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Clinical implications of HIV and hepatitis B co-infection in Asia and Africa

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Hepatitis B virus (HBV) is the leading cause of chronic liver disease and liver-related death worldwide, with the majority of these cases occurring in areas of Africa and Asia where HBV prevalence is high. Many of the countries that are affected by hepatitis B are also affected by a high HIV burden, leading to frequent HIV/HBV co-infection. The consequences of co-infection, including increased liver-related morbidity and mortality, increased hepatitis B viral replication, immune reconstitution to HBV in the setting of antiretroviral therapy, and hepatotoxicity from antiretroviral drugs, are especially important in regions with expanding antiretroviral programmes. Little data, however, are available on HIV/HBV co-infection from regions with high chronic hepatitis B prevalence. This Review discusses the epidemiology, natural history, pathogenesis, and management of HIV/HBV co-infection from these areas. Topics for future research relevant to HIV/HBV co-infection in Africa and Asia are also highlighted.

Introduction

Chronic hepatitis B is the leading cause of chronic liver disease and a leading cause of death worldwide.[1,2] From a total of 400 million hepatitis B virus (HBV)-infected people worldwide, 620 000 people die annually from complications of chronic hepatitis B.[3] In the setting of HIV co-infection, the mortality rate from chronic hepatitis B is increased beyond that of either infection alone.[4] The impact of co-infection is especially apparent in regions with widespread use of highly active antiretroviral therapy (HAART) since competing risks of mortality from opportunistic infections are diminished. In areas with HAART, liver failure has emerged as a major cause of death in HIV-infected individuals.[5–8] As HAART becomes introduced into areas of Africa and Asia that have high HBV endemicity (population prevalence greater than 8%), it is likely that liver disease from chronic hepatitis B will emerge as an even greater problem (see figure). Thus, it is important to understand HIV/HBV co-infection in regions with high chronic hepatitis B endemicity and expanding antiretroviral programmes, especially in view of the implications of using HAART agents that also possess anti-HBV activity. This Review describes the epidemiology, clinical impact, treatment, and future research directions regarding HIV/HBV co-infection with a focus on regions with high chronic hepatitis B endemicity.

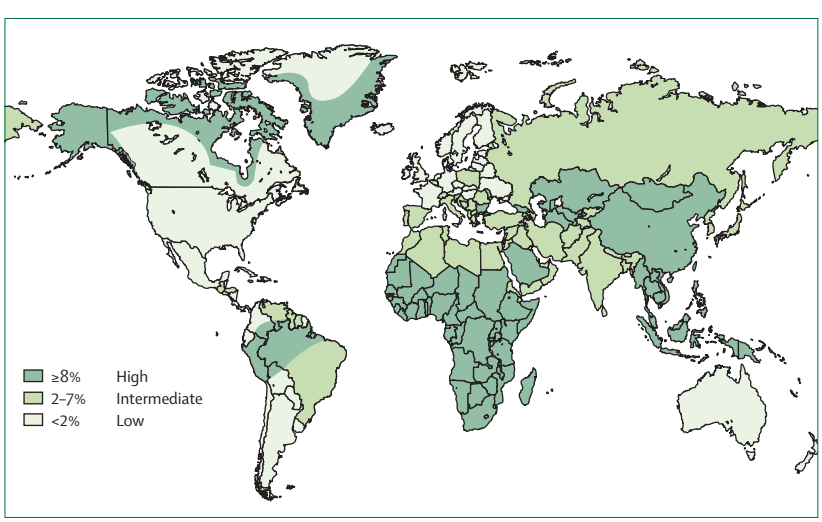

***Figure*: Chronic hepatitis B global distribution**
Colours represent hepatitis B surface antigen prevalence. Adapted from reference 9. CDC. Travelers' health: yellow book, health information for international travel, 2005–2006. Atlanta, GA: Centers for Disease Control and Prevention. http://www.cdc.gov/travel/yb/.

