

## Hepatitis B co-infection in pregnancy

Ronald D. Wilcox, MD, FAAP

Chronic hepatitis is often found in HIV-infected persons. Chronic hepatitis C co-infection is found in approximately 30% of HIV-positive people and chronic hepatitis B in 10%; triple infection with all three viruses occurs in about 1% of HIV-infected persons.

Recently we received a consultation on the appropriate treatment of hepatitis B in an HIV-infected woman who is pregnant in the middle of her second trimester. The patient was currently on no HIV medications but had a long history of prior HIV therapy and had a multiply-resistant strain of virus on her most recent resistance assay. Her CD4 count was in the 500 range, HIV viral load about 15,000 copies/ml, and hepatitis B viral load was over 1,000,000 copies/ml. Her hepatitis B e antigen (HBeAg) was positive in 2005 but her liver transaminases recently were not markedly elevated. As defined by her lab work-up, the patient likely has chronic active hepatitis B, although a more recent HBeAg needs to be assessed.

Hepatitis B is very concerning in pregnancy. Without intervention, a child exposed to a mother with both hepatitis B surface antigen (HBsAg) and HBeAg positivity has approximately a 70-90% chance of chronic hepatitis B infection within the first six months of life with nearly 10% *in utero* transmission. With receipt of hepatitis B immune globulin at birth and all three doses of the standard regimen of hepatitis B vaccination, this chance of chronic infection is decreased by approximately 95%. The higher the maternal hepatitis B viral load, the more likely the chance of transmission even with preventive measures; in a study by van Zonneveld *et al*, mothers with a high hepatitis B viral load had a transmission rate of 28% despite appropriate interventions. It stands to reason that treatment of hepatitis B infection in the third trimester should decrease transmission to the infant by lowering the maternal viral load but strong data is lacking regarding this measure.

DHHS Guidelines suggest that if patients are HIV-infected and require therapy for hepatitis B co-infection, the patients should be given full HAART therapy even if they do not require therapy for their HIV yet. The HAART regimen should contain at least one medication that has activity against hepatitis B also. The reasoning behind this decision is that two medications frequently used to treat chronic hepatitis B, tenofovir and lamivudine, are also FDA-approved for the treatment of HIV. Emtricitabine, although not FDA-approved for hepatitis B therapy, also has strong activity against both viruses. Entecavir, a medication not used for the treatment of HIV but only for hepatitis B, also has some activity against HIV and can lead to resistance development in HIV if used as monotherapy for treatment of hepatitis B in HIV-infected persons.

Acute hepatitis B infection in pregnancy mimics acute disease in the non-pregnant patient but must be differentiated from other causes of liver disease in pregnancy such as intrahepatic cholestasis, acute fatty liver of pregnancy, or the HELLP syndrome. There is no known teratogenic effect of acute hepatitis B in pregnancy, but low birth weight and prematurity incidence have been reported to be increased. In a study in Texas of 455 obstetrical patients with HIV over 11 years, only 1.5% were co-infected with hepatitis B. The co-infected women were noted to have lower CD4 counts when compared to those co-infected with HIV and hepatitis C or those with only HIV infection.

A study by van Zonneveld *et al* published in 2003 evaluated the effectiveness of lamivudine therapy in decreasing transmission of hepatitis B when given in the third trimester in mono-infected patients. The authors evaluated the outcomes of eight HBeAg positive women given lamivudine 150 mg po daily after 34 weeks gestation and compared them to 24 matched historical controls. For five of the mothers, the hepatitis B viral load decreased to less than  $1.2 \times 10^8$  copies/ml. One half of the infants were HBsAg-positive at birth but only one remained positive at one year, giving a 12.5% rate of transmission in this very small study (compared to 28% in the historical controls). In China and the Philippines, a study by Xu *et al.*, done as a randomized,

double-blind, placebo-controlled study evaluating the effectiveness of lamivudine in mono-infected pregnant women, starting at 32 weeks and continuing to 4 weeks postpartum, had a transmission rate of 18% at one year compared to 39% of infants whose mothers received the placebo. Neither study showed an increase in adverse events.

