Background on HIV and HBV

Human immunodeficiency virus (HIV) infection and hepatitis B virus (HBV) infection, which overlap since they are transmitted by similar routes, including sex and injection drug use, have caused large global epidemics. HIV, a retrovirus with an RNA genome that has 2 variants (HIV-1 is most common in the United States), targets CD4 cells and damages the host immune system. HBV, a hepadnavirus with a DNA genome that has 8 genotypes, targets liver cells (hepatocytes), and also damages the host immune system. HBV is 50 to 100 times more infectious than HIV.1,2

While the tests (HIV-1 RNA viral load and CD4 cell counts) and clinical course for HIV infection are somewhat straightforward, the tests and clinical course for HBV are more complex. Chronic HBV infection is characterized by changes in HBV viral load (usually represented by viral counts in log units). Several tests measure HBV viral load and activity. The following are typical tests used to measure HBV viral load:3

• Serum HBV DNA levels, measured in log units
  
  Serum HBV DNA is present at measurable levels during acute infection, but may or may not be detected during chronic infection or during reactivation in hepatitis B “E” antigen (HBeAg)-negative chronic hepatitis.

• Alterations in liver function reflected in alanine transaminase (ALT) levels

• Various HBV-specific antigens and antibodies to them, measured in log units
  
  HBeAg, a peptide normally detectable in the bloodstream when the hepatitis B virus is actively reproducing, associated with increased infectiousness and greater risk of progression to liver disease, is used clinically as a measure of viral replication, infectivity, and severity
  
  Antibody to HBeAg (anti-HBeAg) is used clinically as a marker for reduced replication
  
  Surface antigen (HBsAg) and antibody to core antigen (anti-HBc) are markers of both acute and chronic infection.

The progression of HBV disease after acute infection is very high (>90%) in children, but very low (<5%) in immunocompetent adults.4,5 About 30% of individuals with chronic HBV infection develop cirrhosis, and 5% to 10% develop hepatocellular cancer (HCC).4 About one fourth of patients with cirrhosis decompensate and develop liver failure within 5 years.6 Chronic HBV infection is the sixth leading cause of liver transplantation in the United States.7 It should also be noted that the presence of HBV antigen is considered as antigen “positive,” and lack of antigen is considered antigen “negative.”
Therapy Analysis and Evidenced-Based Treatment Guidelines (Including Review of Antiviral Medications)

**Treatment Guidelines for HBV-Infected and HIV-HBV Co-Infected Patients**

Although many guidelines and consensus statements have been published, the primary source for treatment of patients HBV-infected without HIV co-infection are the American Association for the Study of Liver Diseases (AASLD) 2007 Hepatitis B guidelines.8 The management of anti-HBV therapy in patients with antiviral-resistant HBV is outlined in the AASLD guidelines (Table 1).8

The U.S. Department of Health and Human Services Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, last updated January 29, 2008, are the preferred guidelines for treatment of HIV-HBV co-infected patients. Anti-retroviral therapy (ART) treatment is normally initiated when CD4 counts are less than 350 (Table 2).9

**Impact of Co-Infection With HIV and HBV**

In co-infection, HIV affects HBV disease progression more than HBV affects the course of HIV infection. In molecular terms, HIV decreases the rate at which HBeAg is lost and increases levels of HBV DNA. In clinical terms, HIV increases the progression to cirrhosis, increases the number of liver-related complications, and increases mortality.10-14 On the other hand, HBV affects HIV disease by activating the immune system and by the HBV-X protein (HBV-X protein stimulates viral genome replication), which may induce HIV replication and transcription, but there is typically no change in CD4 cell count and no evidence for clinical impact of HBV on HIV disease.15

