Update on HBV and HIV Coinfection: Pathogenesis and Treatment

Dr. Dieterich began his November 2005 lecture acknowledging that the etiology and pathogenesis of hepatitis B virus (HBV) infection are extremely complex. "HBV is a very complicated organism," he explained. "In some ways it is like HIV, but in many ways it's not. And it has even less in common with the hepatitis C virus. Hepatitis C is relatively straightforward and can be cured, whereas hepatitis B is a very sneaky virus and is much more difficult to eliminate. This kind of uncertainty can be very hard for clinicians to grasp."

All About HBV

HBV belongs to a family of DNA viruses called hepadnaviruses. Each complete virus consists of an inner core (nucleocapsid or hepatitis B core antigen [HBcAg]) surrounded by an outer protein coat or envelope, the hepatitis B surface antigen (HBsAg).

The HBV genome is a circular, partially double-stranded DNA of approximately 3,200 base pairs. There are four overlapping reading frames, which encode the envelope, precore/core, polymerase, and X proteins. The envelope open reading frame encodes the large, middle, and small surface glycoproteins of HBsAg. The precore/core open reading frame is translated either into the precore polypeptide, which is secreted as hepatitis B "e" antigen (HBeAg), or into the viral nucleocapsid, HBcAg.

Upon entering hepatocytes, the HBV genome is transported to the nucleus and is converted to covalently closed circular DNA (ccDNA). The HBV ccDNA serves as the template for transcription of mRNA and the RNA pregenome. "This closed circular DNA is very difficult to get out of the nucleus," Dr. Dieterich said. "This is why HBV is a very difficult virus to eliminate with treatment. At present, eradicating ccDNA only seems possible in rare cases."

Once transferred to the cytoplasm, HBV polymerase uses reverse transcription to convert the RNA pregenome into new circular genomic DNA. "This is where reverse transcriptase inhibitors go to work," Dr. Dieterich commented. "HBV is really a closet retrovirus. It acts much more like a retrovirus than it does a typical DNA virus. In turn, it is sensitive to reverse transcriptase inhibitors."

HBV Genotypes

Like HIV, HBV is a rather clumsy virus. Because of spontaneous errors that occur during reverse transcription of the virus, the HBV genome has evolved into different genotypes throughout the world. Currently, eight genotypes of HBV are defined by greater than 8% divergence in the entire HBV genomic sequence. Recent data also suggest that HBV genotypes can be further segregated into subgenotypes.

For the most part, HBV genotypes have distinct geographical distributions (see Figure 1). For example, genotypes B and C are prevalent in Asia, whereas genotypes A and D occur frequently in Europe. Genotypes F and H are found in Central and South America. "In the United States, given that it truly is a melting pot, we see genotypes A, B, C, and D," Dr. Dieterich pointed out. "Interestingly, the prevalence of a specific genotype in the United States also depends on the geographic area. For example, in the East, approximately 37% have genotype A, whereas only 18% have HBV genotype A in the West. Conversely, 41% in the West have genotype C, compared to 23% in the East. It all seems to depend on where certain immigrant populations are arriving."

Dr. Dieterich also stressed that different genotypes have different responses to treatment, as is touched upon later on in this article. "This raises a very important question," he said. "Should we be genotyping virus in our patients with chronic hepatitis B to see what their response to treatment might be?"

![FIGURE 1. A New Element in the Terminology of Hepatitis B: Genotypes](http://www.prn.org)

There are currently eight HBV genotypes, defined by greater than 8% divergence in the entire HBV genomic sequence. HBV genotypes have distinct geographical distributions. Genotypes B and C, for example, are prevalent in Asia, whereas genotypes A and D occur frequently in Europe. Genotypes F and H are found in Central and South America. In the United States, four genotypes are frequently seen: A, B, C, and D. Different genotypes have different responses to treatment, a finding that has experts questioning whether or not HBV genotyping should be a routine component of hepatitis B clinical management.

Source: Douglas Dieterich, MD
HBeAg-Negative Disease

HBeAg-negative disease generally occurs in the late phase of the natural history of chronic HBV infection. It is more common in patients infected during childhood and in those with HBV genotypes B or D.

