

Review article**HIV/HBV Co-infection - A Global Challenge**Tumpa SI¹, Mamun AA²**Abstract:**

With prevalence worldwide approximately 10% of the HIV-infected population is infected with hepatitis B. In persons with HBV and HIV co-infection, HBV-related liver disease progresses more rapidly than in those with HBV mono-infection leading to increased rates of persistent infection, higher HBV DNA levels, increased cirrhosis and liver-related mortality, increased risk of hepatocellular carcinoma, and decreased efficacy of anti-HBV therapy. Furthermore, HIV-infected patients co-infected with HBV have an increased risk for antiretroviral therapy-related hepatotoxicity. The management of hepatitis B in co-infected patients is complicated because HIV substantially impacts the outcome of HBV. For all of these reasons, effective treatment of HBV in persons co-infected with HIV is clearly high priority. If treatment is indicated in an HBV/HIV co-infected patient, the severity of liver disease, probability of various reactions and potential adverse events should be taken into account. Combination therapy should be used to avoid development of antiviral resistance. Continuous monitoring of HBV patients, the choice of antiviral therapy or history of seroconversion, is vital to recognize reactivation and subsequent need for treatment, to identify drug resistance and viral breakthrough early. Further work is also needed on how to optimize anti-HBV therapy in HIV/HBV co-infected persons and to determine which combinations are most effective and least toxic together with anti-HIV regimens. Little data, however, are available on HIV/HBV co-infection from regions with high chronic hepatitis B prevalence. The authors aim to bring to light the overall status of HIV/HBV co-infection.

Keywords: HIV; hepatitis B; co-infection; chronic

Bangladesh Journal of Medical Science Vol. 14 No. 04 October'15. Page: 316-322

DOI: <http://dx.doi.org/10.3329/bjms.v14i4.25748>

Introduction:

Due to shared modes of transmission like sexual and percutaneous routes, HIV-infected populations have a high prevalence of hepatitis HBV co-infection¹. Some others similar characteristics such as using a reverse transcriptase enzyme in replication; the tendency to develop chronic infections, which are often difficult to treat; and finally, an immense capacity of mutation in their genome, causing rapid appearance of mutant strains, some of which are resistant to widely used anti-viral agents. In addition, both viral genomes can integrate within the host genome, a process which is obligatory for the life cycle of HIV, but not for HBV. While highly active antiretroviral therapy (HAART) has dramatically improved the lives of those with HIV, the consequences of associated illnesses such

as HBV co-infections have become more relevant. Conditions associated with HBV are currently among the leading causes of hospital admission and death in the HIV-infected population².

In addition, persons co-infected with HIV and HBV have a significant increase in liver-related mortality when compared with those who have HBV mono-infection³. Further, HIV-infected patients co-infected with HBV have an increased risk for antiretroviral therapy-related hepatotoxicity, particularly when HBV DNA levels exceed 10,000 copies/ml⁴. Both can lead to chronic disease, cancer and death and neither can be eradicated with the use of current therapies. These data suggest the importance to focus on the impact of HIV-induced changes in innate

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and adaptive immune response and modifications induced by anti-retroviral therapy that may impact on progression of advanced chronic hepatitis B and clinical course of disease.

HBV infection is itself a dynamic disease and co-infection with HIV considerably complicates its diagnosis and management because the more rapid development of circulated HBV virus in the body. But co-infection with HBV is a preventable cause of chronic liver disease among HIV-infected patients. The tools are already available: vaccination and antivirals with dual anti-HIV and anti-HBV activity⁵. Implementation of anti-HBV vaccination in HIV-infected persons is still largely incomplete whilst long-standing recommendations for immunization of persons (with or without HIV infection) at risk for HBV. As a result the prevalence of chronic HBV infection has been largely unchanged over the past decade among patients in all groups⁶.

