

Antiviral Therapy of Chronic Hepatitis B Infection

A Review of Selected Presentations
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2. Describe future endpoints of hepatitis B therapy.
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Introduction

Epidemiology and Pathology

Infection with the hepatitis B virus (HBV) is a globally significant issue, as it affects more than 2 billion people worldwide.¹ Most people exhibit acute infection, from which healthy adults are generally able to recover. However, a large number of people are afflicted with chronic hepatitis B (CHB), which is defined as continued presence of HBV in the blood for over 6 months. CHB is estimated to occur in over 360 million individuals worldwide and between 1.2–2 million individuals in the United States alone.^{1–3} Infants and children infected with HBV are prone to developing CHB, as are adults with weakened immune systems.

CHB infection can result in serious health consequences. The main disease outcome of CHB infection is liver inflammation and damage. Over time, continuous liver inflammation is associated with progression to end-stage liver disease, including cirrhosis and hepatocellular carcinoma (HCC). Accordingly, CHB is one of the leading causes of liver transplantation. The pathogenesis of the liver damage begins with the release of hepatitis B virions, which primarily infect hepatocytes.⁴ Hepatocyte infection leads to an immune response directed against the virus, which then results in liver inflammation and injury. In an attempt to repair the damaged liver tissue and restore normal hepatic function, new tissue is generated. However, continuous cycles of inflammation and tissue repair eventually lead to tissue scarring, which ultimately results in liver fibrosis, a build-up of the excessive fibrous tissue created during liver repair. Progressive liver fibrosis can decrease liver function and is often used as a marker to stage liver disease.⁵ Additionally, liver function can be assayed biochemically by monitoring levels of the alanine transaminase (ALT) enzyme, which is released during liver damage. Elevated levels of ALT, defined as greater than the upper limit of normal (ULN), are generally indicative of liver inflammation and damage. However, normal ALT levels can sometimes occur in patients with liver disease. Normalization of ALT levels is a common parameter measured to determine therapeutic response.

The extent of HBV infection can also be determined by detection of HBV DNA, which represents the presence of actively replicating virus. The expression of several HBV viral proteins (hepatitis B e antigen [HBeAg], hepatitis B surface antigen [HBsAg], hepatitis B core antigen [HBcAg]) or the antibodies that are produced in response to their expression (anti-HBe, anti-HBs, anti-HBc) can be detected by immunologic assay.⁶

Recently, four phases of CHB infection have been described.⁷ The duration of the first phase of infection,

called the “immune tolerance” stage, can vary depending on the route of viral transmission. Patients who were infected perinatally generally exhibit longer durations (10–40 years), whereas patients infected during childhood or as adults experience either shorter durations or do not experience phase 1 at all. During phase 1, a high level of HBV DNA is evident, as is HBeAg-positive status. However, patients have normal ALT levels and little or no signs of liver inflammation. Minimal disease progression occurs in these patients, despite the elevated levels of HBV DNA that may occur over a long period of time. Phase 2, the “immune clearance” stage, is characterized mainly by flares in ALT levels caused by the lysis of HBV-infected hepatocytes, release of the virus, and immune recognition of the viral antigens HBcAg and HBeAg.^{8,9} Patients in phase 2 continue to have high levels of HBV DNA. As a result of the immune response to the release of HBeAg, patients at the end of phase 2 undergo seroconversion of circulating HBeAg to anti-HBe antibodies. Following seroconversion, infection progresses to phase 3 or the “inactive HBsAg carrier state” stage. Patients in phase 3 have normal ALT levels and low or undetectable HBV DNA levels. Although mild liver disease or inactive cirrhosis may be present upon biopsy, it is generally a result of the inflammatory response during phase 2 and is not progressive during this stage. In fact, patients in phase 3 have a favorable prognosis. In the final phase of CHB infection, the “reactivation” stage, HBV replication is reactivated, resulting in increased detectable levels of HBV DNA. These patients remain HBeAg-negative and anti-HBe-positive. Liver disease begins to progress, and ALT levels again become elevated. Transition into phase 4 can be induced either spontaneously or as a result of immune suppression, which can occur in response to chemotherapy or biologic therapy.

