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Hepatitis B virus and human immunodeficiency virus co-infection: impact on transmission and natural history of disease

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There is overwhelming evidence of a strong association between human immunodeficiency virus (HIV) and hepatitis B virus (HBV) infections in areas of low endemicity for both viruses, due to shared risk factors. There is also much evidence that HIV modifies the natural history of HBV infection in these areas: co-infected individuals are more likely to be HBV chronic carriers, with higher levels of HBV infectivity, than HIV-negative individuals. Also, immunosuppression brought about by HIV infection reduces persistence of anti-HBs in previously immune and vaccinated individuals, and can cause HBV reactivation or re-infection in those previously exposed to HBV. Furthermore, HIV infection increases the risk of death from liver disease in HBV co-infected individuals, and this risk increases when these patients are treated with highly active anti-retroviral therapy. However, extensive research has found no convincing evidence that HBV impacts on the transmission and natural history of HIV infection. However, the growing body of literature from sub-Saharan Africa (where both HIV and HBV are endemic, and where the majority of the population have been exposed to HBV long before the time of reaching sexual maturity and being exposed to HIV) stands in sharp contrast with the above findings. In this region, it is clear that the prevalence of HBV in HIV-positive individuals is seldom significantly increased, especially in healthy individuals; and when it is significantly increased, it is not increased to the same extent as in HBV-naïve populations. Also, it is expected that these increases will be caused mainly by reactivation or re-infection.

Introduction

It is well established in areas where human immunodeficiency virus (HIV) and hepatitis B virus (HBV) have low prevalence rates, that there is an increased prevalence of HBV in HIV-infected individuals.[1-6] Populations at risk for both these viruses are similar, due to shared transmission routes, thus specific risk groups in these areas are exposed to both viruses more or less simultaneously, with the transmission and progression of each disease in the presence of the other, being the subject of much research and debate.

In contrast, the growing body of literature from areas highly endemic for both viruses, such as sub-Saharan Africa, has generally not found similar dramatic increases in HBV prevalence. The vast majority of the inhabitants of sub-Saharan Africa have been exposed to HBV as children, with chronic carrier rates almost equal to that of adults being established by early childhood. This is due to the major route of HBV transmission in this region being horizontal (i.e. transmission unrelated to recognised sexual, perinatal, or parenteral exposure),[7] with most children being infected by the age of 5 years.[8] A large proportion of these children becomes chronic carriers of HBV, and in adulthood, transmit HBV in exactly the same manner as HIV. Apart from acquiring HIV vertically from infected mothers, it is at the time when sexual activity commences that exposure to HIV occurs. Thus, it is clear that most sub-Saharan Africans have already been exposed to HBV by the time they become sexually active, with the minority being exposed to both viruses more or less simultaneously.

The purpose of this paper is to review HIV and HBV co-infection, specifically focusing on what is known about the impact of each virus on the other's natural history and transmission, highlighting the data from sub-Saharan Africa.

Impact of HIV on transmission and natural history of HBV infections

Increase in progression to HBV chronic carriage

Many studies in areas of low endemicity have shown that there is an increase in chronic carriage of HBV in HIV-co-infected populations. Reviews of these studies show that this has been reported in patients who previously recovered from HBV infection before being infected with HIV, as well as in patients who were HIV-positive at the time of acquiring HBV, or who were infected with both viruses more or less simultaneously.[9,10]

In patients where HBV infection occurs before HIV infection, reactivation of HBV in 'silent' chronic carriers has been reported.[4,11-13] Some of these patients were previously anti-HBs positive, but lost anti-HBs due to HIV immunosuppression.[13] Also, patients who have previously cleared HBV infections have been re-infected by different sub-types of HBV.[11,12] In most of the patients where re-infection or reactivation of HBV occurs, subsequent sero-conversion to anti-HBs does not occur, and patients remain chronically infected.[11,12]

Where HIV infection precedes HBV infection, the immunosuppression brought about by HIV increases the risk

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of chronic HBV carriage,[1,2,4,6,14-16] and when HBV and HIV are acquired more or less simultaneously, there is an even greater rate of progression to chronic HBV carriage.[14]

An early study found a much higher prevalence of HBsAg (indicating chronic infection) in patients with AIDS than in HIV-positive patients without AIDS.[3] However, in this study on HIV-positive patients, it was not known if HIV infection preceded HBV infection, so this finding may be due to reactivation of a previous HBV infection, or inability to clear a subsequent HBV infection. Support for the latter is given by a study which found that lower mean CD4 counts (as found in more advanced HIV infections) at the time of acute HBV infection are significantly associated with progression to chronic carriage.[14]

