HEPATITIS B AND HIV CO-INFECTION IN SOUTH AFRICA: JUST TREAT IT!

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There are an estimated 350 million hepatitis B carriers worldwide. The prevalence of mono-infection with hepatitis B in South Africa has been estimated at approximately 10% for the rural population and 1% in urban areas.[1,2] The transmission routes of hepatitis B and HIV are similar, but hepatitis B is more efficient. Co-infection with HIV and hepatitis B is therefore not unusual. Recent studies have shown that the prevalence of HIV/HBV co-infection (using HBV surface antigen (HBsAg) as a marker for HBV) in South Africa ranges from 4.8% to 17%, depending on the population studied.[3-5]

The guidelines for the South African HIV Comprehensive Care, Management and Treatment (CCMT) programme do not include viral hepatitis studies.[6] Hepatitis B serology is usually done only if serum aminotransferases are evaluated in the absence of another known cause (e.g. tuberculosis and concomitant medications). The clinical sequelae of HIV/HBV co-infection are multiple and can cause an increase in morbidity and mortality. Awareness of HBV/HIV co-infection with appropriate diagnosis and management is imperative for improved care of our HIV patients.

BIOLOGY

Hepatitis B is a DNA virus classified as a hepadnavirus, which replicates in the liver but is found in other sites of the body.[7] A simplified version of the very complicated HBV life cycle begins with the DNA virus entering into the hepatocyte's nucleus, which then produces and releases RNA into the cell's cytoplasm. A nucleoside reverse transcriptase enzyme is necessary to revert into DNA strand for viral packaging and release from the hepatocyte for further infection. Hence the effectiveness of the nucleoside reverse transcriptase inhibitors (NRTIs) in the use of both HIV and hepatitis B treatment (Fig. 1).

As with HIV, HBV has a high mutation rate. The reverse transcriptase enzyme lacks the proof-reading function that is seen with most DNA polymerases. There are three important clinical mutations in the HB virus: tryosine-methionine-aspartate-aspartate mutant (more commonly known as the YMDD mutant), N236T mutant pre-core mutants, and core promoter mutants. The first two are important for nucleoside reverse transcriptase drug resistance and the last one is important in diagnosis and prognosis of HBV infection. These mutants will be described in more detail further on.[8]

HBV is classified into eight different genotypes using alphabetical nomenclature (A - H). The different genotypes are represented in different geographical locations, and genotype can influence both the prognosis of clinical disease and treatment response rates. In South Africa the common genotypes seen are A1 and E. In Asia B and C genotypes are seen. Genotype C has been noted not to respond as well to interferon treatment as genotypes
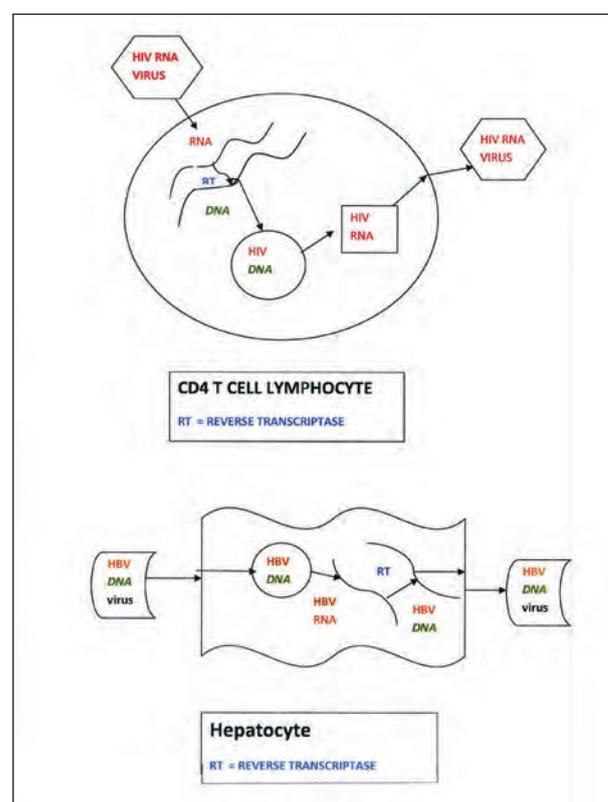

Fig.1. Simplified life cycle comparison of HBV and HIV– use of reverse transcriptase enzyme in viral reproduction.

