Coinfection with HIV and HBV: Diagnosis and Therapy

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It has been estimated that approximately 400 million people worldwide have chronic hepatitis B virus (HBV) infection. In the United States alone, an estimated 1.25 million people—0.35% of the U.S. population—have chronic HBV, defined as patients with a positive hepatitis B surface antigen (HBsAg) serology for more than six months. "Rates are higher when you single out health-care workers, dialysis patients, oncology patients, intravenous drug users, multiply transfused patients, and individuals with multiple sex partners," Dr. Marion Peters said in kicking off her second PRN lecture focusing on HIV and HBV coinfection. "Rates of chronic HBV are highest in immigrants from high-endemic areas, such as Southeast Asia. There are parts of China and Korea where the incidence is as high as 14%."

While hepatitis B vaccination programs are an important component of hepatitis B prevention strategies, they will not have an impact on those already living with this potentially fatal disease. Carriers of HBV are at increased risk of developing cirrhosis, hepatic decompensation, and hepatocellular carcinoma. Although most carriers do not develop hepatitic complications, 25% to 40% do go on to develop serious HBV-related complications during their lifetime.

While chronic HBV disease in the setting of HIV is not listed as an AIDS-defining illness by the U.S. Centers for Disease Control, it is undoubtedly an opportunistic infection and not uncommon in HIV-positive individuals because of similar modes of transmission. Between 50% and 95% of HIV-positive people have serologic evidence of past HBV infection and approximately 5% to 10% are chronic carriers in the U.S.

HIV-positive individuals, particularly those with suppressed immune systems, are less likely to respond to vaccination against hepatitis B and are more likely to develop chronic disease after being exposed to the virus. In addition, individuals coinfected with HIV and HBV are more likely to present with atypical serologies, to have higher HBV-DNA levels, and to experience more profound liver disease as a result of chronic infection.

This article, which expands upon an HIV/HBV-coinfection review published in the December 2002 issue of the *Notebook* and includes many of Dr. Peters' points raised during her June 2004 lecture, highlights much of the current thinking surrounding the pathogenesis, diagnosis, monitoring, and treatment of chronic hepatitis B in HBV-monoinfected and HIV/HBV-coinfected patients.

I. The Virology and Natural History of HBV

HBV belongs to a family of DNA viruses that infect hepatocytes, hence their official classification: hepadnaviruses. When examined under an electron microscope, intact HBV virions—the Dane particles—appear as spheres 42 nm in diameter (see Figure 1). 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]. HBsAg is a 22 nm tubule—or sphere when visualized end on—and is produced in great excess to Dane particles.

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 into a precore polypeptide, which is secreted as hepatitis B "e" antigen (HBeAg), which can be detected in the bloodstream, and into HBcAg, which can only be detected in the liver.

"If you see 'e' antigen in the serum," Dr. Peters commented, "this tells you that core antigen is being made in the liver. Virus is being produced. However, the situation is different when it comes to precore mutants." Mutations in the core promoter and precore region can result in decreased production or loss of serum HBeAg with continued pro-

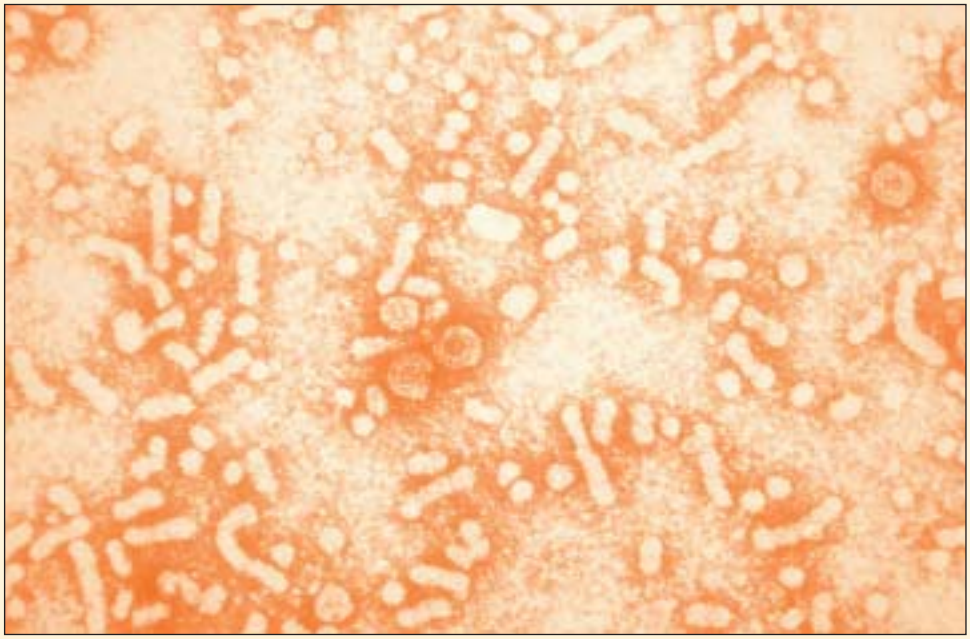

FIGURE 1. **Hepatitis B virus (HBV) "Dane Particles"**
The infective hepatitis B virions are also known as Dane particles. These particles measure 42nm in their overall diameter, and contain a DNA-based core that is 27nm in diameter.

Source: U.S. Centers for Disease Control Public Health Image Library.

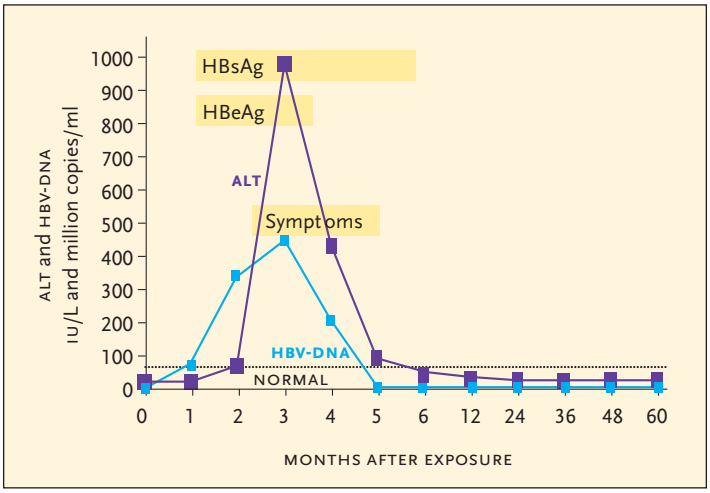

FIGURE 2. Natural History of Acute HBV Infection

HBV infection begins with an acute phase, which can manifest itself as asymptomatic infection, acute hepatitis, or rarely fulminant liver failure. Asymptomatic infection, the most common acute infection course, begins with active HBV replication in hepatocytes. As shown here, detectable HBV-DNA levels in peripheral blood are initially low and limited in time and may precede mild or moderate elevations in serum transaminases. The hepatitis B surface antigen (HBsAg) and hepatitis B "e" antigen (HBeAg) become detectable in blood samples within two to eight weeks and can persist for several weeks. IgM antibodies to the hepatitis B core antigen (HBcAg) occur early and decrease after six months, but total anti-HBc remains for life. Antibodies to HBsAg become positive after loss of active viral replication, usually after six months.

duction of core antigen, which is incorporated into the HBV virion. "The precore mutant increases with time of disease, given that ongoing replication of the virus can lead to mutations," added Dr. Peters.