HBeAg-negative variants have mutations in the core promoter and precore region—often referred to as “precore mutant” HBV—and results in decreased production or loss of serum HBeAg with continued production of core antigen, which is incorporated into the HBV virion. “If you’re measuring e-antigen and you don’t find it, it’s important not to be lulled into a false sense of security,” Dr. Dieterich said. “The virus is still very much detectable, using HBV-DNA assays. Patients with HBeAg-negative variants can still develop severe disease with cirrhosis or hepatocellular carcinoma. And while it does respond to therapy, it’s harder to treat.”

When it comes to treating HBeAg-negative disease, HBeAg seroconversion is not an endpoint, much like it is with HBeAg-positive disease. “Durable suppression of HBV-DNA to low or undetectable levels is a primary goal of treating HBeAg-negative disease,” Dr. Dieterich commented. “While the American Association for the Study of Liver Diseases indicates that treatment should reduce HBV-DNA levels to less than 10,000 copies/mL, striving for undetectable levels is best. Even if there are only 5,000 copies/mL of virus floating around in the serum, we’re still talking about an oncogenic virus. Progression to cirrhosis and cancer can still happen, even with low levels of virus. We need to get where we are with HBV; we shouldn’t be tolerating any detectable virus at all.” He also remarked that, whereas stopping therapy after HBeAg seroconversion is associated with a durable response in patients with HBeAg-positive disease, long-term therapy is the rule with oral agents when treating HBeAg-negative disease.

Sequelae of Chronic HBV Infection

According to a paper published by D. Maxwell Parkin, MD, and his colleagues at the International Agency for Research on Cancer, based in Lyon, France, hepatocellular carcinoma (HCC) is responsible for approximately 500,000 deaths annually worldwide (Parkin, 2001). Approximately 50% of these cases, Dr. Parkin’s group estimates, are associated with chronic HBV infection.

Data presented at the 40th Annual Meeting of the European Association for the Study of the Liver (EASL), and highlighted in Table 1, indicates that the risk of HCC is positively associated with HBV-DNA levels, even in patients with normal ALT levels at baseline (Iloeje, 2005). These data come from a prospective study involving patients with initially asymptomatic chronic HBV infection recruited from seven townships in Taiwan between 1991 and 1992. Of the 3,653 patients who entered the study, 3,601 had normal ALT levels at baseline. Of these patients, 908 had undetectable HBV-DNA levels and 1,825 had HBV-DNA levels that were detectable but below 100,000 copies/mL. Thirteen of the patients with undetectable HBV viral loads progressed to HCC, yielding an adjusted relative risk of 1.0. However, 37 of the patients with detectable viral loads below 100,000 copies/mL progressed to HCC, yielding an adjusted relative risk of 1.6. As for the 250 patients with ALT levels >1 times the upper limit of normal, 43 had undetectable HBV-DNA levels at baseline and 61 had detectable HBV-DNA levels that were below 100,000 copies/mL. Thirteen of the patients with undetectable HBV-DNA levels at baseline progressed to HCC, yielding an adjusted relative risk of 1.9. One patient with baseline HBV viral loads of approximately 10,000 copies/mL developed cirrhosis, yielding an adjusted relative risk of 1.9. Another patient with baseline HBV viral loads of approximately 10,000 copies/mL developed cirrhosis, yielding an adjusted relative risk of 1.5.

Recent data indicate that the risk of HCC is positively associated with HBV-DNA levels, even in patients with normal HCC levels at baseline. These data come from a prospective study involving patients with initially asymptomatic chronic HBV infection recruited from seven townships in Taiwan between 1991 and 1992. Of the 3,653 patients who entered the study, 3,601 had normal ALT levels at baseline. Of these patients, 908 had undetectable HBV-DNA levels and 1,825 had HBV-DNA levels that were detectable but below 100,000 copies/mL. Thirteen of the patients with undetectable HBV viral loads progressed to HCC, yielding an adjusted relative risk of 1.0. However, 37 of the patients with detectable viral loads below 100,000 copies/mL progressed to HCC, yielding an adjusted relative risk of 1.6. As for the 250 patients with ALT levels >1 times the upper limit of normal, 43 had undetectable HBV-DNA levels at baseline and 61 had detectable HBV-DNA levels that were below 100,000 copies/mL at baseline. A total of three cases of HCC were documented in the group of patients with increased ALT but undetectable HBV-DNA levels. Three cases of HCC were also documented in the patients with increased ALT and HBV-DNA levels below 100,000 copies/mL. In both groups, the adjusted relative risk of HCC was 4.3.