Epidemiology and natural history

Epidemiology

Chronic hepatitis B, defined as persistence of hepatitis B surface antigen (HBsAg) for greater than 6 months, has differing epidemiology in regions of high versus low endemicity. In regions with low endemicity, most infections occur in adolescents and young adults. For example, in the USA, a country with low endemicity, sexual transmission accounts for the majority of HBV infections. Sexual transmission is followed by percutaneous transmission as the second most common mode of transmission.[10] Since most HIV and HBV transmission occurs sexually or percutaneously in low endemicity areas, chronic hepatitis B prevalence is higher in HIV-infected populations. By contrast, in regions of Africa and Asia with high HBV endemicity, most HBV infections occur within the first 5 years of life. Perinatal transmission predominates in east and southeast Asia,[11] whereas in Africa most infections are believed to occur in children, with vertical transmission having a less important role.[12] In Africa, most HBV transmission occurs before the age of 5 years through close contact within households, medical procedures, traditional scarification, and possibly additional unidentified mechanisms.[13–16] The lower rate of vertical transmission in Africa than in Asia may be partly because of a lower prevalence of hepatitis B e antigen (HBeAg) in Africa, a major determinant of perinatal transmission.[17] Perinatal infection occurs in 70–90% of women with HBeAg-positive chronic hepatitis B compared with 0–30% in those with HBeAg-negative chronic hepatitis B.[18–21]

In most regions with high HBV endemicity, there is little evidence for substantial adult HBV transmission even among individuals with higher risk sexual behaviour. However, potential causes for adult transmission exist including sexual transmission and blood transfusions because the blood banks in many low-income countries do not screen for hepatitis B.[22] Studies to date report a low number (less than 10%) of HBV infections attributable to adult transmission even in high-risk populations such as sex workers,[23–26] possibly because most adults have already been exposed to HBV and have developed either chronic hepatitis B or immunity. However, some areas might exist where adult transmission is higher; two cross-sectional surveys, one from Ethiopia and the other from Somalia,[27,28] reported a lower prevalence of HBV markers in children than in adults, suggesting either adult infection or a decline in childhood infections over time.

In the setting of HIV infection, even a small number of adult transmissions can be important because of the increased likelihood of developing chronic hepatitis B and the increased risk for long-term adverse outcomes.[4,29,30] Studies have not found evidence of significantly increased history of HBV exposure (immunity indicated by anti-hepatitis B surface antibodies, chronic hepatitis B indicated by HBsAg, or any exposure indicated by hepatitis B core antibodies) in HIV-infected individuals in Asia and Africa. Studies from Tanzania and Uganda show similar population-wide exposure to HBV regardless of HIV status with 51–76% of HIV-uninfected and 61–73% of HIV-infected individuals having serological evidence of exposure.[31,32] Only subset analyses have identified groups with potentially higher exposure; one was a subset limited to HIV-infected antenatal clinic attendees and the other a subset limited to individuals with HIV but without clinical signs of AIDS.[32,33] It is unclear why either of these HIV-infected populations would have increased HBV exposure or if further groups with higher HBV exposure will be identified in future studies. It is notable that three-quarters of the population in much of Asia and Africa have been exposed to hepatitis B, especially since AIDS can lead to reactivation of HBV even after the development of anti-hepatitis B surface antibodies.[34]

Similar to studies of exposure to HBV, studies from the Côte d'Ivoire, Malawi, and Tanzania have reported similar chronic hepatitis B prevalence between HIV-uninfected and HIV-infected individuals (6·0–14·4% and 9·0–16·9%, respectively).[23,35–37] In Thailand, a chronic hepatitis B prevalence of 8·7% (60 of 692 HIV-infected patients tested), was reported among patients receiving antiretroviral therapy, consistent with the population prevalence of 5–10%.[11,38] However, one study from the Central African Republic identified a lower prevalence of chronic hepatitis B in HIV-infected versus HIV-uninfected individuals.[39] The cause of this difference is unclear but perhaps there was greater mortality in those with HIV/HBV co-infection. Further work is clearly needed to better describe chronic hepatitis B epidemiology in areas of high HIV/HBV co-infection. Especially needed are longitudinal studies to evaluate incidence of acute HBV infection in HIV-infected individuals, and incidence of HBsAg seroconversion and chronic hepatitis B reactivation in HIV-infected people.

