

THE NCCC BULLETIN

From the Editors

There has been a major focus in the past several years on the management of patients coinfecting with HIV and hepatitis C virus (HCV). More recently, there has been an emphasis on hepatitis B virus (HBV) coinfection. HIV/HBV coinfection is not uncommon: In a study of HIV-positive homosexual males in the United States, 6% were also positive for the hepatitis B surface antigen (HBsAg).¹ During the last several years, the Food and Drug Administration (FDA) has approved several new anti-HBV agents. In light of these developments, we feel it is timely to address treatment issues of the HIV/HBV-coinfecting patient.

A Warmline clinician recently received a call from a family physician regarding the following:

An asymptomatic 40-year-old white male was coinfecting with HIV and HBV. The HBV DNA viral load was reported as "high," the hepatitis B e-antigen (HBeAg) was positive, and the serum alanine aminotransferase (ALT) was 500 U/L. A liver biopsy showed moderate inflammation and mild fibrosis. The patient's HIV antiretroviral regimen consisted of lamivudine, didanosine, and efavirenz, with a CD4+ count of 500 cells/ μ L and an HIV RNA viral load of <50 copies/mL.

Question:

Are there any clinical trials for pegylated interferon in the treatment of HBV?

Response:

* HBV is a noncytopathic DNA virus that causes liver injury through immune-mediated processes. After acute HBV infection, about 90-95% of patients will clear the infection. The remaining 5-10% become chronically infected. HBV causes chronic infection by incorporating its covalently closed circular DNA (cccDNA) into the nucleus of the infected hepatocytes. In HIV-negative individuals, 25% of untreated patients develop liver failure and hepatocellular carcinoma; the risk may be higher in HIV-positive individuals.²

* There is no evidence that HBV accelerates HIV disease progression; on the other hand, in comparison with HIV-negative individuals with chronic HBV infection, HIV/HBV-coinfecting individuals appear to be at an increased risk for HBV-related end-stage liver disease.³ Furthermore, in HIV-positive individuals, HBV infection increases the risk for liver-related mortality.⁴

Treatment

* The currently available anti-HBV agents do not eradicate the cccDNA, so the goal of anti-HBV therapy is to prevent cirrhosis. It is unknown whether treatment will prevent hepatocellular carcinoma.

* Any HIV/HBV coinfecting patient with evidence of liver damage should be considered for anti-HBV treatment. However, there are no strict recommendations as to which HIV/HBV-coinfecting individuals should be treated.

* For HIV-negative individuals with chronic HBV, the American Association for the Study of Liver Disease (AASLD) recommends treatment in the following circumstances:⁵

- HBeAg positive, ALT >2 times the upper limit of normal
- HBeAg negative, HBV DNA >100,000 copies/mL

Whether these criteria are applicable to HIV-positive individuals is unknown.

* Currently, there are 5 markers available for assessing HBV liver damage and treatment response:

- Serum HBV-DNA
- HBsAg
- HBeAg
- ALT
- Liver histology

* What defines successful therapy is not well delineated, but markers of treatment success include the following:

- A substantial decrease in serum HBV DNA viral load

The NCCC Bulletin

Editors: Jason Tokumoto, MD; Rebecca Poage, MD

Published by: National HIV/AIDS Clinicians' Consultation Center (NCCC)

Contact us at 800/933-3413 or visit our Web site:

<http://www.ucsf.edu/hiventr>

This publication is supported by the Ryan White CARE Act through a grant from the Health Resources and Services Administration (HRSA), HIV/AIDS Bureau, to the NCCC, University of California San Francisco (Award # H4AHA01082).

- Sustained loss of HBsAg
- Loss of HBeAg; +/- the development of hepatitis B e-antibodies (anti-HBe)
- Normalization of ALT
- Improvement in liver histology

* Should a liver biopsy be done prior to treatment?

- For HIV-negative, HBV-infected persons, the AASLD does not routinely recommend liver biopsy prior to treatment.⁵
- In HIV/HBV-coinfected individuals, a liver biopsy is not mandatory before initiating anti-HBV therapy.⁶ However, initial treatment options, further treatment, and length of treatment may be influenced by liver histology.

* How long should treatment continue?

- The optimum length of therapy for HBV treatment is unclear.

* In approaching HBV treatment in an HIV-positive individual, the most important consideration is whether this patient needs to be treated with HIV antiretroviral therapy.

