HIV AND HEPATITIS B COINFECTION IN SOUTHERN AFRICA: A REVIEW FOR GENERAL PRACTITIONERS

Theunis Kotzee[1], *MB ChB, DTM&H, DPH, H Dip Int Med, Dip HIV Man, MCFP*
Paul Pronyk[1], *BSc (Med), MD, FRCP, DTM&H, MSc*
Efthyia Vardas[2], *BSc (Hons), MB BCh, DTM&H, DPH, FCPath (Virol), MMed (Virol)*
Adele Heyer[1], *MB ChB, DCH, Dip Obst, Dip HIV Man, MCFP*
Neil A Martinson[2], *MB ChB, MPH, MFGP, DCH*
[1]*Rural Aids Development and Action Research Programme*
[2]*Perinatal HIV Research Unit, University of the Witwatersrand, Johannesburg*

Sub-Saharan Africa is facing serious HIV and hepatitis B epidemics, with coinfection becoming a major public health problem. In addition, the prevention and treatment of concurrent illnesses such as hepatitis B in HIV-infected people is becoming increasingly important as their life expectancy lengthens due to treatment with highly active antiretroviral therapy (HAART). Despite the important epidemiological burden and clinical consequences of coinfection, there is a paucity of research to inform practice that derives from studies conducted in highly endemic regions. This article reviews the current status and limitations of knowledge on coinfection with the hepatitis B virus (HBV) and HIV. It will examine the basic epidemiology of coinfection; the implications for disease progression of each condition; the therapeutic implications including drug toxicities; and current evidence and guidelines for the use of vaccine-based prevention strategies. In addition the article highlights critical areas for future research on coinfection in sub-Saharan Africa.

his article aims to review important aspects of and recent developments in coinfection with HIV and hepatitis B for general practitioners. Our review starts by briefly reviewing aspects such as the prevalence, transmission, prevention, complications and treatment of hepatitis B disease. The subsequent sections deal in more detail with the various aspects of coinfection, including the prevalence, natural history, serological diagnoses, disease progression, outcome of HAART, and HBV vaccination in HIV-positive patients. Coinfection with these two viruses is a complicated topic and most currently available research is from developed settings where predominant transmission modes are different to most African countries, in particular horizontal spread dynamics. In addition, disease prevalence differs markedly, as does vaccine administration and timing, and the feasibility of therapeutics in developing compared with developed countries.

On the African continent 25.4 million individuals are infected with HIV, and in South Africa 5.6 million people were infected with HIV by the end of 2003.[1] Globally, more than 2 billion people have serological evidence of HBV infection and between 350 and 400 million people, representing over 5% of the world's population, are chronically infected.[2] Sub-Saharan Africa is estimated to have approximately 50 million chronic HBV carriers and around 2.5 million of these live in South Africa.[3] Research from sub-Saharan countries has shown the prevalence of chronic HBV in the general population to vary between 9% and 20%.[4] Based on seroprevalence studies, the estimated HBsAg carrier rate in the South Africa is approximately 9%,[5] with a marked difference in prevalence rates between rural and urban populations. This is demonstrated by prevalence rates in the rural Eastern Cape of 15.5% (in the 0 - 60-month age group), compared with 1% in Soweto in the 1980s.[4] Some of these studies are dated and predate universal HBV infant immunisation, but still no explanation currently exists for the geographical variability of HBV infection in South Africa.

Furthermore, even the basic epidemiology of HBV transmission in sub-Saharan Africa is poorly understood. Transmission is thought to be predominantly horizontal, though the details of transmission and marked urban-rural variation are not well understood. The vast majority of the region's population has been exposed to HBV by the age of 5 years. Thereafter HBV prevalence rates increase slightly when children first attend school, and again when they become sexually active.[6] The exact mechanism of HBV transmission has not been established, but the major risk factors associated with HBV infection include scarification, poor sterilisation techniques, re-use of needles, and close personal contact.[7, 8] This is in contrast to developed countries, where the majority of HBV transmission takes place in adulthood when sexual transmission and intravenous drug use form the predominant modes of transmission. Vertical (*in utero*) HBV transmission is not thought to play a major role in sub-Saharan Africa.[9]