Treatment of Chronic Hepatitis B Infection

One of the first major treatments for CHB was interferon- α , a cytokine with both antiviral and immunomodulatory properties.¹⁰ Over time, standard interferon- α was replaced with a pegylated version of the protein (Peg-IFN- α). The addition of the polyethylene glycol (PEG) moiety led to dramatic improvements in the pharmacologic properties of the drug.¹¹ However, although it is active against HBV, interferon therapy is associated with a number of adverse effects, some of which can be serious. This has led to the development of antiviral agents as more practical treatment alternatives, which often display a higher efficacy.

The major classes of anti-HBV antiviral agents is the oral nucleos(t)ide analogs. These drugs act by mimicking the naturally occurring nucleos(t)ides, competing with them for insertion into a replicating HBV DNA strand. Because these analogs are unable to promote a connection to the next nucleos(t)ide in the DNA strand, DNA strand elongation is inhibited and the virus cannot replicate.¹² The two nucleos(t)ide analogs first approved for treatment of CHB were lamivudine and adefovir.¹³ These were subsequently followed with the addition of entecavir and telbivudine.¹⁴ In addition, tenofovir is currently approved for the treatment of HIV and is under active investigation for the treatment of CHB.

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Antiviral Therapy of Chronic Hepatitis B Infection

A Review of Selected Presentations From the 58th Annual Meeting of the American Association for the Study of Liver Diseases, November 2–6, 2007, Boston, Massachusetts

LB2 A Randomized, Double-Blind, Comparison of Tenofovir DF (TDF) Versus Adefovir Dipivoxil (ADV) for the Treatment of HBeAg-Negative Chronic Hepatitis B (CHB): Study GS-US-174-0102¹

P Marcellin, M Buti, Z Krastev, G Germanidis, KD Kaita, I Kotzev, P Buggisch, F Weilert, HN Trinh, J Sorbel, J Anderson, E Mondou, F Rousseau

LB6 A Randomized, Double-Blind, Comparison of Tenofovir DF (TDF) Versus Adefovir Dipivoxil (ADV) for the Treatment of HBeAg-Positive Chronic Hepatitis B (CHB): Study GS-US-174-0103²

J Heathcote, E Gane, R DeMan, S Lee, R Flisiak, MP Manns, K Tchernev, O Kuras, ML Shiffman, J Sorbel, J Anderson, E Mondou, F Rousseau

Tenofovir disoproxil fumarate is a nucleotide analog reverse transcriptase inhibitor (NRTI) that is structurally similar to another NRTI, adefovir, differing by only one methyl group. However, this slight variation translates into distinct differences in both the safety profile and pharmacologic properties between the two agents.³ Because of its improved safety profile, tenofovir can be administered at much higher doses compared to adefovir, thus allowing higher and more effective antiviral levels to be achieved.⁴ Tenofovir was approved as an HIV therapy in 2001, whereas adefovir is currently indicated for treatment of CHB. During its development, tenofovir was also noted to exhibit anti-HBV properties.^{5,6} A substudy analysis of HIV/HBV co-infected patients enrolled in two randomized phase III trials testing the anti-HIV activity of tenofovir also revealed that the drug had potent anti-HBV activity.⁷ In the first of the two trials, 24 weeks of tenofovir monotherapy reduced HBV DNA levels by 4.9 log₁₀ copies/mL compared with a reduction of 1.2 log₁₀ copies/mL in placebo-receiving patients ($P=.041$). The second study, which randomized patients to receive