- In a patient who is already taking HIV therapy or will be starting HIV therapy, the best treatment option is to include agents that have both anti-HIV and anti-HBV activity. Examples of these agents are lamivudine (3TC), emtricitabine (FTC), and tenofovir (TDF).
- In a patient not requiring HIV therapy, the use of an anti-HBV agent without anti-HIV activity would probably be the best choice. Examples of these agents include interferon alpha and possibly adefovir at a dosage of 10 mg.
- No agent that has both anti-HIV and anti-HBV activity should be used as HBV monotherapy because of the high risk for developing HIV resistance.

Currently FDA-Approved Anti-HBV Agents

Interferon-alpha (IFN-a)

- Data on the effectiveness of IFN-a in the HIV/HBV-coinfected population are limited.
- In HIV-negative, HBV-infected persons, IFN-a has greater efficacy in those who are HBeAg positive, have high ALT (>2 times the upper limit of normal), and have low HBV DNA counts (<28,000,000).
- Compared with HIV-negative, HBV-infected persons, HIV/HBV-coinfected persons have a lower response rate to IFN-a, with loss of HBeAg in <10% of patients. In contrast, about 30% of HIV-negative, HBV-infected individuals lose HBeAg with IFN-a treatment.^{5,7}

- HIV/HBV-coinfected patients most likely to respond to IFN-a have the following parameters:^{6,7,8}

- HBeAg positive
- ALT >2 times the upper limit of normal
- HBV DNA <28,000,000
- Good CD4+ count (at least 300 cells/ μ L)
- Do not require HIV antiretroviral therapy

- Dosage:

- HBeAg positive: 5-6 million units (MU) a day or 9-10 MU 3 times a week for 4-6 months
- HBeAg negative: 5-6 MU 3 times a week for 12 months

- Side effects: flulike illness, psychiatric effects, bone marrow suppression

- Contraindication: decompensated liver disease

Lamivudine (3TC)

(Class: nucleoside analogue reverse transcriptase inhibitor)

- Mechanism of action: HBV requires reverse transcriptase for replication of HBV DNA from a long RNA intermediate.
- 3TC has activity against both HIV and HBV.
- For HIV-negative individuals with chronic HBV, the dosage is 100 mg once a day. For HIV treatment, the dosage is 300 mg once a day, and this dosage should be used in HIV/HBV-coinfected patients. In HIV-positive individuals, 3TC should never be used as HBV monotherapy because of the rapid selection for HIV resistance. 3TC always should be combined with ≥ 2 other anti-HIV medications.
- In HIV/HBV-coinfected patients treated with 3TC, the rate of HBeAg loss is about 22-28%,^{9,10} and the rate of HBV DNA reduction is about 40-87%.⁶
- 3TC resistance to HBV involves mutation at the YMDD domain of the polymerase gene. The development of HBV resistance to 3TC is about 20% per year in HIV/HBV-coinfected patients.¹¹
- Resistance to 3TC can be manifested by an increase in HBV DNA and/or a rise in the ALT.
- Even if the YMDD mutation appears, from the standpoint of HIV treatment, 3TC generally can be continued. For HBV, the benefit of continuing 3TC in the presence of the YMDD mutation is unclear.
- **Caution!** In a patient with detectable HBV DNA, stopping the 3TC can result in severe rebound hepatitis. If 3TC is stopped, it is vital to monitor HBV DNA and ALT.

Adefovir

(Class: nucleotide reverse transcriptase inhibitor)

- Has activity against both HIV and HBV but is not FDA approved for HIV.
- Dosage for HBV treatment is 10 mg once daily. At this

dosage, there is no anti-HIV activity.

- Activity against 3TC-resistant HBV strains:¹²
 - In 35 HIV/HBV-coinfected patients with 3TC-resistant virus, adefovir at 10 mg once a day was added to 3TC.
 - The addition of adefovir resulted in a significant reduction in HBV DNA and normalization of ALT.
 - At 144 weeks of therapy, adefovir resistance mutations had not developed for HIV or HBV.