Currently the most effective way to reduce the acquisition of HBV in sub-Saharan African countries is through early childhood HBV vaccination. In line with this the South African Department of Health added a vaccine against hepatitis B virus (HBV) into the Expanded Programme on Immunisation (EPI) in April 1995.[10] The World Health Organization (WHO) also recommended the inclusion of the HBV vaccine into their Expanded Programme on Immunisation (EPI) and by the year 2000 more than 100 followed this recommendation.[11] Although the oldest of the South African immunised cohort are only 11 years old now, follow-up studies have shown that small cohorts of immunised children were protected against clinical HBV infections,[12] and that that even at low coverage, reductions in indicator diseases such as HBV nephropathies have been recorded.[13] However, more extensive data on the field effectiveness of the current EPI HBV vaccination programme are still outstanding.

A successful HBV vaccination programme could therefore reduce the prevalence of chronic HBV disease and the high mortality rate (20 - 30%) due to hepatic complications. These include liver cirrhosis and hepatocellular carcinoma (HCC),[14] the latter having a 3-year survival rate of less than 20%.[8] The current morbidity and mortality resulting from chronic HBV infection in sub-Saharan Africa is high, with 20% of cirrhosis cases and 70% of all liver cancer cases in the region thought to be due to HBV infection.[5, 6]

In addition to vaccination, antiviral treatment for HBV is available for most patients with chronic HBV in developed countries. Sadly, access to HBV treatments in developing countries has lagged behind that of antiretrovirals (ARVs). The aim of treatment of hepatitis B is sustained viral suppression to a level associated with no or minimal liver damage.[15] The currently approved treatments in developed countries include standard interferon, lamivudine, adefovir dipivoxil, and entecavir. Decisions regarding treatment should balance the benefits (severity of liver disease) against the risks (adverse effects and costs).[15, 16] In most patients, careful monitoring over a 3 - 12-month period is needed to correctly determine the phase of chronic HBV infection and the severity of liver disease before starting treatment. Current guidelines[15] do not recommend treatment for hepatitis B envelope antigen (HBeAg)-positive patients with persistently normal alanine aminotransferase (ALT) but do for patients with ALT > 2 × upper limit of normal or moderate/severe hepatic inflammation if spontaneous HBeAg seroconversion does not take place after 3 - 6 months of observation (Table I). Patients with hepatic flares or decompensation should receive immediate treatment.

TABLE I. ANTIVIRAL TREATMENT GUIDELINES FOR HBV DISEASE

ALT	HBV DNA	Treatment recommendations
HBeAg positive		
<2 × ULN	> 5 $\log_{10}$	No treatment, monitor Treat if ALT 1 - 2 × ULN and moderate/severe inflammation or advanced fibrosis on liver biopsy
>2 × ULN	> 5 $\log_{10}$	Observe 3 - 6 months, treat if no spontaneous HBeAg seroconversion
HBeAg negative		
<2 × ULN	< 5 $\log_{10}$	No treatment, monitor Treat if ALT 1 - 2 X ULN or HBV DNA 4 - 5 $\log_{10}$ with moderate/ severe inflammation or advanced fibrosis on liver biopsy
>2 × ULN	> 5 $\log_{10}$	Treatment

ULN = upper limit of normal.

PREVALENCE OF COINFECTION WITH HBV AND HIV IN SUB-SAHARAN AFRICAN COUNTRIES

Early epidemiological studies did not show an increased prevalence of HBV among HIV-positive individuals. However, it was conducted when HIV prevalence was low, and was limited by small sample sizes.[6] Recently the prevalence of HBV in HIV-infected adults in sub-Saharan Africa was found to be nearly two times that of HIV-negative patients.[6, 17-26] This higher risk is not as great as that in developed countries, where the prevalence of HBV infection is increased by as much as 10 times in HIV-positive patients, possibly owing to different epidemiologies and modes of spread (such as intravenous drug use). Nonetheless, a high proportion of HIV-positive patients will be HBV coinfected in sub-Saharan Africa and more research is needed to allow an accurate estimation of the extent of the problem and to provide more information regarding differences in prevalence between various groups of patients including rural and urban populations, males and females, and children and adults.

