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HIV/HBV coinfection in children and antiviral therapy

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Abstract

Small cohort studies from countries where both HIV and HBV are endemic demonstrate prevalence rates of chronic hepatitis B in HIV-infected children of between 1 and 49%. While data on coinfected children are limited, results from studies in adults with HIV/HBV coinfection raise the concern that coinfected children may be at a higher risk of liver disease, hepatic fibrosis and cirrhosis. With the scale-up of combination antiretroviral therapy worldwide, of which lamivudine is included in most first-line regimens, coinfected children treated with lamivudine risk development of HBV resistance mutations. This article summarizes the current literature relevant to HIV/HBV coinfection in children, the options for treatment and highlights priorities for future research.

Keywords

antiviral treatment; coinfection; drug resistance; HBV; hepatitis B; HIV; pediatrics; vaccine

Epidemiology of HIV/HBV coinfection

Approximately 350 million people are chronically infected with HBV, and 500,000–1,200,000 die each year of HBV-related disease and hepatocellular carcinoma [1–3]. Although the prevalence varies from population to population, approximately 5–10% of HIV-infected adults worldwide also have chronic HBV infection, defined as persistence of hepatitis B surface antigen (HBsAg) for >6 months. HIV/HBV coinfection in some sub-Saharan African populations is believed to be significantly higher [3–5].

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Prevalence of HIV/HBV coinfection in pregnant women

Given that HIV and HBV have common transmission routes (perinatal, horizontal, parenteral, sexual) and that endemic regions of both often overlap, as might be predicted, a number of studies have shown that the prevalence of HBV infection among HIV-positive individuals is significantly higher than in HIV-negative individuals [6–9]. However, information on the magnitude of HBV positivity of different risk groups, including people living with HIV/AIDS, is scarce, especially in high-risk populations, such as pregnant women. Recently, with the availability of nationally approved combination antiretroviral therapy (cART) programs, there has been increased concern regarding the potentially high prevalence of HBV coinfection in HIV-positive pregnant women. This concern has spawned further evaluations into the true seroprevalence of HBV infection on a national level, including in African countries that were previously underrepresented **(TABLE 1)** [10–22]. As demonstrated in **TABLE 1**, prevalence of HBV monoinfection among pregnant women in Africa ranges from 4.0 to 17.1%, and prevalence of HBV/HIV-coinfected pregnant women in Africa is variable with a range from 0.4 to 7.1%.

Prevalence of HIV/HBV coinfection in children

The prevalence of chronic viral hepatitis in HIV-infected children is not well characterized. The authors of this paper examined literature on the coinfection of HIV and HBV in children published since 2000. A Medline search was conducted using Ovid's online search engine. Keywords included 'HIV,' 'AIDS,' 'hepatitis B' and 'children.' The starting year was defined as 2000 and the end date was not defined. Any 'related article' hyperlinks were followed for each retrieved article. The reference list of the retrieved articles was also used to identify related literature. No language priority was chosen. The results of this search yielded the studies listed in **TABLE 2** [23–34]. In highly endemic (≥8% of the population are HBsAg positive) areas of Africa and Asia, most HBV infections occur in the first 5 years of life [35]. It has been estimated that three million people from sub-Saharan Africa are coinfected with HIV and HBV, many of them may be immunotolerant children [29,36]. Given that both HBV and HIV can be transmitted perinatally and infants exposed to HBV are more likely to develop chronic HBV infection, HBV infection in HIV-infected children would be expected to be higher than the prevalence in the general pediatric population.

Coinfection & risk of transmission

Perinatal transmission worldwide is the most common mode of HBV transmission. However, mother-to-infant transmission was not seen as the primary route of pediatric acquisition in sub-Saharan Africa when initial studies were completed in the 1980–1990s. This is thought to be due in part to the relatively low rate of hepatitis B e antigen (HBeAg) and maternal antibody protection [37–39]. However, more recent studies have shown that perinatal transmission of HBV may have been initially underestimated. A study conducted in South Africa found that 8.1% of infants at the age of 0–6 months and 8.9% at the age 7–12 months were HBsAg positive, suggesting that perinatal or early infancy transmission may play a significant role in consequent high-chronic HBV carriage rates [40].

The perinatal transmission rate may be lower in Africa than in Asia, partly because of a lower prevalence of HBeAg in Africa, a major determinant of perinatal transmission. Perinatal infection occurs in 70–90% of infants by the age of 6 months if they are born to a mother who is HBsAg and HBeAg positive, compared with 0–30% of those infants born to mothers who are HBsAg positive and HBeAg negative [41–43].

In addition to HBeAg positivity, high-maternal viral load (HBV DNA) has been seen to significantly increase transplacental transmission of HBV [44–46]. While data on HBV DNA levels in coinfected pregnant women are lacking, in HIV-positive patients, even those on cART, including lamivudine, low CD4 counts are associated with a higher rate of detectable HBV viremia [47]. Another factor affecting the risk of perinatal transmission and development of persistent infection is HBV genotype [45,48]. A discussion of the HBV genotypes and the effect of genotype on transmission and disease progression is beyond the scope of this review.

