

HBV-HIV Coinfection: Key Clinical Management Issues

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Hepatitis B virus (HBV) coinfection is a considerable problem in HIV-infected persons, leading to significant liver-related morbidity and mortality. Optimizing HBV treatment requires balancing the need for antiretroviral therapy and the severity of liver disease with the risk of drug-resistant HBV and HIV variants. Combination therapy with tenofovir plus either lamivudine or emtricitabine is recommended for patients who require treatment for HBV infection and combination antiretroviral therapy for HIV infection. Pegylated interferon alfa and adefovir dipivoxil are HBV treatment options for coinfecting patients who do not require antiretroviral therapy for HIV infection. For patients who have received therapy for HBV infection, the types of HBV mutations should help guide treatment selection. [*Infect Med.* 2007;24:196-206]

Key words: Hepatitis B virus ■ HIV/AIDS ■ HBV-HIV coinfection

Given the shared risk factors for transmission, coinfection with hepatitis B virus (HBV) and HIV is common. HIV infection increases the risk of chronic HBV infection and hastens the progression of liver disease in patients with chronic HBV infection.

The treatment of chronic HBV infection needs to be carefully coordinated with HIV management in HBV-HIV coinfecting patients. The main goals of treatment for HBV infection are to suppress HBV replication, improve liver function, and minimize the emergence of HBV and

HIV drug-resistance.

In this article, we briefly review the epidemiology and natural history of HBV-HIV coinfection, and then we describe the current treatment options.

EPIDEMIOLOGY AND NATURAL HISTORY

An estimated 60,000 persons in the United States have chronic coinfection with HBV and HIV.¹ The highest incidence of acute HBV infection is in adults who are aged 25 to 45 years. Most of these infections are sexually acquired.

The prevalence of past infection (anti-hepatitis B core antigen [HBcAg]-positive) ranges from 10% to 40% among sexually transmitted disease clinic patients and from 10% to 25% among men who have sex with men and are younger than 30 years.² In US and European cohorts of HIV-infected persons, 7% to 10% have chronic HBV infection, which is defined as the persistence of surface antigen in the serum for at least 6 months.^{1,3}

HIV infection increases the risk of chronic HBV infection. Chronic HBV infection develops in 23% of coinfecting adults but in only 4% of those without HIV infection.⁴

In addition, spontaneous hepatitis B surface antigen (HBsAg) and hepatitis B e antigen (HBeAg) seroconversion (the loss of HBsAg with development of anti-HBsAg and the loss of HBeAg with development of anti-HBeAg, respectively) is less likely with coinfection. Elevated and sustained serum HBV DNA levels are often seen in HBV-HIV coinfecting patients, while liver enzyme elevations are usually milder in these patients than in those with HBV mono-infection.⁵

Clinical studies have demonstrated that the risk of end-stage liver disease is increased in HBV-HIV coinfecting patients. A recent population-based prospective study of 3653 HBsAg-positive, HIV-negative patients found that the incidence of he-

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patocellular carcinoma increased with serum HBV DNA level at study entry, independent of HBeAg serostatus, serum alanine aminotransferase (ALT) level, and the presence of liver cirrhosis.⁶ Another study that included 3582 HBV-monoinfected patients found a similar relationship between serum HBV DNA level and cirrhosis.⁷

Among 5293 men in the Multicenter AIDS Cohort Study, coinfecting men were almost 19 times more likely to die of liver disease than those infected with HBV alone and more than 8 times more likely to die of liver disease than those infected with HIV-1 alone.⁸ Among coinfecting men, higher liver-related mortality was observed for each risk factor evaluated, but none was statistically significant. In an observational study of more than 23,000 HIV-infected persons followed in Europe, the United States, and Australia, active HBV infection (defined as HBsAg-positive, HBeAg-positive, or HBV DNA-positive) was an independent predictor of liver-related death (adjusted relative risk, 3.73).⁹

During the initial stage of chronic HBV infection, serum HBV DNA levels are high and HBeAg is present. In most persons with chronic HBV infection, seroconversion from HBeAg to anti-HBeAg eventually occurs,¹⁰ HBV DNA levels decrease, ALT levels normalize, and hepatic inflammation decreases.