either tenofovir with lamivudine or lamivudine alone, revealed similar results after 48 weeks. Patients receiving the combination therapy exhibited greater reductions in HBV DNA levels compared to the monotherapy group ($4.7 \log_{10}$ copies/mL vs $3.0 \log_{10}$ copies/mL, respectively, $P=.055$). Although the tenofovir-induced HBV DNA reductions in each of these studies did not reach statistical significance, the patient sample size was small for both ($n=12$ and $n=11$, respectively). Importantly, tenofovir displayed activity in patients with either wild-type or lamivudine-resistant HBV, signifying its activity in both treatment-experienced and -naïve individuals. In light of its improved pharmacologic properties over adefovir, tenofovir was also directly compared to adefovir in a small trial of 53 CHB patients with high HBV DNA levels ($>6 \log_{10}$ copies/mL) and genotypic resistance to lamivudine.⁸ Significantly, 100% of patients randomized to receive tenofovir displayed HBV DNA levels reduced to $<10^5$ copies/mL compared with only 44% of the adefovir-receiving group ($P=.001$).

Based on the promising anti-HBV activity of tenofovir in these and other trials, two long-term phase III trials were designed to compare tenofovir against the standard anti-HBV therapy, adefovir. The design of each trial includes an initial blinded randomization period of over 48 weeks during which patients receive either tenofovir or adefovir monotherapy in a 2:1 ratio. This is then followed by open-label administration of tenofovir for up to 5 years. Here, the initial results after the first 48 weeks of therapy are presented from each of these clinical trials. The first study (GS-US-174-0102), conducted by Marcellin and colleagues, analyzed the drugs in an HBeAg-negative patient population, whereas the second study (GS-US-174-0103), presented by Heathcote and associates, assessed HBeAg-positive individuals.^{1,2}

Each of these multicenter international studies was double-blind and active-controlled, with control patients receiving the active drug adefovir. To be eligible, patients had to be between 18 and 69 years of age and monoinfected with CHB. Patients had elevated ALT levels (over ULN) and high HBV DNA levels ($>10^5$ copies/mL for HBeAg-negative patients and $>10^6$ copies/mL for HBeAg-positive patients). Additionally, all patients had compensated liver disease, with a Knodell necroinflammatory score ≥ 3 . To assess treatment efficacy, liver biopsies and HBV DNA assessments were performed at both baseline and 48 weeks of therapy.

In the first study by Marcellin and colleagues, 375 HBeAg-negative individuals were randomized to receive either 300 mg daily tenofovir ($n=250$) or 10 mg daily adefovir ($n=125$).¹ The baseline characteristics among the patients were balanced between the two groups, with an overall mean age of 44 years. The majority of patients

were men (77%) and from Europe (62%), and most were white (65%) or Asian (25%). A total of 18% of all patients had previous exposure to either lamivudine or emtricitabine. The mean HBV DNA level was $6.9 \log_{10}$ copies/mL, and 64% of the study population had ALT levels $>2 \times$ ULN. Study individuals had a mean Knodell necroinflammatory score of 7.8, and a mean fibrosis score of 2.3; 19% of the patients had liver cirrhosis. Most of the patients were infected with genotype D HBV.

The primary study endpoint, complete response to therapy, was assessed after 48 weeks (Table 1). Complete response was defined as HBV DNA levels <400 copies/mL combined with a histologic improvement of a ≥ 2 point reduction in the Knodell necroinflammatory score with no associated worsening of fibrosis. A significantly greater percentage of patients in the tenofovir group achieved improvements in both HBV DNA levels and liver histology compared with those in the adefovir group (71% vs 49%, respectively, $P<.001$). However, when distinct responses to therapy were analyzed separately, there were no significant differences between the number of patients experiencing either histologic response or a normalization of ALT levels. Compared with tenofovir-receiving patients, individuals in the adefovir group had a similar improvement in liver histology after therapy (72% vs 69%, respectively, $P=NS$). Similarly, tenofovir induced a normalization of ALT levels in 77% of patients compared to 78% of adefovir-receiving patients ($P=NS$).

