

Preamble

Classical opportunistic complications of severe immunodeficiency have declined dramatically as a result of the widespread use of potent antiretroviral therapies. However, coinfections such as viral hepatitis continue to present challenges in the overall management of the HIV-infected patient.

There are several reasons to highlight hepatitis B virus (HBV) coinfection in HIV-positive individuals. Not only is there more severe HBV-related liver damage in these patients, there is also the higher risk of hepatotoxicity using antiretroviral drugs in these patients. Perhaps most importantly, some nucleos(t)ide analogues are active against both HIV and HBV.

This booklet addresses some important questions regarding the management of the HIV-HBV coinfecting patient. It discusses when anti-HBV therapy should be started, and treatment approaches based on whether the patient is a candidate for HBV therapy alone, or whether treatment is indicated for both HIV as well as HBV. This is a key decision, given that certain nucleos(t)ides have activity against both viruses, whereas adefovir is active against HBV alone. Thus, the treatment regimen depends upon whether therapy is directed towards either one, or both viruses.

In this booklet

This booklet discusses fourteen key questions on HIV/HBV coinfection, as listed in Table 1.

Table 1: Key questions on HBV/HIV co-infection

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1. Burden of HBV and HIV co-infection
 2. Liver disease caused by HBV in HIV-infected patients
 3. HBV as a co-factor for HIV disease progression
 4. HBV therapy: when, goals and monitoring
 5. Interferon alpha
 6. Nucleoside analogues: lamivudine and emtricitabine
 7. Nucleotide analogues: adefovir and tenofovir
 8. New HBV drugs
 9. Hepatotoxicity of antiretroviral drugs in HBV carriers
 10. Prevention of further liver damage in HBV carriers
 11. HBV vaccination: doses and schedules
 12. HBV reactivations: diagnosis and management
 13. Treatment of patients with multiple viral hepatitis (C, D)
 14. Management of end-stage liver disease. Screening for hepatocellular carcinoma and liver transplantation
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Each question is followed by a synopsis that reflects current data. The quality of evidence that forms the basis for this synopsis is graded as follows:

- ① – based on properly randomised, controlled trials
- ② – based on other kinds of publications
- ③ – based on expert opinion

The strength of the recommendation was categorized as follows:

A – good **B** – modest **C** – poor

Burden of HIV and hepatitis B virus co-infection

- Chronic hepatitis B affects nearly 10% of HIV-infected patients, and therefore approximately 4 million people worldwide are HBV/HIV-co-infected.
- In India, estimates of HIV/HBV coinfection range from 3.5% (*Bombay Hospital Journal, April 2005*) to 30% (*Ind J Med Microbiol 2003; 21:268-70*)
- Atypical HBV serological markers may be recognized, particularly among those with more severe immunosuppression.
- HBV genotypes may differ among different risk groups and distinct geographical regions, which may influence the natural history of liver disease and the treatment outcome. In India, genotype A is prevalent.

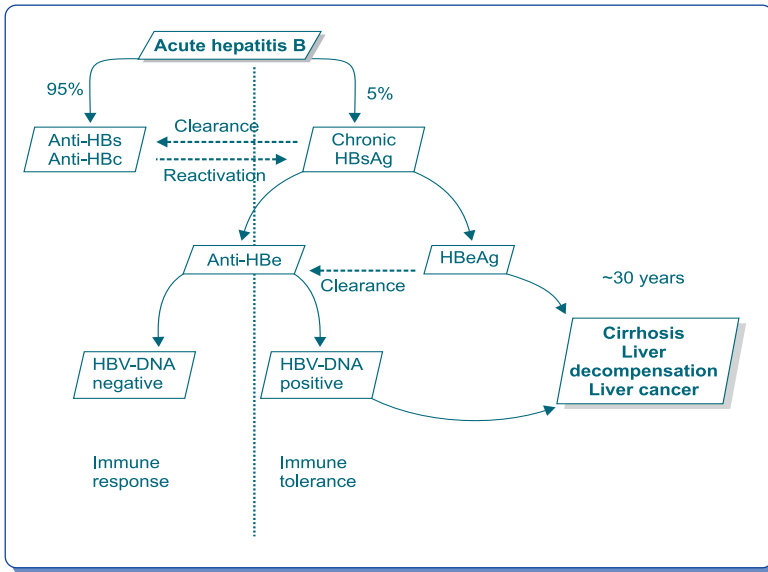
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Liver disease caused by hepatitis B virus in HIV-infected patients

- Elevated serum HBV-DNA levels are frequently seen in HBV/HIV-co-infected patients, whereas liver enzyme elevations are frequently milder than in patients with chronic HBV mono-infection.
- Liver histological damage may progress more rapidly in HBV/HIV-co-infected patients, leading to cirrhosis in a shortened time frame.
- These patients show an increased risk of HBV-related liver complications and death.

