



HIV MEDICAL ALERT

FOR PRIMARY HEALTH CARE PROVIDERS AND HEALTH PROFESSIONALS

March 2007
Vol. 10, Issue No. 3

HIV Medical Alert

provides clinicians with comprehensive and up-to-date information about diagnosis, treatment, and prevention of HIV.

HIV Medical Alert

is published by Upper Hudson Primary Care Consortium, Glens Falls, N.Y., as part of the HIV Clinical Education Initiative. The Initiative is funded by the AIDS Institute of The New York State Department of Health (NYSDOH).

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WELCOME to the *HIV Medical Alert* Newsletter Continuing Medical Education (CME) format. This activity has been planned and implemented in accordance with the Essentials and Standards of the Medical Society of the State of New York through the joint sponsorship of Glens Falls Hospital and Upper Hudson Primary Care Consortium. The Glens Falls Hospital is accredited by the Medical Society of the State of New York (MSSNY) to sponsor continuing medical education for physicians.

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Hepatitis B – Part II

HIV And Hepatitis B Co-infection

by Lyn Stevens, MS, ACRN, NP

Because of the negative impact HIV has on the natural history of chronic hepatitis B, the treatment and prevention of hepatitis B (HBV) in the co-infected patient is essential to the clinical plan of care. This article is the second in a two-part series presented in *HIV Medical Alert: Part I* (September 2006) discussed the principles of *Hepatitis B in Primary Care*; *Part II* will describe the clinical treatment of the patient who is co-infected with HBV and HIV. This article will address the impact of HIV infection on the natural course of Hepatitis B, offer Hepatitis B prevention strategies and discuss recommended Hepatitis B treatment measures in a HBV/HIV co-infected patient that will support healthier outcomes.

Epidemiology

Published data on the overall prevalence of Hepatitis B (HBV) and HIV co-infection in the United States is somewhat limited. Studies have identified prevalence rates of previous or current HBV infection in the following subgroups:

- 45% of HIV-infected men who have sex with men (MSM) aged 22 -29 (CDC unpublished data, 1998-2000)
- 24% of adolescent HIV-infected males and 43% of HIV-infected women, including 76% among HIV-infected female injection drug users (IDUs)

Chronic HBV infection had been identified in 6%-14% of HIV-positive persons from Western Europe and the United States, including 9% - 17% of MSM, 7%-10% of IDU's and 4%-6% of heterosexuals.

The course of HBV infection in the presence of HIV can be modified resulting in a lower incidence of jaundice and a higher incidence of chronic HBV infection. Limited data indicate that HIV-infected patients with chronic HBV infection have an increased risk for liver-related mortality and higher all-cause mortality than HIV-monoinfected patients. (EuroSIDA)

The Consequence of Co-infection

Influence of HIV on HBV

The course of HBV associated liver disease is accelerated by co-infection with HIV disease. HIV/HBV co-infection is known to adversely affect HBV outcomes. The relationship of co-infection and risk appears to be strongest with lower CD4 counts

and with treatment in the post-antiviral therapy treatment era. The natural history of HBV infection is modified by HIV infection and can result in higher rates of HBV persistence and relapse.

Influence of HBV on HIV

The EuroSIDA study found that HBV co-infection does not impair the virologic or immunologic response to antiretroviral therapy. Although hepatotoxicity after initiation of Antiretroviral Therapy (ART) is more common in HIV/HBV co-infected individuals than HIV-monoinfected people, this study showed that most co-infected individuals can be effectively treated for their HIV infection. Therefore, HBV infection should not preclude treatment of HIV. Individuals with co-infection should be carefully monitored for signs, symptoms and laboratory evidence of hepatotoxicity after starting ART.

Screening for HBV

The high prevalence of HIV/HBV co-infection underscores the importance of screening all HIV-infected patients for HBV. If the screened patient is not immune to HBV, the provider can offer HBV vaccine to prevent spread of infection. Providers are urged to test all HIV-positive patients for hepatitis B surface antigen (HBsAg) and anti-HBc antibodies and review patient HBV vaccination history.