Epidemiology of HBV Infection in HIV-infected Patients:

Since both the hepatitis B virus and the HIV virus share similar transmission routes (Table-I), it is not surprising that there is a high frequency of co-infection³.

| Table-I: Transmission routes for both HBV and HIV |
|---|
| Unprotected sex. |
| Sharing of drug needles. |
| Living in a household with an infected person. |
| An infected mother to her newborn child at birth. |
| Sharing earrings, razors or toothbrushes with an infected person. |
| Unsterilized needles, including tattoo or piercing needles. |
| Human bites. |

It is estimated that, worldwide, 39 million people live with HIV infection and that 1.5 million (3.8%) of them die of HIV-related causes⁷. Although HBV is about 100 times more infectious than HIV and more than 240 million people have acute or chronic consequences of hepatitis B^{1, 8-10}, HBV and HIV are endemic in the same world regions (Table-II)¹¹ and

share their routes of transmission.

Table-II: Prevalence of HIV/HBV Co-infection

| Areas of Endemicity | Prevalence |
|--|---------------------|
| Malawi | Highest (20%) |
| Sub-Saharan Africa and the Far East | High (>8%) |
| Eastern and southern Europe, South America and rest of Africa and Asia | Intermediate (2-8%) |
| Northern Europe, North America, and Australia | Low (<2%) |

After acquiring HBV infection, HIV infected individuals are 6 times more likely to develop chronic hepatitis B than HIV negative individuals¹²⁻¹⁴. The progression of chronic HBV to cirrhosis, end-stage liver disease, and/or hepatocellular carcinoma (HCC) is more rapid in HIV-infected persons than in persons with chronic HBV alone³. Men who have sex with men (MSM) show higher rates of HBV/HIV co-infection than injecting drug users (IDUs) or heterosexuals¹⁵. The risk of chronic hepatitis B is greater in congenital and acquired immunosuppression including HIV infection and due to usage of immunosuppressant drugs^{3, 16, 17}.

Factors affecting the prevalence of chronic HBV include age at time of infection and mode of acquisition, which vary geographically. In the United States and Western Europe, HBV often is acquired in adolescence or adulthood via sexual contact or injection drug use¹⁸. In the United States, HIV/HBV co-infection rates are highest among MSM and IDUs. In contrast, in Asia and sub-Saharan Africa the most common modes of transmission are vertical and early childhood exposures¹⁹.

The Influence of HBV on HIV Infection:

HBV co-infection do not reported to have a substantial impact on immunologic or HIV virologic responses to antiretroviral therapy (ART) or on the development of AIDS-defining illness or HIV-related death^{15, 20}. Chronic HBV infection significantly increased liver-related mortality in HIV infected patients but did not impact on progression to AIDS or on viral and immunological responses to HAART. There is evidence that HBV infection itself reduces CD4 cell counts in patients with cirrhosis and hypersplenism²¹.

The Influence of HIV on HBV Infection:

Although the evidence remains conflicting, acute infection with HBV is more likely to be mild or asymptomatic in HIV (+) patients compared with those who are HIV (-)^{12, 22}. Patients with HIV infection can have high levels of HBV DNA and hepatic necro-inflammation with hepatitis B core antibody (anti-HBc) but not Hepatitis B surface antigen (HBsAg), which is called “occult HBV” but lower rates of clearance of the hepatitis B e antigen (HBeAg)²³. HIV infected individuals are more likely to lose previously developed protective anti-HBs antibody and develop acute hepatitis B infection; this risk is also associated with lower CD4 counts^{24, 25}. HIV increases the risk of cirrhosis and end-stage liver disease in HBV co-infection³. Progression to liver cancer is more rapid, with HIV-positive patients with HBV infection developing liver cancer younger than patients with HBV infection alone^{2, 12, 22, 26}. Liver-related disease has emerged as the leading cause of non-HIV-related mortality in parts of the world where effective ART is widely available. The impact of HIV on HBV is summarized in table III.