The decision to treat HBV in a patient with HIV-HBV co-infection depends on whether highly active antiretroviral therapy (HAART) for HIV is indicated, liver disease severity, likelihood of response, and adverse event potential. The goal of HBV therapy is to eradicate the virus (by suppression of HBV DNA to undetectable levels) and to prevent complications of liver disease, including cirrhosis, decompensation, and liver cancer, and finally to reverse chronic carrier state HbsAg/HbsAb seroconversion. Complete response to HBV therapy involves biochemical (serum ALT within normal range), virologic (undetectable serum HBV DNA and loss of HBeAg in HBeAg-positive patients), and histologic improvement.16 The level of detection of HBV DNA depends on the assay used due to the sensitivity of these assays over wide concentrations.16
HBV Antiviral Therapies

While interferon and pegylated interferon have been used to treat HBV infection, 3 additional classes of oral anti-HBV therapy are now available: L-pyrimidine nucleoside analogs, acyclic phosphonates, and a guanosine nucleoside analog. L-nucleoside analogs approved by the FDA include lamivudine, defovir, dipivoxil, and tenofovir disoproxil fumarate, which is approved for use in HIV infection but not yet for HBV infection. Entecavir is a guanine nucleoside analog. A National Institutes of Health (NIH) clinical research workshop estimated the comparative activity of anti-HBV agents on various parameters used to measure response of HBV infection to therapy at 1 year; they used data from various clinical trials. HBeAg-positive patients have a more pronounced decline in HBV DNA in response to therapy than HBeAg-negative patients.

Lamivudine was the first oral nucleoside approved for treatment of HBV infection. The other L-nucleosides are similar to lamivudine. While about half of patients who are HBeAg-positive at baseline become HBeAg-negative by 5 years, resistance to lamivudine in HBV emerges relatively rapidly (24% at 1 year, 49% at 3 years, and 69% at 5 years). As a result, lamivudine is no longer a first-choice therapy for HBV infection. Adefovir is an acyclic phosphonate indicated for HBV but not for HIV infection. An observational cohort followed 35 HIV-HBV co-infected patients resistant to lamivudine for up to 192 weeks. Adding adefovir to ART that included lamivudine was well tolerated and resulted in sustained reductions in both HBV DNA (percentage with <1,000 copies per mL was 6% at 48 weeks, 27% at 96 weeks, 46% at 144 weeks, and 58% at 192 weeks) and ALT (normalization in 14% at 48 weeks, 48% at 96 weeks, 68% at 144 weeks, and 70% at 192 weeks). During therapy for chronic HBV, resistance develops to adefovir over time (3% at 2 years, 11% at 3 years, 18% at 4 years, and 29% at 5 years).

Tenofovir is an acyclic phosphonate that is very similar to adefovir indicated for HIV but not HBV, although tenofovir has been shown to inhibit HBV DNA polymerase. Tenofovir has been shown to have activity against both viruses in patients with HBV or co-infected with both HIV and HBV. For example, in a study of 53 patients with high levels (>6 log copies per mL) of HBV DNA, at week 48 the tenofovir-treated patients (n = 35) had decreased 5.5 log units compared with 2.8 log units for adefovir-treated patients (n = 18). In another study of 52 co-infected patients on stable ART with HIV viral load <10,000 copies per mL (74% had <50 copies per mL at baseline and 94% lamivudine resistant) and serum HBV DNA 5 log copies per mL or higher (86% HBeAg-positive), tenofovir was not inferior to adefovir without safety issues, and the study was terminated early. Other studies have shown that tenofovir was able to reduce HBV viral load despite resistance to adefovir or lamivudine, and no patients developed viral breakthrough while receiving tenofovir therapy.

Entecavir is a guanosine analog that inhibits multiple steps in HBV replication without inhibiting human mitochondrial DNA polymerase-γ. Recent data indicated entecavir also has activity against HIV and tends to target HIV virus resistant to antiretroviral drugs. Over 3 years, the cumulative rate of resistance to entecavir in treatment-naïve HBV-infected patients was 1.1%. Virologic rebound occurred in 20.6% (14/68) lamivudine-refractory patients treated with entecavir. A recent analysis determined that entecavir would be cost-effective versus lamivudine in the treatment of HBeAg-positive HBV infection. The activity of entecavir in HIV-HBV co-infected patients differs depending on prior exposure to ART. Some studies (although based on small patient numbers) have shown good viral suppression in ART-naive patients but much less so in ART-experienced patients. Entecavir was shown to target the M184V (methionine to valine at position 184) mutation in the HIV reverse transcriptase gene. Therefore, entecavir is not appropriate to treat HIV-HBV co-infected patients unless used with a fully suppressive antiretroviral regimen.