**TABLE 1. Adjusted Relative Risk of Liver Cancer for Various Serum HBV-DNA and ALT Levels**

<table>
<thead>
<tr>
<th>HBV-DNA Level</th>
<th>Number of Subjects</th>
<th>Number of Liver Cancer Cases</th>
<th>Adjusted Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT &lt;1 x upper limit of normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>908</td>
<td>13</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt;10⁵</td>
<td>1825</td>
<td>37</td>
<td>1.6 (0.9–3.0)</td>
</tr>
<tr>
<td>&gt;10⁵</td>
<td>868</td>
<td>93</td>
<td>10.2 (5.7–18.4)</td>
</tr>
<tr>
<td>ALT &gt;1 x upper limit of normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>43</td>
<td>3</td>
<td>4.3 (1.2–15.9)</td>
</tr>
<tr>
<td>&lt;10⁵</td>
<td>61</td>
<td>3</td>
<td>4.3 (1.2–15.1)</td>
</tr>
<tr>
<td>&gt;10⁵</td>
<td>146</td>
<td>27</td>
<td>16.9 (8.1–33.7)</td>
</tr>
</tbody>
</table>

P<0.05; †P<0.001

Another study reported at the 40th EASL meeting, by the same study team using the same cohort of patients, suggests that increased HBV-DNA is also a strong predictor of cirrhosis risk (Iloeje, 2005a). Of the patients with normal ALT levels at baseline, 2,072 had HBV-DNA levels <1,000 copies/mL and 632 had HBV-DNA levels of approximately 10,000 copies/mL at baseline. Ninety-seven of the patients with HBV-DNA levels <1,000 copies/mL developed cirrhosis, yielding an adjusted relative risk of cirrhosis of 1.0. Fifty-seven of the patients with baseline HBV viral loads of approximately 10,000 copies/mL developed cirrhosis, yielding an adjusted relative risk of 2.1.

As for the patients with ALT levels >1 times the upper limit of normal, 82 had HBV-DNA levels <1,000 copies/mL and 17 had HBV-DNA levels of approximately 10,000 copies/mL at baseline. Nine patients with normal baseline ALT levels and HBV-DNA levels <1,000 copies/mL developed cirrhosis, yielding an adjusted relative risk of 1.9. One patient with baseline HBV viral loads of approximately 10,000 copies/mL developed cirrhosis, yielding an adjusted relative risk of 1.5.

Both of these studies concluded that HBV-DNA levels—
of ALT levels—are a strong predictor of cirrhosis and cancer risk and that the incidences of these sequelae increase with the HBV-DNA level in a dose-dependent manner. “Just as we see with HIV, it’s the virus that drives disease. Even when ALT levels were increased, it was the viral load that was most strongly associated with both cirrhosis and cancer.”

A lamivudine-treatment study conducted at the Chang Gung Memorial Hospital and National University in Taipei helps to illustrate the clinical benefits of reducing HBV-DNA replication in patients with advanced hepatitis B disease (Liaw, 2004). In this study, 651 patients with chronic HBV infection who had histologically confirmed cirrhosis or advanced fibrosis were randomly assigned in a 2:1 fashion to receive lamivudine (100 mg/day) or placebo for a maximum of five years. The primary endpoint was time to disease progression, defined by hepatic decompensation, hepatocellular carcinoma, spontaneous bacterial peritonitis, bleeding gastrointestinal varices, or death related to liver disease.

The study was terminated after a median duration of treatment of 32.4 months, owing to a significant difference in endpoints reached between the two study groups. Disease progression was seen in 7.8% of those receiving lamivudine versus 17.7% of those receiving placebo. Cirrhosis worsened in 3.4% of the patients receiving lamivudine, compared to 8.8% of those receiving placebo. Similarly, HCC occurred in 3.9% of those in the lamivudine group and 7.4% of those in the placebo group.

Mutations conferring resistance to lamivudine developed in 49% of the patients treated with lamivudine, and cirrhosis was more likely to worsen in patients with these mutations than in the other patients treated with lamivudine (7% vs. <1%). However, patients harboring lamivudine-resistant HBV variants were significantly less likely to experience disease progression compared to placebo recipients. “Just like HIV, mutated HBV with the lamivudine-resistant mutation is less fit,” Dr. Dieterich commented. “I see what happens if it’s allowed to replicate.”