Vaccination coverage & prevention of HBV in HIV-infected children

After the introduction of infant HBV immunization in the WHO-sponsored Expanded Programme on Immunization (EPI) in the majority of countries, HBV immunization coverage has steadily increased throughout most regions of the world [49].

As a result of increased immunization coverage, a decrease in the prevalence of chronic HBV carriers has been documented in many areas of the world [50,51]. While it has significantly improved over the past 10 years, HBV immunization coverage is still only 75% worldwide and is less in many countries where the HIV epidemic is greatest [52].

In addition, there are data to suggest that immunization coverage may be less in HIV-exposed infants. A survey of over 2000 children between the ages of 12 and 23 months in South Africa found maternal HIV status to be a risk factor for decreased immunization coverage for several childhood immunizations, including HBV [53].

HIV-1-infected children may be unprotected from HBV in spite of receiving the full three-dose immunization series, due to a less robust initial immunologic response and waning of anti-HBs antibody titers [54–56]. Immune reconstitution after treatment with cART does not restore anti-HBV immunity in the majority of children, and the response to revaccination is variable. In several small cohorts, 1–40% of HIV-infected children with a history of receiving their primary HBV vaccine series had protective anti-HBsAg antibody levels (>10 IU/ml) detected when measured after initiation of treatment with cART [23,56–60]. In a study conducted by the International Maternal Pediatric Adolescent AIDS Clinical Trials group, only 24% of 204 HIV-infected cART-treated children (median age: 9 years) with a history of previous immunization with three doses of HBV vaccine had protective anti-HBsAg antibody levels prior to receiving a booster vaccine. Forty five percent of the children became seropositive 8 weeks after a booster vaccine [56]. Vaccine response was greatest in those children with higher CD4 counts and undetectable viral loads. Lao-araya *et al.* reported on 64 HIV-infected children (median age: 10 years) on cART for a median of 31 months with a previous history of routine infant HBV immunization. Eighty seven percent had no measurable anti-HBsAg antibody prior to revaccination. The response rate to a repeat

HBV immunization series was 17% after the first vaccine, 82.5% after the second and 92% after the third [60]. After 3 years, 71% of these children maintained protective anti-HBsAg antibody levels, suggesting that HIV-infected children will benefit from a repeat HBV vaccine series after initiation of cART [61].

The decreased vaccine effectiveness suggests that many HIV-infected children remain vulnerable to both intrafamilial and behaviorally acquired hepatitis B infection, even in countries with good HBV vaccine coverage. The percentage of HIV/HBV-coinfected children who acquire HBV perinatally or through intrafamilial transmission in childhood is unknown.

Natural history of HBV monoinfection in children infected perinatally

The risk of developing chronic HBV is significantly affected by the age at the time of primary HBV infection. Studies show that chronic HBV infection develops in up to 90% of infants born to HBsAg- and HBeAg-positive women, and in 20–30% of children infected after the neonatal period but before the age of five [62,63]. In contrast, <5–10% of immunocompetent adults who acquire HBV infection will develop chronic disease [64,65]. Another important determinant of the outcome of HBV infection is the maternal HBeAg/anti-HBe status. Although approximately 5% of babies born to HBeAg-negative/anti-HBe-positive-monoinfected mothers develop acute symptomatic or fulminant hepatitis by 4 months of age, less than 10% of babies become persistently infected [66,67].

HBV infection acquired perinatally or during early childhood is characterized by four phases **(TABLE 3)** [64,68–71]. The initial immune-tolerant phase is marked by high levels of serum HBV DNA and the presence of HBsAg as well as HBeAg [64,72,73]. During this phase, which may last 10–30 years in children infected perinatally, there is little host immune response, normal liver enzyme blood levels and little to no evidence of hepatic inflammation [64,72,73]. The second phase, the immune-active phase, reflects increasing immune activity and loss of tolerance to the virus. This phase is characterized by a decrease in HBV DNA levels, an increase in alanine aminotransferase (ALT) levels and evidence of hepatic inflammation and necrosis on biopsy [72–74]. This phase may be prolonged, leading to hepatic fibrosis and eventual cirrhosis and/or hepatocellular carcinoma [64,73]. After a variable period of time, the majority of patients with perinatally acquired HBV lose HBeAg and seroconvert to hepatitis B e antibody (HBeAb). This seroconversion is accompanied by a decrease in HBV DNA levels, normalization of liver enzymes and resolution of the hepatic necroinflammation [64,73]. Loss of HBeAg leads to the third phase of chronic HBV infection; the low-replicative or inactive HBsAg-positive carrier state. In this phase, liver enzymes remain normal, serum levels of HBV DNA are low or undetectable and patients remain HBeAg negative and HBeAb positive. There is minimal to no evidence of ongoing hepatic inflammatory activity or fibrosis [72,73]. HBV replication may persist or reactivate, leading to the fourth phase of infection; HBeAg-negative chronic hepatitis [67,75]. During this phase, there is continued evidence of hepatic inflammation, which may lead to fibrosis and eventual hepatic cirrhosis. Selection of a precore or core promoter mutation prevents the production of HBeAg but does not interfere with active viral replication [73]. Alternatively, spontaneous loss of HBsAg may occur, although the rate is low (<1–2% per year) [72,73].