Liver-Related Mortality in Co-Infected Patients

The risk of liver-related mortality was estimated in the Multicenter AIDS Cohort Study (MACS) in which about 6% (326/5,293) of the men who had sex with men were HBsAg-positive at baseline. The rate of liver mortality for HIV-HBV co-infected patients was 14.2 deaths/1,000 patient-years compared with 1.7 deaths/1,000 patient-years for HBV-positive, HIV-negative patients and 0.8 deaths/1,000 patient-years for HIV-negative, HBV-positive patients. In MACS, concomitant HIV infection increased the relative risk for liver death from HBV infections 18.7 fold. In the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study that evaluated mortality in 23,441 HIV-infected persons followed for a total of 76,893 patient-years, the relative risk of liver-related death for those with HBV was lower, 3.7 (95% CI =2.4-5.9).

Response to Anti-HBV Therapy in Co-Infected Patients

Anti-HBV therapy is effective in patients with HIV-HBV co-infection. Data from a summary article published in 2006 pre-

### Table 3: Responses to Anti-HBV Agents in Patients with HIV-HBV Co-Infection

<table>
<thead>
<tr>
<th>Agent</th>
<th>HBe seroconversion</th>
<th>HBV DNA decline (log units)</th>
<th>ALT Normalized</th>
<th>Histologic improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interferon</td>
<td>9%</td>
<td>NR</td>
<td>12%-20%</td>
<td>NR</td>
</tr>
<tr>
<td>Lamivudine</td>
<td>11%</td>
<td>2.7</td>
<td>30%-50%</td>
<td>NR</td>
</tr>
<tr>
<td>Entecavir</td>
<td>NR</td>
<td>3.6</td>
<td>49%</td>
<td>33%-50%</td>
</tr>
<tr>
<td>Adefovir</td>
<td>7%</td>
<td>4.7-6.0</td>
<td>35%-66%</td>
<td>NR</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>4%</td>
<td>4.4</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Note: These values are comparisons of the results of various clinical trials, and, therefore, should be taken as only a guide to probable relative activity.
senting a treatment algorithm for HBV in HIV-infected patients are presented in Table 3.29

The following paragraphs summarize key observations about the response rate of HBV infection in selected clinical studies of HIV-HBV co-infected patients.

**Interferon-α** can be used in co-infected patients but seems to have some complications. A retrospective cohort study followed 144 HBeAg-positive patients (69 HIV-positive) for 45 months. HIV infection was associated with poorer response to interferon-α, more frequent HBV reactivations, and increased incidence of cirrhosis and cirrhosis-related death in cases of low CD4 cell count; however, interferon-α therapy reduced the incidence of HBV-related cirrhosis regardless of HIV status.32

**Lamivudine** appeared effective initially as monotherapy in co-infected patients, but resistance has been shown to develop quickly. In a randomized, controlled study of lamivudine therapy in 1,790 patients, the median decrease in HBV DNA level was 2.0 log units at 12 weeks and 2.7 log units at 52 weeks compared with no decrease in the placebo arm.30 A retrospective cohort study of 46 co-infected patients treated with lamivudine documented lamivudine resistance of 25% at 1 year and 52% at 2 years.31

**Emtricitabine** has been used experimentally in co-infected patients with some evidence of effect. In a double-blind, parallel study of co-infected patients, patients were given emtricitabine 25 mg, 100 mg, or 200 mg once daily for 48 weeks and followed for an additional 48 weeks on open-label 200 mg emtricitabine. Emtricitabine was associated with a mean decrease in HBV level of 3.4 log units at 56 days, which was maintained after 48 weeks of treatment in more than half the patients.32,33