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Figure 1: Natural history of hepatitis B virus infection. HBc, Hepatitis B core; HBe, hepatitis B e; HBeAg, hepatitis B e antigen; HBs, hepatitis B surface; HBsAg, hepatitis B surface antigen; HBV hepatitis B virus.



Is hepatitis B virus a co-factor for HIV disease progression?

- Chronic hepatitis B with evidence of active HBV replication might act as a co-factor for HIV disease progression.
- HBV might accelerate HIV disease progression indirectly, enhancing immune activation.
- However, no definitive proof for a role of HBV on HIV disease progression has been reported so far.

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Hepatitis B virus treatment: when, goals and monitoring

- Anti-HBV therapy should be considered for all HIV/HBV-co-infected patients with any evidence of liver disease (i.e. elevated transaminase levels, elevated HBV-DNA titers, necro-inflammatory lesions and fibrosis in the liver biopsy) irrespective of the prevailing CD4 cell count.
- In HIV/HBV-co-infected patients not requiring HAART, HBV therapy should be preferentially based on interferon or adefovir.
- In contrast, in patients presenting with CD4 cell counts of less than 350 cells/ μ l or those already on antiretroviral therapy, the use of agents with double anti-HIV and anti-HBV activity should be preferred.
- When possible, combination treatment with a nucleoside analogue (lamivudine or emtricitabine) plus tenofovir should be administered.
- An earlier prescription of HAART with those agents may be discussed on an individual basis in patients whose criteria to initiate antiretroviral therapy have still not been fulfilled.
- In HBeAg-negative patients with early liver fibrosis stage and without a need for beginning antiretroviral therapy, a watchful waiting strategy could be advisable instead of immediate anti-HBV treatment.

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Table 2: Classification of chronic hepatitis B virus infection

Chronic active hepatitis

HBeAg-positive

HBeAg-negative (with detectable serum HBV DNA)

Inactive carrier state

(HBeAg-negative, normal ALT, negative HBV DNA)

Figure 2: Hepatitis B virus treatment decision algorithm. ALT, Alanine aminotransferase; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; Tx, transplantation

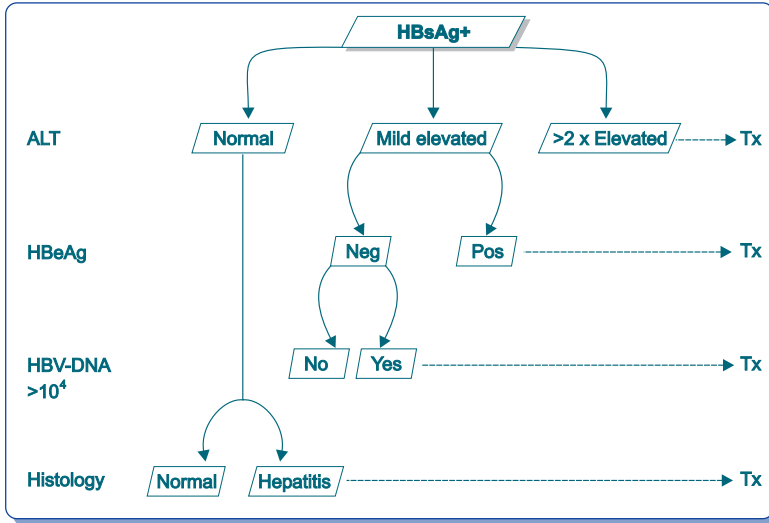
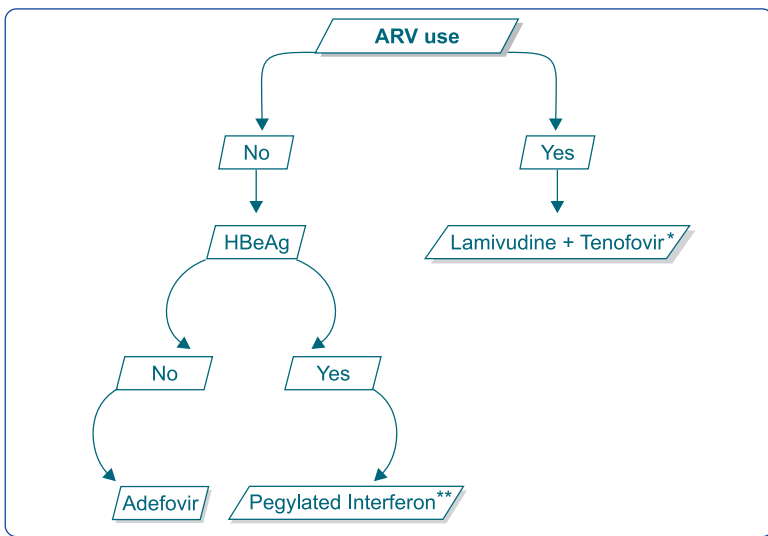