Coinfection Considerations

Although coinfection with HIV and HBV has long been very common, only recently have long-term studies on liver-related mortality in coinfected people been undertaken. In 2002, investigators at Johns Hopkins University School of Medicine used data from the Multicenter AIDS Cohort Study (MACS) to ascertain the risk of liver-related mortality in HIV/HBV-coinfected patients (Thio, 2002). Of the 5,293 men screened, 326 men were HBsAg positive and 213 were coinfected with HIV and HBV. Of the 4,967 HBsAg negative men, 2,346 (47%) were infected with HIV. The liver-related mortality rate was 1.1/1,000 person-years, and was higher in men with HIV and chronic HBV infection (14.2/1,000) than in those with HIV monoinfection (1.7/1,000) or HBV monoinfection (0.8/1,000). In the coinfected individuals, the liver-related mortality rate was highest with lower nadir CD4+ cell counts and was twice as high after 1996, when combination antiretroviral therapy was introduced. “These data are really shocking,” Dr. Dieterich remarked. “Fourteen times the liver-related mortality in HIV/HBV-coinfected patients, compared to HBV-monoinfected patients.”

Another study, involving the EuroSIDA cohort, assessed the prevalence of HIV/HBV coinfection and its possible impact on mortality (Konopnicki, 2005). The study evaluated data involving 9,802 patients being treated at 72 European HIV centers. HBsAg was found in 498 (8.7%) patients. The incidence of new AIDS diagnoses was similar in both HIV/HBV-coinfected and HIV-monoinfected patients (3.3 and 3.4/100 person-years respectively) even after adjustment for potential confounders. However, the incidences of all-cause and liver-related mortalities were significantly higher in HIV/HBV-coinfected patients (3.7 and 0.7/100 person-years respectively) compared with HIV-monoinfected patients (2.6 and 0.2/100 person-years respectively).

A Taiwanese study has also evaluated the impact of chronic HBV infection on outcomes of HIV-infected patients (Sheng, 2004). Between June 1994 and February 2003, a total of 111 HIV/HBV-coinfected patients and 387 HIV-monoinfected patients were prospectively observed to assess the impact of HIV infection on outcomes of HIV-infected patients. After a median duration of observation of 25 months, coinfected patients were more likely to develop hepatitis (adjusted hazard ratio: 2.54) and hepatic decompensation (adjusted odds ratio: 9.94). Although the two patient groups were similar with respect to CD4+ cell count gains and the development of new opportunistic illnesses, the HIV/HBV-coinfected patients had an increased risk for virologic failure and death after combination antiretroviral therapy was initiated.

Occult HBV infection—defined as active infection in the absence of detectable HBsAg—is also believed to be common in HIV-infected patients. In one study, 955 HIV-infected individuals were evaluated for HBV infection (Marino, 2005). Five-hundred eighty-one (60.8%) patients were anti-HBc positive, 64 (6.7%) were HBsAg positive, 361 (37.8%) were anti-HBs positive, and 190 (19.9%) were anti-HBc positive alone. Four-hundred two patients were also coinfected with HCV. Patients with isolated anti-HBc were more likely than patients negative for anti-HBc to be infected the hepatitis C virus (HCV). HBV-DNA was positive in 6.9% of patients positive for anti-HBc, with low levels of detectable HBV replication (usually from 100 to 1,000 copies/mL). Interestingly, follow-up data indicated that viremia was intermittent in these patients, meaning that it was not detectable at all time points, suggesting that repeated evaluation of HBV-DNA is necessary to ensure a correct diagnosis of occult HBV infection in patients who present with anti-HBc (in the absence of HBsAg).

Anti-HBV Therapy

The primary goal of treating chronic HBV infection is to halt progression of liver disease by suppressing viral replication. Numerous questions remain, however, regarding the optimal treatment for chronic HBV infection.

The treatments approved for the management of chronic HBV infection are: interferon alfa-2b (Intron A), pegylated interferon alfa-2a (Pegasys), lamivudine (Epivir-HBV), adefovir (Hepsera), and entecavir (Baraclude). “Interferon alfa-2b is an approved option, but I don’t recommend it,” Dr. Dieterich noted. “Peginterferon is a stronger option, at least in HCV-monoinfected patients. There’s no data in coinfection.”