During seroconversion of HBeAg to anti-HBeAg, precore and core promoter mutant viruses that are ineffectively controlled by the immune response may develop in a subset of patients. Patients with these mutant viruses tend to have more severe hepatic inflammation and a higher likelihood of cirrhosis. The likelihood of these mutant viruses developing is related to the duration of infection, as suggested by an older age at clinical presentation.

Precore and core promoter mutant viruses occur mainly in persons who have HBV genotypes other than A. Therefore, these viruses are uncommon in the United States where genotype A predominates, but they are very common in Asian and southern European countries where other genotypes are prevalent.¹¹ In addition to the association between HBV genotype and precore and core promoter mutations, evidence is mounting that HBV genotype correlates with disease progression and clinical outcomes.^{12,13}

Occult HBV (HBV DNA in the absence of HBsAg) is often marked by the anti-HBc-alone pattern. The reported prevalence of occult HBV infection in HIV-1-infected persons varies widely.^{14,15} Conflicting results have been found concerning whether occult HBV infection in HIV-infected persons increases hepatic flares (elevations of liver enzyme levels) after the start of combination antiretroviral therapy.^{16,17}

Persons who continue to have circulating HBsAg with low or undetectable levels of HBV DNA are inactive carriers. Inactive carriers usually have a benign clinical course, although up to 30% may have reactivation of HBV infection with associated flares and progression of liver disease.¹⁸

CANDIDATES FOR HBV TREATMENT

The ideal time to initiate HBV-specific treatment in coinfecting persons is based on the need for combination antiretroviral therapy; the level of HBV viremia; HBeAg serostatus; degree of liver disease; and consideration of potential adverse events, including drug resistance (Figure).¹⁹ If antiretroviral therapy for HIV infection is indicated, a regimen with both anti-HIV and anti-HBV activity should be strongly considered, especially in patients who have high

serum HBV DNA levels (more than 10^4 copies/mL) and elevated ALT levels.

Patients who are starting HIV antiretroviral therapy and who have HBV DNA levels of less than 10^4 copies/mL and normal ALT levels may not need anti-HBV therapy. However, their serum HBV DNA and ALT levels should be monitored every 3 to 6 months. Close surveillance of serum HBV DNA and ALT levels is important given their fluctuating nature in chronic HBV infection.^{20,21} If antiretroviral therapy for HIV is not indicated, HBV treatment should be considered for patients who have serum HBV DNA levels of greater than 10^4 copies/mL and elevated ALT levels. The use of anti-HBV drugs without HIV activity is preferred in this case.¹⁹

Histological staging of liver disease is useful in the decision to start HBV therapy. Liver biopsy is recommended but not required in all coinfecting patients before starting anti-HBV therapy.²⁰ Patients with HIV-HBV coinfection have been found to have cirrhosis with lower ALT levels than patients with HBV monoinfection.²² Therefore, liver biopsy can sometimes be helpful in the setting of persistently normal transaminase levels.

Recent guidelines for HBV-monoinfected patients recommend liver biopsy for those with HBV DNA levels of 10^4 copies/mL or higher and normal ALT levels, especially for patients older than 35 to 40 years. Treatment for HBV infection should be considered for patients with moderate to severe fibrosis (stage 2 or greater) and/or significant inflammation on liver biopsy.²³

The primary goals of HBV treatment are the reduction of HBV DNA levels, normalization of ALT levels, and improvement in liver histology. Durable HBV suppression will lead to histological improvement and

ALT normalization. Furthermore, treatment may reduce the risk of hepatic decompensation and hepatocellular carcinoma in the setting of advanced fibrosis or cirrhosis.²⁴ Meeting these goals requires long-term therapy because of intrahepatic persistence of HBV DNA in the form of covalently closed circular DNA (cccDNA).²⁵

HBV cccDNA functions as the intracellular template for continued viral replication and is unlikely to be eradicated by current HBV therapy. As a result, indefinite treatment may be necessary to maintain viral suppression. HBeAg seroconversion is another treatment goal in HBeAg-positive patients. HBsAg seroconversion is an ideal but unlikely goal in HBV therapy.