In sub-Saharan Africa, it is expected that HBV infection will precede HIV infection in the majority of co-infections, which could possibly result in an increased number of HBV reactivations/re-infections in the region. However, data on this are scant, with only one study providing this information. This study, in the Democratic Republic of the Congo (DRC), found that despite a similar prevalence of HBV exposure in HIV-positive and -negative pregnant women (n=500, 18 being HIV-positive), there was a significant increase (11.1% in HIV-positive, 2.7% in HIV-negative) in specimens that were positive for all three markers (HBsAg, anti-HBs, and anti-HBc), suggesting re-infection or reactivation. Similarly, the same study found an increase in specimens positive for all three markers in 94 HIV-positive patients (15.9%) compared to 51 HIV-negative blood donors (5.9%).[17]

Very few studies from sub-Saharan Africa have found an increase in chronic HBV carriage in HIV-positive individuals, and this has been mainly in symptomatic HIV-positive patients,[18-20] and HIV-positive patients with hepatocellular carcinoma.[21] In addition, a study on a healthy rural population of the Republic of Equatorial Guinea found increased HBV carriage in HIV co-infected people, but the number of HIV-positives in this study was small (only 12, two of whom were HBsAg-positive).[22] Also, an earlier study (1998) on 100 Tanzanian blood donors reported an increased risk (odds ratio [OR] = 4.0) for HBsAg positivity,[23] but when the same author repeated this study in 2004-2005 on 1,599 blood donors, no increase in HBsAg was found.[24]

A study from Burkina Faso that encapsulates the above findings very well, reported increased HBsAg prevalence in HIV-positive pregnant women (12% *versus* 8.1%), and included 33 AIDS patients amongst the 75 HIV-positives. When these 33 women are removed from the HIV-positive group and analysed separately (5/33 were HBsAg-positive), there is very little difference in HBsAg prevalence between the HIV-positives (4/42 [9.5%]) and HIV-negatives (26/321 [8.1%]).[25] This is also in agreement with studies from non-endemic countries which have found a much higher prevalence of HBsAg in patients with AIDS than in HIV-positive patients without AIDS.[3]

Reduced persistence of anti-HBs and anti-HBc

A number of studies have shown that HIV co-infection decreases anti-HBs persistence in naturally infected[4,13] and vaccinated individuals,[26,27] contradicting an early report that persistence of anti-HBs in responders to the HBV vaccine administered prior to HIV infection, is not affected.[1]

Chronic HBV infection without anti-HBc (i.e. HBsAg-positive and anti-HBc-negative) is a rare serological pattern that is associated with immunosuppression, most often due to HIV co-infection.[28] A correlation between high HIV viral load, low CD4+ count, and absence of anti-HBc was demonstrated in this study, with anti-HBc becoming detectable at lower levels of immunosuppression.

Data on persistence of anti-HBs in HIV-positive individuals in sub-Saharan Africa are scant. The DRC study discussed above,[17] found significantly lower mean levels of anti-HBs (15.7 IU/l *versus* 375.2 IU/l) as well as a significantly higher prevalence of low anti-HBs levels (lower than 25 IU/l: 63.6% *versus* 35.6%), in HIV-positive as opposed to HIV-negative pregnant women. Also, a Kenyan study on AIDS patients found a very low prevalence of anti-HBs (24.4%) compared to the general population (57%).[29] In contrast, however, a South African study (n=1420) found a statistically significant increased prevalence of anti-HBs in HIV-positive pregnant women (29.5% *versus* 20.1%; OR: 1.66).[30]

There are no sub-Saharan data on reduced persistence of anti-HBc in HIV-infected populations.

Increased HBV infectivity

HIV-co-infected chronic HBV carriers have been shown to have a higher HBV replication rate,[2,4,6,31] with increased serum HBV DNA levels, and are more likely to be HBeAg-positive for a longer time than those infected with HBV alone.[2,6,12] As was seen in the progression to chronic carriage, the degree of HIV immunosuppression is related to the degree of HBV infectivity. This is evident from data which show that in HIV-positive patients with AIDS, the prevalence of HBsAg and HBV DNA is higher than in HIV-infected patients without AIDS.[3]

However, HBV DNA and HBeAg levels have been shown to decrease in some (5/9) chronic HBV carriers during the acute phase of HIV infection.[32] Thus, shortly after HIV infection, it is possible that for a short period of time, HBV infectivity is actually reduced. A number of hypotheses was put forward by the authors to explain this phenomenon, but as yet they remain untested.