Entecavir (Baraclude)

(Class: *guanosine nucleoside reverse transcriptase inhibitor*)

- Has no activity against HIV.
- Dosage: 0.5 mg once a day in 3TC-naive patients; 1 mg once a day in 3TC HBV resistance.
- Limited data in HIV/HBV-coinfected patients:¹³
 - Randomized, double-blind, placebo-controlled study in 68 HIV/HBV-coinfected patients who had a rise in the HBV DNA while on a 3TC-containing HIV antiretroviral regimen.
 - Patients either received entecavir 1 mg once a day or placebo for 24 weeks; followed by another 24 weeks in which all 68 patients received entecavir.
 - At the end of 48 weeks, 26% of individuals in the entecavir group had undetectable HBV DNA.

Anti-HBV Agents Not Yet FDA Approved

Polyethylene glycol-modified (pegylated) interferon (PEG-IFN)

- In HIV-negative individuals with HBeAg-positive chronic HBV, PEG-IFN has been shown to be more effective than conventional IFN:¹⁴

* International, multicenter, parallel-group, open-label Phase II study with 194 patients.

* One group received either 90, 180, or 270 µg once a week of PEG-IFN, the other group received 4.5 MU 3 times a week. Therapy was administered for 24 weeks, with a 24-week follow-up period.

* Inclusion criteria: HBeAg-positive, HBV DNA >500,000 copies/ml, ALT 2-10 times the upper limit of normal. HIV-positive patients were excluded.

* Primary end point: loss of HBeAg and appearance of anti-HBe antibodies.

* Combined end points: loss of HBeAg, HBV DNA <500,000 copies/mL, ALT normalization.

* Results: at the end of 24 weeks follow-up post treat-

ment, 29-37% in the PEG-IFN group reached the primary end point compared to 25% in the conventional IFN group. For the combined end points, 24% in the PEG-IFN group achieved the combined points compared to 12% in the conventional IFN group.

* Frequency and severity of side effects were the same in both groups.

- In HIV-negative, HBeAg-negative chronic HBV patients, PEG-IFN was more effective than 3TC.
- The U.S. AIDS Clinical Trials Group (ACTG) will be conducting a study assessing PEG-IFN in HIV/HBV coinfecting patients.

Emtricitabine (FTC)

(Class: *nucleoside reverse transcriptase inhibitor*)

- FDA approved for HIV but also has anti-HBV activity.
- Very similar to 3TC and shares similar HIV and HBV resistance mutations. However, there are some preliminary data to suggest that resistance to HBV occurs less frequently with FTC than with 3TC.¹⁵
- In 1 study involving 98 HIV/HBV-coinfected patients, FTC at a dosage of 200 mg once a day for 1 year resulted in 61% of patients having an undetectable HBV DNA viral load and 50% losing HBeAg.¹⁶
- FTC and 3TC probably should be considered interchangeable, not additive.

Tenofovir (Viread, TDF)

(Class: *nucleotide reverse transcriptase inhibitor*)

- FDA approved for HIV but also has anti-HBV activity.
- Effective against 3TC HBV-resistant strains.
- In HIV/HBV-coinfected patients, 70% had undetectable HBV DNA and 15% lost HBeAg after 2 years on tenofovir.¹⁷
- In a study involving 52 HIV/HBV-coinfected patients, one group received 300 mg of tenofovir and the other group received 10 mg of adefovir. At a median of 75 weeks, in an intent-to-treat analysis, there was a 4.46 log₁₀ drop in copies/mL from baseline in the tenofovir group while in the adefovir group there was 3.35 log₁₀ drop in copies/mL from baseline.¹⁸

Combination Therapy for HBV

- Data for combination therapies are limited.
- In 1 study that involved HIV-negative, HBV-infected patients, the combination of adefovir + 3TC was no more potent than adefovir alone at the end of 1 year of treatment.
- Combination therapy may reduce the evolution of multidrug resistant HBV strains.

General Considerations in the Care of HIV/HBV-Coinfected Patients

- HIV/HBV-coinfected patients are more prone to chemical hepatitis from exposure to certain drugs.
- Alcohol intake should be discouraged.
- Fulminant hepatitis A virus (HAV) has been reported in HIV/HBV-coinfected patients. The HAV vaccine therefore should be administered to patients who are not immune to HAV (i.e., anti-HAV IgG negative).
- Abdominal ultrasound and serum alpha-fetoprotein should be used to screen for hepatocellular carcinoma. Some experts suggest performing these tests every 6 months.⁶

Conclusions

* As with the HIV/HCV-coinfected patient, the HIV/HBV-coinfected patient presents with many treatment challenges.