Data published last year in The Lancet indicate that pegylated interferon is significantly more effective for patients with HBV genotypes A and B than it is for HBV genotypes C and D (see Figure 2), hence it is now generally recommended that patients undergo HBV genotyping prior to commencing interferon therapy.

“As for lamivudine,” Dr. Dieterich continued, “I don’t recommend it for hepatitis B treatment, particularly as monotherapy. Adefovir is better and entecavir is actually quite a good drug. There’s also emtricitabine (Emtriva) and tenofovir (Viread), both of which are approved for HIV, but not for HBV.”
A study conducted in Rotterdam randomized 307 HIV-negative, HBeAg-positive patients with chronic hepatitis B to receive either combination therapy (100 microg/week peginterferon alfa-2b plus 100 mg/day lamivudine) or monotherapy (100 microg/week peginterferon and placebo) for 52 weeks. During weeks 32-52 the pegylated interferon dose was 50 microg/week in both treatment groups. More of the combination-therapy than of the monotherapy group had cleared HBeAg at the end of treatment (44% vs. 29%) but relapsed during follow-up. Of note, response rates (HBeAg loss) varied by HBeAg genotype: A, 42 (47%) patients; B, 10 (44%); C, 11 (28%); and D, 26 (25%). These data, the study authors suggest, indicate that HBeAg genotype is an important predictor of response to peginterferon treatment.


**Lamivudine Concerns**

Dr. Dieterich’s primary concern with lamivudine is the high rate of resistance seen in patients receiving the drug as monotherapy. Follow-up data from clinical trials have demonstrated that resistance mutations occurred in 15% to 32% of patients treated with lamivudine for 52 weeks and as many as 67% of HBV-monoinfected patients (Lai, 2000) and 90% of HIV/HBV-coinfected patients (Benhamou, 1999) treated with lamivudine for a total of four years. Yet, some patients with lamivudine resistance mutations continued to experience HBeAg seroconversions, partial suppression of HBV-DNA, and improved biochemical and histologic parameters, likely because of decreased replicative capacity associated with HBV resistance to lamivudine (Leung, 2001). However, many of these patients relapse when therapy is stopped. Maintaining therapy in the face of resistance is also a problem, as it is also known that HBV can develop compensatory mutations in the A and B domain of its reverse transcriptase gene—notably L180V/I, V173L, and L180M—that can restore HBV’s replication capacity.

Data from the University of Michigan Medical Center suggest that long-term lamivudine therapy is commonly associated with hepatic flares, most notably in patients with HBV harboring the mutation associated with lamivudine-resistance (M204V/I in the YMDD motif) (Lok, 2003). The study reviewed data involving 998 patients with HBV-related compensated chronic hepatitis B who received lamivudine for up to six years and 200 patients who received placebo for one year. Hepatitis flares occurred in 10% of the lamivudine-treated patients in year 1 and in 18%-21% in years 2 through 5. A temporal association between hepatitis flares and lamivudine-resistant mutations increased from 43% in year 1 to greater than 80% in year 3. Ten hepatic decompensation events occurred in eight (<1%) lamivudine-treated patients. Four patients died, two from liver-related causes. The proportion of patients with a documented lamivudine-resistant mutation increased from 23% in year 1 to 65% in year 5. During each year of the study, patients with lamivudine-resistant mutations experienced significantly more hepatitis flares than patients without lamivudine-resistant mutations.

Data comparing long-term use of adefovir, compared to long-term use of lamivudine, also paint an intriguing picture. At the 40th Annual Meeting of the EASL, Dr. Stephen Locarnini and his colleagues confirmed the low resistance rate associated with long-term adefovir therapy, compared to lamivudine therapy, combining data from five studies (Locarnini, 2005). They found that the cumulative probability of adefovir resistance at week 192 was 15% among patients using adefovir monotherapy, compared to 70% among patients using lamivudine monotherapy. Better yet, the cumulative probability of adefovir resistance at week 192 was 0% among patients using adefovir combined with lamivudine. Higher serum HBV-DNA levels at week 48 was the main predictor of subsequent adefovir resistance.