Data from sub-Saharan Africa on this subject are limited but informative. A large Zambian study conducted on pregnant women (n=1861, 340 being HIV-positive) found a slight non-significant increase in HBsAg prevalence in the HIV-positive group (7.1% *versus* 5.4% in the HIV-negative group). Of interest, however, was the high prevalence of HBeAg positivity in the HBsAg-positive/HIV-positive women (25% *versus* 8.5% in the HIV-negative women), suggesting a much higher rate of infectivity.[33]

Similarly, a more recent Côte d'Ivoire study on pregnant women found that although there was no difference in HBsAg prevalence, with 9% (45/499) in HIV-positive versus 8% (40/498) in HIV-negatives, of these HBsAg positives, there was an almost three-fold increase in HBV infectivity in the HIV-positives, with 26.7% *versus* 9.4% being HBV DNA-positive.[34]

In agreement with studies from non-endemic countries,[3] the prevalence of HBV DNA in co-infected AIDS patients was found to be increased in a study on 100 AIDS patients in

South Africa, where six (6%) of the patients were HBsAg positive, with three (50%) of these being HBeAg-positive.[18] The area from which these patients were drawn, has a HBsAg carrier rate of 1.4%, with 0-12% of carriers being positive for HBeAg.[8]

In contrast to these studies, a recent study in South Africa on pregnant women (n=1,420), found no difference in the prevalence of HBsAg between HIV-positives and HIV-negatives (6.2% [44/710] *versus* 5.8% [41/710]) and HBV DNA (2.4% [11/454] versus 2.2% [10/710]), although there was a significant increase in the prevalence of HBV exposure in the HIV-positive group (39.2% [278/710] *versus* 30.1% [214/710]).[30]

The previously discussed DRC study[17] provides a good illustration of the relationship between HBV infectivity and HIV immunosuppression in co-infected individuals: there was a significantly higher prevalence of HBV DNA in AIDS patients (20.4%), compared to asymptomatic HIV-positive patients (8.9%), and HIV-positive pregnant women (0%). Thus, it is clear that as HIV progresses to AIDS, the infectivity of HBV rises in co-infected individuals.

Increased transmission of HBV

It is evident from the increased prevalence of HBV exposure in HIV-positive individuals in non-endemic areas that transmission of HBV must be on the increase in populations who are at risk for these infections. In these areas, there is overwhelming evidence that the association between HIV and HBV positivity is very strong,[1-6] for example an almost seven-fold increase in HBV prevalence in HIV-positive male adolescents has been reported.[5] However, the data from sub-Saharan Africa, which is highly endemic for both viruses, stand in sharp contrast to these studies, with only one study finding as much as a four-fold increase,[23] others finding less than two-fold increases,[30,35-37] and still others finding no increase.[24,29,38-45] Although these conflicting reports make it difficult to draw a definitive conclusion, it is clear that transmission of HBV in HIV-positive individuals, when it is increased, is not increased to the same extent as in non-endemic areas.

Studies on sub-Saharan hospitalised patients may shed more light on the subject, although a common problem with these studies is the lack of a comparison HIV-negative group, so it is not always possible to say whether the prevalence of HBV is increased or not. For example, a recent Nigerian study found an HBV prevalence of 70.3% (211/300) in hospitalised HIV-positive patients.[46] Thus, when taken together with the increased HBV infectivity of symptomatic HIV-positive patients as discussed above, it is clear that, theoretically at least, HBV transmission should be increased in these patients. However, it is questionable whether this will be so in reality, given that these patients are often gravely ill, and will most likely not be engaging in sexual activity. Also, in countries where highly active anti-retroviral therapy (HAART) is available and these patients recover and lead normal lives, it is likely that they will be receiving intensive counselling about safe sexual practices, once again lowering the risk of HBV transmission.

Ultimately, the question is whether increased transmission, when it is present, is due to shared risk factors alone, or whether the presence of HIV infection facilitates HBV transmission. This can be answered when taking into account that HIV infection is associated with HBV re-infection and reactivation, increased progression to HBV chronic carriage, reduced persistence of anti-HBs in naturally infected and vaccinated individuals, and an increased HBV infectivity rate. Thus, it is clear that HIV immunosuppression facilitates transmission of HBV.

