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An Update in the Management of Hepatitis B/HIV Coinfection

Monika N. Daftary, PharmD, Tiffany Goolsby, PharmD, and Faria Farhat, MD

With growing numbers of hepatitis B virus (HBV)/HIV-coinfected patients and the complexity of treating both diseases together, new treatment options and guidelines are

available. This article reviews treatment and management options for HBV/HIV-coinfected patients.

KEY WORDS: HIV, hepatitis B, coinfection, treatment.

HEPATITIS B/HIV COINFECTION OVERVIEW

Worldwide, a staggering 350 million people are affected with hepatitis B virus (HBV), and approximately 40 million are affected by HIV.¹⁻³ With coinfection of HBV/HIV rates at nearly 10%, it is estimated that about 4 million people are affected by this coinfection around the world.¹⁻³ Furthermore, in the Western world compared to the general population, chronic HBV infection is 10-fold greater among HIV-infected individuals.^{1,2} This may be because HBV and HIV are transmitted through similar transmission routes, which include blood and bodily secretions.^{1,4} It is known that coinfecting HBV/HIV patients are at a higher risk for developing liver-related complications and mortality, that is, cirrhosis and hepatocellular carcinoma, than are those with HIV infection alone.^{2,3,5-7} HIV can have a negative impact on the outcome of chronic hepatitis.^{1,2} However, the information regarding the role of HBV infection causing progression to AIDS in the coinfecting population remains conflicted.^{3,6}

The complexity of treating HBV/HIV coinfection has been noted in the literature.^{1,2,5,7} One issue is the HIV drug resistance seen when using monotherapy with nucleoside or nucleotide reverse transcriptase inhibitors that have activity against both HBV and HIV.^{1,2,5,7,8} In addition, there is a less than optimal response noted with interferon α in coinfecting patients.^{1,2} Availability of newer agents to manage these patients and new management guidelines continues to make the treatment of HBV/HIV coinfection a dynamic arena.

All patients infected with HBV, regardless of HIV status, should be evaluated for the need of anti-HBV

therapy.^{1,7} Currently, anti-HBV therapy goals are to suppress HBV replication and to stop the progression of liver disease.^{1,2,4} Treatment response is gauged by reduction in serum of HBV DNA, reversal of serum hepatitis B surface antigen (HBsAg), normalization of alanine aminotransferase (ALT), improvement in liver histology, and change in hepatitis B e antigen (HBeAg)-positive status.^{1,2,5}

TREATMENT OPTIONS

The Food and Drug Administration (FDA) has approved 5 drugs for the treatment of chronic hepatitis B. They include interferon α , lamivudine, adefovir dipivoxil, entecavir, and more recently, peginterferon α -2a (Table 1).^{1,4,8} Treatment of HBV/HIV coinfection varies according to whether HBV alone needs treatment, HIV alone needs treatment, or both HBV and HIV need treatment in a particular patient.⁷ After each drug

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section, a recommendation, based on recent literature, is provided.^{1,2,5,7}

Interferon α and Peginterferon α

Interferon- α (IFN- α) are cytokines that have activity against HBV through antiviral, immunomodulating, and antiproliferative mechanisms.⁹ There are 2 IFN- α subtypes, 2a and 2b, and both subtypes have activity against HBV.⁹ This agent was the first approved treatment of chronic hepatitis B, and it is given by subcutaneous injection.^{1,2,4}

It is recommended that IFN- α be used in patients with the following clinical presentations: HBV/HIV-coinfected patients who are candidates for treatment of chronic hepatitis B disease but not HIV, patients with high ALT levels (more than 2 times the upper limit of normal), detectable HBV DNA levels, circulating HBeAg, chronic hepatitis on liver biopsy, compensated liver disease, HBeAg-positive patients with chronic hepatitis B, and HBeAg-negative patients with chronic hepatitis B.^{1,5,10,11}