Prognosis in individuals who clear HBsAg is usually excellent, although a small risk for development of hepatocellular carcinoma remains [73].

Due to the prolonged immune tolerant phase in children who acquire HBV perinatally or in early childhood, the risk of developing complications of HBV infection during childhood is low. Nevertheless, studies conducted in Asian populations suggest the life time risk of development of hepatocellular carcinoma for a child with chronic HBV is 15–40% [67].

Natural history of HBV-monoinfected adults

HBV acquired in older childhood or adulthood is more likely to be symptomatic and less likely to develop into a chronic infection [65,67]. Symptomatic hepatitis occurs in about 30% of cases of adult HBV infection [67,76]. While the risk of progression to chronic HBV is <5–10% acquired after the first few years of life, this risk is significantly increased in immunocompromised individuals, including those with HIV infection [65]. The immune tolerant phase is uncommon in postnatally acquired HBV. Most adults who develop chronic infection have immune active disease and experience seroconversion to HBeAg negative/HBeAb positive at the rate of 14–16% per year and loss of HBsAg at the rate of 1% per year [73]. HBV-infected adults in the inactive HBsAg carrier state who do not clear HBsAg remain at risk for periodic reactivation with subsequent ongoing risk for advancing fibrosis and cirrhosis [73].

Natural history of HBV in children who are also infected with HIV

The authors of this paper examined literature on the coinfection of HIV and HBV in children published since 2000, as described above. The results of this search yielded two reports with longitudinal data on a small cohort of coinfected children in the Ivory Coast, one on a cohort of Romanian adolescents and eight additional small cross-sectional cohort studies **(TABLE 2)** [23–34].

The only available HBV/HIV-coinfected pediatric cohort with longitudinal data is from the Ivory Coast, where 34 coinfected children were followed with serology and HBV DNA levels for up to 30 months [29,30]. ALT levels were not reported, but 14 out of 19 (74%) with available specimens at 18 months follow-up were HBeAg positive and had elevated HBV DNA levels. On further follow-up, 26% of the samples tested showed an unusual pattern of HBeAg positive/anti-HBeAg positive/HBV DNA positive, indicating that development of anti-HBeAg did not result in control of viral replication [30]. The mean HIV-1 RNA level was higher and the CD4% was lower in the children who had detectable HBV DNA levels, suggesting that children with more active HIV disease have less immune control of HBV. There was one additional cohort of coinfected adolescents from Romania with 1 year of follow-up. In this cohort, 126 of 161 (78%) had evidence of HBV infection as determined by the presence of anti-hepatitis B core antibody. Forty three percent were HBsAg positive, of which 25% were HBeAg positive. Adolescents with more severe immune suppression had higher levels of HBV DNA and were more likely to be HBsAg positive. After 1 year, 31% seroconverted to HBeAb with the clearance rate significantly less in those with severe immune suppression [33]. The remaining studies were cross-sectional reports on small cohorts. ALT levels were mildly elevated in 30–50% of the coinfected

children [23,24,26–28,34]. The two studies that reported HBeAg testing found 83–88% of the coinfected children to be HBeAg positive [23,34].

HIV/HBV coinfection in adults

Extrapolating from studies in adults with HIV/HBV coinfection, there is concern that HBV/HIV-coinfected children may have more active liver disease and progress more quickly to hepatic fibrosis and cirrhosis than monoinfected children. The progression of and complications from HBV hepatitis occur at an increased rate in HIV/HBV-coinfected adults [77,78]. Patients with HIV, especially those with a lower number of CD4 cells, are up to six times more likely to develop chronic hepatitis B after acquiring infection than those without HIV [6,79]. Studies in coinfected adults have shown more severe liver fibrosis with an increased risk of the development of cirrhosis and end-stage liver disease in spite of evidence of less hepatic necroinflammatory pathology and lower ALTs [80,81]. HIV/HBV coinfection also reduces the rate of spontaneous HBeAg and HBsAg seroconversion, consequently leading to a higher prevalence of HBeAg positive disease [80,82] and elevated HBV DNA levels [80]. Follow-up of over 5000 adult men in the Multicenter AIDS Cohort Study for a mean of 10.5 years found those coinfected with HIV/HBV had an eightfold greater risk of mortality due to liver disease compared with those with HIV infection only, and a 19-fold greater increase compared with those with HBV infection only [81].

Conversely, chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 cell responses following cART. With the advent and increased availability of cART worldwide and, thus, decreased risk of death from HIV disease itself, liver disease has emerged as an important cause of death in patients coinfected with HIV/HBV.

Importantly, immune reconstitution hepatitis can occur after initiation of cART, which may lead to anti-HBeAg seroconversion and loss of HBsAg or severe hepatic decompensation and death [83,84]. An additional risk in coinfected patients is HBV reactivation following withdrawal of cART, which includes HBV-active agents [85]. In one study, 29% of 147 patients had increased ALT levels within 6 months of discontinuation of lamivudine [86].

