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Strategies for managing coinfection with hepatitis B virus and HIV

ABSTRACT

Hepatitis B virus (HBV) infection is more aggressive in individuals coinfected with human immunodeficiency virus (HIV): in the presence of HIV, HBV carrier rates and viremia levels are higher, episodes of activation are more frequent, cirrhosis progresses more quickly, and hepatocellular carcinoma occurs more often than with HBV infection alone. As in HBV monotherapy, the objective of treatment is suppression of viral replication. Standard or pegylated interferon may be appropriate treatment for chronic HBV infection for patients who have not yet started highly active antiretroviral therapy (HAART) for their HIV. When treatment is required for both diseases, the use of a combination of nucleoside and nucleotide analogues is prudent, with careful selection of therapy to reduce the risk of antiviral resistance—a particular concern for patients receiving antiretroviral therapy for both HIV and HBV. HBV DNA levels should be monitored every 3 months; the frequency can be extended to every 6 months once the viral load becomes stable or undetectable.

KEY POINTS

Patients with HBV/HIV coinfection are at relatively high risk of frequent HBV activation, progression to cirrhosis, and death from liver-related causes.

If the patient does not yet require HAART but requires treatment for HBV, this is itself an indication for HAART, since monotherapy for HBV is associated with development of resistance to HIV therapy.

Nucleoside and nucleotide analogues should not be used as monotherapy in the HBV/HIV-coinfected patient because of the risk of inducing HIV resistance.

Worldwide, 40 million people are infected with the human immunodeficiency virus (HIV). As many as 4 million of them are coinfected with hepatitis B virus (HBV).[1]

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In North America and Europe, the highest prevalence of HBV/HIV coinfection is in men who have sex with men. Approximately half of HIV-positive men who have sex with men have evidence of prior or active HBV infection, and 5% to 10% have chronic HBV infection. Among those who acquire HIV through injected drug use or through heterosexual transmission, the coinfection rate is much lower.[2,3]

Coinfection with HBV and HIV follows a different course elsewhere in the world. For example, in Africa and Asia, HBV is usually acquired first through neonatal or childhood infection, with either vertical or horizontal transmission after birth.[4,5] In parts of Africa, ritual scarification is likely a major player in the adolescent transmission of HBV. (Ritual scarification is the practice of creating small incisions in the skin of adolescents and rubbing black ash in the wounds to form scars; the cutting instruments are not sterilized between rituals.)

NATURAL HISTORY

In general, HBV tends to be more aggressive in HIV-positive individuals than in monoinfected individuals,[2,6] with higher HBV carrier rates, higher levels of HBV viremia, more frequent episodes of activation, and faster progression to cirrhosis.

Hepatocellular carcinoma occurs more often, its onset is earlier, and its course is more aggressive in coinfected individuals than in monoinfected individuals.[7,8] Using data from a prospective cohort study, Thio et al[9] found that among men coinfected with HIV and HBV, liver-related mortality was almost 19 times greater compared with men infected with HBV only and more than seven times greater compared with those infected with HIV only.

In an observational longitudinal cohort study,[10] the risk of death from liver disease in HIV-positive persons was nearly three times greater among those also infected with HBV ($P < .0001$).

ASSESSING WHEN TO TREAT

The objectives of HBV therapy in individuals coinfected with HIV are similar to those in the population infected with HBV alone. Suppression of viral replication is the major goal. Ideally, the viral load should be reduced to

an undetectable level, which will result in normalization of alanine aminotransferase (ALT) level, improved liver histology, reduced risk of progression to cirrhosis and liver failure (although supportive evidence from controlled clinical trials is lacking), and likely reduced incidence of hepatocellular carcinoma.

For those who are hepatitis B e antigen (HBeAg) positive, seroconversion may be a convenient end point for treatment, although for many patients seroconversion is not associated with remission of disease activity or viral replication.