HBV TREATMENT OPTIONS

Six drugs have been approved by the FDA for the treatment of chronic HBV infection: interferon (IFN) alfa 2b in 1992, pegylated IFN (Peg-IFN) alfa 2a in 2005, lamivudine (at 100 mg daily) in 1998, adefovir dipivoxil in 2002, entecavir in 2005, and telbivudine in 2006. In addition, 3 drugs active against HBV have been approved for HIV treatment: lamivudine (at 300 mg daily), tenofovir, and emtricitabine.

IFN alfa

HBV-HIV-coinfected patients have a poorer response to IFN alfa than HBV-monoinfected patients. Published data evaluating the response to IFN alfa in patients with HIV coinfection are from the pre-HAART era involving significantly immunosuppressed patients. One retrospective study showed that coinfecting patients treated with IFN had lower rates of HBV DNA loss and HBeAg seroconversion and a higher rate of HBV reactivation than HBV-monoinfected patients had.²⁶ A poorer response was observed in coinfecting

patients who had low CD4⁺ T-cell counts.²⁶

The duration of treatment is 4 to 6 months for HBeAg-positive patients and up to 12 months or more for HBeAg-negative patients, since IFN alfa is more effective in HBeAg-positive patients with chronic HBV infection.²⁰ High ALT levels (more than 2 times the upper limit of normal) and low serum HBV DNA levels are the best predictors of response.²⁷ Treatment duration is limited by adverse effects, including bone marrow suppression, flu-like symptoms, depression, and thyroid dysfunction.

IFN alfa should be used with caution in patients who have compensated cirrhosis, because hepatic necroinflammatory flares with therapy may lead to decompensation. Treatment is contraindicated in patients with decompensated cirrhosis.

Peg-IFN alfa has now supplanted standard IFN alfa. To date, no data have been published regarding the effectiveness of Peg-IFN in coinfecting patients. In HBeAg-positive HBV-monoinfected patients, a 24-week course of Peg-IFN was found to be more effective than 24 weeks of standard IFN, with a comparable adverse-event profile.²⁸ Peg-IFN alfa was also found to be more effective than lamivudine over 48 weeks of therapy in both HBeAg-positive and HBeAg-negative patients without HIV infection. The combination of Peg-IFN alfa plus lamivudine was not more effective than Peg-IFN alfa alone.^{29,30}

Peg-IFN alfa is a potential option for initial HBV treatment in coinfecting patients who have high CD4⁺ T-cell counts, high ALT levels, and low HBV DNA levels. In addition, the lack of anti-HIV activity makes IFN alfa a good treatment choice in suitable coinfecting patients who do not yet require antiretroviral therapy for HIV infection. Clinical trials of Peg-

IFN alfa for chronic hepatitis C in HIV-infected persons reported adverse-event rates similar to those for patients with hepatitis C virus monoinfection.^{31,32}