Figure 3: Preferred anti-hepatitis B virus agents in drug-naïve hepatitis B virus/HIV-co-infected patient candidates for hepatitis B virus therapy. ARV, Antiretroviral drug; FTC, emtricitabine; HBeAg, hepatitis B e antigen; 3TC, lamivudine.

*In patients already on highly active antiretroviral therapy without tenofovir/lamivudine (emtricitabine), adefovir might be added (but not if on tenofovir), and 6-12 month course of interferon might be considered.

** With caution in cirrhotic patients.



Interferon alpha

- The efficacy of IFN- α therapy is greater in HBeAg-positive than in HBeAg-negative chronic hepatitis B.
- However, the response rate is much lower in HIV-co-infected patients. The poor tolerance of IFN- α usually limits its use, and CD4 cell drops may be of particular concern in HIV-positive individuals.
- Results using pegylated IFN- α alone or in combination with nucleos(t)ide analogues are awaited.
- In the meantime, IFN- α may be the best choice for HIV/HBV-co-infected patients not requiring antiretroviral therapy.
- However, IFN- α should be used cautiously in HBeAg-positive patients with advanced liver disease and is contraindicated in patients with decompensated cirrhosis.

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Nucleoside analogues: lamivudine and emtricitabine

- Lamivudine and emtricitabine are pyrimidine analogues with excellent safety profiles, and both anti-HIV and anti-HBV activities.
- They should be considered interchangeable and not additive.
- Given their low genetic barrier for resistance, they should not be used as monotherapy in HIV/HBV-co-infected patients.
- They are particularly recommended in patients on antiretroviral therapy and in those taking other concomitant antiretroviral drugs, particularly in HBeAg-negative chronic hepatitis B patients, who will often need prolonged periods of therapy.

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Nucleotide analogues: adefovir and tenofovir

- Adefovir at a dose of 10 mg a day is active against HBV but not against HIV.
- In contrast, tenofovir at a dose of 300 mg a day is active against both viruses.
- These drugs show a more robust genetic barrier to resistance than lamivudine and emtricitabine.
- Moreover, adefovir resistance mutations in HBV are selected at different positions than for lamivudine or emtricitabine.
- When possible, combination therapy with one nucleoside and one nucleotide analogue should be preferred to monotherapy with any of these drugs in HIV/HBV-co-infected patients.

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New anti-hepatitis B virus drugs

- New nucleoside analogues show strong ant-HBV activity and do not inhibit HIV.
- They may be used as monotherapy in HBV/HIV-co-infected patients not taking antiretroviral drugs.
- Entecavir, clevudine and telbivudine are the most promising agents, with a good safety profile.
- The activity of clevudine and telbivudine is halted in the presence of YMDD mutants, whereas the activity of entecavir is only slightly reduced in the face of lamivudine resistance.
- None of these compounds show cross-resistance with adefovir or tenofovir.
- Particularly in combination, they may further improve efficacy and avoid viral breakthroughs.