A and D. C has also been reported to have an increased tendency to be associated with liver failure and hepatocellular carcinoma.[8-10]

TRANSMISSION

Transmission of HBV follows the same blood/body fluid patterns of HIV, but is much more efficient. For example, the rate of HIV transmission from a needle stick is 0.03%, whereas the rate of transmission of hepatitis B can be as high as 30%. Serum but also semen and saliva are effective infectious agents.[7,11] Horizontal transmission due to close contact between young children is a major modality of HBV spread in southern Africa.[12,13] Perinatal transmission is very important in Asia and is thought to occur mainly during delivery and not during breastfeeding.[7] Most of these data come from the literature on HBV mono-infection. HIV-related immunosuppression increases the viral replication and viral load of HBV. HIV/HBV co-infected people have higher HBV viral loads, so co-infection would be likely to make transmission of HBV more efficient.[14]

SEROLOGY AND DIAGNOSIS

The diagnosis of hepatitis B disease is complicated, and multiple laboratory evaluations of serology, HBV viral load, hepatic transaminase levels and/or histological studies are often required. Serological markers have been the standard method of diagnosis of HBV infection for more than 30 years and have been the cause of great confusion among many an intern over this time. The traditional interpretation of serological markers is as follows:

- Anti-HBs – antibody to hepatitis surface antigen confers immunity (either through the vaccine or through exposure). Anti-HBs alone is seen with immunity acquired through vaccination. Anti-HBs + anti-HBc is usually seen with immunity acquired through HBV infection.
- HBsAg – hepatitis B surface antigen (infectious agent) is the first serological marker to appear after infection, and persistence for more than 6 months indicates chronic HBV infection.
- Anti-HBc – antibody to the hepatitis core antigen becomes positive when exposed to hepatitis B virus.
- HBeAg – e antigen represents active replication of hepatitis B (it can be viewed as a poor man's HBV viral load).
- Anti-HBeAg – antibody of e antigen indicates that HBV replication is not occurring and has been considered an end-point of HBV treatment.

PRECORE AND PROMOTER MUTANTS

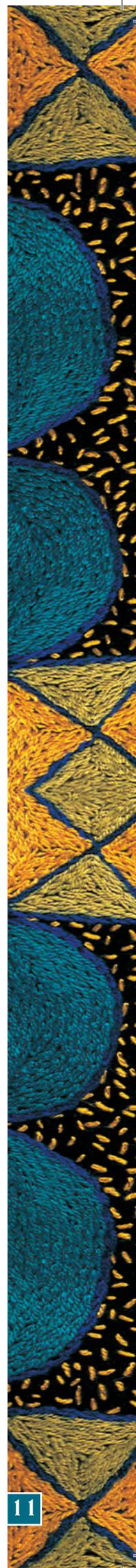These mutations occur in the wild-type hepatitis B replicating virus in the precore and/or promoter regions of the virus. In these regions there are mutations leading to changes in the DNA code which form stop codons in the templates, preventing HBeAg production. A replicating HBV that should be producing the e antigen therefore cannot do so, and is called HBeAg-negative chronic hepatitis B.[8]
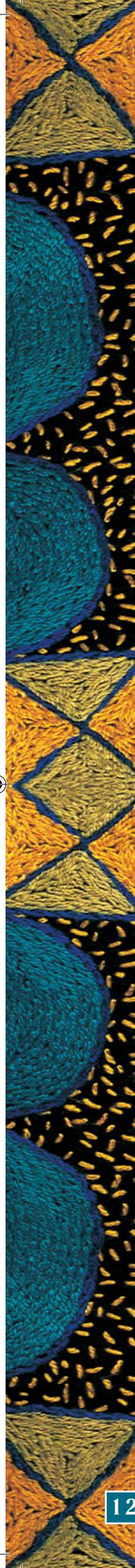
With the wider availability of sensitive molecular biological techniques for detecting HBV DNA in serum and liver tissue, increased attention is being paid to occult (silent) HBV infection. Occult HBV DNA is defined as DNA found in liver or serum in HBsAg-negative patients, and detection of two regions of the hepatitis virus DNA via PCR is required for an infection to be considered occult. The clinical importance of occult HBV infection is unclear and debated. In a co-infected HIV/occult hepatitis B cohort in Philadelphia, no significant increase in liver transaminases was seen after controlling for confounders such as alcohol exposure and hepatitis C.[15] An Italian cohort found an increased frequency of elevated liver transaminases in HIV-seropositive patients who were co-infected with occult hepatitis B. There was a statistically significant increase in hepatitis flares during highly active antiretroviral therapy (HAART). In addition, with the discontinuation of lamivudine in these co-infected patients, there were hepatic exacerbations (defined as greater than twofold increase in transaminases from basesline) when compared with HIV-seropositive patients who did not have occult HBV DNA (64.7% v. 24.6%, $p<0.005$).[16] If occult HBV DNA in HIV is found to be clinically significant, the greater prevalence of HIV/HBV co-infection will have significant consequences for the antiretroviral (ARV) treatment programme in resource-poor settings such as southern Africa. Department of Health and Human Services (DHHS) guidelines and World Health Organization (WHO) recommendations for the treatment of HBV include the use of more than one medication active against HBV in combination therapy for HIV infection.[17]

