen (HBsAg) ranged between 12% and 14% with infections beginning at approximately 5–6 months of age (Figure 1). A serosurvey using similar methodology conducted shortly thereafter in children living in Soweto, a large city immediately adjacent to Johannesburg, found a much lower seroprevalence of HBsAg, with the highest rate being 1.4–1.5% among children aged between 15 and 19 years [2] (Figure 1). A serosurvey published in 1999 in children from both the urban and rural areas of the Eastern Cape of South Africa found that the prevalence was the same in these areas at 10.4% with a very high rate of infection of 15.7% in the 5–6 year old range [3]. In adults, HBV prevalence ranges from approximately 8.3% in pregnant women [4] to 10% in men working in mines [5].

HIV in South Africa

Much local and international attention has been directed at the HIV epidemic in southern Africa. Briefly, HIV began to emerge in the late 1980s and early 1990s in South Africa. Multiple spot surveys combine to give a relatively accurate picture of the extent of the epidemic in South Africa. Some of these spot surveys have shown towns or small areas with an HIV seroprevalence as high as 65%, but there is considerable geographical variation [6]. The lowest prevalence has been found in inland rural areas of the Northern Cape (1.9%), whereas the highest is in the northwestern parts of KwaZulu-Natal (20.6%) [6]. A recent publication showed that the prevalence of HIV was associated with ethnicity, urban status and unemployment [7]. Heterosexual transmission appears to be the major route of transmission and women appear to be disproportionately affected [8].

ART has only recently become widely available in South Africa. The South African National Department of Health has established national guidelines for initiation of ART, both in adults and children. According to these guidelines, ART is indicated for patients with HIV infection and CD4⁺ T-cell count <200 cells/mm³, irrespective of World Health Organization (WHO) stage, or with a WHO stage IV AIDS-defining illness, irrespective of CD4⁺ T-cell count. There are two recommended ART regimen lines for use in the South African public sector (Table 1). Note that the primary first-line regimen includes the use of lamivudine, a drug with activity against both HIV and HBV.

HIV–HBV coinfection in South Africa

At present, there are few publications regarding HIV–HBV coinfection in South Africa. We conducted a prospective study evaluating the prevalence of HIV–HBV in the Themba Lethu Clinic, a public sector HIV care management and treatment facility supported by the US

President's Emergency Plan for AIDS Relief in Johannesburg, South Africa. The clinic currently provides HIV care to over 20,000 HIV-infected adults, according to the South African Department of Health National Antiretroviral Treatment Guidelines. Full results from this prospective study are available elsewhere [9]. Here, we summarize the serosurveys including our prospective study done in HIV–HBV-coinfected patients in South Africa.

Results of serosurvey for HBV infection in HIV-seropositive patients

The demographic characteristics and HBV distribution from the 502 participants in this serosurvey are summarized in Table 2. Approximately 5% of patients were seropositive for HBsAg; however, nearly 50% had some serological evidence of previous or active HBV infection. Of note, baseline activities of alanine aminotransferase (ALT) and aspartate aminotransferase were within the normal range in 84% and 57% of these HBsAg-positive patients, respectively. Lower CD4⁺ T-cell counts were positively associated with hepatitis B e antigen (HBeAg) positivity. We found three other studies that evaluated HBV in HIV-seropositive patients in South Africa. A prospective study done in HIV patients admitted to a large government hospital in Johannesburg found a similar coinfection rate as our study of 6% [10], A retrospective unmatched control laboratory-based study showed a rate of 16.2% from a more rural area of the country [11], which is also consistent with a study from the rural mines in 2007 that revealed a prevalence of 17% [12]. These rates seem to follow that the rural areas tend to have higher rates of HBV than the urban areas.