Upon entering hepatocytes, the HBV genome is transported to the nucleus and is converted to covalently closed circular DNA (cccDNA). The HBV cccDNA serves as the template for transcription of mRNA and the RNA pregenome. Once transferred to the cytoplasm, HBV polymerase uses reverse transcription to convert the RNA pregenome into new circular genomic DNA.

HBV is usually not a cytopathic virus. Replicative HBV, either during the acute or chronic stages of infection, causes liver disease because of vigorous cytotoxic T-lymphocyte (CTL) and/or cytokine killing of HBV-infected hepatocytes. However, some researchers have determined that HBV can be cytopathic in fibrosing cholestatic hepatitis.

Natural History of HBV: Acute Infection

HBV INFECTION BEGINS WITH AN ACUTE PHASE, WHICH CAN MANIFEST itself as asymptomatic infection, acute hepatitis, or rarely fulminant liver failure. Asymptomatic infection, the most common acute infection course, begins with active HBV replication in hepatocytes. As illustrated in Figure 2, detectable HBV-DNA levels in peripheral blood are initially low and limited in time and may precede mild or moderate elevations in serum transaminases. HBsAg and HBeAg become detectable in blood samples—the core antigen cannot be detected in peripheral blood samples, only in hepatocytes—within two to eight weeks and can persist for several weeks. IgM antibodies to HBcAg occur early and decrease after six months, but total anti-HBc remains for life. Anti-HBs becomes positive after loss of active viral replication, usually after six months.

Clinical disease in acute HBV infection may be asymptomatic, mild, moderate, or severe. Symptomatic HBV infection can exist in the icteric and anicteric forms. Anicteric infection is typically associated with a flu-like illness without jaundice. Icteric infection is associated with symptoms ranging from mild jaundice to nonfatal subacute hepatic necrosis (3% of all acutely infected patients), to fatal fulminant hepatitis (less than 1% of all acutely infected patients). In those with acute hepatitis, HBV-DNA levels, along with serum transaminases, may be high and prolonged. Serum levels of HBeAg and HBsAg may remain detectable for several months before seroconversion to anti-HBe and anti-HBs.

Regardless of the clinical course taken, most HBV-infected adults are capable of generating broad-based CTL and antibody responses to the virus. Once these develop, the infection becomes latent, with serum evidence of immunity, which usually remains with the patient for the rest of his or her life. Under unusual circumstances, such as immune suppression or organ transplantation, HBV can be reactivated, as intact virions may be hidden from the immune system in the nucleus of hepatocytes as cccDNA.

Dr. Peters pointed out that the outcome of acute HBV infection is largely determined by host factors, particularly age and immune competence at the time of exposure. In infants exposed to HBV at birth or shortly thereafter, chronic infection is established over 90% of the time. The risk of chronic HBV infection declines as the exposed individual increases in age, falling to 25% to 50% in young children, to less than 5% of people exposed during adulthood. In adults, the risk of chronic infection is largely dependent on the general health of the immune system; hence the increased prevalence of chronic infection among transplant patients, patients receiving hemodialysis, patients receiving corticosteroid treatment, and HIV-infected patients.

Natural History of HBV: Chronic Infection

THE NATURAL HISTORY OF CHRONIC HBV IN ADULTS CAN BE BROKEN down into replicative and nonreplicative phases. In the replicative phase of infection, HBeAg is usually present (unless precore mutants are present), HBV-DNA levels are elevated (above 100,000 copies/mL), and transaminases may be either persistently or intermittently elevated (see Figure 3 on page 16).

Hepatic flares—characterized by decreases in HBV-DNA followed by spikes in ALT levels—are common during the replicative phase of infection. These spikes indicate that the immune system is making ongoing attempts to eliminate HBV from infected hepatocytes. With each flare, HBV-DNA is decreased and usually, over time, there is a spontaneous HBeAg to anti-HBe shift. Once this occurs, chronically infected patients move into the nonreplicative phase—or the inactive carrier state—of infection, in which transaminases stabilize and symptoms are minimal. "The chances of this happening are approximately 10% per year in HBV-monoinfected subjects," Dr. Peters added. "The chances increase with treatment."

As is touched upon in the virology section above, the absence of HBeAg is not necessarily synonymous with inactive infection. HBeAg-negative chronic HBV infection, characterized by ongoing HBV-DNA replication and continued necroinflammation in the liver, is the most prevalent form of liver disease in some parts of the world. The vast majority of HBeAg-negative chronic hepatitis B cases involve HBV variants harboring mutations in the precore open reading frame or basic core

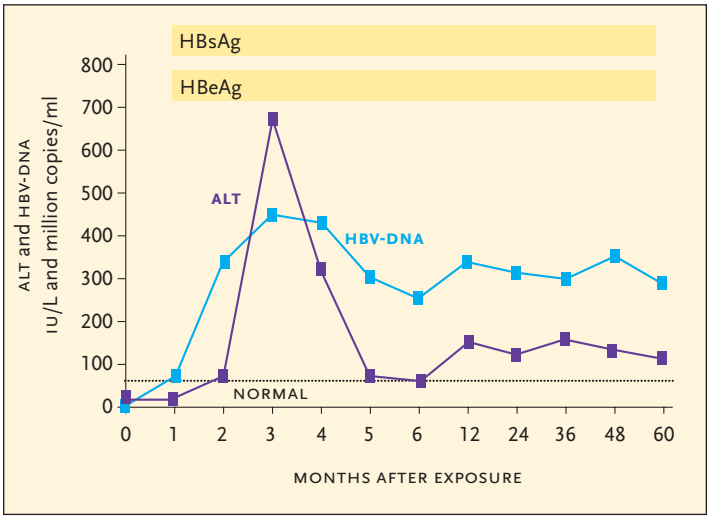

FIGURE 3. Natural History of Chronic HBV Infection

The natural history of chronic HBV in adults can be broken down into replicative and nonreplicative phases. In the replicative phase of infection, HBeAg is usually present (unless precore mutants are present), HBV-DNA levels are elevated (above 100,000 copies/mL), and transaminases may be either persistently or intermittently elevated. Hepatic flares, characterized by decreases in HBV-DNA followed by spikes in ALT levels, are common during the replicative phase of infection. These spikes indicate that the immune system is making ongoing attempts to eliminate HBV from infected hepatocytes. With each flare, HBV-DNA is decreased and usually, over time, there is a spontaneous HBeAg to anti-HBe shift. Once this occurs, chronically infected patients move into the nonreplicative phase—or the inactive carrier state—of infection, in which transaminases stabilize and symptoms are minimal.

promoter (BCP) region, the most common being G1896A in the precore region. This mutation creates a premature stop codon in the precore region, which hinders production of HBeAg. It is most commonly associated with HBV genotypes B and D, which are prevalent in the Mediterranean basin and parts of Asia, and is uncommonly detected in patients with HBV genotype A, which is the most prevalent strain in the United States and Northern Europe. Patients with HBeAg-negative chronic HBV infection tend to have lower HBV-DNA levels and are more likely to run a fluctuating course characterized by persistently elevated or fluctuating ALT levels.