THE NATURAL HISTORY OF HBV DISEASE IN HIV COINFECTED PATIENTS

The natural history of both HIV and hepatitis B infection appears to be influenced by the other, but depends on which infection was acquired first.[7] The more common scenario in sub-Saharan Africa is where children are first infected with HBV and subsequently infected with HIV as adults. In this setting HIV-positive patients with previous cleared HBV infections may lose their protective HBV antibodies due to HIV immunosuppression,[23, 27] and may therefore be at an increased risk of reinfection with HBV.[22, 27] In addition HIV-induced immunosuppression may cause reactivation of recovered (previously anti-HBs positive) as well as 'silent' chronic infections.[21, 27]

In sub-Saharan countries, the minority of patients are HIV-infected by the time they are exposed to HBV for the first time. Most of this sub-group would be children who acquired HIV vertically and are subsequently infected by HBV. HIV-negative children infected with HBV are more prone to develop chronic HBV disease; as many as 90% of those infected as infants and 50% of those infected as young children may become chronic carriers of the virus and are at high risk of liver disease later in life.[28] The effects of HIV infection in these children are unknown at present and require further study.

Research from developing countries suggests that HIV-positive adults who are subsequently infected with HBV are at a higher risk of becoming HBV carriers,[8, 19, 21, 23, 24] are more likely to have high HBV replication rates,[21, 24, 29] and are more likely to be HBeAg-positive for a longer time[21] than HIV-negative patients. All these factors could increase the risk of HBV transmission.

Almost all research looking at the natural history of coinfected patients has been conducted in developed countries, and research documenting disease progression in endemic African populations is needed as transmission dynamics of HBV and HIV differ significantly in these populations.

ISOLATED ANTI-HBc ANTIBODY AND SEROLOGICAL SCREENING STRATEGIES FOR HBV IN HIV-INFECTED PATIENTS

For a reminder of the interpretation of HBV serology, see Table II.[30]

TABLE II. INTERPRETATION OF HBV SEROLOGY

Serological markers	Clinical significance
HbsAG +	Acute or chronic infection
Anti-HBc IgM +	Acute infection; chronic disease with poor prognosis
Anti-HBc IgG and HBsAg +	Chronic infection
Anti-HBc IgG and Anti HBs +	Resolved infection
Anti-HBc only +	Exposure; low-level carrier; senescence of anti-HBs; false positive
Anti-HBs only +	Immunity (natural or vaccine)

Historically, screening strategies for HBV infection test for the presence of HBsAg and anti-HBs only. This strategy overlooks individuals with isolated anti-HBc antibodies. This pattern may represent resolved HBV infection, with loss of antibody to hepatitis B surface antigen (anti-HBs) or occult chronic HBV infection, with levels of the hepatitis B surface antigen (HBsAg) below the limits of detection.[31] Although isolated anti-HBc antibodies are less commonly seen in HIV-negative patients[32] they have increasingly been detected in HIV-positive individuals throughout the world.[33] This has been well researched in regions of low HIV/HBV endemnicity, particularly Europe and the USA.[34, 35] In these settings, it has been estimated that 10 - 20% of all individuals who are serologically positive for HBV have an 'anti-HBc alone' serological pattern. Of these, about 10% are HBV DNA positive.[34]

In areas of high endemnicity such as sub-Saharan Africa, mechanisms resulting in 'occult' HBV infection and the burden of these infections are less well understood.[36] The importance of this sub-group of patients is demonstrated by the finding that as many as 85% of these 'anti-HBc alone' HIV-positive patients have been found to be positive for HBV DNA.[25] Work from South Africa's Limpopo province suggests that 33.3% of HIV-positive adults with an 'anti-HBc alone' serological pattern were also HBV viraemic, compared with 0% of HIV-negative controls.[37]

No associated increased risk for mortality or progression of HIV infection in patients with isolated anti-HBc has been documented, either before or after the introduction of HAART.[38] Research suggests that the prevalence of isolated anti-HBc will vary with the epidemiological characteristics of the patients enrolled and the background seroprevalence of HBV infection. In addition it is proposed that the prevalence of isolated anti-HBc will be high among patients at a late stage of HIV infection, in areas of hyper-endemnicity of HBV infection.[25]

In conclusion, these findings strongly support the concept that HIV infection is a risk factor for occult HBV infections, and the clinical importance of HBc only is still to be studied. In the future, screening for HBc only may be recommended as standard of care for HIV-infected patients. In addition more research, documenting how HIV-1 infection alters the serological response to HBV infection and the frequency of and factors associated with isolated anti-HBc in endemic patient populations, are needed to increase our understanding of this complex interaction.[31]

IS HIV DISEASE PROGRESSION ACCELERATED BY HBV COINFECTION?