Classification of anti-hepatitis B medications for pregnancy safety is as follows: category C for adefovir, entecavir, lamivudine, interferon alfa-2b, and pegylated interferon alfa-2a; category B for telbivudine and tenofovir. Lamivudine is associated with a 2.2-2.4% risk of birth defects (no higher than baseline) and tenofovir with 1.5% in second trimester use and 2.3% in third trimester use (similar to background rates). Telbivudine received its rating based on animal studies with little human pregnancy registry data. The interferon alfa formulations have not been studied for treatment in co-infected patients and have been noted to induce spontaneous abortions in rhesus monkeys so should *only* be used during pregnancy when the risk of the disease in the fetus is great.

Although there are no clear guidelines as to the decision to offer therapy in the mono-infected pregnant patient, one algorithm decides depending on two factors: the hepatitis B viral load at 28 weeks gestation and a history of previous hepatitis B perinatal transmission. If there is no history of prior perinatal transmission, therapy is recommended in the third trimester if the hepatitis B viral load is  $>10^8$ - $10^9$  copies/ml. For those with a positive history for previous perinatal transmission, the recommended level is  $>10^6$  copies/ml. Medications should be held after delivery if the mother decides to breast-feed the infant but the woman must be monitored closely for a flare-up of transaminase elevation after discontinuation of the medications.

The Opportunistic Infections treatment guidelines released by DHHS in June, 2008, state "treatment of chronic HBV infection is generally not indicated in pregnancy (DIII)" but also that in "women having indications for ART for their own health and expected to continue antiretrovirals postpartum, a regimen including two agents with activity against hepatitis B should be used (AIII)." In general, lamivudine is used as a part of the HAART and hepatitis B therapy unless resistance to lamivudine has previously been demonstrated and tenofovir may be added as a second agent.

The case patient had previously been on many different HIV medications. Her latest genotype showed possible resistance to tenofovir and resistance to most of the nucleoside reverse transcriptase inhibitors. Although the latest genotype did not show the M184V mutation which gives resistance to lamivudine and emtricitabine, the patient likely is harboring a resistant strain that is not the most prevalent strain. This author/consultant recommended the use of tenofovir + emtricitabine to decrease the hepatitis B viral load to be used with a boosted protease inhibitor regimen and possibly an integrase inhibitor (although there is very limited data on integrase inhibitor use in pregnancy) that could be added after delivery. This will hopefully decrease the chances of transmission, both of the hepatitis B and the HIV, to the infant. ❖

*Dr. Wilcox is Director/Principal Investigator, Delta Region AETC; Associate Professor, Infectious Disease and Pediatrics, LSUHSC; Staff Physician, Interim LSU Hospital HIV Outpatient Program (HOP) Clinic.*

#### REFERENCES

Department of Health and Human Services. "Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents." Released June 18, 2008. Pages 113-126.

Jonas MM. "Hepatitis B and pregnancy: an underestimated issue." *Liver International* 2009; 29(s1): 133-9.

Santiago-Munoz P *et al.* "Prevalence of hepatitis B and C in pregnant women who are infected with human immunodeficiency virus." *Am J Obstet Gynecol* 2005; 193(s1): 1270-3.

Tran TT. "Management of hepatitis B in pregnancy: weighing the options." *Cleveland Clin J Med* 2009 May; 76(s3): S25-9.

van Zonneveld M *et al.* "Lamivudine treatment during pregnancy to prevent perinatal transmission of hepatitis B virus infection." *J Viral Hepat* 2003; 10: 294-7.

Xu WM *et al.* "Efficacy and safety of lamivudine in late pregnancy for the prevention of mother-child transmission of hepatitis B: a multicentre,

randomized, double-blind, placebo-controlled study [AASLD abstract 246]. *Hepatology* 2004; 40: 272A.