Overall, the clinical course of chronic infection is variable and ranges from mild to severe. On average, patients with chronic HBV infection maintain high HBV-DNA levels for five to ten years and a detectable HBV-DNA viral load for 20 years. Approximately 0.5% to 1% of HBsAg carriers clear HBsAg yearly, most of whom will seroconvert to anti-HBs. There is a 25% to 40% lifetime risk of end-stage liver disease in chronically infected patients. "Among those infected with HBV at birth, the end-stage liver disease (ESLD) risk is closer to 40%, whereas for those who acquired the infection in adulthood, the risk is closer to 25%," Dr. Peters said. To put these numbers into perspective, she added: "With chronic hepatitis C virus, the risk of death is probably 10% to 12%. So it's much higher with chronic hepatitis B infection."

Hepatocellular carcinoma (HCC) is statistically more likely to occur in chronically infected men and develops in less than 1% of patients per year. And because HBV can integrate into the human genome and is an oncogenic virus, HCC can occur in the absence of cirrhosis.

II. HBV Serologies

OF ALL THE VIRAL HEPATITIS INFECTIONS, HBV INFECTION IS THE MOST complex with respect to interpretation of serologic test results. What's more, atypical serologies are common among HIV-positive patients.

As was reviewed by Dr. Peters—and is illustrated in PRN's HBV clinical care algorithm (see pages 18 and 19)—both acute and chronic HBV infection are characterized by the presence of hepatitis B surface antigen (HBsAg) and absence of antibodies to the surface antigen (anti-HBs). "When surface antigen is lost and surface antibody is gained, the textbooks refer to this as 'recovered'," Dr Peters said. "For the vast majority of people, this truly is 'recovered'. However, if you take a liver from a recovered person and transplant it into a naive individual, they may develop acute hepatitis B and, unfortunately, this has been done a number of times. So we know this really isn't recovered, but rather 'latent.' If you're immune competent, this doesn't matter. The immune system is controlling the infection, even though there may be HBV-DNA in the nuclei of hepatocytes. But for immune-compromised individuals, there is the possibility of reactivation, because of dwindling immunologic control."

Also of importance is the hepatitis B 'e' antigen (HBeAg). As explained by Dr. Peters, the value of HBeAg — in the presence of HBV-DNA— is in deciding how long to treat patients. "In the old days," she recalled, "we couldn't get HBV-DNA. It is still $200, whereas HBeAg and anti-HBe are approximately $30. Obviously it's a bargain over HBV-DNA. If 'e' antigen is present, then you know that HBV is replicating in the liver and you will invariably see high viral replication and elevated ALT levels. If anti-HBe is present, there are two possible scenarios. The most desirable is no viral replication and normal ALT levels; the other possibility is a precore mutant, which means high viral replication and high ALT levels." As is reviewed in the treatment discussion below, anti-HBV treatment can be discontinued if an HBeAg-to-anti-HBe seroconversion is maintained for three to six months. For patients with a precore mutant, HBeAg is absent from the start and anti-HBe — if already present — cannot be used to signify recovery; thus, in these individuals, therapy will likely need to be continued indefinitely.

Dr. Peters spent some time discussing atypical serology results, including the presentation of anti-HBc alone, in the absence of both HBsAg and anti-HBs. She explained that approximately 48% to 50% of immune-competent, HIV-negative individuals who present with anti-HBc alone are false-positive for the infection. In another 48% to 50%, anti-HBc alone can mean latent infection, in which titers of anti-HBs have dropped below the level of detection. "Less than 2% of these patients have detectable HBV-DNA in their serum," Dr. Peters pointed out.

In HIV-positive patients, the presentation of anti-HBc alone is much more complicated. This was certainly the observation of investigators associated with the Swiss HIV Cohort Study, in an analysis involving frozen serum specimens that were sequentially obtained over time from a cohort of 57 HIV-infected patients (Hofer, 1998). All tested positive only for anti-HBc, and were retested for other HBV markers, including HBV-DNA (Hofer, 1998). During a median of 31 months from the first to the last serum collected, anti-HBc remained the sole marker of HBV infection in 98.2% of the patients. PCR to detect HBV core and HBV surface gene was positive in 126 (62.4%) and 121 (59.9%) of all 202 serum samples, respectively. Over time, HBV-DNA was detected at least once in 51 (89.5%) patients. In contrast, decomplexed HBsAg was detected at least once in 14 (24.6%) patients. Among patients positive for HBV-DNA — and negative for HCV antibodies — 8/22 (36.4%) had necroinflammatory disease that was attributable only to persistent HBV infection. In other words, anti-HBc alone in HIV-positive patients is significantly more likely to be in-

dicative of active infection than anti-HBc alone in HIV-negative patients. "For HIV-positive patients," Dr. Peters concluded, "HBV-DNA testing is very much necessary when atypical serologic results occur."

III. The Treatment of Chronic HBV Infection

THE PRIMARY GOAL OF TREATING CHRONIC HBV INFECTION IS TO HALT progression of liver disease by suppressing viral replication. Even though HBV is considered not to be a cytopathic virus, the immune system continues to respond and cause damage if viral replication continues unabated. In essence, persistent viremia portends liver disease and, as is the case with HIV, therapy should focus on halting viral replication.

"With HBV treatment," Dr. Peters pointed out, "we can decrease viral replication. Whether these treatments eradicate cccDNA from the nuclei of hepatocytes is still controversial. My feeling is that they don't. Once viral replication has been turned off, surface antigen is lost and there will be no evidence of viral peptides on the surface of hepatocytes. But cccDNA may still be in the nucleus. In turn, if a patient gets chemotherapy, high-dose steroids, a transplant, is HIV infected, or experiences immune reconstitution, viral replication can potentially start up again. And this is what causes reactivation of disease."