As mentioned above, diagnosis of chronic hepatitis B may need a variety of testing for accuracy, and serological studies alone may not be adequate. HBV PCR is not readily available in South Africa and is very expensive, but could be considered if there is concern about possible occult infection or HBeAg-negative chronic hepatitis B. Raised levels on liver function tests can be helpful, but 'normal' liver function test results do not rule out chronic hepatitis B infection.[18]

CLINICAL COMPLICATIONS OF HIV/HBV CO-INFECTION

As with most co-infections with HIV, there are interactions between the viruses that can affect the clinical course. HIV increases the risk of an acute hepatitis B infection progressing to a chronic active infection (defined as positive HBsAg for over 6 months) by at least threefold. These co-infected individuals will have significantly higher HBV viral loads, and HIV-infected individuals will have a higher risk of reactivating the latent HBV infec-

tion. Occult hepatitis B infection is also seen more commonly in HIV-positive individuals and co-infection may escape diagnosis, especially in resource-limited countries where it is not possible to measure the HBV DNA viral load. Clinically these viral interactions lead to an increased risk of hepatic cirrhosis caused by hepatitis B and of hepatic-related deaths in HIV patients (hepatocellular carcinoma and cirrhosis) if not treated.[14]

Hepatitis B *per se* does not interfere with the disease course of HIV, as CD4 immune reconstitution and viral load suppression in patients on HAART are similar to those in hepatitis B-negative patients. However, HBV co-infection can increase complications with treatment of HIV patients with HAART or other concomitant medications. A retrospective study in miners in South Africa showed that hepatotoxicity was more likely to occur with HAART initiation if the baseline HBV DNA was above 1×10^4 copies/ml, and a higher proportion of these patients had hepatotoxicity 12 weeks after initiating HAART.[19] The HIV/HBV-co-infected patients who had the highest degree of hepatotoxicity were taking HAART and antituberculosis treatment. Patients who were HBsAg positive had 100% increase in hepatotoxicity (0.11 to 0.22 proportion of patients) compared with patients on TB medication without HBsAg during the first 6 months of TB/ARV treatment.[3] These hepatic exacerbations can be related to several mechanisms: direct drug-related liver damage, seroconversion from HBeAg or HBsAg positivity, immune reconstitution in patients with HBsAg, and an HBV viral load rebound after effective ARV therapy (tenofovir/lamivudine) for HIV/hepatitis B is withdrawn. Co-infected patients can also be at increased risk of hepatic steatosis and lactic acidosis from ARVs.[12,14]

Careful observation is needed in the co-infected patient if anti-hepatitis B antiretroviral drugs are removed. Significant hepatic exacerbations (alanine aminotransferase >200 U/l) were reported in 4% of a European HIV/HBV-co-infected cohort, and 1/147 deaths from fulminant hepatic failure (0.7%) occurred. Hepatitis exacerbations were seen about 5 - 8 weeks after removal of the antiretroviral agent. Re-institution of the agent in these situations is the treatment of choice.[20]

CLINICAL FOLLOW–UP

HBV viral load is the major factor that determines progression to liver cirrhosis, hepatocellular carcinoma and death in patients with chronic hepatitis B. However, serum hepatitis B DNA is costly and not routinely performed in South Africa, especially in the public sector. The degree of liver fibrosis is also important in determining prognosis and treatment decisions. As in mono-infections, the patient with hepatic cirrhosis carries a high risk of developing hepatocellular carcinoma. Liver biopsy has been used to stage fibrosis, but more recently new non-invasive methods such as elastometry and serum biochemical indices have been used. Neither of these methods is well validated in co-infected patients.[21]