Several studies looking at HIV and HBV interactions have been published recently. Findings are conflicting. Some show no impact of HBV coinfection on HIV disease progression,[39-42] while others suggest that HBV co-infection was associated with reduced survival in patients with clinical AIDS.[43] More recently several studies have shown no convincing evidence that HBV hastens progression to AIDS.[19, 23, 24, 33, 44-45] A reason for these conflicting results could be that the majority of clinical studies conducted have only considered HBsAg as a marker of chronic HBV disease,[33, 44] and many of these studies suffer from a number of limitations such as small sample sizes, lack of standardisation of important variables, and confounding variables such as the introduction of HAART.[17] While most available evidence does not show a significant impact of HBV on HIV disease progression, further research is required. In particular, HBsAG-positive patients should be stratified into subgroups according to other variables such HBV DNA levels to determine whether their HIV disease progresses differently.

IS HBV LIVER DISEASE PROGRESSION ACCELERATED BY HIV COINFECTION?

Several studies from developing countries show evidence that coinfection with HIV alters progression of HBV infection. This includes an increased progression of HBV towards chronicity,[8, 46-48] higher levels of HBV replication,[8, 23, 44, 48-50] and a reduced rate of spontaneous loss of HBeAg and/or HBsAg and seroconversion to anti-HBe and anti-HBs.[48] Individuals

who are HBeAg positive and/or have high HBV replication rates generally have more rapid liver disease progression and are more infectious.[30]

Conflicting data exist regarding the degree of liver inflammation in coinfected patients. The pathogenesis of hepatic damage in chronic HBV disease is predominantly immune mediated, with CD8 cells targeting HBV antigens on infected hepatocytes, resulting in inflammation and necrosis.[51] Immune deterioration due to HIV leads to reduced necro-inflammatory activity and reduced ALT levels.[51] Research involving men who have sex with men from developed countries supports the hypothesis for a reduction in liver inflammation in HIV-coinfected patients.[49, 52] Thus, despite higher HBV DNA viral levels in coinfected patients, liver inflammation appears less[39] and may be undetected by routine transaminase screening. Reasons for this could be that HIV immunosuppression may reduce liver damage as a result of a less aggressive HBV-specific immune response.[21] In contrast, other research involving mostly injecting drugs users in developed countries shows increased inflammatory activity.[53, 54]

There are contradictory data regarding the impact of HIV on progression towards cirrhosis and hepatocellular carcinoma in coinfected patients. Some studies from developed countries failed to show any negative impact of HIV coinfection on hepatitis B disease progression.[8, 49, 55] However, numerous studies have shown that HIV infection exacerbates liver disease in patients with HBV co-infection.[29, 39, 43-45, 50, 54, 56-64] In addition, several clinical reports have shown that the risk of end-stage liver disease is significantly increased in HIV-infected patients with chronic HBV.[43, 56, 58, 62, 65-71] The MACS cohort study found that the liver-related mortality rate was higher in men with HIV-1 and HBsAg than in those with only HIV-1 infection or only HBsAg. They further found that the liver-related mortality rate in coinfected individuals was highest in those with lower nadir CD4+ cell counts.[56] This increased risk of HBV disease progression should be considered in any HIV/HBV-co-infected patient with detectable HBV-DNA.[48] South Africa would be an ideal country to perform well-designed and well-funded studies to evaluate this issue.