Although there are numerous studies that evaluate the efficacy of IFN- α in the treatment of chronic hepatitis, there are limited data on the efficacy of chronic hepatitis B treatment among HIV-1 infected persons.^{1,5} Wong and colleagues, in a meta-analysis conducted to determine the effectiveness of IFN- α , found IFN- α to be effective in stopping HBV viral replication in patients with HBeAg-positive chronic hepatitis B monoinfection.¹² Similarly, in a study by Perrillo and associates,¹³ treatment with IFN- α for chronic hepatitis B monoinfection was effective in inducing a sustained loss of viral replication in more than a third of patients studied, and in 10% of the patients, HBsAg disappeared from the serum. However, a retrospective follow-up study evaluating the response to IFN- α therapy found differences in the HBV/HIV-coinfected patients versus the hepatitis B monoinfected groups. The coinfecting group had an inferior response to IFN- α therapy and more reactivations of HBV, cirrhosis, and cirrhosis-related deaths, especially in patients with low CD4 counts. However, it should be noted that regardless of HIV status, IFN- α therapy reduced the number of cirrhosis cases associated with HBV.¹⁴

The recommended adult dose is 5 million units (MU) per day or 10 MU 3 times a week for 16 to 24 weeks for HBeAg-positive patients and greater than or equal to 48 weeks for HBeAg-negative patients.⁵ IFN- α side effects are varied. The side effects of flulike symptoms, or leukopenia, or depression usually limit the use of IFN- α .^{1,11}

Pegylated interferons are formed by the attachment of a large inert polyethylene glycol (PEG) to interferon proteins.⁹ As a result, the pharmacokinetic profile of interferons are changed; plasma concentrations are prolonged, allowing once-weekly dosing, longer half-life, and less renal clearance.⁹ There are 2 clinically tested pegylated interferons, PEG α -2a (Pegasys) and PEG α -2b (PEG-Intron), and both are approved by the FDA for the treatment of chronic hepatitis C virus in combination with oral ribavirin.⁹ However, more recently, pegylated IFN- α has generated attention because of recent studies that show superiority when compared to currently available treatments (IFN- α and lamivudine) for chronic hepatitis B infections.¹⁵⁻¹⁷ In May 2005, PEG α -2a, or Pegasys, became the only pegylated interferon to be FDA approved for the treatment of HBeAg-positive and HBeAg-negative chronic hepatitis B.⁸ Two major studies were key to the approval of this agent for the treatment of chronic hepatitis B.^{15,16}

Lau and colleagues conducted a study of 814 patients with HBeAg-positive chronic hepatitis B who were randomized to receive PEG α -2a monotherapy (180 μ g once a week) plus placebo, PEG α -2a (180 μ g once a week) plus lamivudine (100 mg daily) combination therapy, or lamivudine monotherapy (100 mg daily).¹⁵ Patients were treated for 48 weeks and followed for an additional 24 weeks.¹⁵ In this study, PEG α -2a therapy resulted in higher rates of sustained HBeAg seroconversion, HBV DNA suppression to less than 100 000 copies per milliliter, lowering of ALT levels, and HBsAg seroconversion than with lamivudine monotherapy in HBeAg-positive patients.¹⁵ At the end of follow-up (week 72), HBeAg seroconversion occurred in 32% of patients on PEG α -2a monotherapy, 27% in persons receiving combination therapy, and 19% for those treated with lamivudine alone in HBeAg-positive patients.¹⁵ HBeAg-positive chronic hepatitis B patients' response to PEG α -2a monotherapy was superior to combination therapy and lamivudine monotherapy even at the end of treatment. HBsAg conversion was not seen in patients receiving lamivudine monotherapy.¹⁵ All results were statistically significant.

Marcellin and associates¹⁶ evaluated the effectiveness of PEG α -2a monotherapy (180 μ g once a week), PEG α -2a (180 μ g once a week) plus lamivudine (100 mg daily) combination therapy, or lamivudine monotherapy (100 mg daily) in an HBeAg-negative chronic hepatitis population. PEG α -2a therapy was found to have higher percentages of sustained response than lamivudine monotherapy in ALT normalization,

Table 1
Treatments for Hepatitis B Currently Approved
by the Food and Drug Administration

Name	Brand	Year Approved
Interferon α -2b	Intron A	1983
Lamivudine	Epivir-HBV	1998
Adefovir	Hepsera	2002
Pegylated interferon α -2a	Pegasys	2005
Entecavir	Baraclude	2005