Treatment decisions depend on whether or not the patient requires highly active antiretroviral therapy (HAART) for HIV infection. If HAART is indicated, then HIV agents that have HBV activity are incorporated into the regimen. If the patient does not yet require HAART for HIV but requires treatment for hepatitis B, this is itself an indication for HAART, since monotherapy for HBV is associated with the development of HIV resistance.

Viral load and ALT

As with treatment of chronic HBV infection, the approach to the patient coinfected with HBV and HIV starts with an assessment of HBV DNA level **(Figure 1)**.[2] Those with HBV DNA levels less than 2,000 IU/mL, indicating the absence of active replicating disease, do not require anti-HBV therapy as long as their viral load remains low. These patients should have their HBV DNA levels monitored regularly for a change in status. If the HBV DNA level is 2,000 IU/mL or higher, the treatment decision should be based on the ALT level. If the ALT is elevated, even intermittently, anti-HBV treatment should be instituted.

Liver biopsy

If the ALT is normal in the presence of a high HBV DNA level, a liver biopsy is recommended, partly because the ALT level is an inadequate indicator of the severity of liver disease. If significant fibrosis is present, treatment is recommended. No treatment is required if fibrosis is mild, but liver biopsies should be repeated every 3 to 5 years in this group because a hallmark of HBV infection is its variability in time to progression. The extent of fibrosis may influence the choice of therapy.

Often in the coinfected patient, HBV-related liver injury must be distinguished from other forms of liver injury. For instance, some of the drugs used to treat HIV infection can induce nonalcoholic fatty liver disease and lipodystrophy. Because the risk of advanced fibrosis is higher in the coinfected patient than in the patient infected only with HBV, the threshold for biopsy in the coinfected patient should be lower.

At present, noninvasive tools to assess the extent of liver injury have not been validated in chronic HBV infection, unlike in hepatitis C virus infection.

Case: HIV/HBV with resistance to tenofovir

A 43-year-old man who is coinfected with human immunodeficiency virus (HIV) and hepatitis B virus (HBV) presents to your office. In 1998, he was treated with lamivudine for his chronic HBV infection and with tenofovir for his HIV infection. In 2006, he was hepatitis B e antigen (HBeAg) negative, and his lamivudine was discontinued, but by 2007 he was again HBeAg positive. In 2007, his HBV DNA level was extremely high, 10^9 IU/mL, and his alanine aminotransferase (ALT) level was 252 U/L. His serum creatinine level ranged from 2.2 mg/dL to 2.5 mg/dL from 2006 to 2008. A drug resistance profile was performed in March 2008, at which time the L180M and M204V resistance mutations were discovered. He had also developed moderate renal insufficiency, presumably from tenofovir. His ALT was 90 U/L at this time. His HIV was under moderately good control at the last visit (HIV RNA: 51 copies/mL). He was still taking tenofovir for his HIV. What HBV therapy should be tried next?

TREATMENT OPTIONS

The potential therapies for HBV in the coinfected patient are the same as those for the patient infected with HBV alone (see "Hepatitis B treatment: Current best practices, avoiding resistance," page S14), with the addition of tenofovir and emtricitabine in combination.

Interferon

Early studies of interferon for the treatment of chronic HBV infection included many patients who were also HIV positive. These early studies revealed a lower rate of HBeAg seroconversion in HIV-positive patients compared with HIV-negative patients. Di Martino et al[11] found that approximately half (26 of 50) of HIV-negative patients treated with interferon seroconverted at 6 years, compared with only 4 of 26 interferon-treated patients with chronic HBV who were coinfected with HIV. Based on results such as these, interferon therapy in the HBV/HIV-coinfected patient should be limited to patients who are likely to seroconvert: ie, those who are female and younger than 40 years with high ALT levels, low serum HBV DNA levels, and active liver histology (a subgroup that is more likely to undergo spontaneous seroconversion than other HBV-infected groups).