Natural history

Age at time of HBV infection is inversely correlated with the risk of developing chronic hepatitis B. After an acute HBV infection, up to 90% of newborn infants (32 of 35 infants born to mothers with high HBsAg titres)[40] and 30% of children (six of 21) under the age of 5 years develop chronic hepatitis B[41] compared with only 1–5% of adults with intact immune systems. In the setting of HIV infection, infected adults progress to chronic hepatitis B at a rate approximately five times higher than HIV-uninfected adults (chronic hepatitis B developed among seven of 31 HIV-infected adults versus two of 46 HIV-uninfected adults following acute infection, p=0·026).[29,42]

After progression to chronic hepatitis B, the course of disease can be divided into four phases—immunotolerant, immunoactive, inactive carrier, and reactivation—and an additional category of occult hepatitis B.[43,44]

In perinatally acquired HBV, the immunotolerant phase can last for decades and is characterised by high HBV DNA levels, normal liver enzymes, and low hepatic necroinflammatory activity. This phase is shorter in childhood-acquired HBV, and usually absent in adult-acquired HBV. A study from Taiwan showed a low risk for developing cirrhosis or hepatocellular carcinoma during this phase (less than 0·5% per year).[45]

The second phase, the immunoactive phase, is characterised by liver enzyme elevations, fluctuating HBV DNA levels, and pronounced hepatic necro-inflammation. Hepatic inflammation during this phase is believed to be immunologically mediated with the duration and the severity of the liver enzyme fluctuations correlated with the extent of liver damage. In HIV/HBV co-infection, a paradox exists of lower average serum liver enzyme levels but a higher risk of progression to cirrhosis.[46] During the immunoactive phase a proportion of individuals develop a mutation in either the pre-core or core domain causing HBV to no longer express HBeAg, although these individuals continue to have HBV replication and high levels of serum HBV DNA.[43]

The third phase of chronic hepatitis B, the inactive carrier phase, is traditionally identified by presence of anti-HBe antibodies, absence of HBV DNA, and potentially indefinite duration. Seroconversion in adults to the inactive carrier phase occurs at a rate of 8–15% per year in HIV-uninfected individuals, but occurs less frequently in HIV-infected populations.[46–48] Among pregnant women in Zambia with chronic hepatitis B, those co-infected with HIV were twice as likely to have detectable HBeAg levels (25%) compared with HIV-uninfected individuals (among HIV-infected women with chronic hepatitis B, six of 24 were HBeAg positive versus seven of 82 HIV-uninfected

women with chronic hepatitis B, p<0·05), suggesting that HIV infection delays transition to the inactive carrier phase.[24] HBV DNA, another marker of active chronic hepatitis B, was detected in 26·7% of pregnant women in the Côte d'Ivoire with HIV co-infection versus 9·4% of those with chronic hepatitis B alone (12 of 45 versus three of 32, p=0·06), also suggesting lower rates of transition to the inactive carrier phase.[35] For those individuals who do have transition to the inactive carrier phase, it is during this phase that AIDS-related immune suppression increases frequency of reactivation with reappearance of HBeAg and reversion to the immunoactive phase.

Occult hepatitis B, which is defined by undetectable serum HBsAg and measurable serum HBV DNA, probably lies in the continuum between the inactive carrier and reactivation phases. HIV-infected individuals appear to have increased prevalence of occult hepatitis B in some studies. Among South African hospitalised patients tested for HIV and HBV, 22% of HIV-infected people without HBsAg had detectable HBV DNA compared with only 2·4% of HIV-uninfected people (31 of 140 versus two of 85).[48] Other studies have not confirmed higher rates of occult hepatitis B in HIV-infected individuals.[49] Occult hepatitis B may be associated with progression to cirrhosis and hepatocellular carcinoma, although the risk compared with chronic hepatitis B is uncertain.[50,51] Further research is needed to characterise occult hepatitis B and to determine whether liver-related complications are increased in people with occult hepatitis B, a topic best studied in regions of high HBV endemicity.

Some individuals with chronic hepatitis B eventually achieve HBsAg seroconversion. Among individuals not co-infected with HIV, but infected with HBV as adults, this seroconversion occurs at a rate of 1–2%.[42] HBsAg seroconversion occurs at a lower rate in those infected by HBV earlier in life. Even with development of anti-hepatitis B surface antibodies, many individuals have persistence of covalently closed circular DNA (cccDNA) in the hepatocytes.[52] Thus, AIDS-related immunosuppression can cause reactivation to chronic hepatitis B.[46,53,54] This is sometimes referred to as reverse seroconversion. The incidence of reactivation in the setting of HIV infection is unknown but is important to determine in areas of high chronic hepatitis B endemicity.