In patients who are HBsAg –positive, further evaluation of the severity of HBV disease and the virologic profile is important. Table 1 outlines the screening tests for HBV. Also, each patient should have an examination for signs and symptoms of advanced liver disease and Alanine aminotransferase (ALT) determination.

Vaccination

The Advisory Committee on Immunization Practices (ACIP) guidelines for Hepatitis B published December 8, 2006 in Morbidity and Mortality Report (Vol.55, No. RR-16) recommends that HBV vaccination be provided for all HIV-infected patients who do not have evidence of prior HBV infection.

TABLE 1		
Screening in an HIV Infected Individual for Hepatitis B		
	HIV negative	HIV positive
Suspected Acute HBV	HBsAg IgM anti-HBc	HBsAg IgM anti-HBc HBV DNA
Suspected Chronic HBV	HBV Total anti-HBc	HBsAg Total anti-HBc If positive, HBV DNA

Table 2			
Dose, Route, and Schedule for HIV-infected Adults >20 years old			
Vaccine	Dose and Route	No. Doses	Schedule
Hepatitis B Vaccines			
Engerix-B	20 ug (1mL IM)	3	0,1,6 months
Recombivax	10ug (1 mL IM)	3	0,1,6 months
Combined Hepatitis A and B Vaccine			
Twinrix	Havrix 720 EL U plus		
	Engerix 20 ug (1 mL IM)	3	0,1,6 months
<i>EL U indicates enzyme-linked immunosorbent assay units; IM, intramuscular</i>			

Treatment

Treatment of chronic HBV infection is generally recommended for all HBV/HIV co-infected patients. However, the best strategy for management of HBV infection has not been defined. Since infection with HBV cannot be totally eliminated, the primary goal of treating chronic HBV infection is to halt progression of liver disease by suppressing viral replication.

Viral clearance in the form of conversion to HBV surface antigen-negative (HBsAg-) status, is a rare event in co-infected patients. HBV therapy is also used to prevent HBV disease flares in patients with immune re-constitution syndrome after initiating ART for HIV .

There are six drugs approved for the treatment of chronic hepatitis B: standard interferon alfa, pegylated

TABLE 3
Medications approved by the FDA for the Treatment of Chronic HBV Infection

Drug	Dose	Duration	Indicated for Chronic HBV infection in HIV-infected patients	Active against HIV and HBV	FDA approved
Interferon alpha (Intron A)	5MU daily or 10 mu 3 times per week by injection	4-6 months	No	No	1991
Peginterferon alfa-2a (Pegasys)	180ug weekly by injection	6-12 months	No	No	2005
Lamivudine (Epivir-HBV)	300mg/day in HIV positive patients	Minimum 12 months	No	Yes	1998
Emtricitabine (Emtriva)	200 mg/ day	Optimal duration unknown	No	Yes	
Adefovir (Hepsera)	10 mg/ day	Optimal duration unknown	No	No	2002
Tenofovir (Viread)	10 mg/ day	Optimal duration unknown	No	No	
Entecavir (Baraclude)	0.5 mg/ day in lamivudine-naïve patients 1.0 mg/day in lamivudine-experienced patients	Optimal duration unknown	Yes	No	2005
Telbivudine (Tyzeka)	600 mg/ day	Optimal duration unknown	No	No	2006

interferon alfa-2a, lamivudine, adefovir, entecavir and telbivudine. Other drugs with anti-HBV activity such as tenofovir and emtricitabine are FDA approved for treatment of HIV infection and are frequently used in co-infected patients as anti-HBV agents.

Treatment of HBV in HIV-infected patients is similar to patients with HBV alone. The need for treatment is based on the presence of viremia, the extent of biochemical abnormalities, and the severity of liver disease.