As highlighted in practice guidelines published by the American Association for the Study of Liver Disease (AASLD) practice guidelines, the endpoints used to assess treatment response include normalization of serum ALT levels, undetectable HBV-DNA in peripheral blood using an unamplified assay, loss of HBeAg with or without detection of anti-HBe, and improvements in liver histology (Lok and McMahon, 2001; 2004). The practice guidelines also point out that it is currently difficult to compare response rates in clinical trials of the treatment of chronic HBV infection, as there have long been inconsistencies in the definition of response, lack of standardization of HBV viral load assays, and significant baseline differences in the patient populations studied. Still, improvements have been made in the therapy of chronic HBV infection, most notably the addition of adefovir dipivoxil (Hepsera) to the therapeutic armamentarium.

Dr. Peters was quick to point out that the success of therapy is highly dependent on baseline transaminases, even when using nucleoside/nucleotide analogues. "High ALT levels indicate that an immune response is occurring in the liver. Antiviral agents will decrease the level of HBV, but the immune response is required to clear virally infected hepatocytes." Generally speaking, anti-HBV therapies are most efficacious in patients with ALT levels greater than two times the normal limit.

Dr. Peters also offered a few words about HBV-DNA testing. "When you order an HBV-DNA, at most institutions you get the HBV-DNA assay *du jour,*" she said. "The hospital or laboratory has contracted to get the cheapest deal. The frustrating thing is that none of the assays correlate. If I send the same serum to four different testing facilities, I may get four different answers." Qualitative PCR testing can confirm the presence of HBV, provided that no fewer than 200 copies/mL of HBV-DNA is present in a sample. As for quantitative PCR, Roche's Cobas Amplicor HBV Monitor (version 2.0) can quantify HBV-DNA over a range of 200 to 200,000 copies/mL. Bayer's Versant HBV DNA 3.0 Assay has a linear range of quantification, starting at 2,000 copies/mL and ending at 100 million copies/mL. Other assays, including Abbott's and Digene's hybridization tests, are rarely used or recommended today, given their high cutoffs. "The bottom line here is that clinical trials of different HBV therapies were performed with different tests, using different cutoffs, which makes it very difficult to directly compare one drug to another."

Lamivudine

GLAXOSMITHKLINE'S LAMIVUDINE, FIRST APPROVED FOR THE TREATMENT of HIV in the mid-1990s, was awarded a second FDA approval for the treatment of chronic HBV infection in December 1998 (Epivir-HBV). The dose of lamivudine typically used to treat chronic HBV is 100 mg once daily, compared to the 300 mg once-daily schedule used to treat HIV. If used to treat HIV/HBV-coinfected patients, the 300 mg QD dosing schedule—as a component of combination antiretroviral therapy— should be used.

In patients with HBeAg-positive chronic HBV infection who have persistent or intermittent ALT elevations, three clinical trials involving a total of 731 treatment-naive patients who received lamivudine for one year reported that HBeAg seroconversion (including loss of HBV-DNA based on non-PCR assay) occurred in 16% to 18% of patients compared with 4% to 6% of untreated controls ((Dienstag, 1999; Lai, 1998; Schalm, 2000). Histologic improvement, defined as a reduction in necroinflammatory score greater than two points, was observed in 49% to 56% of treated patients and in 23% to 25% of controls.

In patients with HBeAg-negative chronic HBV infection who have elevated ALT levels prior to starting therapy, one study demonstrated a virologic and biochemical response in 34/54 (63%) patients who received 24 weeks of lamivudine therapy, compared to 3/53 (6%) of patients who received placebo (Tassopoulos, 1999). Of the 54 patients who completed one year of lamivudine treatment, HBV-DNA was undetectable by bDNA assay in 65% and by PCR assay in 39% of patients, and histologic improvement was seen in 60% of patients. Other studies have reported similar findings, although it should be noted that the vast majority of patients relapsed when lamivudine treatment was stopped.

Dr. Peters pointed out that HBeAg seroconversion, with reductions in HBV-DNA, is more likely to occur over time with lamivudine therapy. A study in Chinese patients with chronic hepatitis B showed that treatment with lamivudine for one year significantly improved liver histology and enhanced HBeAg seroconversion compared with placebo (Leung, 2001). Fifty-eight patients from this one-year study have received long-term treatment with lamivudine 100 mg. After three years of continuous treatment with lamivudine 100 mg daily, 23/58 (40%) patients achieved HBeAg seroconversion. In patients with baseline serum ALT greater than two times the upper normal limit, the rate of HBeAg seroconversion was 65%. Median HBV-DNA concentrations were below the level of detection, and median ALT concentrations were within the normal range throughout the three years of treatment.

While long-term therapy with lamivudine increases the possibility of HBeAg seroconversion, it also comes with the risk of developing key mutations in the YMDD motif, a highly conserved domain of the HBV reverse transcriptase required for HBV-DNA polymerase activation. The primary mutation associated with drug resistance is M204I/V in the C domain of the HBV polymerase.

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 capactity associated with HBV resistance to lamivudine (Leung, 2001). But Dr. Peters was quick to point that HBV can develop compensatory mutations in the B domain of its polymerase—notably V173L and L180M—that can restore HBV's replication capacity, "which almost always causes HBV-DNA levels to eventually increase to pre-treatment levels."

CHRONIC HBV INFECTION: A PRN CLINICAL CARE ALGORITHM

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Initial HBV Screening				
HBsAg	**Anti-HBs**	**Anti-HBc**	**Anti-HBc (IgM)**	
–	–	–	–	Needs vaccine
–	+	–	–	Established immunity (vaccinated)
–	+	+	–	Latent or prior infection
–	–	+	–	Usually either latent infection or false positive. Small percentage may reflect active infection; HBV-DNA follow-up testing recommended (only for immune-compromised patients).
+	–	+	+	Acute HBV infection
+	–	+	–	**Chronic infection**

Chronic HBV Infection Follow-Up Screening				
HBeAg	**Anti-HBe**	**HBV-DNA**	**ALT**	
–	+	–/low	Normal	Virus not replicating/inactive infection
–	+/–	+	Elevated	**Chronic infection with viral replication — precore mutant**
+	–	+	Elevated	**Chronic infection with viral replication**

Screen for Hepatoma and Cirrhosis

- **Referral to gastroenterologist/hepatologist**
- **AFP screen (every six months to 12 months)**
- **Abdominal ultrasound (every six months to 12 months)**
- **MRI if AFP abnormal or ultrasound is suspicious**

HBeAg-Positive	HBeAg-Negative
HBV-DNA <100,000 copies/mL; normal ALT: **FOLLOW**	HBV-DNA <10,000 copies/mL; normal ALT: **FOLLOW**
HBV-DNA >100,000 copies/mL; normal ALT	HBV-DNA >10,000 copies/mL; normal ALT
Liver Biopsy	
Moderate or severe disease	No or mild disease: **FOLLOW**
HBV-DNA >100,000 copies/mL; elevated ALT	HBV-DNA >10,000 copies/mL; elevated ALT