In sub-Saharan Africa, because of the high prevalence of HBV exposure, the prevalence of exposure to HBV in HIV-infected individuals is not expected to be much higher than it is in HIV-negative individuals. The reduced persistence of anti-HBs in HIV-positive individuals seen in non-endemic areas and reported by a few sub-Saharan authors[17,29] may, however, lead to increased re-infection in previously immune individuals. Reactivation in these individuals is also possible, as it has been previously shown that HBV DNA can be detected in sera positive for anti-HBs alone, in healthy Africans.[47] This will have the effect of increasing HBV transmission from HIV-positive individuals who are well enough to remain sexually active. Pregnant women with active HBV infection are likely to infect their babies perinatally, a route of transmission that is not common in sub-Saharan Africa due to low HBeAg carriage.[8] However, there is very little evidence as yet to support an increase in reactivation or re-infection,[17] and no data to support increased HBV perinatal transmission. Whether this will become evident later on in the HIV pandemic when HIV morbidity is more prevalent, or whether it is already happening but remains hidden because this is an under-researched topic in the region, or whether this will not occur in sub-Saharan Africa, remains to be seen.

Impact on liver disease

HIV immunosuppression was thought to reduce liver damage, due to a less aggressive HBV-specific immune response.[2,6,48,49] This is supported by reports of a reduction in icteric illness in acute HBV infections in HIV-positive patients,[1,4,14] although this reduction was not always significant,[1] and one study did not support these findings.[15] However, HIV infection has been found to exacerbate liver disease, with an early study finding death from liver failure in four of five HIV-positive HBV carriers, compared to two of six HIV-negative HBV carriers.[31] More recently, it was found that HIV- and HBV-co-infected patients have a significantly increased risk of dying from liver disease. This risk was found to increase after starting treatment for HIV using HAART.[50] However, hepatocellular cancer, although more prevalent in HIV- and HBV-co-infected patients, does not appear to be accelerated by HAART.[51]

Thus, it is apparent that in HIV-infected patients, although acute HBV infections are largely asymptomatic with little apparent liver damage, once the virus has established chronic infection in hepatocytes, liver disease is accelerated and the risk of mortality from liver failure is increased. The exact mechanism for this acceleration of liver disease in co-infected patients is not yet clearly understood.

There are no data from sub-Saharan Africa on this area of research, although there is a growing body of research on the effects of HAART in these patients. This topic is dealt with extensively in a companion article in this issue of the journal.[52]

Impact of HBV on transmission and natural history of HIV infections

Because of the high prevalence of HBV in AIDS patients, there were early speculations that HBV infection may be a co-factor in AIDS,[53-55] and some studies found that HBV infection hastened progression to AIDS.[56,57] However, extensive research has shown that there is no convincing evidence that HBV hastens progression to AIDS,[1,3,4,16,58,59] in HIV- and HBV-co-infected patients. Most of the early speculations were based on very small studies, whilst larger studies have shown no association between HBV infection and progression to AIDS.[4,59]

More recently, a retrospective study on the effect of HBV on the course of HIV infection in 458 HIV-positive patients, revealed that HIV viral loads were lower over time in HBsAg-positive patients. However, there was no effect on the progression of HIV to AIDS or death.[60] The first finding leads to speculation that the transmission of HIV from co-infected patients may be decreased due to lower levels of replication, but there is no evidence to support this. There are no data from sub-Saharan Africa on this area of research.

Conclusion

In areas of low endemicity for both viruses, several studies have shown that HIV co-infection reduces inflammation in acute HBV infections, but accelerates liver disease in chronic infections and increases the risk of death from liver failure. This has not been investigated in HAART-naïve patients in sub-Saharan Africa.

Decreased anti-HBs persistence, increased HBV reactivation and re-infection, increased progression to chronic HBV carriage, and increased HBV infectivity, are all common findings in these studies from areas of low endemicity. There is also some evidence of this from sub-Saharan Africa.

In sub-Saharan Africa, it is expected that if there is an increased prevalence of HBV in HIV-infected individuals, it will not be as pronounced as in HBV naïve populations, because of the high background of exposure to HBV, and this is supported by the studies that have been undertaken. It is also expected that any increase in HBV prevalence in HIV-positive individuals that may occur, will be due mainly to reactivation or re-infection.

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