Standard or pegylated interferon is a treatment option for coinfected patients who do not yet require HAART, especially patients who have high ALT levels, low viral loads, and positive HBeAg status without liver decompensation.[12]

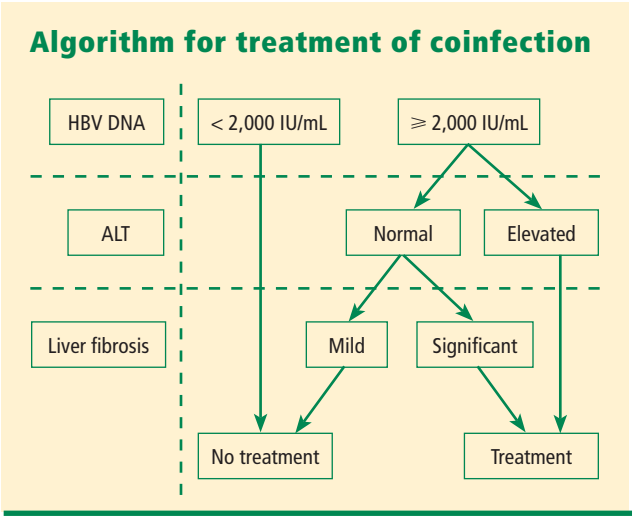

FIGURE 1. The decision to treat hepatitis B virus (HBV) infection in the patient coinfected with HBV and human immunodeficiency virus starts with a measurement of HBV DNA.[2] A normal level (< 2,000 IU/mL) does not require immediate treatment; the decision to treat patients with a high HBV DNA level rests on measurement of alanine aminotransferase (ALT) and the degree of fibrosis on liver biopsy. The algorithm is not static, in that HBV is highly variable in its time to progression and requires constant monitoring.

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Nucleoside and nucleotide analogues

The nucleoside and nucleotide analogues used for HBV therapy have different degrees of effectiveness against HIV polymerase, but none can be used as monotherapy because of the risk of inducing HIV resistance. Lamivudine and tenofovir are used as part of the standard cocktail for the treatment of HIV (see "Case: HIV/HBV with resistance to tenofovir," page S31). Entecavir is now recognized as a partial inhibitor of HIV replication. Both lamivudine and entecavir induce the YMDD mutation, an indication of resistance to therapy, in HIV polymerase. Tenofovir also may select for resistance mutations in HIV polymerase.

At dosages used for the treatment of HBV infection, adefovir has weak activity against HIV, and therefore HIV would not be under significant selective pressure to develop resistance mutations. In HIV polymerase, the mutations that confer resistance to adefovir also confer resistance to tenofovir, and therefore use of adefovir may induce tenofovir resistance.

Telbivudine has not been studied in HIV-infected patients, but its resistance profile is similar to that of lamivudine.

Treating both infections

When both HBV and HIV infections require treatment, HAART is necessary for HIV.[12] The treatment strategy for coinfection is to use standard therapy for HIV, selecting two agents that are effective against HBV infection.

Case revisited

Lamivudine and tenofovir are no longer useful for our case patient. Despite uncertainty about whether tenofovir is the cause of his renal dysfunction, he cannot be maintained on tenofovir. The choices then become entecavir or adefovir. Adefovir is associated with a slightly higher risk of renal dysfunction than tenofovir, but tenofovir-induced renal toxicity cannot be assumed to translate to adefovir.

The need to avoid antiviral resistance complicates the selection of active agents. Resistance to HIV therapy limits the choices for treatment of HBV infection. The immediate aim of therapy, an undetectable level of HBV DNA, eliminates the use of less potent agents. The best choice for therapy is the most potent agent that can be used, such as tenofovir plus lamivudine or tenofovir plus emtricitabine.

Antiviral resistance

For the coinfected patient who develops resistance to lamivudine, the recommendation is to treat with tenofovir plus entecavir (the preferable choice because of absence of cross-reactivity between the two agents) or tenofovir plus lamivudine or emtricitabine. There is some evidence that lamivudine resistance predisposes to entecavir resistance, but the studies that generated these results were conducted in patients who had very high baseline viral loads[13]; the effectiveness of entecavir in patients with low baseline viral loads is unknown. Presumably, when entecavir is used in combination with another potent nucleoside analogue in coinfected patients, the sensitivity of HBV will be more durable than when entecavir is used as monotherapy.