Clinical response to ART among HIV–HBV-coinfected patients

At present, there are few published data regarding the clinical outcomes of HIV–HBV-coinfected patients treated with ART in South Africa. In the Themba Lethu Clinic cohort studied here, all patients had initiated ART with stavudine, lamivudine and efavirenz. Of the 24 HBsAg-positive patients, 18 completed the 6-month follow-up. At their 1- and 6-month visits, ART was found to be well tolerated with no clinical or laboratory evidence of liver flare (defined as a twofold increase in ALT levels from baseline). At 6 months, 14 of the 18 participants had a normal serum ALT activity (<40 IU) and the median HBV DNA viral load dropped from 100,100 to 374 copies/ml. Seven patients had an undetectable HBV viral load. Only three patients had slight worsening of serum aminotransferase activities but none greater than grade 1 (<100 IU). Additionally, no correlation between serum HBV DNA viral load levels and liver function tests was demonstrated. Positive HBeAg correlated with high HBV DNA replication ($>\log_{10} 7.0$) and CD4⁺ T-cell count <100 cells/mm³. HIV response to ART in this cohort was robust with a mean CD4⁺ T-cell count of 153 cells/mm³ at baseline and a mean of 241 cells/mm³ 6 months later. The first 6 months of follow-up in this small cohort of coinfecting patients did not demonstrate any cases of hepatitis flare or hepatotoxic complications of ART. HBV resistance to lamivudine was not yet seen in this small cohort; however, lamivudine resistance takes at least 6 months to develop. Further follow-up of these patients is needed in this cohort to determine the incidence and rate of lamivudine resistance in the South African context.

In this study we demonstrate high rates of HBV coinfection, but good clinical response and tolerance to ART among a cohort of HIV–HBV-coinfected adults. In a larger retrospective study done in miners elsewhere in South Africa, the CD4⁺ T-cell response to ART was also similar in patients with or without HBV. However, this cohort of miners demonstrated that hepatotoxicity associated with initiation of HAART was more likely to occur in HBV-coinfected HIV patients with HBV viral loads $>1 \times 10^4$ cells/mm³ [12]. Additionally, hepatic complications related to taking ART were also more likely to occur in HIV–HBV-coinfected patients who were also taking anti-tuberculosis drugs during the first 6 months of ART treatment. Patients who were HBsAg-positive had a 100% increase in hepatotoxicity (11–

22% of patients) compared with HIV patients on tuberculosis drugs and ART without HBsAg [13]. There were no early deaths caused by complications of HBV infection in HIV patients starting HAART in either cohort.

HBV resistance in South Africa

At present, there are no data published regarding HBV drug resistance or vaccine-escape mutant virus in HIV–HBV-coinfected patients in South Africa. However, there are reports of lamivudine resistance in HBV-monoinfected patients, both in those who are drug-naïve and those treated with lamivudine in South Africa. In a study by Selabe *et al.* [14], the YMDD motif of the hepatitis reverse transcriptase gene was sequentially evaluated in 17 HBV-monoinfected patients on lamivudine treatment. A total of 13 patients had carried YMDD mutations; however, only 5 of these patients developed clinically significant resistance and treatment failure [14]. Selabe *et al.* [14] also reported the detection of YMDD mutations in HBV treatment-naïve patients (both HIV-seropositive and -seronegative). Overall, 20% (3/15) of monoinfected HBV patients and 50% (10/20) of HIV–HBV-coinfected patients were found to have lamivudine resistance without any known therapy given to the patients [15].

Because of the evidence in the developed world indicating a high rate of lamivudine resistance occurring in HIV–HBV-coinfected patients receiving lamivudine as monotherapy against hepatitis B in their ART regimen (40% resistance rate by year 2 of therapy), the current recommendations include initiating treatment with tenofovir/lamivudine as the NRTI backbone for coinfecting patients until there is evidence from the resource-limited countries for their HIV treatment regimen. Both the US Department of Health and Human Services and WHO guidelines on HIV treatment recommend the use of more than one medication active against HBV in combination therapy for HIV infection in HIV–HBV-coinfected patients [16,17]. However, as in most resource-limited countries, ART options are very limited in South African government sector programmes. Tenofovir, has become available in South Africa, but consistent access remains difficult in these programmes.