Table-III: Impact of HIV on HBV

| |
|---|
| Prolonged alanine aminotransferase (ALT) elevation. |
| Reduced rate of spontaneous HBeAg and HBsAg seroconversion. |
| Increased rate of HBeAg-positive disease. |
| Higher HBV DNA levels |
| Lower ALT elevations. |
| Increased rates of persistent infection. |
| Milder hepatic necroinflammation. |
| Decline in liver enzyme levels. |
| Increased progression to cirrhosis. |
| Increased risk of hepatocellular carcinoma (HCC). |
| Decreased response to interferon. |
| Decreased efficacy of anti-HBV therapy. |

Indications for Treatment of HBV in HIV Infection:

HBV therapy is recommended for all HIV/HBV co-infected patients with abnormal ALT values or HBV DNA levels of >2,000 IU/mL. Some guidelines cite >20,000 IU/mL as the threshold for treatment of HBeAg-positive patients²⁷. However, many experts recommend treatment of HBV for all HIV co-infected patients in whom any HBV replication is present.

HBV treatment may be considered when the CD4 count is <350 cells/mm³ or in case of symptomatic HIV and antiretroviral treatment is indicated or when there are no clinical signs of cirrhosis and the CD4 count is >350 cells/mm³,²⁸. It is discreet to test all HIV infected persons for both HBsAg and anti-HBc and if either is positive, to test for HBV DNA. Persons who are negative for all HBV seromarkers should receive HBV vaccine.

Indications for Treatment of HIV in HBV Infection:

ART should be initiated for all HIV-infected persons who have a CD4 count less than 200 cells/mm³ and considered initiating therapy for those with a CD4 count of 200-350 cells/mm³ and also irrespective of CD4 count²⁴. Patients with HIV and HBV co-infection should be advised against self-discontinuation of ART, since discontinuation of antiviral agents that have HBV activity may cause serious hepatocellular damage as a result of HBV reactivation²⁹.

Treatment:

The long-term treatment goals are the same for HBV/HIV co-infected patients as for HBV mono-infection: delay development of end-phase liver disease (ESLD), reduce the risk of HCC and improve survival. Until further research emerges on the optimal treatment for HIV/HBV co-infected population, data from HBV mono-infected persons will need to be extrapolated. In this setting, the clinician must carefully select a course of therapy that does not have significant overlapping anti-HIV activity.

Interferon

In HBV mono-therapy (treatment of HBV only), suppression of viral replication is the aim of therapy. Interferon (IFN) is most effective treatment for chronic HBV infection in patients who have not yet started HAART for their HIV³⁰. INF is more effective in patients who are positive for HBeAg (in whom liver decompensation has not occurred yet), have elevated ALT levels more than twice the upper limit of normal and low HBV DNA levels³¹⁻³⁴. It is also a major concern that interferon therapy is just effective with HBV infection not HIV and a durable treatment response is rarely achieved after treatment with IFN in HBV/HIV co-infected patients³⁵. It therefore may be less useful in patients with HIV/HBV co-infection than in those with HBV alone^{33, 36}.

Telbivudine

Telbivudine is a thymidine analogue that also selects for the HBV rtM204 mutation, which leads to

lamivudine (3TC) cross-resistance. Telbivudine as a single agent is limited to treat HBV by a moderately high risk of developing drug-resistant HBV³⁷. Telbivudine also may have anti-HIV activity³⁸ and limited data in HIV/HBV co-infected population and is not recommended for use without fully suppressive ART. Thus, most experts do not recommend use of telbivudine mono-therapy.

Adefovir

Of agents with activity against HBV, adefovir (ADF) is the least potent. At lower dosages, ADF suppresses HBV replication but is less effective than telbivudine or tenofovir (TDF). In addition, ADF at low doses (10mg) does not have activity against HIV but higher doses do have activity against HIV³⁹. ADF appears to be active against 3TC-resistant HBV⁴⁰. The use of ADF largely has been deposed in favor of treatment with TDF, a related but more potent agent and active against HIV. Although low-dose ADF does not appear to be active against HIV, it is the least potent of the available anti-HBV drugs and thus an inferior option⁴¹.

Treating HIV and HBV Infections Concomitantly

Co-treatment remains as a topic of debate in the medical community. Some researchers focus on treating one virus at a time, while others declare it safe to treat both simultaneously. If treatment is indicated in an HBV/HIV co-infected patient, some factors such as combination ART for HIV infection, the severity of liver disease, probability of various reactions and potential adverse events should be taken into account⁴². When treatment is necessary for both HBV and HIV infections, HAART is needed for HIV. Entecavir, a partial inhibitor of HIV replication along with 3TC are applied to induce mutation in HIV polymerase which is an indication of resistance to therapy. Entecavir should not be used without a fully suppressive ART regimen as it can select for the HIV mutation M184V that result in HIV resistance to 3TC and emtricitabine (FTC)⁴³. 3TC works for both HIV and HBV, but studies have demonstrated a high degree of resistance and hepatic “flares” when removed⁴⁴.