Many people with HIV disease also have chronic hepatitis B, and vice versa. It is extremely important to screen for coinfection in either case. This algorithm was developed by the editorial faculty of *The PRN Notebook* to illustrate the various steps involved in the screening, diagnosis, and clinical care of patients with chronic HBV infection. PRN does not seek to make any recommendations, per se, but rather to define the current standard of medical care — and the evolving options — for both HBV-monoinfected and HBV/HIV-coinfected patients. Expert clinicians involved in the development of this algorithm were:

- James Braun, DO
- Russell Chieffe, RPAC
- Raymond Chung, MD
- Edward Goldberg, MD
- Stephen Locarnini, BSc(Hons), MBBS, PhD, FRC(Path)
- Marion Peters, MD

- Joe Sasadeusz, MBBS(Hons), PhD, FRACP, FRCC
- Sharon Stancliff, MD
- Hans L. Tillmann, MD

Consider liver biopsy to grade and stage disease

Consider liver biopsy to grade and stage disease

TREATMENT

HBeAg-positive: Treat until four to six months after anti-HBe seroconversion

HBeAg-negative (pre-core mutant): Long-term treatment necessary

HIV/HBV-Coinfected Patients

HAART

- Initiate therapy with a lamivudine- and/or tenofovir-containing regimen when treatment is indicated (DHHS Guidelines).
- Closely monitor LFTs, especially when using drugs associated with hepatotoxocity in the setting of chronic HBV infection (e.g., nevirapine).

Interferon-alfa (5 MU QD x 16 weeks)

- Not as effective in coinfected patients; most effective in patients with CD4+ counts >350 cells/mm^3.
- Side effect profile difficult.
- Should be combined with HAART (e.g., lamivudine- and/or tenofovir-containing regimen).

Lamivudine (Epivir) (150 mg BID or 300 mg QD)

- Use dose indicated for HIV infection.
- Should be used as part of a HAART regimen with/without tenofovir when antiretroviral treatment is indicated.
- Resistance develops in 25% of patients after one year and in 90% after four years.

Tenofovir (Viread) (300 mg QD)

- *Not FDA approved for the treatment of HBV.*
- Limited data in HIV/HBV-coinfected patients.
- Should be used as part of a HAART regimen, with or without lamivudine, when antiretroviral treatment is indicated.
- Adjust dose for renal dysfunction.

Adefovir dipivoxil (Hepsera) (10 mg QD)

- Effective for the treatment of HBV in coinfected patients, including lamivudine-resistant HBV.
- Use as monotherapy before a tenofovir-/lamivudine-inclusive HAART regimen is indicated?
- Adjust dose for renal dysfunction.

Experimental Agents

- Pegylated interferon, emtricitabine (for lamivudine-naive patients), telbivudine, entecavir, etc.
- Combination therapies.
- Few studies open to coinfected patients.
- Studies listed with Hepatitis Resource Network (http://www.h-r-n.org) and AIDS Clinical Trials Information Service (http:///www.actis.org).

HBV-Monoinfected Patients

Interferon-alfa (5 MU QD x 16 weeks)

- Side-effect profile difficult.

Lamivudine (Epivir-HBV) (100 mg QD)

- Safe and effective anti-HBV treatment.
- Use in combination with adefovir dipivoxil?
- Resistance develops in 15% to 32% of patients in one year and in 67% after four years.

Adefovir dipivoxil (Hepsera) (10 mg QD)

- Safe and effective anti-HBV treatment, including lamivudine-resistant HBV.
- Use alone or in combination with lamivudine for cirrhotic patients.
- Prolonged antiviral activity; limited resistance with prolonged administration.
- Adjust dose for renal dysfunction.

Experimental Agents

- Pegylated interferon, emtricitabine (for lamivudine-naive patients), tenofovir, telbivudine, entecavir, etc.
- Combination therapies.
- Studies listed with Hepatitis Resource Network (http://www.h-r-n.org).

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Adefovir Dipivoxil

THE MOST RECENT ADDITION TO THE HBV THERAPEUTIC LANDSCAPE IS adefovir dipivoxil (Hepsera). It is being manufactured by Gilead Sciences and is the same drug that was studied previously, at higher doses, as a treatment for HIV, and subsequently rejected by the FDA because of high rates of renal toxicity—proximal renal tubular necrosis—at the 60 mg dose studied. The FDA-approved 10 mg adefovir dose has not been associated with renal toxicity, at least not in patients with normal renal function prior to initiating therapy.

Laboratory evaluations have suggested that the drug is effective against both wild-type and lamivudine-resistant HBV. There have also been a handful of phase I and phase II studies demonstrating that adefovir is associated with a 4 log reduction in HBV-DNA and is associated with HBeAg to anti-HBe seroconversion rates of 20% to 27% (Gilson, 1996; Heathcote, 1998; Jeffers 1998). It was the successful completion of two phase III studies involving patients with both HBeAg-positive and HBeAg-negative chronic hepatitis B that led to the approval of adefovir earlier this year. Highlights from these two studies, as well as those from a small open-label study involving HIV/HBV-coinfected patients, are reported here.

Study 437 was a double-blind, placebo-controlled Phase III clinical trial evaluating the safety and efficacy of adefovir once daily as monotherapy compared to placebo in patients with HBeAg-positive chronic HBV infection (Marcellin, 2003). The study randomized 515 patients in the United States, Canada, Europe, Australia and Southeast Asia to receive 10 mg adefovir (172 patients), 30 mg adefovir (173 patients), or placebo (170 patients) daily for 48 weeks.

After 48 weeks of treatment, significantly more patients who received 10 mg or 30 mg of adefovir per day, compared to those receiving placebo, had histologic improvement (53%, 59%, and 25% respectively). There were also statistically significant reductions in HBV-DNA, compared with placebo: –3.52 $\log_{10}$ copies/mL in the 10 mg adefovir group, –4.76 $\log_{10}$ copies/mL in the 30 mg adefovir group, and –0.55 $\log_{10}$ copies/mL in the placebo group. As for rates of undetectable HBV-DNA (<400 copies/mL) after 48 weeks of therapy, this was documented in 21%, 39%, and 0% respectively. ALT normalization occurred in 48% of patients receiving 10 mg adefovir, 55% of patients receiving 30 mg adefovir, and 15% of patients receiving placebo. HBeAg seroconversion occurred in 12%, 14%, and 6% respectively.

No adefovir-associated resistance mutations were identified in the HBV polymerase gene during the 48 weeks of treatment. The safety profile of the 10 mg dose of adefovir was similar to that of placebo. Among patients receiving 30 mg adefovir, there was a higher frequency of adverse events and renal laboratory abnormalities.