Importantly, when reductions in HBV DNA levels were analyzed separately, a significant improvement induced by tenofovir treatment compared with adefovir therapy was evident. A greater percentage of patients receiving tenofovir achieved reductions in HBV DNA levels to <300 copies/mL compared with patients receiving adefovir (92% vs 59%, respectively, $P<.001$). Additionally, tenofovir treatment resulted in a superior number of patients exhibiting undetectable levels of HBV DNA compared with adefovir therapy (91% vs 56%, respectively, $P<.001$). HBV DNA levels were assessed using a polymerase chain reaction-based assay with a lower limit of detection of 169 copies/mL.

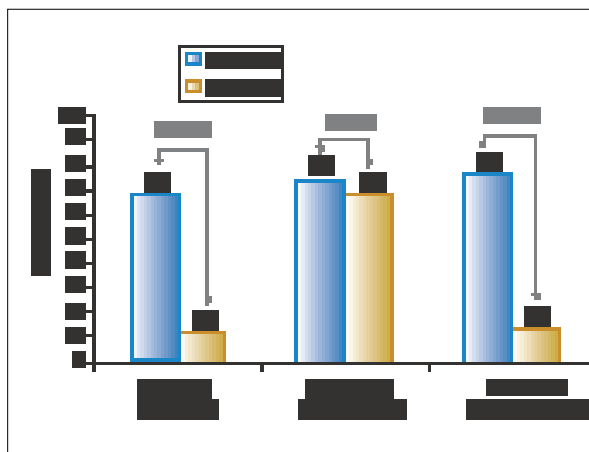
The second study, presented by Heathcote and associates, used the same treatment randomization in 266 HBeAg-positive CHB patients.² A total of 176 patients received tenofovir (300 mg daily), and 90 patients received adefovir (10 mg daily). The mean age of all patients was 34 years, and 69% were men. White and Asian individuals made up the majority of the study population (52% and 36%, respectively), and 55% were European. Most patients were infected with either genotype D (33%) or genotype C (26%) HBV. The baseline mean HBV DNA level was $8.72 \log_{10}$ copies/mL, and most patients had ALT levels $\leq 4 \times$ ULN. The average Knodell necroinflammatory

Table 1. Endpoint Measures in Study GS-US-174-0102

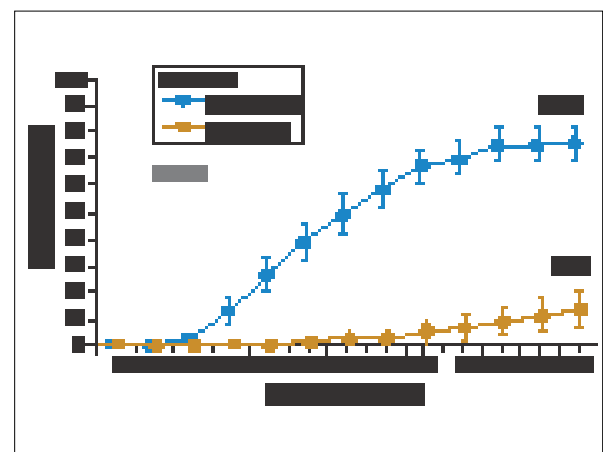
Efficacy endpoints	TDF 300 mg (n=250)	ADV 10 mg (n=125)	P
Primary composite endpoint	71%	49%	<.001
Histologic response	72%	69%	NS
% HBV DNA <169 c/mL (LLQ)	91%	56%	<.001
% HBV DNA <300 c/mL	92%	59%	<.001
Normal ALT	77%	78%	NS

ADV=adefovir; ALT=alanine aminotransferase; HBV=hepatitis B virus; TDF=tenofovir.