While adefovir appears not to select for resistance mutations that are cross-resistant to lamivudine, new data indicate that HBV resistance to adefovir is more common in lamivudine-pretreated patients (Osiowy, 2005). Resistance to lamivudine is typically associated with the V173L, L180M, or M204V/I mutations in HBV’s polymerase. Resistance to adefovir has been documented in individuals with HBV variants harboring A181V/T, N236T, K241E, or K318Q mutations. “In this study evaluating a switch from lamivudine to adefovir, four out of five patients had HBV variants with the V236T mutation at baseline,” Dr. Dieterich explained. “Clearly, lamivudine monotherapy may increase the chances of adefovir resistance. Failing lamivudine monotherapy can shut therapeutic doors down the line, which is something we don’t want. Cross resistance with HBV therapies is a significant concern” (see Figure 3).

Dr. Dieterich also discussed a study evaluating pegylated interferon alfa-2b in combination with lamivudine (Janssen, 2005). The study enrolled 307 HBeAg-positive patients and assigned them to receive either combination therapy (1.0 mg/kg/week pegylated interferon alfa-2b and 100 mg/day lamivudine) or monotherapy (1.00 mg/kg/week pegylated interferon alfa-2b and placebo) for 52 weeks. During weeks 32 through 52, the pegylated interferon dose was 50 mg/kg/week in both treatment groups. According to the study team’s report in The Lancet, 49/136 (36%) patients assigned monotherapy and 46/130 (35%) patients assigned combination therapy had lost HBeAg at the end of follow-up. Of particular interest were the varying response rates among patients with different HBV genotypes. Forty-two (47%) patients with HBV genotype A lost HBeAg at the end of follow-up, compared to 10 (44%) with HBV genotype B, 11 (28%) with HBV genotype C, and 26 (25%) with genotype D. “As we’ve seen in other treatment studies, HBV genotype D is much less responsive to treatment,” Dr. Dieterich commented. “Patients with genotype D were half as likely to respond to treatment, compared to those with genotype A.”

Hepatitis B genotype also influences the efficacy of lamivudine therapy as a component of liver transplant surgery. In one study, HBV genotype was identified by direct sequencing from pre-transplant sera of 119 patients who underwent liver transplantation using lamivudine prophylaxis. The baseline characteristics and outcome of 43 genotype B and 74 genotype C patients were compared. Genotype B patients had significantly more pre-transplant acute flares, worse liver functions, and higher end-stage liver disease scores. Fewer genotype B patients had HBeAg (13% vs. 32%), but HBV-DNA positivity was comparable (26% vs. 23%). The three-year graft survival was 83% for genotype B and 89% for genotype C, a difference that was not statistically significant. The rate of HBeAg clearance or seroconversion was also the same.
The cumulative rate of viral breakthrough due to lamivudine-resistant mutants at three years was 4% for genotype B and 21% for genotype C. Liver biopsy after viral breakthrough showed recurrent hepatitis B in 7/10 genotype C patients, including two with fibrosing cholestatic hepatitis, and no histologic recurrence in two genotype B patients. In conclusion, HBV genotypes B and C are associated with different patterns of end-stage liver diseases that required transplantation, and genotype C may carry a greater risk and severity of recurrence due to lamivudine-resistant mutants.

"Just like grades, A or B is better than C or D," Dr. Dieterich noted. "Patients with HBV genotypes A or B respond better to treatment, and appear less likely to develop resistance to either lamivudine or adefovir than those with genotypes C or D. This is definitely important for clinicians to know." However, further studies with larger patient numbers are required to confirm these trends.

Lamivudine-resistant HBV infection has also been documented in treatment-naive individuals, suggesting that, like HIV, the transmission of drug-resistant virus is a very real risk. A study reported at the 12th Conference on Retroviruses and Opportunistic Infections (CROI) evaluated 12 occult HIV/HBV-coinfected patients, 10 HIV/HBsAg-positive patients, and 12 HBsAg-positive HBV-monoinfected patients (Selabe, 2005). HBV strains harboring the lamivudine-resistant mutation M204V/I were documented in 3/12 (25%) patients with occult HIV/HBV coinfection and 5/10 (50%) patients with HIV/HBsAg-positive coinfection, compared to none of the HBsAg-positive HBV-monoinfected patients. "Here we have evidence of resistant strains emerging without therapy," Dr. Dieterich said. "Resistant strains such as this need to be monitored and evaluated in HBsAg-negative and HBsAg-positive patients coinfected with HIV. This really shouldn’t come as a surprise to anyone, especially clinicians familiar with the transmission of lamivudine-resistant HIV."