Gilead Study 438 was an international, multicenter, double-blind, placebo-controlled Phase III clinical trial that enrolled 185 patients with HBeAg-negative chronic HBV infection and compensated liver function (Hadziyannis, 2003). The study was conducted in Australia, Canada, France, Greece, Israel, Italy and Southeast Asia. Patients were randomized to receive adefovir 10 mg once daily or placebo for 48 weeks.

After 48 weeks of treatment, 77/121 (64%) patients who had baseline liver biopsy specimens available in the adefovir group had improvement in histologic liver abnormalities, compared with 19/57 (33%) patients in the placebo group. HBV-DNA levels became undetectable (<400 copies/mL) in 63/123 (51%) patients in the adefovir group, compared to 0% of patients in the placebo group. Transaminases had normalized after 48 week of treatment in 84/116 (72%) patients receiving adefovir, compared with 29% percent of those receiving placebo. And much like Study 437, no HBV polymerase mutations associated with resistance to adefovir were identified during the 48 weeks of follow up in Study 438.

Also of importance are data from a small open-label study of adefovir conducted in HIV/HBV-coinfected patients with lamivudine-resistant HBV (Benhamou, 2004). This study enrolled 35 coinfected patients receiving lamivudine therapy as part of their anti-HIV regimen. Patients received a 10 mg once-daily dose of adefovir while maintaining their existing antiretroviral regimen, including the lamivudine. Patients had received lamivudine for a median of 42 months and had developed HBV resistance to the drug approximately 22 months before starting therapy with adefovir.

All 35 patients enrolled in the study had evaluable data after 48 weeks of treatment. Thirty patients completed 96 weeks of treatment, 28 completed 144 weeks of treatment, and 22 completed 192 weeks (four years) of treatment. At week 48, the median change in HBV-DNA was –3.97 $\log_{10}$ copies/mL. At 96, 144, and 192 weeks, the median changes were –4.80, –5.55, and –5.62 $\log_{10}$ copies/mL, indicating a slow but continual effect on HBV viral load. As for undetectable HBV-DNA levels (<1,000 copies/mL), this was documented in 6% of patients after 48 weeks, 27% of patients after 96 weeks, 46% of patients after 144 weeks, and 59% of patients after 192 weeks. Rates of ALT normalization were also remarkable: 19% after 48 weeks, 37% after 96 weeks, 64% after 144 weeks, and 67% after 192 weeks.

Of the three patients who lost HBeAg by 48 weeks of treatment, two developed detectable antibodies (anti-HBe). These seroconversions remained durable through the four years of follow up. What's more, no adefovir-associated polymerase mutations were identified at any time during the study and there have been no reports of nephrotoxicity, or any other serious adverse events for that matter.

"Studies have consistently demonstrated that HBV-DNA is reduced slowly, over time, with the use of either lamivudine or adefovir," Dr. Peters commented. "A three-log drop at twelve weeks is a good response and a four-log drop at 24 weeks is the usual scenario. Less that 10% of patients will experience a very weak response to therapy, meaning an HBV-DNA reduction less than one log."

In vivo resistance to adefovir can arise with the N236T mutation in the D domain of HBV's polymerase. However, resistance to adefovir does not occur nearly as frequently as HBV resistance to lamivudine. In contrast to the rates of lamivudine resistance reported above, no cases of adefovir resistance have been reported among patients receiving the drug for a year. After two years of adefovir therapy, resistance has been documented in 1.8% of patients. And after three years of adefovir therapy, the resistance rate is 3.9%. "Resistance has only been seen in patients with HBeAg-negative, precore mutant HBV infection," Dr. Peters clarified. "Resistance has not yet been documented in any patients with HBeAg-positive HBV infection, although it's probably just a matter of time."

One final issue to consider when prescribing adefovir: it can result in hepatic flares. "We've known about flares associated with interferon therapy and now know that adefovir therapy can result in flares," Dr. Peters explained. "These flares usually occur six to eight weeks into treatment. ALT levels increase, a sign that the immune system is recognizing the viral infected hepatocytes, which is a good indicator of clearance." Care should be taken in patients with cirrhosis who might experience flares and develop decompensated liver disease.

As is discussed below, there is the possibility of 10 mg adefovir monotherapy in HIV/HBV-coinfected patients who do not yet require combination antiretroviral therapy for HIV, as 10 mg probably has a limited effect with respect to HIV-resistance development.

Tenofovir

BASED ON PROMISING *IN VITRO* AND *IN VIVO* STUDIES SUGGESTING THAT tenofovir (Viread)—Gilead Science's approved nucleotide analogue for the treatment of HIV—is also active against HBV, clinicians have been partial to prescribing tenofovir over adefovir for their HIV/HBV-coinfected patients as a component of combination HIV therapy.

"There have been very few studies of tenofovir for the treatment of HBV," Dr. Peters said. "None of them have been controlled, so it hasn't yet been studied adequately." However, data do exist.

Substudies of the safety and efficacy of tenofovir for HBV/HIV coinfection were undertaken within two Gilead-sponsored phase 3 randomized controlled trials involving antiretroviral therapy-experienced (Study 907) and antiretroviral-naive (Study 903) HIV-infected patients (Dore, 2004). In Study 907, the mean decrease in HBV-DNA was 4.9 $\log_{10}$ copies/mL after 24 weeks among 10 patients randomized to receive tenofovir, compared with a mean increase of 1.2 $\log_{10}$ copies/mL among two patients randomized to receive placebo. The mean decrease in HBV-DNA during tenofovir treatment was similar for patients with wild-type and lamivudine-resistant HBV strains. In Study 903, the mean decrease in HBV-DNA was 3.0 $\log_{10}$ copies/mL after 48 weeks for six patients randomized to receive lamivudine, compared with a 4.7 $\log_{10}$ copies/mL decrease among five patients randomized to receive lamivudine and tenofovir combined. Four patients developed drug-resistant HBV mutations, all in the lamivudine-only treatment arm.

Two-year follow-up data from Study 903 were reported at the XV International AIDS Conference in Bangkok (Dore, 2004a). Combination therapy with tenofovir and lamivudine had greater sustained anti-HBV activity than lamivudine alone. Improvements in ALT levels were also more likely to occur among patients receiving the tenofovir/lamivudine combination than those receiving lamivudine alone. And, as was seen during the initial 24-week phase of the study, lamivudine-resistance mutations emerged solely in the lamivudine-only group within two years of therapy.