Cirrhosis and hepatocellular carcinoma

An estimated one-quarter of HIV-uninfected individuals with chronic hepatitis B are expected to develop cirrhosis or hepatocellular carcinoma, or both.[55,56] Independent predictors for both cirrhosis and hepatocellular carcinoma are elevated serum HBV DNA level and HBe antigenaemia, as shown in recent studies from Taiwan.[57,58] Both HBV DNA and HBe antigenaemia are increased in HIV/HBV co-infected people, which may help to explain the 18-fold increased risk of liver mortality in HIV/HBV co-infected men compared with HBV mono-infected men in a US cohort.[4] Although no significant increase in hepatocellular carcinoma has been noted thus far in areas with both high HIV prevalence and chronic hepatitis B endemicity,[59] further work is needed to determine the contribution of HIV co-infection to hepatocellular carcinoma risk. As HAART becomes introduced into Africa and Asia, it will be important to evaluate the risk of cirrhosis and hepatocellular carcinoma in co-infected individuals on HAART.

HBV genotype and natural history

Currently, there are eight known HBV genotypes (A–H), which are clustered geographically. Increasing evidence suggests that HBV genotype is a factor in determining HBV disease progression. Genotype A is found in North America, southern Africa, and east Africa; however, the genotype A viruses in these regions are of differing subtypes and accumulating evidence suggests that their natural histories differ.[60] For example, in southern Africa, an increased risk of hepatocellular carcinoma has been linked to genotype A1.[61] Genotype E is the predominant genotype in west Africa, and genotypes B and C are present in Asia. In HBV mono-infected patients in east Asia, genotype C infection increases the risk for hepatocellular carcinoma, lowers rates of HBeAg clearance, and increases the frequency of acute HBV exacerbation.[62–64] However, in individuals younger than 50 years of age, genotype B is reported to increase the risk of hepatocellular carcinoma the most.[65] Genotypes B, C, and D are more likely to develop the core and pre-core mutants because of a nucleotide sequence that favours development of these mutants. Therefore, studies that more clearly define the role of genotype on the natural history are warranted and need to be undertaken globally since all the genotypes are not found in one area of the world. It is also unknown how HBV genotype and HIV interact in terms of liver disease progression, making this an important area for research.

HAART and chronic hepatitis B

HAART and liver enzyme elevations

There are several important causes of liver enzyme elevations in HIV/HBV co-infected individuals on HAART that can limit the tolerability of antiretroviral drugs. The causes of liver enzyme elevations can be divided into three categories: HAART-related, chronic hepatitis-B related, and miscellaneous. Determination of the aetiology of the liver enzyme elevation is important because it guides correct therapy. HAART-related causes are a result of toxicity from the drugs. Antiretroviral therapy may cause liver injury through direct toxicity, inhibition of mitochondrial DNA polymerase gamma, and idiosyncratic reactions such as those that occur with nevirapine and abacavir.[66]

Co-infection with chronic hepatitis B increases the risk of hepatotoxicity from antiretroviral drugs three-fold to

five-fold.[67–69] Studies of HIV co-infection with hepatitis B from Thailand and Taiwan showed an increase in hepatotoxicity to 15·3–16·0 episodes per 100 person-years in those HIV-infected individuals with chronic hepatitis B compared with 4·5–8·0 episodes per 100 person-years in those without either chronic hepatitis B or hepatitis C.[70,71] A further concern in many countries with high chronic hepatitis B endemicity is use of multiple hepatotoxic drugs, especially for antituberculosis therapy. Tuberculosis therapy and HAART are more likely to cause liver enzyme elevations in HIV/HBV co-infected people than either therapy alone.[72] In patients on tuberculosis therapy and HAART, chronic hepatitis B increases the risk for severe liver enzyme elevations three-fold above that for antituberculosis therapy and HAART.[73] Further studies are needed to determine if hepatotoxicity episodes cause progression of chronic liver disease as do chronic hepatitis B-associated flares.[74]