Treatment

HBV treatment in children

Hepatitis B replication itself is not considered to be cytopathogenic to hepatocytes. Instead, it is the host immune responses against the virus that lead to hepatocyte damage [87]. As discussed above, during the immune tolerant phase of chronic HBV infection, although HBV DNA levels are high, ALT levels remain normal and there is little or no histologic evidence of liver damage [88]. In HBV-monoinfected children, there is little evidence that treatment during the immune-tolerant phase impacts outcome, and treatment is not currently recommended during this phase of infection **(TABLE 3)** [71]. Response rates are improved when children are treated during the immune-active phase of the disease. Given the low risk of progression during childhood [89] and the higher likelihood of response to treatment for children with signs of active hepatitis, the Hepatitis B Foundation expert panel of pediatric

liver specialists recommends that children with chronic HBV are monitored with ALT levels every 6–12 months, and those developing ALT levels persistently greater than the upper limit of normal for the testing laboratory be evaluated by liver biopsy. Those with histologic evidence of necroinflammation should be considered for treatment **(Table 3)** [71]. Noninvasive measures of hepatic fibrosis, such as transient elastography and serum biomarkers, have shown promise and may replace liver biopsy for determining the stage of liver fibrosis to guide the need for HBV treatment in the future [90,91].

Because of the concern for a potentially higher risk of progression of liver fibrosis, the Hepatitis B Foundation expert panel included HIV coinfection in the list of circumstances for which HBV treatment should be strongly considered, regardless of the phase of infection [71]. However, other groups suggest that the indications for treatment of chronic HBV infection in HIV/HBV-coinfected children should be the same as in HBV-monoinfected children [92–94]. As discussed above, there are insufficient data on the risk of progression of liver disease in coinfected children to recommend one treatment strategy over the other.

No published studies on HBV treatment in children have included HIV/HBV-coinfected children, and no antivirals are labeled for the treatment of HBV/HIV-coinfected children. Antiviral treatment options for HBV-infected children include IFN-α, and the nucleos(t)ide analogues lamivudine, emtricitabine, adefovir, entecavir, telbivudine and tenofovir **(TABLE 4)** [95–98].

IFN-α is the agent with the most data on safety and efficacy in HBV-infected children. A meta-analysis of randomized trials published prior to 1996 involving 240 children found that 28 and 23% of interferon-treated children had clearance of HBV DNA and HBeAg, respectively, at longest follow-up [99]. The response rate was highest in those with ALT levels >two-times the upper limit of normal. Similarly, in a large multicenter trial of interferon versus no treatment in HBV-monoinfected children in the immune-active phase with evidence of hepatitis on liver biopsy, 26% of treated children were negative for HBeAg and HBV DNA at the end of therapy compared with 11% for controls [100]. Extrapolating from data in adults, IFN-α may be less effective in coinfected children, particularly in those with significant HIV-associated immune suppression. Nevertheless, IFN-α is the preferred treatment, particularly in younger children and in those who meet indications for HBV but not HIV treatment [92,101]. PegIFN-α, which can be given once weekly, has not been approved for treatment of HBV-infected children; however, data in adults suggest it may be more efficacious [102]. Interferon treatment is poorly tolerated, with development of flu-like symptoms of fever, fatigue, myalgias, rigors and headache occurring in most patients.

Lamivudine has an excellent safety profile for extended use in HIV- and HBV-infected children, and it is recommended as a part of a combination antiretroviral regimen for coinfected children who require both HIV and HBV treatment [92,103]. However, therapy with lamivudine as the only anti-HBV agent is problematic due to the high risk of development of HBV resistance mutations after prolonged therapy in monoinfected adults and children and in coinfected adults with uncontrolled HBV viremia [104–107]. In a large randomized trial of lamivudine monotherapy in HBV-infected children, 23% had undetectable HBV DNA and loss of HBeAg after 52 weeks of treatment; however, 64%

developed lamivudine resistance after 3 years of treatment [104,108]. Due to the increased risk of resistance and the lack of clear longterm efficacy in HIV/HBV-coinfected adults, lamivudine as the only anti-HBV active agent in a regimen is not recommended in coinfected adults [35,92,109]. Importantly, lamivudine and the similar agent, emtricitabine, are active against HIV, and HIV resistance develops rapidly when they are used as single agents. Thus, lamivudine and emtricitabine should not be used for treatment of HBV in coinfected individuals in the absence of additional antiretroviral agents.

Adefovir dipivoxil is the third antiviral agent for which there are data from a randomized treatment trial in HBV-infected children. One hundred and seventy three children aged 2–17 years with HBeAg and ALT levels at least 1.5-times the upper limit of normal were randomized to receive adefovir versus placebo. In the 12–18-year age group, 23% of the adefovir-treated children achieved the primary end point of HBV DNA <1000 copies/ml and a normal ALT versus 0% in the placebo arm at 48 weeks. The outcome in adefovir-treated children <12 years of age was not different from placebo [110]. Continued antiviral response was seen with prolonged adefovir therapy and development of resistance was uncommon [103]. Increased creatinine has been noted in up to 50% of adults with prolonged adefovir treatment [111]. Adefovir is labeled for treatment of chronic HBV in children aged 12 years and older. Adefovir has minimal anti-HIV activity. Therefore, it could be used in older coinfected children who require HBV but not HIV treatment.