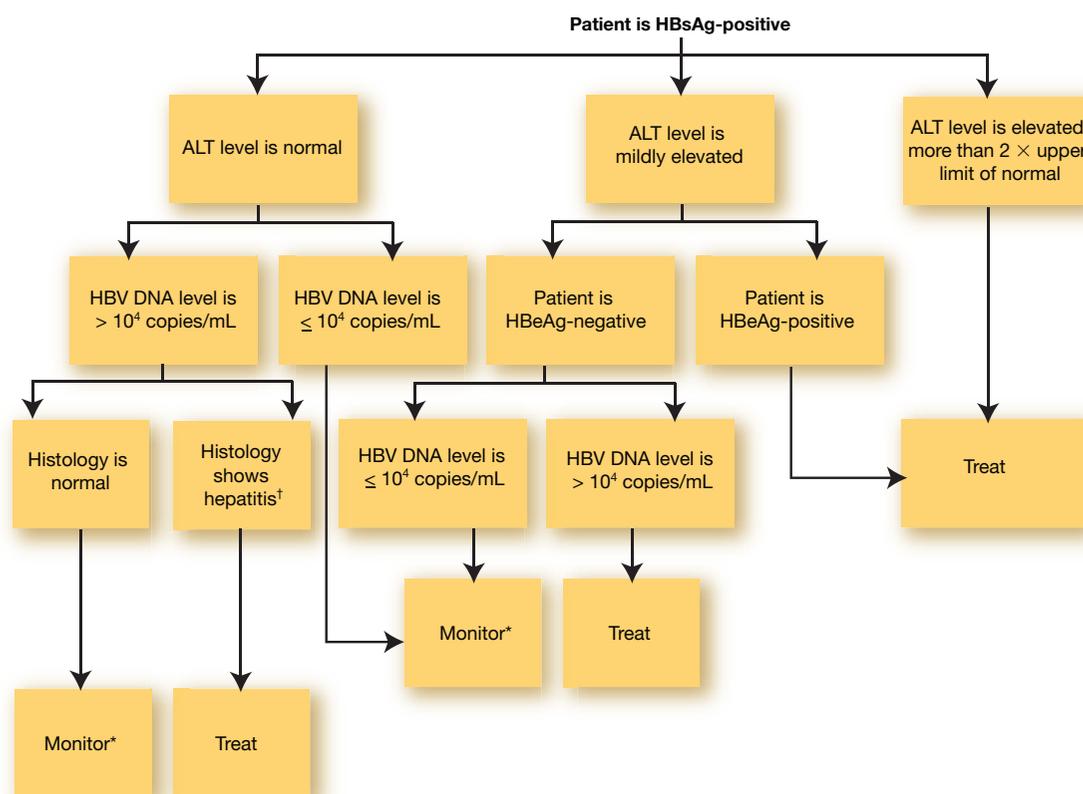
Lamivudine

This cytosine analogue reverse transcriptase inhibitor has activity against both HBV and HIV. The approved dosages for lamivudine are 100 mg once daily for chronic HBV infection and 300 mg daily for HIV infection. In HBV-HIV coinfecting patients, lamivudine should be given only at the 300-mg daily dose (either 300 mg once daily or 150 mg twice daily) and in the setting of combination antiretroviral therapy to prevent the appearance of lamivudine-resistant HIV.

Lamivudine is associated with significant viral suppression and improvement in ALT levels in both HBV-HIV coinfecting and HBV-monoinfected patients. Undetectable HBV DNA was documented in 40% to 87% of coinfecting patients treated with lamivudine 300 mg/d for 13 to 24 months.^{33,34} HBeAg seroconversion rates with lamivudine treatment in coinfecting patients have ranged from 22% to 29%.^{33,34}

Lamivudine-resistant HBV with mutations in the YMDD motif of the polymerase gene emerges at a high rate with lamivudine monotherapy in both coinfecting and HBV-monoinfected patients. The cumulative risk of lamivudine resistance in coinfecting patients is linear, with a 20% annual incidence and an estimated 4-year resistance rate of 90%.³⁵ Selection of YMDD mutants may lead to acute exacerbation of HBV infection with flares in ALT levels and progression of liver disease.²⁰

Because of the high potential for resistance, recent treatment guidelines for HBV monoinfection no longer recommend lamivudine monotherapy as first-line therapy.²³

Figure – Treatment algorithm for hepatitis B virus infection

HBsAg, hepatitis B surface antigen; ALT, alanine aminotransferase; HBV, hepatitis B virus; HBeAg, hepatitis B e antigen.