HBV DNA suppression, and HBsAg seroconversion in HBeAg-negative patients.¹⁶ Patients were treated for 48 weeks and followed for an additional 24 weeks.¹⁶ Normalization rates of ALT levels at the end of follow-up for the HBeAg-negative population were 60% for persons treated with combination therapy, 59% in patients treated with PEG α -2a monotherapy, and 44% for those on lamivudine monotherapy.¹⁶ At week 72 (end of follow-up), suppression of HBV DNA levels to less than 20 000 copies/mL occurred in a significantly higher percentage of HBeAg-negative patients receiving combination therapy (44%) and PEG α -2a monotherapy (43%) than lamivudine monotherapy (29%).¹⁶ The rates of HBV DNA suppression at the end of follow-up peaked for HBeAg-negative patients who received combination therapy. Also identified at the end of follow-up or week 72 was HBsAg seroconversion. This occurred in 7 patients receiving PEG α -2a alone and in 5 receiving the combination therapy.¹⁶ HBsAg seroconversion was not identified in any patients receiving lamivudine monotherapy.¹⁶ All results were statistically significant.¹⁶

Although the studies evaluating PEG α -2a therapy in the coinfecting HBV/HIV population are lacking, the results that are available for HBeAg-positive and HBeAg-negative mono-infected patients are promising.^{1-2,15-17} IFN- α and pegylated IFN- α are currently recommended for use in coinfecting HBV/HIV patients who require treatment of HBV and not HIV.^{1,2,7}

Lamivudine and Emtricitabine

Lamivudine is a nucleoside analog that inhibits HIV reverse transcriptase and HBV DNA polymerase and was the first oral agent approved for the treatment of chronic hepatitis B.^{1,9} Patients who are potential candidates for lamivudine use include HIV-1-infected persons who are antiretroviral therapy naïve and require antiretroviral therapy or patients with HBeAg-positive or HBeAg-negative chronic hepatitis B with or without

compensated or decompensated cirrhosis.^{5,7,11} Lamivudine should be administered with other antiretroviral agents in an HBV/HIV coinfecting population.^{1,2,5} The recommended dose for adults with HBV/HIV coinfection is 150 mg twice daily or 300 mg daily.^{1,2,5,7} The lamivudine 100-mg daily dose should not be used in the HBV/HIV coinfecting population.^{1,2,5} Lamivudine should be dose adjusted according to renal function.^{5,18}

Several studies have evaluated the effectiveness of lamivudine in the HBV/HIV-coinfecting population.¹⁹⁻²¹ One randomized, double-blind, placebo-controlled study evaluated 1895 HIV/HBV-coinfecting patients.¹⁹ A total of 1895 patients was included in the study, but only 1790 patients had baseline HBsAg results, done retrospectively. Of 1790 patients, only 122 were positive for HBsAg. The CD4 count ranged from 25 to 250 CD4 cells/ μ L for the total study population. Patients were randomized to placebo, lamivudine (150 mg twice daily), or lamivudine (150 mg twice daily) plus zidovudine (100 mg 3 times daily) and to either zidovudine monotherapy or zidovudine plus didanosine or zalcitabine combination regimen.¹⁹ The groups that received lamivudine had greater reductions in the HBV DNA and loss of HBeAg than did the placebo group. Also, the groups receiving lamivudine achieved greater ALT normalization and reduced HIV disease progression than the placebo group did.¹⁹ Although in 1 study of 19 patients, HBV/HIV-coinfecting patients receiving lamivudine as a component of their antiretroviral therapy had reduction in HBV DNA (87%) and 35% had seroconversion to anti-HBe, resistance mutations to lamivudine were reported.²⁰ Similarly, a study by Hoff and colleagues²⁰ evaluating 66 HBV/HIV-coinfecting patients who were treated with lamivudine along with other antiretrovirals found that 86.4% of patients did respond to therapy; however, resistance mutations to lamivudine were also noted in 22 (33.3%) patients.²¹