Entecavir is a nucleoside analogue with greater potency against HBV than lamivudine and adefovir. In the only published study of entecavir in HBV-monoinfected children, 30 children who had failed previous anti-HBV therapy had a decrease in their mean HBV DNA levels and improvement in their ALT levels after 24 weeks of entecavir. Clearance of HBV DNA was seen in seven out of eight (78%) of the HBeAg negative children and five out of 22 (23%) of the HBeAg positive [112]. No safety data were presented in this pediatric study, however adverse effects of entecavir in adult studies have been minimal [105,106]. As with all the nucleos(t)ide analogues, lactic acidosis with severe hepatomegaly and steatosis has been reported [113]. Several small studies in HIV/HBV-coinfected adults failing previous anti-HBV treatment have similarly shown significant decreases in HBV DNA after the addition of entecavir [114,115]. While insufficiently potent to be considered an HIV therapy, entecavir has activity against HIV such that monotherapy entecavir results in the development of the M184V mutation and should not be used as monotherapy in HIV-coinfected individuals in the absence of additional antiretroviral agents [84]. Entecavir is labeled for treatment of HBV-monoinfected adolescents aged 16 years and older.

Tenofovir, another oral nucleotide analogue, was recently labeled for HBV treatment in adults. Tenofovir has significant activity against both lamivudine-resistant and wild-type HBV. Tenofovir also has a higher barrier to HBV resistance than lamivudine and has been shown to be more effective than adefovir and equally effective to entecavir in chronic HBV infection in monoinfected adults [116,117]. Adult treatment guidelines recommend inclusion of tenofovir plus lamivudine in the ART regimen for coinfected adults who require treatment for HIV [35,92,118]. Tenofovir was found to be safe and effective in a recently completed randomized study of tenofovir versus placebo in adolescents (age: 12–18 years) with chronic HBV monoinfection. At the end of 72 weeks, 86% of the 52 tenofovir-treated adolescents

had HBV DNA viral loads <400 copies/ml versus zero out of 54 treated with placebo [119]. Tenofovir has recently been labeled for treatment of HIV-infected children down to 2 years of age. However, the potential renal and bone toxicity associated with long-term use of tenofovir may be of particular concern in younger children. As with lamivudine, tenofovir also has significant HIV activity and should not be used as a single agent in coinfected individuals without additional antiretroviral agents.

Telbivudine is labeled for the treatment of chronic HBV infection in adults and adolescents aged 16 years and older. However, there are little data in HIV/HBV-coinfected adults and no published data in HBV-infected children. Similar to lamivudine, resistance develops during chronic therapy, so monitoring of HBV DNA levels during treatment is indicated.

Treatment issues in coinfected adults & children

HIV treatment guidelines recommend HIV therapy for all infected infants and for children with CD4 counts <350 (WHO) and <500 (US Department of Health and Human Services) and includes lamivudine as one of the agents in all first-line regimens [120,121]. The scale-up of cART in poor resource settings, particularly with lamivudine-containing regimens as first-line ART, along with lack of testing for chronic HBV prior to the initiation of ART, will likely result in more HIV/HBV-coinfected adults and children being treated with monotherapy lamivudine. Studies in adult cohorts have demonstrated lamivudine resistance mutations in up to 50% of coinfected patients with continued HBV viremia within 2 years of lamivudine monotherapy and in greater than 90% at 4 years [105,122,123]. In the coinfected Thai adolescents included in the report by Aurpibul *et al.*, 69% had HBV DNA levels above 10^5 copies/ml in spite of lamivudine therapy, and the lamivudine resistance mutation rtM204V/I was found in 75% of the adolescents tested [23]. Similarly, in the cohort of HIV/HBV-coinfected children described above from the Ivory Coast, six out of 11 (54%) treated with lamivudine-containing cART failed to show a response to therapy, based on continued high HBV DNA levels and/or persistent HBeAg, suggesting a high likelihood of lamivudine resistance developing in these children [29].

The accumulation of lamivudine resistance mutations has implications for future HBV therapy in the individual patient as well as raising the concern for perinatal and horizontal transmission of lamivudine-resistant HBV. The mutations L180M and M204V/I **(TABLE 4)**, which are the most frequently present mutations, confer decreased susceptibility to entecavir and a decreased response to entecavir therapy has been shown in HIV/HBV-coinfected adults with prior resistance to lamivudine [114]. Fortunately, there does not appear to be decreased susceptibility to tenofovir, and coinfected adults with lamivudine-resistant HBV respond effectively to tenofovir or tenofovir plus continued lamivudine [84,124,125]. Lamivudine-resistant HBV has been demonstrated in therapynaive coinfected adults in South Africa, which suggests transmission of resistant HBV and the potential of perinatal transmission of HBV-resistant virus [126].