*Monitor HBV DNA and ALT levels every 6 - 12 months. On initial diagnosis, monitor every 3 months for 1 year to ensure stability.

†Fibrosis stage 2 or higher or significant inflammation.

Lamivudine withdrawal may result in a spectrum of subclinical and clinical hepatic responses, ranging from asymptomatic elevation of ALT levels to fulminant hepatic failure.

Emtricitabine

This cytosine analogue is similar to lamivudine in molecular structure, antiviral activity, and resistance pattern. The effective dosage of emtricitabine for HBV is the same as for HIV—200 mg once daily.³⁶ Emtricitabine can be used in place of lamivudine unless lamivudine-resistant HBV has been selected.

Both drugs share the same mechanism of resistance through YMDD motif mutations, but in HBV-

monoinfected patients, the incidence of resistance mutations at 1 year seems to be lower with emtricitabine (about 9%).³⁶ Available efficacy data in HIV-HBV coinfection are limited.

Entecavir

This is a purine nucleoside analogue with potent anti-HBV activity that was recently found to have anti-HIV activity and to select for M184V drug-resistant variant virus.³⁷ The recommended dosage of entecavir in HBV-HIV-coinfected patients is 1 mg once daily in lamivudine-experienced patients.

In a group of 43 coinfecting patients with lamivudine-resistant HBV, the addition of entecavir re-

sulted in a 4.20 log₁₀ copies/mL drop in HBV DNA levels, and HBV DNA levels of less than 300 copies/mL were achieved in 9% of patients at 48 weeks.³⁸ Resistance to entecavir requires the preexistence of lamivudine resistance mutations plus an additional mutation in the HBV reverse transcriptase (rtT184, rtS202, or rtM250). In the above-mentioned study, 2 of the 43 coinfecting patients had entecavir resistance mutations (rtT184S and rtS202C) present at study entry, but no new mutations associated with phenotypic entecavir resistance appeared during treatment.³⁸

Entecavir should not be used in HIV-HBV-coinfecting persons who

are not on a fully suppressive HIV regimen.

Adefovir dipivoxil

This nucleotide analogue reverse transcriptase inhibitor has activity against both wild-type and lamivudine-resistant HBV in HBeAg-positive and HBeAg-negative patients. The approved dosage of adefovir dipivoxil for chronic HBV infection is 10 mg once daily.

In a group of 35 HBV-HIV-coinfected patients with lamivudine-resistant HBV, adefovir added to lamivudine produced median reductions in serum HBV DNA levels of 4.7 log₁₀ copies/mL and 5.9 log₁₀ copies/mL at weeks 48 and 144, respectively.³⁹ Undetectable HBV DNA (limit of detection less than 2.3 log₁₀ copies/mL) was found in 25% of patients, with 45% of patients achieving HBV DNA levels of less than 3 log₁₀ copies/mL.³⁹ No HBV polymerase mutations associated with adefovir resistance (N236T or A181V) or HIV reverse transcriptase codon mutations (K65R or K70E) were found at 144 weeks.³⁹

Primary resistance to adefovir has

been described in a small proportion of patients. Adefovir treatment failure was reported in 3 coinfecting patients who had lamivudine resistance in the absence of any known adefovir resistance mutations.⁴⁰ These coinfecting patients subsequently responded to tenofovir. In HBV-monoinfected patients, a novel rtI233V mutation in the reverse transcriptase domain is associated with primary adefovir resistance.⁴¹

Tenofovir disoproxil fumarate

Tenofovir is another nucleotide analogue reverse transcriptase inhibitor active against wild-type, lamivudine-resistant, and adefovir-resistant HBV.^{19,40} The drug is not yet licensed in the United States for treatment of chronic HBV infection, but it has been approved for HIV therapy at a dosage of 300 mg once daily.