There are several HBV-related causes of liver enzyme elevations. First, HBeAg seroconversion can be heralded by flares in alanine transaminase and aspartate aminotransferase. Second, individuals with chronic hepatitis B are at risk for acute infection with hepatitis D virus, which causes acute hepatitis. Third, acute hepatitis or fulminant hepatic failure can occur if HBV replication is suddenly uninhibited by discontinuation of an active anti-HBV agent or by emergence of drug-resistant HBV. In these settings, the time to symptom onset, duration, and clinical course is similar to that of acute hepatitis B.[75] Ideally, this situation can be avoided by knowing the HBV status of the patient and avoiding withdrawal of an HBV-suppressive agent. Whether a combination of two HBV-active HAART agents reduces the risk of drug-resistant HBV is unknown. If rebound hepatitis does occur, then the appropriate treatment is prompt institution or re-institution of an active anti-HBV agent. Fourth, in some individuals with chronic hepatitis B, antiretroviral therapy may lead to a paradoxical flare of hepatitis during immune recovery caused by the immune reconstitution syndrome. This syndrome occurs because of increased immune activity against antigens from ongoing or resolved infections. It has been reported to occur with chronic hepatitis B, although the frequency and predictive factors are unknown.[76–78] Further investigation is needed to determine the extent to which immune reconstitution contributes to hepatic morbidity during antiretroviral therapy and whether it can be eliminated by pharmacological suppression of HBV replication before initiation of HAART or with HAART.

The miscellaneous causes of liver enzyme elevations in HIV-infected populations need to be distinguished from chronic hepatitis B-related causes to initiate appropriate therapy. These causes include alcoholic hepatitis, acute hepatitis A, acute hepatitis C, acute hepatitis E, AIDS cholangiopathy, *Schistosoma mansoni* infection, visceral leishmaniasis, malaria, and opportunistic infections and malignancies including *Mycobacterium tuberculosis*, *Mycobacterium avium* complex, Kaposi's sarcoma, lymphoma, opportunistic fungal infections (*Candida albicans*, *Cryptococcus neoformans*, *Histoplasma capsulatum*, and *Penicillium marneffei*), and opportunistic bacterial infections (*Bartonella henselae*, salmonella, *Listeria monocytogenes*, and others).[79–81] These causes can often be identified with a thorough history, serological testing, and occasionally, abdominal imaging.

Response to HAART

An area with special relevance to low-income settings with high HBV endemicity is the potential for chronic hepatitis B to blunt immune recovery after initiation of HAART. Current data conflict regarding the effect of chronic hepatitis B on CD4 lymphocyte recovery. Among the HIV-NAT cohort in Thailand a lower mean increase in CD4 lymphocyte count was identified in HIV/HBV co-infected (29 cells per μL) versus HIV-mono-infected (62 cells per μL) individuals after 4 and 8 weeks of HAART. But by week 48, CD4 lymphocyte increases were similar regardless of hepatitis B status.[38] In Nigeria, HIV RNA suppression and absolute CD4 rise was similar between HBsAg-positive and negative patients started on HAART.[82] Results from an Italian cohort showed increasing divergence of mean CD4 lymphocyte count up to 36 weeks after HAART initiation between patients with and without chronic hepatitis B, with those with chronic hepatitis B having a lesser CD4 increase ($p=0·03$).[83] More studies are needed, especially in areas of high chronic hepatitis B endemicity, to characterise the effect of chronic hepatitis B co-infection on CD4 lymphocyte recovery during antiretroviral therapy. If reduced immune recovery is found to occur in co-infected populations in Asia and Africa, current WHO guidelines for antiretroviral monitoring may not be optimal because of delayed CD4 recovery.[84] Adjusting expectations for goal CD4 lymphocyte improvement in co-infected patients may prevent changes of regimen or discontinuation of HAART because of suspected drug failure. For this reason, additional studies of the effect of chronic hepatitis B on immune recovery with HIV therapy are necessary.

Management of chronic hepatitis B

HBsAg seroconversion is the ultimate, but elusive, goal of chronic hepatitis B therapy. A more achievable objective is to halt the progression of chronic hepatitis B-associated liver disease.[85,86] In view of the suppressive, rather than curative, nature of most chronic hepatitis B therapy, treatment is usually prolonged and may need to be continued indefinitely to maintain benefit through persistent HBV suppression. Treatment is most beneficial and efficacious for those in the immunoactive phase. Patient characteristics that favour treatment success are low HBV DNA levels, HBeAg positivity, or evidence of hepatic inflammation noted either on liver biopsy or by liver enzyme elevations.[87] In Africa and Asia, large