Of particular concern, because of the overlap between the HBV polymerase gene and the envelope gene, antiviral resistance mutations also result in changes to the HBsAg. The resultant so-called antiviral drug-associated potential vaccine-escape mutants have reduced antigenicity and are able to escape neutralization by hepatitis B vaccines [127]. One such

mutant, the triple polymerase mutant (rtL173V, rtL180M, rtM204V), occurred in 17% of viremic coinfected adults treated with prolonged lamivudine monotherapy in the USA and Australia [105]. Similar mutations have been found in up to 24% of HBV-monoinfected adults in Turkey treated with lamivudine [128]. While any reduction in the effectiveness of HBV vaccination programs as a result of these vaccine-escape mutants has yet to be demonstrated, continued monitoring for the emergence and clinical effect of these viruses will be important [129].

To prevent the accumulation of LMV mutations, options for treating HIV/HBV-coinfected children would be to initiate LMV-sparing cART in those who would not otherwise require HBV treatment or to include additional anti-HBV medications in the cART regimen [94]. Use of LMV-sparing cART regimens has been advocated for initial HIV therapy independent of HBV sero-status in order to preserve lamivudine for future cART options [130]. Due to concerns of hepatic flares after initiating cART in coinfected individuals, adult guidelines recommend that HBV-active agents be included in any cART regimen for coinfected adults regardless of stage of HBV disease [92]. Specifically, tenofovir plus lamivudine or emtricitabine are recommended to decrease the risk of HBV mutations. However, although up to 25% of HBV/HIV-coinfected adults experience hepatic flares after starting cART, the role of HBV specific treatment in preventing or treating hepatic flares has not been delineated [83,84]. The risk of symptomatic hepatitis after cART initiation in coinfected children in the immune tolerant phase of HBV infection is not known.

Expert commentary & five-year view

Although prevalence of HIV and HBV varies from region to region, many of the countries impacted by the HIV epidemic are also those with endemic HBV, resulting in significant impact on the progression of liver disease and associated complications in the HBV/HIV-coinfected adult patient population. Coinfected individuals have been shown to have higher levels of HBV viremia, increased hepatotoxicity and overall liver-related morbidity and mortality. However, much more information is needed to fully uncover the scope of HIV/HBV coinfection in the pediatric population in order to understand the impact coinfection has in this population now and in the future.

First and foremost, more comprehensive data on the prevalence of HIV/HBV coinfection in pregnant women and their infants and children needs to be published, especially from regions where chronic HBV is highly endemic. Basic serological and quantitative data, such as HBsAg and HBeAg status and HBV DNA viral loads in mothers and their offspring, collected in prospective longitudinal studies, will be necessary to fully examine the natural history of HIV/HBV coinfection in children. Without this information, it remains unclear whether frequent and/or expensive HBV monitoring is needed, and whether this unique population of HBV-immunotolerant, HIV-infected children will develop significant liver-related morbidity and mortality over the course of their lifetime.

The introduction of HBV immunizations into the national Expanded Programme on Immunization is promising, but it has not become universal. Advancements in timely vaccination, ideally within the first 24 h of life, and completion of the three-dose series

needs continued support and accessibility. In addition, as research has shown, HIV-positive children are less likely to respond to vaccination against HBV, even when completed in a timely manner. Thus, vaccination schedules and recommendations for revaccination in this population should be established.

The management and treatment plans of chronic HBV infection in light of HIV infection in infancy and childhood also poses specific problems, and treatment approaches to both HBV and HIV need to be considered. Given that most national cART programs include lamivudine as a single HBV-active agent, it is critically important to assess the impact of prolonged lamivudine use and the development of lamivudine resistance on perinatal HBV transmission and HBV progression in women and children. Even though the addition of new anti-HBV treatment options in cART regimens, such as tenofovir and emtricitabine, is encouraging, issues around testing, monitoring, access, cost and licensing for pediatric use prohibit their widespread use [92,131].

HIV/HBV coinfection in children is an evolving problem for which there are many unanswered questions. But given what is known about increased liver-related disease in coinfected adults, the implications of prolonged lamivudine therapy and consequent resistance, lack of comprehensive HBV immunization coverage and unknown natural history, further research is essential to adequately inform the management of HBV/HIV coinfection in an increasingly at-risk pediatric population.