The occurrence of lamivudine resistance is more common in HBV/HIV-coinfecting patients than in those patients with HBV alone.^{1,2} There is an increased risk of developing resistant strains of HBV as treatment with lamivudine is prolonged.^{1,2,5} Resistance mutations to lamivudine have been associated with exacerbations in hepatic disease, including liver failure and rises in aminotransferases. Emtricitabine is another nucleoside analogue that has activity against both HIV and HBV, but it is FDA approved only for the treatment of HIV.^{1,2,22} It is being evaluated for its activity against hepatitis B.^{2,23} A 2-year follow-up study found emtricitabine's dose for HBV activity to be 200 mg

daily, similar to the HIV dosing, and it should be adjusted in renal dysfunction.^{7,23} Lamivudine and emtricitabine share traits not only in mechanism of action and side effects but also in resistance patterns. If a patient is resistant to lamivudine, emtricitabine should not be given. The resistance patterns seen with both lamivudine and emtricitabine have not been seen with adefovir and tenofovir.^{1,2,7} Therefore, lamivudine or emtricitabine plus tenofovir is recommended in HBV/HIV-coinfected patients who need treatment of both HBV and HIV along with other antiretroviral agents.⁷ It is also recommended that lamivudine and emtricitabine not be used in HBV/HIV-coinfected patients who need treatment only for HBV.⁷

Adefovir Dipivoxil and Tenofovir Fumarate

Adefovir dipivoxil is a nucleotide reverse transcriptase inhibitor that has activity against both HBV and HIV.^{1,4,24} Adefovir dipivoxil works by inhibiting HBV DNA polymerase in hepatitis B infection.^{4,24} It is FDA approved at a 10-mg/d dosage and is effective in the treatment of wild-type HBV and lamivudine-resistant HBV.^{1,2,4,24} Adefovir dosing needs adjustment in renal dysfunction.²⁴ At the approved 10-mg dosage of adefovir, there is no reported significant antiviral effect against HIV.^{1,2} An advantage of adefovir therapy is the limited resistance seen with the drug.⁵ However, recently, the possibility, although not common, of HIV drug resistance with adefovir monotherapy in coinfecting HBV/HIV patients has been cited.²⁴⁻²⁶ The issue of HIV drug resistance should be evaluated in coinfecting HBV/HIV patients prior to initiation of therapy.^{1,2,24-26}

An evaluation of patients who were HBeAg positive found that 48 weeks of adefovir therapy resulted in normalization of ALT and reduction in HBV DNA levels when compared to placebo.²⁷ Adefovir also has been studied in 185 patients who were HBeAg negative. Similar to patients who were HBeAg positive, patients receiving adefovir were significantly more likely than the placebo group to have normalization of liver function tests and undetectable HBV DNA levels.²⁸ In one study of HBV/HIV-coinfected patients with lamivudine resistance to HBV, adefovir was added to the existing regimen, and reductions in HBV DNA levels were seen.²⁹

Tenofovir is another nucleotide analogue that has activity against both HIV and HBV, but it is only FDA approved for the treatment of HIV.^{1,2} However, it has

been studied in HBV/HIV coinfecting patients, and it is being evaluated for its activity against hepatitis B at a dose of 300 mg daily, similar to the approved HIV dosing.^{1,2} One study evaluating tenofovir in 10 HBV/HIV-coinfected patients found a reduction of 4.9 log₁₀ copies/mL of HBV DNA at 24 weeks of therapy.³⁰ Similarly, in an evaluation of 5 HBV/HIV-coinfected patients with noted lamivudine resistance, a reduction of 4.5 log₁₀ copies/mL of HBV DNA was also found at 24 weeks of therapy.³¹ It is recommended that if tenofovir is to be used in HBV/HIV coinfecting patients, it should be used in combination with either lamivudine or emtricitabine plus other antiretroviral agents.^{1,2,7} Tenofovir needs dosage adjustments in renal dysfunction.^{4,7}

Adefovir and tenofovir are recommended for use in different circumstances in HBV/HIV-coinfected patients.^{1,2,7} Adefovir is recommended for use in coinfecting patients who need treatment of only HBV and not HIV infection.⁷ However, adefovir may also be used in the HBV/HIV-coinfected patient who has an existing antiretroviral regimen without HBV activity but needs treatment of HBV.^{1,7}