Long-term monitoring

Long-term monitoring for the coinfected patient is similar to that for the patient infected with HBV only. HBV DNA levels should be monitored every 3 months for signs of resistance until levels have plateaued or become undetectable. Once the HBV DNA level is stable or undetectable, the monitoring interval can be extended. Ultrasonographic screening for hepatocellular carcinoma should be conducted every 6 months. Patients with cirrhosis should be screened for esophageal varices.

SUMMARY

HBV in the setting of HIV is more aggressive than in a patient infected with HBV only, and treatment must be comparably aggressive and carefully selected. The primary goal of HBV treatment in a coinfected patient is the same as in a patient with HBV infection only: reduction of viral load to undetectable levels. Treatment decisions are based on viral load, ALT level, findings on liver biopsy, the need for HAART, and the drug's resistance profile. None of the nucleoside or

nucleotide analogues can be used as monotherapy in the coinfected patient because of the risk of inducing resistance to HIV therapy. When the patient requires HAART, then the general recommendation is to select a combination of two drugs that have activity against HIV. If resistance develops, the preferred strategy is treatment with tenofovir plus entecavir. Monitoring includes measurement of HBV DNA levels every 3 months and ultrasonographic screening for hepatocellular carcinoma every 6 months.

DISCOSURES

Dr. Sherman reported that he has received consulting fees and honoraria for teaching and speaking from Bristol-Myers Squibb Company, Gilead Sciences, Inc., and Roche Laboratories, Inc.

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REFERENCES

1. **Alter MJ.** Epidemiology of viral hepatitis and HIV co-infection. J Hepatol 2006; 44(suppl 1):S6–S9.
2. **Soriano V, Puoti M, Peters M, et al.** Care of HIV patients with chronic hepatitis B: updated recommendations from the HIV-Hepatitis B Virus International Panel. AIDS 2008; 22:1399–1410.
3. **Núñez M, Soriano V.** Management of patients co-infected with hepatitis B virus and HIV. Lancet Infect Dis 2005; 5:374–382.
4. **Modi AA, Feld JJ.** Viral hepatitis and HIV in Africa. AIDS Rev 2007; 9:25–39.
5. **Hoffman CJ, Thio CL.** Clinical implications of HIV and hepatitis B coinfection in Asia and Africa. Lancet Infect Dis 2007; 7:402–409.
6. **Puoti M, Torti C, Bruno R, Filice G, Carosi G.** Natural history of chronic hepatitis B in co-infected patients. J Hepatol 2006; 44(suppl 1):S65–S70.
7. **Puoti M, Bruno R, Soriano V, et al.** Hepatocellular carcinoma in HIV-infected patients: epidemiological features, clinical presentation and outcome. AIDS 2004; 18:2285–2293.
8. **Bräu N, Fox RK, Xiao P, et al.** Presentation and outcome of hepatocellular carcinoma in HIV-infected patients: a US-Canadian multicenter study. J Hepatol 2007; 47:527–537.
9. **Thio CL, Seaberg EC, Skolasky R Jr, et al.** HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). Lancet 2002; 360:1921–1926.
10. **Mocroft A, Soriano V, Rockstroh J, et al.** Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? AIDS 2005; 19:2117–2125.
11. **Di Martino V, Thevenot T, Colin J-F, et al.** Influence of HIV infection on the response to interferon therapy and the long-term outcome of chronic hepatitis B. Gastroenterology 2002; 123:1812–1822.
12. **Iser DM, Sasadeusz JJ.** Current treatment of HIV/hepatitis B virus coinfection. J Gastroenterol Hepatol 2008; 23:699–706.
13. **Sherman M, Yurdaydin C, Sollano J, et al; AI463026 BEHoLD Study Group.** Entecavir for treatment of lamivudine-refractory, HBeAg-positive chronic hepatitis B. Gastroenterology 2006; 130:2039–2049.

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