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Key issues

- Approximately, 350 million people are chronically infected with HBV, and 500,000–1,200,000 die each year of HBV-related disease and hepatocellular carcinoma.
- The prevalence of chronic viral hepatitis in HIV-infected children is not well characterized.
- Perinatal transmission worldwide is the most common mode of HBV transmission to children.
- Factors impacting the risk of perinatal transmission and development of persistent infection include maternal hepatitis B e antigen (HBeAg) status, HBV DNA viral load and HBV genotype.
- HBV immunization coverage may be less in HIV-exposed/infected infants, and even those HIV-infected children who receive the full three-dose immunization may be unprotected from HBV due to a less robust initial immunologic response and waning of anti-hepatitis B surface antibody titers.
- The risk of developing chronic HBV is significantly affected by the age at the time of primary HBV infection, with chronic HBV infection developing in up to 90% of infants born to hepatitis B surface antigen and HBeAg positive women and in 20–30% of children infected after the neonatal period but before the age of five.
- Extrapolating from studies in adults with HIV/HBV coinfection, there is concern that HBV/HIV-coinfected children may have more active liver disease and progress more quickly to hepatic fibrosis and cirrhosis than monoinfected children.
- Chronic HBV does not substantially alter the progression of HIV infection and does not influence HIV suppression or CD4 cell responses following combination antiretroviral therapy.
- Lamivudine has an excellent safety profile for extended use in HIV- and HBV-infected children, and it is recommended as a part of a combination antiretroviral regimen for coinfected children who require both HIV and HBV treatment, but its use is problematic due to the high risk of development of HBV resistance mutations after prolonged therapy.
- Adult treatment guidelines recommend inclusion of lamivudine (or emtricitabine) plus tenofovir in the antiretroviral regimen for HBV/HIV-coinfected adults.
- The accumulation of lamivudine resistance mutations has implications for future HBV therapy in the individual patient, as well as raising the concern for perinatal and horizontal transmission of lamivudine-resistant HBV.

- HBV antiviral resistance mutations also result in changes to the HBeAg, called antiviral drug-associated potential vaccine-escape mutants, which have reduced antigenicity and are able to escape neutralization by hepatitis B vaccines.

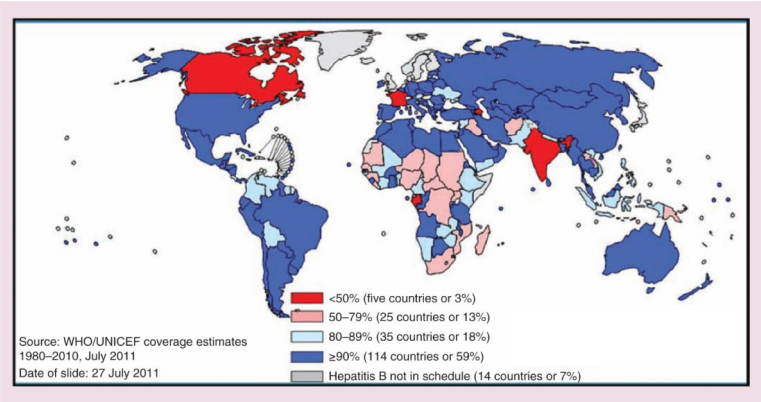

Figure 1.

Immunization coverage with third dose of hepatitis B vaccines in infants, 2010. Reproduced with permission from [52].

Table 1

HIV/HBV coinfection seroprevalence in pregnant women in African countries.

Study (year)	Country	Years study completed	Number of pregnant women enrolled	% HIV infected (number HIV infected)	% HBV infected (number HBV infected)[†]	% total pregnant women coinfected with HIV/HBV	% HIV-positive pregnant women coinfected with HBV	Ref.
Eke *et al.* (2011)	Nigeria	2009	480	11.9 (56)	8.3 (40)	4.2	35.7	[10]
Sangaré *et al.* (2009)	Burkina Faso	2009	307	6.5 (20)	11.4 (35)	2.0	30.0	[11]
Cho *et al.* (2012)	Ghana	2008–2009	1226	5.0 (75)	10.6 (133)	1.1	18.7	[12]
MacLean *et al.* (2012)	Mali	2008–2009	3659[‡]		8.0 (298)	0.4		[13]
Mamadou *et al.* (2012)	Niger	2008	495	2.0 (10)	16.2 (80)	0.6	30.0	[14]
Adesina *et al.* (201)	Nigeria	2006–2008	721[§]	100.0 (721)	8.9 (64)		8.9	[15]
Tiruneh *et al.* (2008)	Ethiopia	2006	480	11.9 (57)	7.3 (35)	0.6	5.3	[16]
Ilboudo *et al.* (2007)	Burkina Faso	2005–2006	379	12.7 (48)	7.9 (30)	1.3	10.4	[17]
Simpore *et al.* (2006)	Burkina Faso	2004–2005	336	61.6 (207)	9.8 (33)	7.1	11.6	[18]
Collenberg *et al.* (2006)	Burkina Faso	2003–2004	492[¶]	4.2 (33 of 790)	17.1 (84)	1.7	24.2	[19]
Simpore *et al.* (2004)	Burkina Faso	2002–2003	429	25.5 (108)	9.3 (40)	3.3	13.0	[20]
Pirillo *et al.* (2007)	Uganda and Rwanda	2001–2004	247[§]	100 (247)	4.0 (10)		4.0	[21]
Kfutwah *et al.* (2012)	Cameroon	2000–2003	650[#]	46.3 (301)	7.9 (51)	4.3	9.3	[22]

[†]Defined as hepatitis B surface antigen positive.

[‡]No information provided on number of HIV-infected pregnant women in the entire population (of 3659 women enrolled).

[§]All enrolled pregnant women were HIV positive.

[¶]In the study from both sites, a total of 790 women were tested for HIV, but only 492 completed both HIV and HBV testing.

