New paradigms for treating hepatitis B in HIV/hepatitis B virus co-infected patients

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Until the advent of tenofovir, many HIV/hepatitis B virus (HBV) co-infected patients had been treated with lamivudine as the only agent active against HBV. Selection of lamivudine-resistant HBV strains occurred in many of these patients, complicating clinical prognosis and rescue therapy. These individuals might also transmit HBV-resistant strains. Moreover, a subset of these lamivudine-resistant HBV isolates may behave as vaccine escape mutants, complicating diagnostic accuracy (e.g. producing ‘occult’ hepatitis B) and reducing the efficacy of preventive measures (causing infection in vaccinated persons). Nowadays, periodic monitoring of HBV viral load in co-infected patients should be mandatory. It may allow the early recognition of HBV viraemic individuals who may benefit from either initiating or switching antiviral therapy. In any situation, the use of anti-HBV therapies more potent than lamivudine alone is warranted.

Keywords: liver, tenofovir, drug resistance, vaccine escape mutants

Chronic hepatitis B occurs in 10% of HIV-infected individuals worldwide, with large variations across distinct geographical regions. It is ~5% in Western countries but it may rise to 20% in some sub-Saharan nations. A detrimental effect of HIV on the natural history of chronic hepatitis B is well demonstrated, with increased rates of chronic infection following hepatitis B virus (HBV) exposure, greater levels of HBV viraemia, faster progression to liver cirrhosis and higher liver-related and overall mortality rates. By contrast, the influence of chronic HBV infection on the natural history of HIV is less well known and often considered as negligible, although recent studies have claimed that there is a more pronounced CD4+ T cell decline, slower CD4 recovery under antiretroviral therapy and increased incidence of AIDS and non-AIDS events in HIV/HBV co-infected individuals than in HIV mono-infected persons. The appreciation of this significant negative impact of chronic hepatitis B on prognosis of HIV/HBV co-infected patients clearly demands more attention. The advent of new diagnostic procedures to manage HBV infection, including periodic viral load monitoring, drug resistance testing and use of non-invasive tools for assessing liver fibrosis, and especially the availability of tenofovir, an antiviral agent much more potent than prior anti-HBV drugs, are helping to build a new paradigm for managing chronic hepatitis B in HIV-infected persons, in which early recognition and treatment are cornerstones. Clearly, chronic HBV infection should no longer be disregarded or be a neglected disease in HIV-infected individuals.

HBV surface antigen (HbsAg) testing is mandatory as part of first HIV evaluation. In all individuals with positive serum HBsAg, delta co-infection must be ruled out and serum HBV-DNA and HBV genotype should be tested. Patients with serum HBV-DNA >2000 IU/mL are at increased risk for liver fibrosis progression and accordingly may benefit from antiviral therapy. On the other hand, differences in disease progression and treatment response are seen regarding genotype. For example, genotypes A and B are associated with better response to interferon and slower fibrosis evolution. In the past, selection of the most convenient regimen was mainly driven by the need for antiretroviral therapy, based on current CD4 counts. In subjects with relatively high CD4 counts, pegylated interferon or adefovir were considered as the preferred choices. In contrast, in patients with intermediate to low CD4 counts, initiation of antiretroviral therapy including drugs active against HBV (and preferably including tenofovir) was recommended. The recent recognition that mortality, both overall and liver related, may be higher in HIV/HBV co-infected patients compared with HIV mono-infected individuals, even when HIV replication has been suppressed with antivirals in the former group, has prompted a reassessment of when to start anti-HBV active antiretroviral therapy in co-infected individuals. With the current knowledge, the message is clear: it should be as soon as possible.

Not all antivirals have the same efficacy against HBV and the role of combination therapy is still unclear. Tenofovir has shown the greatest potency in terms of HBV-DNA suppression. When provided alone, however, nearly 20% of patients on tenofovir may not reach undetectable viraemia after 1 year of treatment, a situation that hypothetically makes them prone to select resistance mutations. A A194T change in the polymerase...
Table 1. Consequences of the development of lamivudine resistance in HIV/HBV co-infected patients

- Liver enzyme flares, occasionally severe (and life-threatening in cirrhotics).
- Cross-resistance to emtricitabine, to telbivudine and to a lesser extent to entecavir.
- Transmission of drug-resistant HBV strains.
- Seronegative or occult forms of chronic hepatitis B.
- Evasion of vaccine protection.

Some studies, although it has not been confirmed in others, tenofovir is co-formulated with emtricitabine as Truvada; emtricitabine is another antiretroviral drug active against HBV. Patients receiving Truvada experience faster serum HBV-DNA decline than those treated with tenofovir or emtricitabine alone. Thus, Truvada is the preferred choice for co-infected patients. Once treatment has started, monitoring of HBV-DNA at least every 6 months should be warranted. Furthermore, antiviral resistance testing is indicated when virological breakthrough or lack of primary response is seen. Virological breakthrough is defined as a 1 log increase in serum HBV viral load from nadir in a patient with previous response, while primary response is defined as a 2 log decrease in HBV viral load during the first 6 months.