Slowing disease progression is important in HIV/HBV co-infected patients in light of increased morbidity and mortality secondary to liver disease. Potential benefits derived from HBV treatment also include improved tolerance of highly active antiretroviral therapy (HAART) since several studies suggest that chronic hepatitis B is a risk factor for drug associated toxicity and decreased risk of HBV transmission to others.

For patients who need HIV treatment, agents with HBV activity should be considered as part of the antiretroviral regimen in an effort to avoid immune constitution syndromes which can occur with rising CD4 counts and ongoing HBV viremia. The risk of HBV-related immune reconstitution is increased in patients with high levels of HBV and CD4 counts less than 200 cells/ul.

The treatment recommendations for HBV/HIV co-infected patients provide guidance for treatment in each of the possible scenarios. (Please refer to Table 4, next page.)

Combination therapy for HBV can lead to decreased HBV drug resistance, although it has not improved the overall efficacy of HBeAg seroconversion in patients with HBV alone. The role of combination therapy in patients with HIV/HBV infection is unclear. It may be best suited for patients who are candidates for HAART.

For comprehensive guidelines on treatment of HIV/HBV co-infection link to: HIV and Hepatitis http://www.hivandhepatitis.com/hep_b/news/2007/020907_a.html or www.uptodate.com "Treatment and prevention of hepatitis B in the HIV-infected patient".

Patient monitoring

Laboratory monitoring includes serial liver function tests, HBeAg and HBV DNA. A reasonable schedule is to obtain liver function tests monthly, HBeAg every six months, and HBV DNA quarterly while on therapy. The goal is to improve biochemical function, suppress HBV DNA, and attain seroconversion (in patients with HBeAg positive infections). In patients with HBeAg negative infection, aminotransferases and HBV DNA should be monitored on a similar schedule.

TABLE 4: Treatment Recommendations for HBV/HIV Co-infected patients

Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, October, 10, 2006

All Patients with HBV should:

- ◆ Be advised to avoid alcohol;
- ◆ Receive hepatitis A vaccine, if found not to be immune at baseline (ie absence of hepatitis A antibody);
- ◆ Be advised of methods to prevent Hepatitis B transmission
- ◆ Be evaluated for the extent of HBV infection.

Need to treat HIV and not HBV

The combination of tenofovir + emtricitabine or tenofovir+lamivudine can be used as the NRTI backbone of an antiretroviral regimen. To avoid development of HBV resistant mutants Lamivudine, tenofovir or emtricitabine should not be the only agents with anti-HBV activity in a regimen.

Need to treat HIV and HBV

The combination of tenofovir +lamivudine or tenofovir +emtricitabine are considered first-choice NRTI backbones. Additional options include entecavir alone or in combination with one of the three nucleosides with activity against both viruses. The use of lamivudine , emtricitabine, or tenofovir as the only active anti-HBV agent should be avoided because of the risk of resistance.†

Treatment of HBV and not HIV

Pegylated interferon-alpha is an option that does not lead to development of drug-resistant HIV or HBV mutants. Entecavir is a nucleoside analogue that is not active against HIV, so it is another option in this situation. Adefovir dipivoxil is active against HBV but not against HIV at the 10 mg dose; however, a theoretical risk for development of HIV mutants exists, because it is related to tenofovir. The use of emtricitabine, lamivudine, or tenofovir without a full HAART regimen should be avoided because of the rapid development of drug-resistant HIV mutations.

†Entecavir may be linked to a risk for HIV resistance in patients co-infected with HBV and HIV who are not currently receiving HAART according to the US Food and Drug Administration (FDA) and Bristol-Myers Squibb. A similar warning has also been issued by Health Canada. (Medscape Medical News 2007). (14th CROI: Abstract 136LB. Presented February 28, 2007.)

Need to discontinue lamivudine, tenofovir, or emtricitabine

Monitor clinical course with frequent liver function tests, and consider the use of adefovir dipivoxil or entecavir to prevent flares, especially in patients with marginal hepatic reserve.