"The fact is, more research needs to be conducted," Dr. Peters said. "We don't know the correct tenofovir dose for the treatment of HBV. We know, for instance, that the adefovir dose needed to control HIV replication was 60 to 120 mg, which caused renal problems. But the dose for hepatitis B is only 10 mg. And the dose of tenofovir needed to treat HIV is 300 mg daily. Is this too much for the treatment of HBV? Not for HIV-positive patients, most likely, but possibly for patients only infected with HBV."

Fortunately, studies looking at tenofovir in HIV/HBV-coinfected patients are currently under way. These include a study being performed by the AIDS Clinical Trials Group (A5127), a randomized comparison of adefovir dipivoxil (10 mg) and tenofovir in HIV/HBV-coinfected patients. More will be learned from the ACTG study about the comparability of the two drugs.

A Few Words on Cross-Resistance

WITH LAMIVUDINE, RESISTANCE TO THERAPY IS ASSOCIATED WITH MUTATIONS in the YMDD motif. With adefovir, resistance to therapy is associated with N236T mutation in HBV polymerase. More importantly, there hasn't been any evidence of cross-resistance between these two compounds in clinical trials or the real-world management of HBV infection. But what about cross-resistance between lamivudine, adefovir, and compounds in development for the treatment of HBV, such as Bristol-Myers Squibb's entecavir, Gilead's emtricitabine, and Idenix Pharmaceuticals' telbivudine?

It is already known that adefovir is active against HBV strains harboring the YMDD mutants and that lamivudine is active against HBV strains harboring the N236T mutation, indicating little, if any, cross-resistance between these two drugs. *In vitro*, HBV harboring the YMDD mutation is less sensitive to entecavir, but *in vivo* data suggest that YMDD mutants retain sensitivity to this drug. *In vitro* data also indicate that N236T mutants are still sensitive to entecavir, although *in vivo* data are not yet available.

As for emtricitabine, it appears to be less active against *in vitro* isolates harboring YMDD mutations and fully active against strains harboring N236T; no *in vivo* data are yet available. Telbivudine, unfortunately, is not active against YMDD mutants, either *in vitro* or *in vivo*, with no data available yet with respect to activity against HBV strains harboring the N236T mutation.

Interferon-Alpha and Pegylated Interferon

INTERFERON-α HAS BEEN APPROVED FOR MORE THAN A DECADE. USED AT a dose of 5 million units every day or 10 million units three times weekly for 16 weeks, interferon-α monotherapy is associated with HBeAg clearance in approximately 30% of immunocompetent patients and HBsAg clearance in up to 10% of patients. Studies have also suggested that it is effective in reducing HBV-DNA levels and normalizing ALT levels in patients with HBeAg-negative chronic hepatitis B, although high rates of relapse are seen. Interferon-α is less effective in patients with high baseline HBV-DNA levels and patients with normal ALT levels prior to initiating treatment, which is often seen in HIV/HBV coinfected individuals

Unfortunately, the drug is associated with significant side effects including fever, myalgia, thyroid abnormalities, bone marrow suppression, and a litany of psychiatric symptoms. What's more, the drug must be used cautiously in patients with cirrhosis, as it may exacerbate the immune response to the virus and lead to decompensation. Patients most likely to benefit from interferon-α therapy are those with normal synthetic function, no cytopenias, elevated transaminases, consistent liver biopsy results, and no decompensation. As for HBV/HIV-coinfected patients, only those with CD4+ counts greater than 350 to 400 CD4+ cells stand a good chance at an effective response (Wong, 1995; MacDonald, 1987).

"The truth is, interferon has really fallen out of favor among clinicians, given the limited effectiveness and the high toxicity rates," Dr. Peters commented. "I started my career studying interferon, so I've maintained a lifelong fondness for it. Fortunately, we're seeing some good results using pegylated interferon."

Because of the improved results of pegylated versions of interferon-alpha over standard versions of interferon in the management of chronic hepatitis C infection, both Schering-Plough and Roche Pharmaceuticals—the manufacturers of Peg-Intron- and Pegasys-brand pegylated interferons, respectively—have their eyes set on an expanded indication to include patients with chronic HBV infection.

A clinical trial of Pegasys was carried out by Dr. Graham Cooksley of the Royal Brisbane Hospital Research Foundation in Brisbane, Australia, and his colleagues and published in 2003 (Cooksley, 2003). In this phase II study, 194 patients with chronic hepatitis B not previously treated with conventional interferon-alpha were randomized to receive weekly subcutaneous doses of Pegasys—either 90, 180 or 270 μg weekly—or conventional interferon alpha-2a 4.5 MIU three-times-weekly. Twenty-four weeks of therapy were followed by 24 weeks of treatment-free follow-up. All subjects were assessed for loss of HBeAg, seroconversion to anti-HBe, suppression of HBV-DNA, and normalization of ALT levels.

At the end of follow-up, HBeAg was cleared in 37%, 35%, and 29% of patients receiving Pegasys 90, 180 or 270 μg respectively, compared

with 25% of patients on conventional interferon alpha-2a. The combined response (HBeAg loss, HBV-DNA suppression, and ALT normalization) of all Pegasys doses combined was twice that achieved with conventional interferon alpha-2a (24%vs 12%). All treatment groups were similar with respect to frequency and severity of adverse events.

"Clinicians who have patients who may tolerate interferon and have strong CD4+ cell counts may want to consider pegylated interferon for hepatitis B," recommended Dr. Peters. "These results are encouraging and we'll definitely be studying it more in the future."

Treating HIV/HBV Coinfection: General Considerations

IT IS IMPORTANT THAT ALL PATIENTS DIAGNOSED WITH HIV UNDERGO serologic testing for HBV coinfection, and vice versa. Given the similar routes by which both viruses are transmitted and the high prevalence rates of HIV and HBV in certain populations, all efforts should be made to promptly diagnose—and, if necessary, treat—both infections.

When is anti-HBV therapy necessary? Any patient who meets the criteria for antiretroviral therapy for HIV—for example, a CD4+ count below 350 cells/mm^3—should initiate a regimen consisting of drugs active against HBV and HIV. This means taking into consideration the overlap in antivirals available to treat both infections, most notably lamivudine (Epvir; Epivir-HBV), which has been approved by the U.S. Food and Drug Administration for the treatment of both infections, and tenofovir (Viread), which has shown promise in clinical trials for patients coinfected with HIV and HBV.

For HBV/HIV-coinfected patients who do not yet meet the criteria for starting antiretroviral therapy for HIV, anti-HBV treatment may still be necessary. Any patient with active liver disease—loosely characterized by high ALT levels and/or necroinflammatory disease—or high HBV-DNA levels should be considered for therapy. A high viral load, warranting treatment, for HBeAg-positive patients is an HBV-DNA titer over 100,000 copies/mL; for HBeAg-negative (precore mutant) patients, treatment is warranted for patients with a value over 10,000 HBV-DNA copies/mL. "It's important to remember that individuals with precore HBV mutants are more likely to be individuals who have had the disease for a long period of time," Dr. Peters said. "They tend to have more aggressive disease and lower HBV-DNA. These are individuals we would normally treat."