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**Tenofovir Dreams**

There have been a handful of studies reported over the past few years indicating that tenofovir is effective in patients with lamivudine-resistant HBV infection. Based on these preliminary studies, a team of investigators in Berlin conducted a study comparing adefovir to tenofovir in 53 volunteers—some of who were HIV-coinfected—with high HBV-DNA levels (> 6 log_{10} copies/mL) and genotypic evidence of lamivudine resistance (van Bommel, 2004). Thirty-five patients received tenofovir for 72 to 130 weeks, and 18 received adefovir for 60 to 80 weeks.

Early viral kinetics was compared on matched subgroups consisting of five patients each. All tenofovir-treated patients showed a strong and early suppression of HBV-DNA within a few weeks, whether they were coinfected with HIV or not. In contrast, considerable individual variations in HBV-DNA decline were observed in the adefovir group. At week 48, 44% of the adefovir-treated patients had HBV-DNA levels below 400 copies/mL, compared to 100% of the tenofovir-treated patients. The mean decline in HBV-DNA levels after 48 weeks in the adefovir group was 2.8 log_{10} copies/mL, compared to a median decline of 5.5 log_{10} copies/mL in the tenofovir group. No evidence of phenotypic viral resistance could be demonstrated in the tenofovir-treated patients in the long term (up to 130 weeks).

"These are really impressive data that are beginning to seep into the CI and liver world," Dr. Dieterich noted. "Tenofovir looks to be a much better drug than adefovir for the treatment of chronic HBV infection. These data, and others like it, also speak to the limited efficacy of adefovir. In HIV/HBV-coinfected patients, the HBV-DNA decay rate is very slow upon switching to adefovir from lamivudine. Meanwhile, there’s been a lot of talk about using adefovir monotherapy in HIV/HBV-coinfected patients who do not yet require regimens containing tenofovir, emtricitabine, or lamivudine to treat their HIV. Adefovir monotherapy likely isn’t strong enough to use in this way. Combining it with entecavir, which doesn’t have activity against HIV, may be the way to go. And once antiretroviral therapy is indicated, switching off of the adefovir and entecavir to a regimen that contains tenofovir and emtricitabine or lamivudine is probably best."

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**Entecavir Makes its Debut**

Entecavir was approved by the U.S. Food and Drug Administration in March 2005. Its safety and efficacy were evaluated in three phase III controlled clinical trials. All three studies included 1,633 patients 16 years of age or older with chronic hepatitis B infection. Patients had persistently elevated ALT levels 1.3 times the upper limit of normal and chronic inflammation on liver biopsy compatible with a diagnosis of chronic viral hepatitis. The safety and efficacy of entecavir were also evaluated in a study of 68 HIV/HBV-coinfected patients.

Study A463022 was a multinational, randomized, double-blind study of entecavir (0.5 mg once daily) versus lamivudine (100 mg once daily) for 52 weeks in 709 nucleoside-naive patients with chronic hepatitis B infection and detectable HBeAg (Chang, 2004). Study A463027 was a multinational, randomized, double-blind study of entecavir versus lamivudine for 52 weeks in 638 nucleoside-naive patients with HBeAg-negative chronic HBV infection (Shouval, 2004).

In Studies 022 and 027, entecavir was superior to lamivudine on the primary efficacy endpoint of histologic improvement. In Study 022, histologic improvements were seen in 72% of patients receiving entecavir and 62% of patients receiving lamivudine. In Study 027, histologic improvements were documented in 70% of entecavir recipients and 61% of lamivudine recipients. While fibrosis scores also in 35% to 39%
of patients in both studies, no statistically significant differences between entecavir or lamivudine were reported.

As for virologic, biochemical, and serologic endpoints, 67% of patients in Study 022 receiving entecavir had HBV-DNA levels below 300 copies/mL after 28 weeks, compared to 36% of patients receiving lamivudine. And in Study 027, 90% receiving entecavir, vs. 72% receiving lamivudine, had HBV-DNA levels below 300 copies/mL after 48 weeks. ALT normalization occurred in 68% of entecavir recipients, vs. 60% of lamivudine recipients, in Study 022, and in 78% vs. 71% of entecavir and lamivudine recipients respectively in Study 027. All of these reported differences between entecavir and lamivudine were statistically significant.