A retrospective study evaluated the HBV virological response of 65 coinfecting patients receiving tenofovir disoproxil fumarate for more than 6 months.⁴² The median decline in serum HBV DNA level was 4.56 log₁₀ copies/mL and 2.53 log₁₀ copies/mL in HBeAg-positive and

HBeAg-negative patients, respectively. Serum HBV DNA became undetectable in 29.6% of HBeAg-positive patients and 81.6% of HBeAg-negative patients.⁴² Among 4 patients who did not have a decrease in serum HBV DNA level from baseline, genotyping analysis did not reveal tenofovir- or adefovir-related HBV resistance mutations.⁴²

The AIDS Clinical Trials Group A5127 was a prospective, randomized, controlled study that compared tenofovir disoproxil fumarate with adefovir in 52 coinfecting patients who were receiving stable antiretroviral therapy. The mean decline in serum HBV DNA level at 48 weeks of treatment was 4.44 log₁₀ copies/mL with tenofovir and 3.21 log₁₀ copies/mL with adefovir. No difference in toxicity was seen between the 2 groups.⁴³

Telbivudine

This L-nucleoside analogue of thymidine without anti-HIV activity was recently approved for chronic HBV infection. The effective dosage of telbivudine in HBV monoinfection is 600 mg once daily.

No efficacy data in HBV-HIV-coinfected patients have been published. In HBV-monoinfected patients, telbivudine achieves significantly greater reduction in serum HBV DNA levels and higher rates of undetectable HBV DNA by polymerase chain reaction, compared with both lamivudine and adefovir.⁴⁴ However, telbivudine shares cross-resistance with lamivudine via M204 variants in the YMDD motif.^{20,44}

Combination therapy

The use of combination therapy for HBV in HBV-HIV-coinfected patients is being evaluated in clinical trials. An ideal HBV treatment regimen would maximize HBV suppression, prevent the emergence of HBV and HIV reverse transcriptase muta-

Table – Possible causes of hepatic flares in HBV-HIV-infected persons receiving combination antiretroviral therapy

- Immune reconstitution syndrome
- Hepatotoxicity from antiretrovirals
- Hepatotoxicity from other drugs (including isoniazid, rifampin, and pyrazinamide) or alcohol
- Hypersensitivity
- Emergence of lamivudine-resistant HBV strains
- Reactivation or exacerbations of HBV (reported after stopping lamivudine)
- HBeAg or HBsAg seroconversion
- Superinfection with another hepatitis virus (hepatitis A or D virus)

HBV, hepatitis B virus; HBeAg, hepatitis B e antigen; HBsAg, hepatitis B surface antigen.

tions that lead to drug resistance, and minimize toxicity. While combination therapy is theoretically attractive as a strategy to achieve viral suppression and prevent the emergence of drug resistance, trials have not consistently shown improved antiviral activity with drug combinations. Data are not available to evaluate long-term drug resistance rates in combined regimens.

Emerging data support the use of tenofovir/lamivudine combination therapy for coinfecting patients. Among HBV-HIV-coinfecting patients who were lamivudine-naïve, tenofovir/lamivudine combination therapy was superior to tenofovir or lamivudine alone. For lamivudine-experienced patients, adding tenofovir to lamivudine or switching to tenofovir was superior to continuing lamivudine.⁴⁵ In coinfecting persons, combination therapy with tenofovir and lamivudine appeared to more effectively suppress both HBV replication and the development of lamivudine resistance compared with lamivudine alone.⁴⁶

The decision to use combination therapy for coinfecting persons should be based on the need for antiretroviral therapy. For those who need HBV treatment but not antiretroviral therapy, Peg-IFN and adefovir are potential treatment options. IFN treatment should be limited to coinfecting patients who are HBeAg-positive and have high CD4⁺ T-cell counts, high ALT levels, and low serum HBV DNA levels.