* While all HIV/HBV-coinfected patients with evidence of liver damage should be considered for treatment, the indications for treatment as well as optimal treatment regimens and duration of treatment are not known.

References

1. Thio CL, Seaberg EC, Skolasky R, et al. Liver disease mortality in HIV-HBV coinfecting persons. Abstract 656. 9th Conference on Retroviruses and Opportunistic Infections; February 2002; Seattle, WA.
2. 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
3. Puoti M, Airoidi M, Bruno R, et al. Hepatitis B virus co-infection in HIV-infected subjects. *AIDS Rev* 2002; 4:27-35.
4. Konopnicki D, Mocroft A, deWit S, et al. Hepatitis B and HIV: prevalence, ADIDS progression, response to highly active antiretroviral therapy and increased mortality in EuroSIDA. *AIDS* 2005; 19: 593-601.
5. Lok ASF. HBV treatment guidelines: questions and controversies. *iMedOptions*; posted 9/10/2004. Available at: <http://clinicaloptions.com/hep/conf/ccohep2004/#lok>.
6. Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV international panel. *AIDS* 2005; 19:221-240.
7. Thio CL. Hepatitis B in the human immunodeficiency virus-infected patient: epidemiology, natural history, and treatment. *Semin Liver Dis* 2003 May; 23(2):125-36.
8. Nunez M, Puoti M, Camino N, Soriano V. Treatment of chronic hepatitis B in the human immunodeficiency virus-infected patient: present and future. *Clin Infect Dis*; 2003; 37: 1678-1685.
9. Benhamou Y, Katlama C, Lunel F, et al. Effects of lamivudine on replication of hepatitis B in HIV-infected men. *Ann Intern Med* 1996; 125: 705-712.
10. Dore GJ, Cooper DA, Barret C, et al. Dual efficacy of lamivudine treatment of human immunodeficiency virus-hepatitis B coinfecting persons in a randomized, controlled study(CAESAR). *J Infect Dis* 1999; 180:607-613.
11. Benhamou Y, Bochet M, Thibault V, et al. Long term-incidence of hepatitis B virus resistance to lamivudine in HIV-infected patients. *Hepatology* 1999; 30:1302-1306.
12. Benhamou Y, Thibault V, Vig P. Long-term treatment with adefovir dipivoxil 10 mg (ADV) in patients with lamivudine-resistant (LAM-R) HBV and HIV co-infection results in significant and sustained clinical improvement. Abstract 1329. XV International AIDS Conference; July 2004; Bangkok, Thailand.
13. Chang T, Hadziyannis S, Cianciara J, et al. Sustained viral load and ALT reduction following 48 weeks of entecavir treatment in subjects with chronic hepatitis B who failed lamivudine. *Hepatology* 2002; 36:300A.
14. Cooksley WGE, Piratvisuth T, Lee S-D, et al. Peginterferon alpha-2a(40 kDa): an advance in the treatment of hepatitis B e antigen-positive chronic hepatitis B. *J Viral Hepat* 2003; 10:298-305.
15. Gish R, Leung N, Wang C, et al. Resistance to emtricitabine may develop less frequently than to lamivudine. Abstract 838. 53rd American Association for the Study of Liver Diseases; 2002. Boston, MA.
16. Sykes A, Wakeford C, Rousseau F, et al. Antiviral efficacy and rate of development of resistance in patients treated for one year for chronic HBV infection with FTC. Abstract 674. 9th Conference on Retroviruses and Opportunistic Infections; February 2002; Seattle, WA.
17. Gilleece Y, Nelson M, Clarke A. Tenofovir in the treatment of hepatitis B/HIV coinfecting individuals. Abstract 3298. XV International AIDS Conference; July 2004; Bangkok, Thailand.
18. Peters M, Anderson J, Lynch P, et al. Tenofovir disoproxil fumarate is not inferior to adefovir dipivoxil for the treatment of hepatitis B virus in subjects who are coinfecting with HIV: results of ACTG A5127. Abstract 124. 12th Conference on Retroviruses Opportunistic Infections; February 2005, Boston, MA.



**National HIV Telephone Consultation Service
(Warmline) 800/933-3413**

**National Clinicians' Post-Exposure Prophylaxis Hotline
(PEPline) 888/448-4911**

**National Perinatal HIV Consultation and Referral
Service
(Perinatal Hotline) 888/448-8765**