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Hepatotoxicity of antiretroviral drugs in hepatitis B virus carriers

- Liver enzyme elevations after beginning antiretroviral therapy are more frequent in patients with underlying chronic hepatitis B.
- Therefore, drugs with more hepatotoxic profiles (i.e. nevirapine, efavirenz, full-dose ritonavir) should be used cautiously in co-infected patients.
- Treatment should be discontinued in patients with symptoms or grade 4 increases in aminotransferase levels.
- In certain cases, immune reconstitution phenomena may lead to liver enzyme elevations after starting HAART.
- Close monitoring of these patients during the first weeks may allow them to be kept on therapy, because they tend to experience a progressive resolution of liver abnormalities without discontinuing treatment.
- Mitochondrial toxicity of some nucleoside analogues (mainly zidovudine, stavudine or didanosine) may result in steatohepatitis.

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Prevention of further liver damage in hepatitis B virus carriers

- All non-immunized HBV carriers should be vaccinated for HAV.
- HAV serostatus should be checked in pre-vaccinated individuals and if low or absent titers are found, re-vaccination should be offered, particularly to patients with rising CD4 cell counts in response to HAART.
- Proper hygiene counselling should be offered to avoid exposure to HAV and hepatitis E virus.

- With respect to HCV and HDV, for which there are no prophylactic vaccines, counselling should be focused on avoiding risky injection practices and unprotected sex.
- When necessary, pharmacological and psychological support should be instituted to reduce alcohol consumption. Hepatotoxic drugs, such as anti-tuberculous agents, should be given with caution.

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Hepatitis B virus vaccination: indications and schedules

- HBV vaccination should be provided to all HIV-positive individuals with no serum HBV markers.
- In the case of negative HAV markers, combination vaccination is advisable.
- The response to HBV vaccine is lower in HIV-positive individuals, particularly among those with lower CD4 cell counts.
- Anti-HBsAb titers should be checked 12 weeks after ending the vaccination cycle and booster doses or extra cycles are advisable when no appropriate humoral responses have been obtained.
- In patients with CD4 cell counts of less than 500 cells/ μ l, intensive schedules are initially warranted.

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Diagnosis and management of hepatitis B virus reactivations

- HIV-infected patients with serum markers of previous hepatitis B (anti-HBsAb) or anti-hepatitis B core antibody) or HBsAg-positive carriers with complete suppression of HBV replication under antiviral agents may experience abrupt flare-ups in transaminase levels, which may occasionally be fatal.
- In most instances, HBV reactivations rather than reinfections are the cause.
- The withdrawal of anti-HBV agents, the development of resistance, or the use of immunosuppressive agents often account for most of these episodes.

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Treatment in patients with multiple viral hepatitis (hepatitis C or hepatitis D)

- Multiple chronic hepatitis virus infections are not rare in HIV-infected patients, particularly among IDU.
- In patients with uncontrolled HIV infection, the escape (replication) of multiple viruses rather than competition between them is often seen.
- More severe liver damage in patients with multiple hepatitis leads to a greater urgency to treat them; however, convenient drugs, doses and schedules have not yet been defined, and overall response rates tend to be much worse than for single hepatitis virus infections.

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Management of end-stage hepatitis B virus-related liver disease; screening for hepatocellular carcinoma and liver transplantation (OLT)

- All HIV-infected patients with end-stage HBV-related liver disease should be considered as candidates for liver transplantation as long as they do not have advanced HIV disease.
- In those with severe immunodeficiency (< 100 CD4 cells/ μ l) the control of HIV replication and immune restoration should be prioritised.
- The evaluation and the pre- and post-operative medical management of HIV-positive candidates for OLT must include an interdisciplinary team composed of hepatologists, infectious disease specialists, surgeons, psychologists and social workers.
- HIV-positive candidates should have no previous history of opportunistic infections (except tuberculosis and perhaps oesophageal candidosis), and current CD4 cell counts greater than 100 cells/ μ l and plasma HIV-RNA levels below 200 copies/ μ l or with optional drugs for successful treatment in the future.
- Moreover, they should have abstained from the consumption of alcohol or illegal drugs for at least 6 months.
- The administration of oral anti-HBV agents before transplantation followed by these compounds plus hepatitis B immunoglobulin after transplantation is critical to avoid HBV recurrence in the allograft.

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