The most potent agent such as TDF plus entecavir or TDF plus 3TC or TDF plus FTC is recommended as the best choice^{33, 34}. In co-infected patients who develop resistance to 3TC, this is recommended because there is no cross-reactivity between these agents. It is assumed that when entecavir is used along with another strong nucleoside analogue in co-

infected patients, the sensitivity of HBV would be more durable than when entecavir is used alone as monotherapy³⁰. Though TDF and ADF are related, TDF has more potent HBV activity than ADF and also can be used for HIV treatment. According to Lacombe (2008), decline in HBV DNA more pronounced in TDF (66%) than ADV (53%)⁴⁵. TDF should be used only for patients who are on fully suppressive ART. In combination with 3TC or FTC it is usually used as first-line therapy. HBV that is resistant to 3TC or ADF can be treated efficiently with TDF therapy^{36, 46}. This was strengthened by the later report of Matthews (2009)⁴⁷. He showed that, TDF plus either 3TC or FTC more likely to have undetectable HBV DNA than TDF or 3TC alone. ADF is an option for HBV treatment in HIV-infected patients who decline or cannot take ART, but it should be used with care. The combination of telbivudine and ADF decrease the rate of developing telbivudine-resistant HBV, but limited data exist with this combination and there is a possibility of anti-HIV activity with telbivudine³⁶.

Management of HBV in HIV Co-infected Individuals:

Liver disease may progress more rapidly in those patients co-infected with HBV/HIV and could lead to serious liver disease complications such as cirrhosis and liver cancer at younger ages. In addition, HIV infection can increase the amount of circulated HBV in the body. So the patient’s health should be carefully monitored by, a CD4 count every three to six months; clinical monitoring of HIV-related symptoms every three to six months; and ALT measurements every three to six months for patients with inactive HBV infection (since liver disease may reactivate even after many years of quiescence)²⁸.

Vaccination:

All children and adolescents younger than 18 years old and not previously vaccinated should receive the vaccine if they live in countries where there is low or intermediate endemicity. In those settings it is possible that more people in high risk groups may acquire the infection and they should also be vaccinated. They include^{48, 49}:

Conclusion:

The synergistic relationship between HIV and HBV accelerates the complications of HIV/HBV co-infected patients. Despite the availability of cheap, efficacious therapy and HBV vaccine for about three decades there has been a significant case of HIV/HBV co-infection and mortality rate in the past decade. The effects of HBV/HIV co-infection emphasize

Table-IV: Selective vaccination of individuals with identified risk factors

- People who frequently require blood or blood products, dialysis patients, recipients of solid organ transplantations;
- Injecting drug users;
- Household and sexual contacts of people with chronic HBV infection;
- Travelers who have not completed their hepatitis B vaccination series should be offered the vaccine before leaving for endemic areas;
- Health care workers and emergency personnel;
- Individuals who have had multiple sex partners or who have been diagnosed with an STD
- Men who have sex with men;
- Individuals who received a blood transfusion prior to 1972;
- Individuals who have tattoos or body piercings;
- Individuals who travel to countries where hepatitis B is common (Asia, Africa, South America, the Pacific Islands, Eastern Europe, and the Middle East);
- People interned in prisons;
- Allpregnant women should be tested for hepatitis B infection.

the importance of close working relationships between hepatologists, virologists, infectious disease specialists and primary-care providers in order to optimize patient outcomes.

Acknowledgements:

We gratefully acknowledge Dr. Selina Akter, assistant

professor, Department of Microbiology, Jessore University of Science and Technology for valuable discussions and support. We also wish to offer our thanks to our supervisors Tasneema Ishika and Md. Tanvir Islam for their suggestions and co-operation.

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