Data adapted from Marcellin P, et al.¹

**Figure 1.** Primary and secondary endpoints in Study GS-US-174-0103.

Data adapted from Heathcote J, et al.²

**Figure 2.** HBV DNA <400 c/mL in Study GS-US-174-0103.

Data adapted from Heathcote J, et al.²

score was 8.4, and the average fibrosis score was 2.4. Liver cirrhosis was evident in 20% of all patients.

At 48 weeks after randomization, the primary study endpoint of treatment response was measured. A significantly higher percentage of patients successfully achieved a primary composite endpoint in the tenofovir group compared with the adefovir group (67% vs 12%, $P<.001$; Figure 1). When response endpoints were analyzed separately, there was no significant difference in the rate of histologic response between the two treatment groups (tenofovir: 74% vs adefovir: 68%, $P=NS$). However, there was a statistically significant improvement in the percentage of patients achieving HBV DNA levels <400 copies/mL in the tenofovir group compared with the adefovir group (76% vs 13%, respectively, $P<.001$; Figure 2). There was also a dramatic improvement in the number of individuals who exhibited undetectable HBV DNA levels after tenofovir therapy compared with adefovir treatment (69% vs 9%, respectively, $P<.001$).

Several secondary endpoints were also assessed after 48 weeks. Compared with adefovir, tenofovir treatment resulted in higher numbers of patients exhibiting ALT normalization (54% vs 69%, respectively, $P=.018$), loss of HBeAg (17.5% vs 22.2%, $P=NS$), and loss of HBsAg (0% vs 3.2%, respectively, $P=.018$). Additionally, though when compared with adefovir, tenofovir-treated patients had higher rates of HBeAg seroconversion (20.9% vs 17.5%, respectively, $P=NS$) and HBsAg seroconversion (1.3% vs 0%, respectively, $P=NS$), compared to adefovir, these differences were not statistically significant. A preliminary assessment revealed that no patients developed tenofovir-resistant mutations, even when including patients who exhibited a viral breakthrough while receiving tenofovir.

In both studies, a safety analysis revealed that the drugs had equal tolerability. No tenofovir-treated individual exhibited renal toxicity, measured as a 0.5 mg/dL increase in creatinine levels or a creatinine clearance of <50 mL. This was especially notable, given previous evi-

dence of nephrotoxicity induced by tenofovir.⁹⁻¹¹ In the second trial of HBeAg-positive patients, flares in ALT levels of either grade 3 or 4 in magnitude were more evident in tenofovir-receiving patients than in the adefovir group (19% vs 10%, respectively). These transient flares were associated with strong decreases in HBV DNA levels and occurred early in treatment (within the first 8 weeks).

Tenofovir displayed higher efficacy in CHB patients compared to adefovir using several response assessments, including improvements in histology and HBV DNA levels. Importantly, tenofovir was active in both HBeAg-positive and -negative patients, indicating that a wide number of CHB patients would benefit from this therapy. No tenofovir-resistant mutations emerged with tenofovir treatment, even in patients who had a viral breakthrough while on therapy. These results, taken together with the favorable safety profile of the drug, provide further evidence for the use of tenofovir to treat CHB. The long-term efficacy of tenofovir will continue to be assessed over a continued 5-year treatment period, and these data are expected at a later date.

83 First Multicenter Evaluation of the Efficacy of Tenofovir in Nucleos(t)ide Analog Experienced Patients with HBV Monoinfection¹²

F Van Bömmel, RA De Man, A Erhardt, D Hüppe, K Stein, P Buggisch, W Böcher, C Sarrazin, J Trojan, U Spengler, JG Reijnders, B Möller, HE Wasmuth, P Rohde, HH Feucht, B Wiedenmann, T Berg

The anti-HBV activity of tenofovir has been most extensively studied in patients co-infected with HIV and HBV.¹³⁻¹⁶ However, studies of single-agent tenofovir activity in HBV monoinfected patients are more limited.^{8,17} To further determine the activity of tenofovir in HBV monoinfected individuals, Van Bömmel and colleagues performed a retrospective study of tenofovir monotherapy.¹² This trial was distinct from previous studies in monoinfected patients, as it was the first multicenter evaluation focused on individuals with prior exposure to other antiviral agents, namely lamivudine and adefovir.