**Entecavir** has shown some effect in lamivudine resistant virus. In co-infected patients with the tyrosine-methionine-aspartate-aspartate (YMDD) lamivudine-resistance mutation treated with entecavir, the mean decrease in HBV DNA level was 3.66 log units at 6 months, and 84% (57/68) had either an HBV DNA level <400 copies per mL or a 2 log or greater reduction from baseline.34

Combination therapy with **adefovir** and ART has been studied in co-infected patients and shown to reduce HBV viral load. For example, when adefovir was added to ART that included lamivudine in 35 co-infected patients with a median baseline HBV DNA level of 9.76 log copies per mL, the HBV DNA level dropped 5.08 log units at 48 weeks, 4.52 at 96 weeks, and 3.86 at 144 weeks, all P<0.001. Of the 29 who completed 144 weeks of therapy, 7 (25%) had HBV DNA levels <2.3 log units.20

In substudies, patients co-infected with HIV and HBV in the phase III studies of **tenofovir therapy** for treatment of HIV, there was a difference in response between ART-naïve (substudy 903) and antiretroviral-experienced (substudy 907) patients.35 In the ART-naïve patients, the mean decrease in HBV DNA at 48 weeks was 4.7 log units for the 5 patients receiving tenofovir and lamivudine compared with 3.0 log units for the 6 patients receiving only lamivudine. In the ART-experienced patients, the mean change in HBV DNA at 24 weeks was a decrease in 4.9 log units for the 10 patients who received tenofovir compared with an increase of 2.1 log units for the 2 patients randomized to receive placebo.

**Resistance of HBV to Anti-HBV Agents**

Resistance of HBV to drug treatment arises because of the high rate of viral production (1 to 10 trillion virions per day) combined with the high rate of spontaneous mutations due to the lack of proof-reading capacity of the HBV reverse transcriptase, which is necessary to the replication of this DNA virus that contains a single-stranded region in its 3,200 base pair genome. The base substitution rate of 1 in 100,000 means that all possible single-base changes in the HBV DNA are produced many times each day so that antiviral resistance mutations are present prior to therapy.

HBV resistance may be characterized as genotypic, viral, or clinical.

- Genotypic resistance identifies specific mutations in vitro or in vivo using molecular testing. These mutations underlie viral and clinical resistance. Interestingly, the mutations associated with lamivudine, emtricitabine, entecavir, and telbivudine (most commonly M204I/V, that is, a change from methionine to either isoleucine or valine at position 204 in the HBV polymerase gene in the YMDD region), do not overlap with those associated with resistance to adefovir or tenofovir (A181V and N236T). Genotypic testing should be used to confirm viral or clinical resistance.
- **Viral resistance** is characterized by an increase in HBV DNA levels by more than 10-fold (>1 log unit) from the lowest level achieved (the nadir) while adherent to therapy. Serum HBV DNA should be monitored frequently—every 3 to 6 months—during therapy.
- **Clinical resistance** is defined as a rise in serum ALT by more than 2-fold (100%) with a simultaneous rise in HBV DNA levels.16 Resistance may be prevented or reduced by avoiding unnecessary treatment and initiating treatment with an appropriate antiviral agent (one to which the virus is not already resistant) or with combination therapy. Maximizing patient adherence and checking carefully for medication adherence in patients with virologic breakthrough is crucial. Switching to an alternative drug in non-responders will also minimize emergence of resistance.8

**Summary**

Treatment of HBV infection reduces risk of liver complications, including cirrhosis and hepatocellular carcinoma, and death. Suppression of serum HBV DNA to the lowest levels achievable is important because HBV disease progression can occur even when HBV DNA levels are less than 10,000 copies per mL, which corresponds to about 2,000 International Units/milliliter (IU per mL). Available antiviral agents may need to be used in combination to achieve this goal, and improving adherence is important. Emergence of resistance to anti-HBV agents is a key consideration. Treatment of HBV infection should be considered in HIV-infected persons using available agents. It is important to consider the activity of the antiviral agents used against both viruses when selecting treatment regimens.