Occult HBV infection in South Africa

Occult HBV DNA is well described in HIV-infected patients in other parts of the world [18,19]; however, there is little information in the setting of resource-limited countries. We studied patients for occult HBV DNA using real-time PCR in patients who had isolated antibodies against to hepatitis B core antigen (anti-HBc) [20]. In that study, 43 patients were in this category and occult DNA was detected in 38 of the 43 samples (88.4%) [20]. In most instances, the viral load was quite low; however, interestingly, in 19% of the patients, levels were >10,000 copies/ml serum [20]. A retrospective laboratory study done by Mphahlele *et al.* [11] in 2006 found a lower rate of occult HBV DNA in only one-third (5/15) of HIV-positive patients with isolated anti-HBc was found. By contrast, none of the 31 HIV-negative patients with anti-HBc alone tested positive for occult HBV DNA [11]. More recent data out of this group has retrospectively found similar results of 37.9% (11/29) of the patients starting ART with isolated anti-HBc had detectable HBV DNA [21]. In HIV-seropositive pregnant women, 3.2% (6/187) had detectable HBV DNA, of which 3/187 were HBsAg-negative [4]. The significance of these findings remains to be determined, but the presence of ongoing HBV replication at levels sufficient to produce these viral levels in serum suggests that clinically significant HBV infection might be present in some of these individuals. Further characterization of these patients is necessary with regard to HBV occult infection in terms of serum aminotransferases, clinical hepatic disease course, transmission of HBV disease and the possibility of developing resistant HBV in the context

of only treating HIV–HBV-coinfected patients with lamivudine monotherapy in the NRTI backbone of ART.

Conclusions

In summary, the situation in South Africa presents a potential ‘perfect storm’ because of the frequency of both HBV and HIV infection. We found that HBsAg was detected in 4.8% of our urban South African cohort with HIV infection presenting for ART. In addition, HBV DNA was detectable in 88% of patients with antibodies against hepatitis B core antigen alone. The use of lamivudine-based ART appears to be safe initially in these coinfecting patients; however, the development of HBV resistance is likely. Now that ART is being used with increasing frequency, it seems appropriate that all patients initiating ART should be screened for HBV infection (this is not currently standard of care and this strategy is not included in official recommendations in the South African government guidelines). Furthermore, wherever possible, tenofovir should be used rather than lamivudine for patients with HBV and HIV coinfection in this setting. Finally, the clinical effect of occult HBV infection in this setting is unknown and requires further study. Poor compliance with ART could accelerate development of HBV resistance to antiviral drugs, including lamivudine and perhaps even tenofovir, enforcing the need for optimal compliance in these coinfecting patients.

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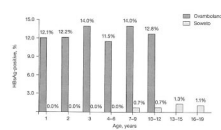


Figure 1.
Historical prevalence of HBsAg among Black children in southern Africa
Data from [1] and [2]. HBsAg, hepatitis B surface antigen.

Table 1

Antiretroviral therapy regimens recommended for use in the public sector by the Department of Health of South Africa

Regimen priority	Drugs
1a	Stavudine/lamivudine/efavirenz
1b	Stavudine/lamivudine/nevirapine
2	Zidovudine/didanosine/lopinavir/ritonavir

Table 2

Demographic and serological data on 502 patients screened for hepatitis B who were initiating antiretroviral therapy at a PEPFAR-supported clinic in South Africa

Characteristic	All patients	Female	Male
Mean age, years	37.0	35.9	39.9
Mean CD4 ⁺ T-cell count, cells/mm ³	128.6	129.1	127.4
Black race, <i>n</i>	475	338	137
HBsAg, <i>n</i> (%)	24 (4.8)	15 (4.2)	9 (6.1)
Anti-HBs alone, <i>n</i> (%)	13 (2.6)	7 (2.0)	6 (4.1)
Anti-HBc alone, <i>n</i> (%)	53 (10.6)	29 (8.2)	24 (16.2)
Anti-HBs and anti-HBc, <i>n</i> (%)	124 (24.7)	88 (24.9)	36 (24.3)
Any marker positive, <i>n</i> (%)	214 (42.6)	139 (39.3)	75 (50.7)

Anti-HBc, antibodies against hepatitis B core antigen; anti-HBs, antibodies against hepatitis B surface antigen; HBsAg, hepatitis B surface antigen; PEPFAR, US President's Emergency Plan for AIDS Relief.