Entecavir

Entecavir is a nucleoside analogue recently approved for the treatment of chronic hepatitis B, and it works by inhibiting HBV DNA polymerase.^{1,4} The recommended dose for treatment-naïve patients is 0.5 mg/d and for lamivudine-resistant patients is 1.0 mg/d.^{1,4} Similar to the other nucleoside analogues, dose adjustments are necessary in renal dysfunction.^{1,4} This agent has been evaluated for use in HBeAg-positive, HBeAg-negative, and lamivudine-resistant patients and was found to have favorable results in the treatment of hepatitis B.³² Entecavir treatment has also been evaluated in 68 HBV/HIV-coinfected patients receiving lamivudine-containing antiretroviral therapy.³² The entecavir dose in this study was 1 mg/d. At 24 weeks, HBV DNA reductions were 3.65 log₁₀ from baseline in the group receiving entecavir plus a lamivudine-containing antiretroviral backbone.³² Normalization of ALT was seen in 34% of the group receiving entecavir versus 8% of the placebo group.³² Entecavir is recommended for use in HBV-HIV-coinfected patients who need treatment of only the HBV infection and not the HIV infection.⁷ However, similar to adefovir, entecavir may also be used in the HBV/HIV-coinfected patient who has an existing antiretroviral regimen without

HBV activity but needs treatment of HBV.^{1,7} Entecavir's advantage over adefovir may be its apparent lack of activity against HIV.^{1,4}

Combination Therapy

Combination therapy for chronic HBV infection is currently being evaluated for monoinfected patients.^{1,2} The rationale for combination therapy is to limit resistance and improve treatment efficacy. The data on combination therapies are limited.³³ This may be less of an issue in HBV/HIV-coinfected patients because many patients who need treatment of both HBV and HIV infection are recommended to receive 2 drugs as part of antiretroviral therapy.^{1,2}

New Drugs

With a growing number of agents in the pipeline, including some in phase 2/3 trials, the treatment options for chronic HBV, specifically HBV/HIV coinfection, are sure to expand.^{1,2,34} Many of the potential agents are nucleoside/nucleotide analogues including telbivudine,^{1,2} clevudine,^{1,2} elvucitabine, valtorcitabine, and pradefovir.^{1,2,34} Recent results show good clinical activity against chronic HBV infection for some of these agents.^{1,2,34} In a phase 2b trial, telbivudine, a nucleoside analogue, was found to have enhanced normalization of ALT and HBeAg loss when compared to lamivudine.^{34,35} Telbivudine also is currently being studied in a phase 3 trial evaluating both HBeAg-positive and HBeAg-negative decompensated chronic HBV infection.³⁴ Similarly, clevudine, a nucleoside analogue, is also being studied for both HBeAg-positive and HBeAg-negative chronic HBV infection in phase 3 trials, and preliminary results have found the drug to be effective in the reduction of HBV DNA.³⁴ Recently, results from a phase 2 trial of the prodrug of adefovir dipivoxil, pradefovir, a nucleotide analogue, also found the drug to be effective in the reduction of HBV DNA.³⁴ Although it seems that the availability of only nucleoside and nucleotide analogues are on the horizon, other drug classes are being investigated, which include a monoclonal antibody, HepX-B, and immune stimulants, including HE 2000, thymosin- α , and theradigm, all of which are in phase 2 trials.³⁴ Most of the new treatments being studied are primarily for HBV mono-infection, although many of these new drug entities may provide a wide range of treatment options for HBV/HIV coinfection.

CONCLUSION

The HBV/HIV-coinfection treatment arena is continuously changing with the availability of new agents, new treatment modalities, and new guidelines. There is no doubt that the treatment of this population is complex, especially given resistance issues related to both HBV and HIV. However, the availability of nucleotide analogues, adefovir and tenofovir, which have activity in lamivudine resistance, is promising. Although IFN- α has a poor response in this population, the pegylated IFN- α product may provide another viable treatment option in this setting.

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