Some patients with coinfection therefore seem to have more aggressive liver disease (i.e. progression to cirrhosis or liver failure), while other patients have minimally active liver disease with little or no evidence of progressive liver disease.[72] The reason for this discrepancy is unclear and no correlation has been found with any specific clinical factor or laboratory tes.[63] Mechanisms to explain the progressive liver disease despite less liver inflammation are unknown at present, but include potential direct toxicity of high HBV viral levels on hepatocytes[73] or the fact that liver cirrhosis and cancer take years to develop and might be masked by the premature death of patients with HIV/AIDS in the absence of HAART.[74] Other possible explanations to explain these differences include the variety of infecting HBV genotypes in different geographical areas; differences in the degree of HIV immune suppression; and confounding by other factors related to liver damage, such as alcohol use and other infective agents e.g. HCV and HDV. In addition further research needs to be done to clarify the current uncertainty regarding HBc-only patients, the role of HBeAg and HBV DNA levels and whether they carry a similar prognosis among coinfected patients.

ANTIVIRAL TREATMENT OF HIV AND HBV IN COINFECTED PATIENTS

Lamivudine, adefovir, entecavir and alpha-interferon are antiviral drugs used for the treatment of chronic HBV infection in developed countries.[75] Of these, only lamivudine, which is active against both HBV and HIV, is readily available in sub-Saharan Africa. Most countries in the sub-Saharan region use antiretroviral regimens that include lamivudine, and some recommend lamivudine as the drug of choice in HIV/HBV coinfection.[21] Unfortunately HBV resistance to lamivudine occurs in up to 20% of cases per year[56] with long-term use.[21, 45, 76] This has potentially serious implications in HIV-endemic areas, where the majority of HBV chronic carriers are likely to be HIV-positive. Others advocate against the use of lamivudine in coinfected patients, because of the development of resistance that is often signaled by late occurring hepatic flares.[39] As an alternative, it has been suggested that in HBe antigen-positive coinfected patients, lamivudine should be reserved for those who develop clinical hepatitis.[77] This recommendation was based on the finding that the risk for long-term lamivudine resistance is greater in HBeAg-positive patients.[77] Long-term studies in areas with high levels of coinfection are necessary to understand the optimal timing of lamivudine introduction to HAART regimens better.

Tenofovir and emtricitabine also have dual antiviral activity against HIV and HBV and it is hoped that they will soon become available in southern Africa, broadening the armamentarium against HBV in coinfected patients. The nucleotide analogues (adefovir and tenofovir) have the advantage of a higher genetic barrier to the development of HBV resistance than the nucleoside analogues (lamivudine and emtricitabine). As these drugs do not share the same resistance profile, they can be used for salvage therapy.

Sadly, access to HBV treatments in developing countries has lagged behind that of ARVs, but once more drugs become readily available the best option may be to ensure that combination antiviral therapy for HBV is administered in conjunction with antiretroviral therapy, thus avoiding the selection of resistant viral species for either or both viruses.[78] Such a combination could be tenofovir and lamivudine as part of HAART,[74] which could be used for patients with liver cirrhosis, HBsAg-positive patients, patients with active HBV disease with HBV viral replication, and possibly even for all coinfected patients.[77, 79]

HAART TOXICITIES IN COINFECTED PATIENTS

The most common drug-related toxicity in HIV/HBV-coinfected patients on HAART remains hepatotoxicity.[39, 56, 61, 78, 80-86] The

development of severe hepatitis has been reported with HAART regimens containing nevirapine, efavirenz and ritonavir at full doses.[61] Liver damage is thought to result indirectly from immune restitution after the commencement of HAART,[56] or directly from liver toxicity caused by protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs).[61, 73, 78] Problems with regulation of restored immune system in the first 6 months of HAART can lead to atypical presentations of various infections including hepatitis B and may occur in 30 - 40% of individuals that initiate HAART at low CD4 counts.[85] Regimens containing NNRTIs or full-dose ritonavir, should be used cautiously in coinfected patients and discontinued if symptoms or grade 4 increases in aminotransferase levels (>10 × upper limit of normal) develop. Close monitoring of coinfected patients initiating HAART during the first few weeks of therapy is recommended. Despite the increased incidence of hepatotoxicity most of these patients tend to experience a progressive resolution of liver abnormalities without interruption of treatment.[58, 61, 78, 80, 84-87]