In the South African public sector context HBV/HIV co-infected patients should have liver function tests 1, 3 and 6 months after initiation of HAART, and close monitoring should be performed with any change or discontinuation of HAART. Education regarding transmission of hepatitis B (including condom use), avoidance of alcohol and herbal medications is needed. All concomitant medications should be reviewed for hepatic toxicity and if possible switched to a less hepatotoxic drug. Partners of HBV-infected HIV patients should be evaluated for HBV. If seronegative, they should be vaccinated. Serum HBeAg and anti-HBe can be used as a limited surrogate marker for HBV DNA replication, and a clinical history and examination, measurement of the serum albumin, prothrombin time and platelet count, and an abdominal ultrasound scan can be done to evaluate for liver cirrhosis.[14,22]

TREATMENT

Treatment for HBV in HIV-seropositive patients is usually not curative because viral reserves are not eradicated. Treatment is done to reduce the HBV DNA viral load with the goal of preventing or reducing the risk of liver disease progression, cirrhosis and hepatocellular carcinoma. There are several drugs available for treatment of hepatitis B mono-infection: interferon-alpha, lamivudine, adefovir, tenofovir, emotricitabine, entecavir, telbivudine and interferon.[8,14]

In public sector CCMT sites in South Africa only lamivudine and tenofovir are available for treatment. As the majority of people in South Africa come in for evaluation of their HIV late in the disease (the average CD4 count on initiation at the Helen Joseph clinic is approximately 90 cells/μl), most will need treatment for their HIV. DHHS guidelines recommend treatment for HBV when the viral load is >20 000 IU/ml in HBeAg-positive patients and 2 000 copies/ml in HBeAg-negative patients.[14] However, since HBV DNA is not readily available, the clinician should just treat for both infections. Patients who need treatment for HBV infection should also be started on a fully suppressive antiretroviral regimen that contains NRTIs with activity against HBV including dual therapy for hepatitis B to prevent resistance: for example, tenofovir plus either emtricitabine or lamivudine. Monotherapy with lamivudine for hepatitis B in co-infected patients will result in resistance in 60 - 80% of patients within 12 months. If tenofovir cannot be used, another agent with anti-HBV activity should technically be used in combination with lamivudine or emtricitabine for treatment of HBV infection. However, in the public health sector other drugs are not available.[17] Hepatitis B infection in HIV-seropositive patients may respond poorly to interferon-alpha, and this drug should not be used in any patient with cirrhosis as it can trigger fulminant liver failure. When patients have failed the first-line therapy for HIV with treatment containing lamivudine,

it is recommended that lamivudine be included in the second-line therapy.[8,14]

In instances when HIV treatment is not an option or is not desirable, pegylated interferon-alpha (excluding cirrhosis) may be used for the treatment of HBV infection, as it does not lead to the emergence of HIV or HBV resistance. Adefovir dipivoxil is active against HBV but not against HIV at the 10 mg dose; however, there is a theoretical risk of development of HIV resistance, as it has anti-HIV activity at higher doses and is related to tenofovir. Adefovir is not available in the public sector.[17]

VACCINATION

Benjamin Franklin's 'An ounce of prevention is worth a pound of cure' could not have been more prophetic than in the situation of HIV/HBV. With the addition of the hepatitis B vaccination to the Expanded Programme on Immunization (EPI) in 1995 for all infants at 6, 10 and 14 weeks, HBV/HIV coinfection will begin to decrease.[13] For those who were born before 1995, vaccination is imperative for prevention. In those already infected with HIV, the vaccine is not as effective. With a CD4 count >500 cells/µl the response rate is 87%, and with a count of 200 - 500 cells/µl it falls to 33%. Vaccination is recommended when the CD4 count is above 350 cells/µl. However, vaccination should not be delayed if the CD4 count is low, as there are some patients who do respond with lower CD4 counts. Vaccination response rates improve when the HIV viral load is suppressed to <50 copies/µl on HAART. Doubling the dose of the vaccine from 20 µg to 40 µg per injection or adding a fourth immunisation also helps response rate.[22]

CONCLUSION

Hepatitis B co-infection is prevalent in our population and can make HAART more complicated. However, most of our patients tolerated HAART without difficulty, and with close monitoring the simple combination of tenofovir/lamivudine with efavirenz is very effective in treating both HIV and hepatitis B and should be considered first-line therapy in these patients.

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