For coinfecting patients who need both HBV and HIV treatment, the antiretroviral regimen should include agents with dual activity (tenofovir, lamivudine, emtricitabine). These patients should receive a nucleotide analogue (tenofovir) combined with a nucleoside analogue (either lamivudine or emtricitabine) to prevent long-term resistance.^{20,21}

Antiretroviral toxicity

Flares in the elevation of liver enzyme levels in HBV-HIV-coinfecting persons who are receiving combination antiretroviral therapy have a variety of possible causes that are important to consider before changing any antiretroviral agent (Table).¹⁹ Chronic HBV infection is associated with increased hepatic flares in patients who have begun antiretroviral therapy.⁴⁷

Early flares, usually occurring within the first 3 months of starting combination antiretroviral therapy, may be the result of an immune reconstitution syndrome and not necessarily direct antiretroviral hepatotoxicity.⁴⁸ Immune reconstitution flares may be followed by normalization of ALT levels and clearance of HBV DNA. Close monitoring of patients with suspected immune reconstitution flares may allow the continuation of therapy, since abnormalities in liver enzyme levels progressively improve while the patient continues combination antiretroviral therapy.

Coinfecting persons who are receiving antiretrovirals that have more significant hepatotoxic profiles (nevirapine, efavirenz, or full-dose ritonavir) necessitate more frequent monitoring. Steatohepatitis mediated by inhibition of mitochondrial DNA polymerase gamma may occur in patients receiving nucleoside analogues, especially stavudine, didanosine, and zidovudine. Hypersensitivity reactions to abacavir, nevirapine, or amprenavir are not reported more frequently in persons with chronic HBV infection.²⁰

In patients with chronic HBV infection, flares have been reported with discontinuation of nucleoside or nucleotide analogues^{49,50} and with the emergence of lamivudine- or emtricitabine-resistant strains.²⁰ Less likely causes of flares in dual-infecting persons are HBeAg or HBsAg

seroconversion and superinfection with another hepatitis virus (such as hepatitis A or D virus).

HBV VACCINATION

All HIV-infected persons should be screened for HBV markers soon after HIV diagnosis. HBV vaccination is indicated for all HIV-infected persons who lack evidence of previous infection or immunity. A national survey of HIV outpatient study sites in 7 US cities found that only 32% of patients eligible for the hepatitis B vaccine had received at least 1 dose.⁵¹

Household, sex, and needle-sharing contacts of HBsAg-positive persons should be identified, tested for susceptibility to HBV infection, and given the first dose of HBV vaccine after collection of blood for serological testing. The sex partners of HBsAg-positive persons should be counseled to use condoms unless they are immune or were previously infected.²

HIV-infected persons, especially those with advanced immunosuppression, have weaker antibody responses to HBV vaccination and lose protective antibodies after vaccination more quickly. After completing the 3-dose HBV vaccine series, the response rate (defined as greater than 10 IU/mL) is 87% in HIV-infected persons with CD4⁺ cell counts greater than 500/ μ L, compared with only 33% in persons with CD4⁺ cell counts between 200 and 500/ μ L.²⁰ In a retrospective cohort study of factors that predicted HBV vaccination success in HIV-infected persons, only undetectable plasma HIV RNA at the time of vaccination was associated with a protective antibody response.⁵² Therefore, immune reconstitution with combination antiretroviral therapy should be attempted before HBV vaccination.

Postvaccination antibody levels (1 to 3 months after completing the se-

ries) and periodic monitoring of antibody levels are recommended in vaccinated HIV-infected patients. Booster doses of vaccine or a new series with double the conventional dose should be attempted in patients in whom adequate antibody levels do not develop. ♦

Therapeutic agents mentioned in this article

- Abacavir
- Adefovir dipivoxil
- Amprenavir
- Didanosine
- Efavirenz
- Emtricitabine
- Entecavir
- Interferon
- Isoniazid
- Lamivudine
- Nevirapine
- Pyrazinamide
- Rifampin
- Ritonavir
- Stavudine
- Telbivudine
- Tenofovir
- Zidovudine

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