Two-hundred eighty-six lamivudine-refractory patients were evaluated in Study A1463026. Patients receiving lamivudine at study entry either switched to entecavir (1 mg once daily) or continued on lamivudine for 52 weeks. Entecavir was superior to lamivudine on the coprimary endpoint of histologic improvement. As for virologic and biochemical endpoints, 19% receiving entecavir, compared to 1% receiving continued lamivudine treatment, had HBV-DNA levels below 300 copies/mL. ALT normalization was documented in 61% of entecavir recipients, vs. 15% of lamivudine recipients. These data were all statistically significant.

Study A1463038 was a randomized, double-blind, placebo-controlled study of entecavir versus placebo in 68 patients coinfected with HIV and HBV who experienced recurrence of HBV viremia while receiving an antiretroviral regimen containing lamivudine (Pessoa, 2005). Patients continued their lamivudine-containing antiretroviral regimen (lamivudine dose 300 mg/day) and were assigned to add either entecavir (1 mg once daily) or placebo for 24 weeks followed by an open-label phase for an additional 24 weeks. Median HIV-RNA level remained stable at approximately 2 log_{10} copies/mL through 24 weeks of blinded therapy. ALT normalization was documented in 34% of the entecavir-treated patients, vs. 8% of the placebo recipients, although this difference was not statistically significant. As for virologic endpoints, 6% of entecavir-treated patients, compared to no patients receiving placebo, had HBV-DNA levels below 300 copies/mL. While the rates of undetectability were not statistically significant, there were significant differences between the two groups with respect to HBV-DNA reductions (~3.65 vs. + 0.11 log_{10} copies/mL in the entecavir and lamivudine groups respectively).

Dr. Dieterich also took some time to present encouraging resistance data that has been released by the Bristol-Myers Squibb Pharmaceutical Research Institute (Colomino, 2005). Samples from more than 600 nucleoside-naive and lamivudine-refractory patients participating in clinical trials of entecavir were monitored for entecavir resistance. In the nucleoside-naive studies, none of the participants experienced a virologic rebound due to resistance, and entecavir resistance-associated mutations at reverse transcriptase positions 184, 202, and 250 were not observed in any of the nucleoside-naive patients. Virologic rebound, due to entecavir resistance, was observed in 1% of the entecavir-treated lamivudine-refractory subjects. Approximately 6% of the lamivudine-refractory patients saw the emergence of mutations at positions 184, 202, and/or 250 occur by week 48, but without obvious signs of virologic failure. “Despite the presence of lamivudine-associated drug-resistance mutations at baseline,” Dr. Dieterich said, “treatment with entecavir did not lead to rapid entecavir resistance or virologic failure. These substitutions resulted in a range of entecavir susceptibility changes”.

### Conclusion

In concluding his lecture, Dr. Dieterich remarked that the current goal of therapy is simply “suppression,” meaning the reduction of HBV-DNA, improvement of ALT, the potential for resistance, hope for seroconversion, and an indefinite course of therapy. “We now have our eyes set on loftier goals, mainly a complete response to treatment” he said. “The goal should be undetectable HBV-DNA, normalization of ALT, minimal resistance, HBeAg loss/seroconversion, and sustained viral load reduction off-treatment. The future, we hope, will involve not only complete response, but also eradication of cccDNA, no hepatic flares off treatment, and reduction of progression of liver disease. We’ve seen a couple of papers involving a small percentage of patients with complete responses plus eradication of cccDNA. HBV may not be nearly as curable as hepatitis C, but I think if we treat it long enough—and I don’t mean 48 weeks or 96 weeks of therapy, I mean five, eight, ten years of suppressive treatment—we may be able to eradicate cccDNA in a significant number of people.”

### References

- Colombo RJ, Rose LE, Levine SM, et al. Entecavir (rvrt) resistance is not observed in nucleoside-naive subjects and is observed infrequently by week 48 in lamivudine-refractory subjects with chronic rvrt infection. J *Hepatol* 42(suppl 2):173, 2005.