***Panel:* Research topics in HIV/HBV co-infection for regions of high chronic hepatitis B endemicity**

- Regional prevalence of HIV/HBV co-infection
- Incidence of acute HBV and reactivation of HBV in HIV-infected individuals
- Prevalence of hepatocellular carcinoma in HIV-infected and HIV-uninfected populations
- Effect of HIV on mother-to-child HBV transmission
- Effectiveness of nucleoside analogues to reduce mother-to-child HBV transmission
- Natural history of chronic hepatitis B acquired during childhood in people with later-acquired HIV infection
- Effect of chronic hepatitis B on HIV complications and HAART response
- Effect of HBV genotypic differences on HAART and HBV therapy
- Incidence and effect of drug-resistant HBV on liver disease progression and HIV outcomes
- Incidence and prevention of HBV-related immune reconstitution syndrome
- Efficacy of treatment with an HBV-active agent as part of HAART
- Efficacy of anti-HBV combination therapy as part of HAART
- Effect of occult HBV on liver disease mortality in HIV-infected individuals and HAART-related hepatotoxicity

numbers of young people are in the immunotolerant phase with high HBV DNA levels and minimum hepatic inflammation and are unlikely to receive substantial benefit from HBV treatment. But, whether these rules are the same in HIV co-infection is not known because HIV-infected people have higher HBV DNA and lower liver enzyme elevations, but more cirrhosis. Thus, further work needs to be done to determine the best possible time to treat co-infected people.

When considering management of chronic hepatitis B in HIV/HBV co-infected patients in low-income countries, modifications in management recommendations are required to account for limited availability of anti-HBV agents and diagnostics. Of the seven agents used for treating chronic hepatitis B in the USA, only one, the nucleoside analogue lamivudine, is widely available throughout most of Africa and Asia. Two others currently have limited availability—tenofovir disoproxil fumarate, a nucleotide analogue also used to treat HIV, and adefovir dipivoxil, a nucleotide analogue with activity only against HBV at currently used doses. Tenofovir disoproxil fumarate may become more available in Asian and African antiretroviral programmes. Several reviews provide guidelines for management of co-infection in high-income regions.[87–90]

The following are our management recommendations for use in regions with limited resources. First, HBsAg and liver enzymes should be tested before starting HAART. Second, routine monitoring of liver enzymes should ideally occur once or twice during the first 3 months of HAART and when CD4 or HIV RNA is assayed. The presence of HBsAg and repeatedly elevated liver enzymes suggest active disease with necroinflammatory activity and the need for anti-HBV therapy. Detection of HBV DNA is also helpful, but this assay is unlikely to be available in resource-limited settings. The presence of HBeAg adds further weight to starting anti-HBV therapy, but this assay also might not be available to many treatment programmes. In high-income countries, HBV-specific agents, such as adefovir dipivoxil and interferon α, are available for use for HBV suppression in patients who have not reached immunological criteria for HAART. These agents are not available in most low and middle-income countries, leading to the need to consider using lamivudine or tenofovir disoproxil fumarate-containing HAART for management of both chronic hepatitis B and HIV.

In countries where tenofovir disoproxil fumarate is available, tenofovir disoproxil fumarate and lamivudine is a reasonable combination of nucleosides to include as a part of a HAART regimen; however, research is needed to determine whether this combination increases the potency or decreases the risk of developing drug-resistant HBV. Unless HBeAg seroconversion occurs, once lamivudine or tenofovir disoproxil fumarate are started as part of HAART they should be continued indefinitely to maintain HBV suppression. If co-infected individuals are switched to a second-line HAART regimen, discontinuation of the anti-HBV active agent can be considered in patients who achieved HBeAg seroconversion a minimum of 6 months earlier. Premature discontinuation of an HBV-suppressive nucleoside/nucleotide analogue can result in acute hepatitis. Studies in HBV mono-infected patients have reported acute hepatitis in 17% of patients (seven of 41 patients) stopping a nucleoside analogue,[91] with a higher risk in those with pre-existing fibrosis or cirrhosis.[92]

Acute hepatitis can also occur during continuation of nucleoside therapy if resistance develops. During lamivudine therapy, HBV resistance occurs at a rate of 25% per year with nearly 100% resistance by 4 years of therapy in HIV co-infected people.[93–95] Resistance to tenofovir disoproxil fumarate has been described, but its incidence in HIV/HBV co-infection is unknown.[96]