As progression to liver cirrhosis in coinfected patients takes 20 years on average,[71] the prevention of death from opportunistic illness in patients treated with HAART increases the likelihood of sequelae of HBV coinfection. In the EuroSIDA cohort, longer exposure to HAART was associated with an increased death rate from liver-related disease in patients with similar CD4 counts. This could be a consequence of direct liver toxicity of HAART or due to progression of HBV/HBC disease.[71] In addition HAART could possibly potentiate the flare-up of HBV directly or indirectly because of mutations resulting from immune pressure,[61, 62, 88] explaining reactivation that develops independent of lamivudine resistance or withdrawal of lamivudine.[62] Little evidence is available regarding the efficacy of HAART in coinfected patients. A cohort study from Thailand reported a delayed CD4 count recovery after coinfected patients were initiated onto HAART, but this was not sustained and there was no associated increased progression of HIV disease.[40]

As discussed previously, the studies highlighted above were conducted in developed countries with significant differences in the profile of HIV and HBV disease. Additional research from developing countries to establish the outcome and toxicities of HAART in coinfected patients is needed to shed light on these important questions.

HBV VACCINATION IN HIV-POSITIVE PATIENTS

T-cell-dependent and independent antigens are affected by HIV immune suppression, and worsen as HIV disease progresses. Owing to this deterioration in immune response, studies of HBV vaccination in HIV-infected infants suggest reduced vaccine efficacy.[89] This reduced immune response pertains both to the antibody titre and its durability.[33, 90-96] Fortunately, in the HAART era evidence suggests that individuals' immune responses to vaccines can be restored to those of HIV-uninfected persons.[97] High CD4 cell counts and low levels of HIV viraemia improve the immunological response to the HBV vaccine.[90, 98] Guidelines from developing countries recommend HBV immunisation for all HIV-positive individuals who have not been exposed to HBV.[90, 98] Strategies to improve response rates include increased dosages of vaccine, prolonging the vaccination schedule, or both.[33, 90, 99, 100] In general there is no harm in vaccinating HIV-infected patients with inactivated HBV vaccines despite the transient increase in HIV viraemia immediately following HBV immunisation.[99, 101, 102] Most guidelines recommend monitoring anti-HBs every 6 - 12 months, after completion of HBV vaccination schedules, to establish efficacy and the need for booster doses.[103]

SUMMARY OF IMPORTANT POINTS

- Coinfection with HIV and hepatitis B is a becoming a major public health problem in sub-Saharan Africa.
- Recent evidence from sub-Saharan Africa shows the prevalence of HBV in HIV-infected adults to be nearly two times that of HIV-negative patients.
- The natural history of both HIV and hepatitis infections is influenced by the other, but this complex interaction is not well understood at present.
- HIV infection is a risk factor for occult HBV infections and it is therefore recommended that anti-HBc antibody testing be included in HBV screening for all HIV-positive patients.
- Available evidence from developed countries does not show a significant impact of HBV on HIV disease progression. Further research is required.
- HIV reduces the immune response to HBV infection, but there is evidence of a paradoxical acceleration of HBV disease progression.
- Future treatment options for coinfected patients could include combination antiviral therapy such as tenofovir and lamivudine, which are active against HBV as well as HIV, thus avoiding the selection of resistant viral species for either of the viruses.
- Close monitoring of coinfected patients initiating HAART is recommended, as these patients have an increased incidence of hepatotoxicity.
- Guidelines for developing countries recommend HBV immunisation for all HIV-positive individuals who have not been exposed to HBV.
- Most research on coinfection has been done in developed countries where HIV and hepatitis disease prevalence, transmission modes and therapeutic options differ markedly and more research from developing countries is urgently needed.

CONCLUSION

HIV and HBV infection are two of the most prevalent infectious disease currently affecting the sub-Saharan region, and coinfection with these two viruses is a common occurrence. The effects that coinfection with these two viruses have on the transmission, natural history, diagnosis and treatment of both diseases are not clearly defined in this setting. Most research has been conducted in developed countries with very different transmission modes, disease prevalence, vaccine administration timing, and availability of certain therapeutics. Data from these settings are therefore difficult to extrapolate to developing countries with endemic

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