A total of 121 individuals participated in this study, and 101 patients were included in the final trial analysis. The average age was 45 years (range: 19–74 years), and 70 patients were HBeAg-positive. Beginning with a mean baseline HBV DNA level of 6.7 log₁₀ copies/mL, tenofovir therapy decreased HBV DNA levels by a mean of 3.8 log₁₀ copies/mL at 24 weeks and 4.1 log₁₀ copies/mL at 48 weeks. Importantly, 72% and 91% of patients at

Weeks 24 and 48, respectively, achieved undetectable HBV DNA levels. The average duration of tenofovir monotherapy was 14.8 months (range: 6–63 months).

Secondary treatment outcomes also showed that tenofovir was active in these treatment-experienced patients. One of the most dramatic responses occurred in ALT levels, which were elevated in 70% of patients at baseline and normalized in 78% of patients at Week 48 of therapy. HBeAg seroconversion occurred in 23%, after an average tenofovir duration of 9 months (range: 2–33 months). Additionally, 4% experienced a loss of HBsAg. Importantly, there was no evidence of resistance to tenofovir within this study, as no virologic rebound was reported.

The response induced by tenofovir was not significantly affected by most baseline parameters, including age, gender, HBeAg status, or presence of liver cirrhosis. Additionally, the presence of lamivudine resistance had no effect on response to tenofovir. However, the tenofovir-induced decrease in HBV DNA levels was significantly affected by the patient's baseline HBV DNA levels. Every patient with an HBV DNA level of <10⁷ copies/mL achieved undetectable levels at Month 12, whereas only 76% of those with >10⁷ copies/mL were undetectable at the same follow-up (*P* = .01).

No serious adverse effects were reported to be associated with tenofovir administration. According to the study investigators, the virologic activity of tenofovir in these patients is significant, as these antiviral-experienced individuals represent a difficult-to-treat patient population.

956 Adefovir Dipivoxil Plus Lamivudine Combination Treatment is Superior to Adefovir Dipivoxil Monotherapy in Lamivudine-Resistant Hepatitis B E Antigen-Negative Chronic Hepatitis B Patients¹⁸

T Vassiliadis, O Giouleme, G Koumerkeridis, C Koumaras, K Tziomalos, K Patsiaoura, A Mpoumponaris, D Gkissakis, K Theodoropoulos, N Grammatikos, A Panderi, N Nikolaidis, N Evgenidis

The NRTI adefovir has been shown to potently suppress both wild-type and lamivudine-resistant HBV in vitro, as well as in several clinical studies.¹⁹⁻²³ However, whether lamivudine therapy should be discontinued in these patients or continued with adefovir treatment is still a matter of debate. One study in HBeAg-negative CHB patients with lamivudine resistance concluded that combining the two agents was more efficacious

Table 2. Results in Both Groups at Median Follow-Up

	Overall (n=60)	ADV+LAM (n=45)	ADV (n=15)	P
Virologic response	47/60 (78.3%)	36/45 (80.0%)	11/15 (73.3%)	0.856
Time to virologic response (months)	8 (4–36)	8 (4–36)	8 (4–16)	0.259
Virological breakthrough	3/47 (6.4%)	0/36 (0.0%)	3/11 (27.3%)	0.011
Biochemical response	48/58 (82.8%)	40/44 (90.9%)	8/14 (57.1%)	0.012
Time to biochemical response (months)	6 (2–36)	6 (2–36)	7 (2–18)	0.888

ADM=adefovir; LAM=lamivudine.