Summary

Significant progress has been made in the treatment of HBV/HIV co-infection. Patients with co-infection, who usually experience more rapid and severe liver damage, now have expanded therapy options that are more convenient to use and have fewer adverse effects.

The broad array of recently approved treatments as well as those in the pipeline will contribute to improved long-term HBV suppression and thus can be expected to prevent or significantly delay the onset of liver complications in most HIV/HIV co-infected patients.

Resources:

1. "A Comprehensive Immunization Strategy to Eliminate Transmission of Hepatitis B Virus Infection in the United States" MMWR, December 8, 2006/ Vol. 55/ No. RR-16.
2. Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults. www.aidsinfo.nih.gov
3. HIV/HBV Co-Infection: Treatment and Management of HBV-HIV Co-infection: The Goals of Therapy for HBV. www.hivandhepatitis.com/hiv
4. V Soriano, P Barreiro and M Nunez. Management of chronic hepatitis B and C in HIV-co-infected patients. *Journal of Antimicrobial Chemotherapy* 57(5): 815-818. May 2006.

Author

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Continuing Education Test

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To earn credit:

1. Read the CME article.
2. Review the objectives
3. Study and apply the content to the objectives and to your practice.
4. Complete the Post-Test.

5. Return the answer sheet as directed at the bottom of the evaluation page.

Objectives: At the conclusion of this activity, the learner will be able to:

1. Discuss influence of HIV on the natural course of Hepatitis B.
2. Name a resource for schedules of Hepatitis B vaccination and recommended doses in HIV-infected patients.
3. State the name of the FDA approved medication for treatment of Hepatitis B in an HIV-infected patient.
4. Discuss the Guidelines for Use of Antiretroviral Agents in HIV-1 Infected Adults co-infected with Hepatitis B.

Note: This CME activity and quiz is designated for 1 credit. CME credit expires September 5, 2008

Select the best answer for each of the following.

1. The course of HBV associated liver disease is _____ by co-infection with HIV:
 a. Unaffected
 b. Slowed
 c. Accelerated
2. The Web site where further information may be obtained regarding Hepatitis B schedules and doses in patients co-infected with HIV / HBV is:
 a. www.hivguidelines.org.
 b. www.immunize.org/catg.d/2081ab.htm
 c. www.anacnet.org
 d. www.cdc.gov
3. The drug approved by the FDA for treatment of Hepatitis B in HIV-infected adults is:
 a. Peginterferon
 b. Lamivudine
 c. Entecavir
 d. Telbivudine t
4. According to the Guidelines for Use of Antiretroviral Agents in HIV-infected Adults Co-infected with Hepatitis B, all patients should:
 a. Be advised to avoid alcohol
 b. Receive a Hepatitis A vaccine, if found not to be immune at baseline
 c. Be advised of methods to prevent Hepatitis B transmission
 d. Be evaluated for the extent of HBV infection
 e. All of the above
5. The EuroSIDA study found that HBV co-infection does not impair the virologic or immunologic response to antiretroviral therapy.
 a. True
 b. False

Evaluation of CME Activity

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	Excellent	Good	Fair	Needs Improvement
Overall Activity				
1. Was the subject matter well balanced in fact and theory?	1	2	3	4
2. Was the format clear and easy to read?	1	2	3	4
3. Did subject matter have sufficient detail?	1	2	3	4
4. Was subject matter valuable for practical application?	1	2	3	4
5. Were objectives listed on test page met?	1	2	3	4
6. Was the writer clear in content, sequence and style?	1	2	3	4
7. Overall program was? _____				

Comments/Topic Suggestions:

PLEASE PRINT CLEARLY TO ASSURE ACCURATE DOCUMENTATION OF CME CREDIT

Profession: Physician PA NP CNM RN LPN Other _____

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(please sign legibly for CME records)

Return the completed test and evaluation form to:
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