[#]Case–control study with 301 patients were HIV positive, 349 patients were HIV negative.

Table 2

HIV/HBV coinfection seroprevalence in children.

Study (year)	Country	Years study completed	Type of study	Number of pediatric patients enrolled	% HIV infected (number of HIV infected)	% HBV infected (number of HBV infected)†	% Total children coinfected with HIV/HBV	% HIV-positive children coinfected with HBV	Ref.
Asia									
Aurpibul *et al.* (2012)	Thailand	2010–2011	Multicenter cross-sectional	521‡	100.0 (521)	3.3 (17)		3.3	[23]
Zhou *et al.* (2010)	China	2005–2009	Cohort	1082‡	100.0 (1082)	4.9 (53)		4.9	[24]
Bhargava *et al.* (2009)	India	2005–2007	Cohort	803§	12.6 (101)			29.7	[25]
Africa									
Mutwa *et al.* (2012)	Rwanda	2010	Cohort	88‡	100.0 (88)	15.9 (14)		15.9	[26]
Ashir *et al.* (2009)	Nigeria	2007	Cross-sectional case–control	560	50.7 (284)	14.5 (81)	9.6	19.0	[27]
Telatela *et al.* (2007)	Tanzania	2006	Cross-sectional	167‡	100.0 (167)	1.2 (2)		1.2	[28]
Rouet *et al.* (2008); Rouet *et al.* (2009)	Ivory Coast	2000–2003	Observational cohort	280‡	100.0 (280)	12.1 (34)		12.1	[29,30]
Chakraborty *et al.* (2003)	Kenya	2000	Cross-sectional	54‡	100.0 (54)	3.7 (2)		3.7	[31]
Nacro *et al.* (2001)	Burkina Faso		Cross-sectional	103	57.3 (59)	39.8 (41)	28.2	49.1	[32]
Europe									
Ruta *et al.* (2005)	Romania	2002–2003	Cross-sectional case–control	517	31.1 (161)	19.0 (98)	13.5	43.4	[33]
North America									
Toussi *et al.* (2007)	USA	2003–2005	Retrospective chart review	228‡	100.0 (228)	2.6 (6)		2.6	[34]

†Defined as hepatitis B surface antigen positive.

‡All subjects enrolled were HIV positive.

§Subjects enrolled were considered high risk for HIV (children of HIV-positive parents or those referred by pediatrician suspecting HIV infection). Hepatitis B surface antigen testing was only reported in the 101 HIV-positive children.

Table 3

Phases of chronic HBV infection: serum markers, HBV viral load and indications for treatment.

Phases	Immune tolerant	Immune active	Inactive HBsAg positive carrier	HBeAg negative chronic hepatitis
HBsAg	Positive	Positive	Positive	Positive
HBeAg	Positive	Positive	Negative	Negative
Anti-HBeAg	Negative	Negative	Positive	Positive
HBV DNA median (IU/ml) [68–70]	10^6–10^8	10^5–10^8	10^2–10^3	10^4–10^5
ALT	Normal	Increased	Normal to mildly elevated	Increased
Liver inflammation	Absent to minimal	Moderate to severe	Absent to minimal – fibrosis may regress	Moderate to severe
Treatment recommended [71]	No	Yes	No	Yes

ALT: Alanine aminotransferase; HBsAg: Hepatitis B surface antigen; HBeAg: Hepatitis B e antigen.

Table 4

Antiviral agents for treatment of hepatitis B.

Generic name	Trade name	US FDA labeled indications and ages	HIV-1 activity[†]	HBV resistance mutations [95–97]
Lamivudine	Epivir® Epivir–HBV®	HIV: birth and older HBV: ≥2 years	Yes	M204I/V L180M A181T/V V173L
Emtricitabine	Emtriva®	HIV: birth and older HBV: not labeled for HBV treatment	Yes	M204I/V L180M A181T/V
Adefovir	Hepsera®	HBV: ≥12 years	No[‡]	N236T A181T/V
Telbivudine	Tyzeka®	HBV: ≥16 years	No	M204I A181T/V
Tenofovir	Viread®	HIV: ≥2 years HBV: ≥18 years	Yes	A194T[§] A181T/V N236T
Entecavir	Baraclude®	HBV: ≥16 years	Yes[¶]	M204I/V[#] L180M T184I/A/G/L S202I/G I169T
IFN-α-2b	Intron A®	HBV: ≥1 year	No	
PegIFN-α-2a	Pegasys®	HBV: ≥18 years	No	

[†]Agent also has activity against HIV-1 and can lead to development of HIV resistance mutations if used as monotherapy in an HIV/HBV-coinfected individual. Additional antiretrovirals should always be included in a treatment regimen.

[‡]While adefovir does have minimal HIV-1 activity, development of HIV-1 resistance mutations has not been demonstrated.

[§]Tenofovir mutations have not been clearly associated with decreased anti-HBV efficacy.

[¶]Entecavir does not have sufficient antiretroviral activity to be used for HIV-1 therapy [98].

[#]Presence of several mutations is necessary to decrease efficacy for entecavir.