Access to tenofovir is limited in many developing countries in south-east Asia, sub-Saharan Africa and Latin America where the highest rates of chronic hepatitis B are seen. There, the use of lamivudine as single anti-HBV agent continues to be the rule. Although a subset of these individuals may reach undetectable serum HBV-DNA under lamivudine, a large proportion will fail and select lamivudine-resistant HBV strains. This situation is particularly frequent in HIV/HBV co-infected individuals, in whom baseline serum HBV-DNA levels are more elevated than in HBV mono-infected persons. Selection of lamivudine resistance in chronic hepatitis B is associated with poor outcomes (see Table 1). First is the occurrence of liver enzyme flares, which occasionally may be life-threatening. Secondly, there is the production of broad cross-resistance to many other anti-HBV agents, such as emtricitabine, telbivudine and to some extent entecavir. Reduced susceptibility to adefovir has also been reported following selection of the rtA181S+M204I mutational pattern under lamivudine. Thirdly, transmission of drug-resistant HBV strains may increase; cases of primary infection with lamivudine-resistant viruses have already been reported. Finally, the HBV envelope (S) gene is completely overlapped by the polymerase gene, which explains how polymerase resistance mutations may occasionally result in changes in the envelope gene, which may affect the antigenicity of the HBsAg.

The clinical relevance of changes in HBsAg antigenicity as a result of lamivudine resistance-associated mutations warrants further assessment. Selection of viruses with either poor or null binding affinity to hepatitis B surface antibody (anti-HBs) may mask the identification of HBV persistent infections, causing seronegative or occult chronic hepatitis B. Occult chronic hepatitis B is defined as the presence of HBV-DNA in the blood without HBsAg. It is more prevalent in HIV and hepatitis C virus co-infected patients and in those with hepatitis B core antibody (anti-HBc) as the only HBV marker. False resolution of chronic hepatitis B following seroclearance in subjects with mutant HBsAg has been reported. More worrisome is the description of fatal cases of hepatitis B reactivation among anti-HBs immune persons with lymphoma receiving chemotherapy. Because of its higher prevalence among HIV co-infected patients (between 0% and 36% depending on the study), we recommend testing for HBV-DNA in individuals positive for anti-HBc alone, especially if they have transaminase flares and/or are going to receive any immunosuppressive therapy. Another consequence of altering HBsAg antigenicity is evasion of vaccine protection, since neutralizing antibodies against HBsAg may miss their target. It is noteworthy that resistance mutations to nucleotide analogues (e.g. adefovir) do not result in significant changes in the antigenicity of HBsAg.

Other drugs approved for treating chronic hepatitis B, such as entecavir or telbivudine, should only be considered in special situations in HIV/HBV co-infected individuals and only when tenofovir cannot be used for any reason. Entecavir displays minimal anti-HIV activity, but it is enough to select M184V in HIV. Therefore, entecavir must be used along with a potent antiretroviral regimen in HIV/HBV co-infected individuals, to ensure complete HIV suppression. However, there are scarce data about the potential for inhibitory competition between entecavir and other nucleoside analogues, such as lamivudine or emtricitabine, whose antiretroviral activity could be impaired in the presence of entecavir. Moreover, abacavir is a guanosine analogue, and both drugs might compete in the phosphorylation pathway when given together. In the absence of additional data, it may be worth choosing a nucleoside analogue sparing regimen if entecavir needs to be used in HIV/HBV co-infected individuals. With respect to telbivudine, recent evidence has also raised an alert about its potential anti-HIV activity. As with entecavir, the use of telbivudine in HIV/HBV co-infected persons should be limited to special circumstances, always ensuring that a completely suppressive antiretroviral regimen is given.

At this time, the only anti-HBV drugs that could be used without significant clinical interference with HIV are interferons and adefovir. Their prescription may be considered when for any reason antiretroviral therapy needs to be avoided. A course of 12 months of pegylated interferon may be considered mainly in patients who test positive for the hepatitis B e antigen (HBe). Up to one-third of HBV mono-infected individuals obtain HBe seroconversion; but this rate could be much lower in HIV/HBV co-infected persons. Adefovir at doses of 10 mg daily exerts anti-HBV activity without any significant antiretroviral effect. Moreover, there is no selection of K65R in HIV. However, adefovir displays low antiviral activity against HBV and does not permit the achievement of undetectable serum HBV-DNA in most subjects with elevated baseline viraemia. Thus, the benefit will only be transient in most instances, steadily vanishing as a result of selection of adefovir resistance.

Finally, in HIV/HBV co-infected patients who have already failed lamivudine and display elevated serum HBV-DNA, tenofovir is the best option for regaining complete suppression of HBV replication. Rather than replacing lamivudine with tenofovir, addition of tenofovir or use of the tenofovir/emtricitabine co-formulation (Truvada) is the best strategy, given that liver enzyme flares have occasionally been reported during the
transition period and combination therapy may further reduce the risk of subsequent drug resistance.8,10,21

In summary, HIV/HBV co-infected patients experience a worse prognosis of both HIV and HBV infections compared with individuals mono-infected with either virus. Optimal management of these patients requires knowledge of baseline HBV viraemia and liver fibrosis staging as well as periodic monitoring. Early initiation of antiretroviral therapy with drugs active against HBV is currently encouraged. In the absence of contraindications, tenofovir-based regimens should be considered the preferred choice in any situation. The prospects for a halt or even a regression of liver fibrosis in subjects with long-lasting suppression of HBV replication with nucleoside therapy33,34 is very compelling. On the other hand, in resource-poor settings where HBV infection in HIV: new diagnostic tools and more weapons. AIDS 2006; 20: 863–70.


References