Resistance should be suspected if an unexplained liver enzyme elevation occurs, or if serum HBV DNA levels are found to be elevated during therapy with an HBV-active agent. Liver enzymes frequently rise after resistance develops, occurring in 40% of HIV-uninfected patients who develop resistance (13 of 32 patients who developed resistance to lamivudine).[97] If resistance to lamivudine develops, adding or switching to another HBV-suppressive agent with a different pattern of resistance is likely to provide the best outlook for the patient. Continuation of lamivudine leads to development of compensatory mutations that could potentially limit future treatment options.[98] In HIV/HBV co-infected individuals who do not need HIV treatment but who need to be treated for chronic hepatitis B, monotherapy with an agent that is active against both HIV and HBV (such as lamivudine, emtricitabine, entecavir, or tenofovir disoproxil fumarate) should not be used because of the rapid development of drug-resistant HIV. A drug that only has anti-HBV activity such as adefovir dipivoxil can be used, if available. Needing further evaluation is whether HAART should be started

for management of chronic hepatitis B in co-infected individuals before WHO immunological criteria for HAART are met.

In high-income countries, further management of co-infected patients includes hepatocellular carcinoma screening with liver ultrasound and serum α fetoprotein measurements. Early detection of hepatocellular carcinoma can allow for effective surgical management making routine annual ultrasound appropriate where surgical care is available.

Prevention

Childhood and adult HBV infection can be prevented by vaccination, whereas perinatal infection can be prevented by a combination of vaccination and hepatitis B immune globulin. Administration of hepatitis B immune globulin and HBV vaccine to infants born to mothers with chronic hepatitis B is 85–95% effective in preventing development of chronic hepatitis B in healthy infants born to mothers without HIV.[19] Unfortunately, HBV immune globulin is expensive, HBV vaccination is incomplete, and HIV-infected babies respond poorly to immunisation;[99] thus, less expensive and more convenient methods of preventing vertical transmission are needed.[100] Theoretically, nucleoside/nucleotide analogues could meet this need, but to date, only scant data exist suggesting that lamivudine is efficacious at decreasing HBV transmission.[101] Universal infant HBV vaccination is effective in reducing infant and adult transmission and is an important component of the Expanded Program of Immunization.[102,103] Vaccination should also be considered for adults, especially those who are HIV-infected. Those most likely to respond are individuals with low HIV RNA and higher CD4 counts.[104] Especially important to consider for vaccination might be individuals who had low nadir CD4 counts and have experienced immune recovery after starting HAART. These individuals may have lost previously acquired HBV immunity and are at risk for reinfection. In recognition of lower rates of vaccination response in HIV-infected individuals, various modified vaccination approaches have been suggested including double-dose vaccines, assaying titres for response, and repeating vaccination series.[104,105]

Conclusion

The introduction of HAART in middle and low-income settings has substantially improved the long-term outlook for millions of people with AIDS. Chronic conditions and co-infections have replaced acute opportunistic infections as leading causes of mortality in settings with established antiretroviral programmes. In many regions with more recently initiated antiretroviral programmes, chronic hepatitis B is a highly endemic infection with prolonged lead-time before HIV infection. The full consequences of high endemicity and potentially advanced liver disease before HIV infection in these regions are unknown. It is clear that co-infected individuals have much higher mortality, increased toxicity from HAART, more complications because of interruptions or changes in antiretroviral therapy, and possibly, a blunted immune recovery. Whether these complications of co-infection can be effectively reduced through the use of specific chronic hepatitis B management guidelines needs to be determined. Studies are still required to characterise chronic hepatitis B epidemiology and chronic hepatitis B/HIV interactions. The panel lists some important areas for further research that have been highlighted in this paper. Further understanding could provide the knowledge with which to create new guidelines for the monitoring and treatment of HIV/HBV co-infected patients in areas of high chronic hepatitis B endemicity and thus lead to greater improvements in morbidity and mortality.

Search strategy and selection criteria

Data for this Review were identified by Medline searches, references from articles, and the authors' files. Search terms used were "hepatitis B", "Africa", "Asia", "HIV", "AIDS", "antiretroviral therapy", "hepatotoxicity", "hepatotocellular carcinoma", and "perinatal." Only English language papers were reviewed. No date restrictions were set in the search.

Conflicts of interest

CLT has served on an independent expert panel supported by an educational grant from Bristol-Myers Squibb. CJH has no conflicts of interest.

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