As for liver biopsies, Dr. Peters indicated that they may be necessary for patients with atypical laboratory results, such as an HBV-DNA titer below 10,000 copies in the presence of elevated ALT levels, or consistently high HBV-DNA titers in the presence of normal ALT levels in HIV-coinfected subjects. "We tend to see atypical results in immune-compromised patients," Dr. Peters indicated. "In HIV, we see a number of patients with normal ALT levels, high HBV-DNA, and a lot of inflammation of the liver on biopsy."

Hepatotoxicity is an important issue to consider when selecting drug regimens to treat HIV and HBV in patients coinfected with both viruses. There have been reports suggesting that nevirapine may be problematic for patients with underlying liver disease, including HCV or HBV infection, and there has been no shortage of data indicating that ritonavir, particularly in high doses, is associated with an increased risk of hepatotoxicity in HIV-positive patients coinfected with HBV and hepatitis C virus (HCV). Another potential concern is hepatic steatosis, which is associated with nucleoside analogue therapy, most notably didanosine (Videx), zalcitabine (Hivid), and stavudine (Zerit).

It's also important to remember that HBV is much slower to develop resistance to lamivudine—and possibly tenofovir—than HIV. Thus, continuing both drugs may still be beneficial for the treatment of HBV, even when genotypic or phenotypic assays determine that HIV resistance to either of these drugs is present. There is also the risk of hepatic flares if either drug is discontinued prematurely. "It is critical that therapy with an anti-HBV drug be continued to control HBV replication, irrespective of the HIV drug-resistance profile," Dr. Peters recommended.

Questions remain regarding the use of adefovir dipivoxil in HIV/HBV-coinfected patients. One possibility that has been considered by clinicians—and was discussed by Dr. Peters—is the possibility of using adefovir monotherapy when HBV treatment is indicated but antiretroviral therapy for the management of HIV is not (i.e., patients with CD4+ counts above 350 cells/mm^3). At present, there are no data indicating that adefovir induces resistance—the dose approved for the treatment of chronic HBV infection is believed to be too low to select for resistance—or cross-resistance to any of the antiretrovirals used to treat HIV. Thus, employing adefovir earlier in the course of HIV infection—provided that therapy for chronic HBV is indicated—may be beneficial in terms of controlling HBV replication, with the knowledge that a second-line, even more powerful regimen consisting of tenofovir and/or lamivudine can be called upon when HIV therapy becomes necessary.

In summarizing some of the finer points of anti-HBV treatment in HBV/HIV-coinfected patients, Dr. Peters stressed that the goal of treatment is to suppress HBV for a prolonged period of time. "If you have an HBeAg-positive patient, treatment can be stopped six months after seroconversion to anti-HBe," she said. "Unfortunately, seroconversion is less common in HIV-positive patients." As for HBe-Ag-negative patients, therapy needs to be continued indefinitely.

As for the selection of agents, interferon should only be used in patients with compensated liver function, whereas the nucleoside/nucleotide analogues can be used in patients with compensated and decompensated liver function. As for prescribing combinations of drugs that are active against HBV—such as tenofovir paired with lamivudine—Dr. Peters indicated that they may maximize antiviral suppression and work in a synergistic manner to enhance the immune response to the virus. "However, this approach hasn't been well studied," she cautioned. "More data is needed to find out if there truly is a clinical benefit associated with combination anti-HBV therapy."

A Few Words on Vaccination

VACCINATION AGAINST HEPATITIS A AND B IS STRONGLY RECOMMENDED for HIV-positive people who have not been exposed to either of these viruses. However, it is important to note that vaccination success is lower in HIV-positive patients, particularly those with compromised immune systems. According to one study published in 1992, standard schedules of the HBV vaccine (20 μg at months 0, 1, and 6) induce immunity in 30% to 40% of HIV-infected patients (Bruguera, 1992). Generally speaking, patients with a CD4+ count below 200 cells/mm^3 have a very poor chance of response, whereas patients with counts of more than 500 CD4+ cells/mm^3 can achieve antibody response in up to 70% of cases.

One study team has tested the hypothesis that doubling the number of hepatitis B vaccine injections might increase the anti-HBs response rate in HIV-positive patients (Rey, 2000). Twenty-eight HIV-infected patients with CD4+ counts greater than 200 cells/mm^3, all of whom were on stable HAART and had never been vaccinated against HBV, were given three intramuscular injections of Genhevac B (20 μg) at one-month intervals. Initial nonresponders were given three additional monthly injections.

The response rate after three 20 μg injections was 55%, with the response rate being lowest (33%) among patients with CD4+ counts between 200 and 500 cells/mm^3, compared to a higher response rate

(87.5%) among patients with CD4+ counts above 500 cells/mm^3. Among nine initial nonresponders, only two failed to respond to three additional doses; thus, the overall response rate was 90%. But one year later, only 10/17 (58.8%) evaluable patients had protective anti-HBs. While the study authors concluded that doubling the number of hepatitis B vaccinations in HIV-infected patients might significantly improve anti-HBs response rate, it is not likely to be recommended, given its short-lived persistence.

"The ideal time for vaccinations is before the age of 20," Dr. Peters pointed out. "Older adults, no matter how their health is, are not going to respond to vaccination as well as younger adults. But certain conditions can further decrease the likelihood of effective immunization, including chronic liver disease, HIV infection, and other causes of immune suppression." Dr. Peters did indicate that she is collaborating with other investigators to further explore the possibility of using GM-CSF to augment vaccination to hepatitis B—a strategy that yielded encouraging results in a small study involving dialysis patients. Plus, a number of different adjuvants are currently in clinical development.

Conclusion

IN SUMMARIZING HER TALK, DR. PETERS REITERATED SOME OF THE MORE important recommendations regarding the diagnosis and care of HIV-patients coinfected with HBV. For starters, she stressed the importance of testing all HIV-positive patients for HBV, HAV, and HCV and being careful not to dismiss atypical serologies, such as the presentation of core antibodies alone in the absence of other serologic markers of infection. "For patients with serologies that are not indicative of previous or current infection, vaccination should be provided." she said.

Regarding the natural history of chronic HBV in HIV-infected patients, Dr. Peters reminded PRN members that the immune response to HBV predicts disease outcome and that while immunodeficiency may decrease necroinflammation, it allows for increased replication of HBV. "The immune recovery promoted by antiretroviral therapy allows for necroinflammation to continue. There's no doubting the importance of treating HBV. Treatment should be considered where there is HBV viremia and elevated transaminases. And remember, HBV should be treated along with HIV and combination regimens should involve antiviral compounds active against both viral infections." prn

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