Data adapted from Vassiliadis T, et al.¹⁸

than adefovir monotherapy and resulted in fewer cases of virologic breakthrough.²⁴ However, a second trial of HBsAg-positive lamivudine-resistant patients which compared adefovir monotherapy to adefovir plus lamivudine found similar viral responses in both treatment groups.²⁵ The average reduction in HBV DNA levels was similar between both groups ($-2.45 \log_{10}$ copies/mL vs $-2.46 \log_{10}$ copies/mL), and both were significantly superior to lamivudine monotherapy ($-0.07 \log_{10}$ copies/mL, $P<.001$). Here, Vassiliadis and colleagues aimed to determine whether lamivudine should be discontinued during adefovir therapy in lamivudine-resistant HBsAg-negative CHB patients.¹⁸ Additionally, the researchers evaluated the long-term activity of adefovir in these patients.

This prospective study randomized 60 patients to receive either 10 mg daily adefovir combined with continued 100 mg daily lamivudine (n=45) or 10 mg daily single-agent adefovir with discontinuation of lamivudine. All patients had previously displayed lamivudine resistance and had experienced a virologic breakthrough while on lamivudine for an average of 40 months.

Patient characteristics were evenly distributed between both treatment groups. The median patient age was 56 years (range: 22–74 years), and the vast majority of participants were men (90%). At baseline, the median HBV DNA level was 5.3 ± 10^6 copies/mL, and the median ALT level was 2.9 ± 3 ULN.

At a median follow-up of 41.5 months (range: 8–46 months), virologic response (defined as reduction in HBV DNA levels to <400 copies/mL) was observed in 78.3% of the total patient population (Table 2). When patients within each treatment group were analyzed separately, there was no significant difference in virologic response between either combination or monotherapy patients (80.0% vs 73.3%, respectively, $P=NS$). Additionally, the median time to virologic response was the same between both treatment groups (8 months for both, $P=NS$). However, a significantly greater percentage of patients receiving adefovir combined with lamivudine experienced a nor-

malization of ALT levels compared with those receiving adefovir only (90.9% vs 57.1%, respectively, $P=.012$).

Perhaps the most notable difference between the two treatment groups was the greater number of virologic breakthroughs in the monotherapy (n=3) group compared to the combination (n=0) group (27.3% vs 0.0%, respectively, $P=.011$). These virologic breakthroughs occurred at 12, 20, and 36 months of adefovir monotherapy after these patients had achieved virologic response at 4, 4, and 8 months, respectively. Interestingly, adefovir-resistant mutations were identified in 2 patients (4.4%) in the combination group and 5 patients in the monotherapy group (33.3%). The 2 identified patients with resistance mutations in the combination group were classified as suboptimal responders, and increasing the adefovir dose to 20 mg daily resulted in improved virologic response.

The study authors concluded that although both single-agent adefovir and adefovir combined with lamivudine produced similar rates of virologic response, combination therapy should be considered the treatment of choice. This assessment was based partly on the greater rate of biochemical response (ALT level normalization) evident in this treatment group. Additionally, despite the emergence of resistance mutations in these patients, none of the patients receiving combination therapy experienced virologic breakthrough, unlike the adefovir-only group.

542 A Prospective Study on the Safety and Efficacy of Lamivudine and Adefovir Dipivoxil Prophylaxis in HBsAg-Positive Liver Transplantation Candidates²⁶

E Gane, SI Strasser, S Patterson, GW McCaughan, PW Angus

In CHB patients, a major complication following liver transplantation is the recurrence of HBV. Currently, the standard prophylaxis therapy for HBsAg-positive liver

transplant candidates is a combination of lamivudine with high-dose intravenous HBV immunoglobulin (HBIG).²⁷⁻²⁹ However, this regimen is long-term, often occurring over the lifetime of the patient, and is therefore associated with a high therapeutic cost.³⁰ Recently, one group attempted to reduce the cost of this prophylactic regimen by testing the efficacy of low-dose HBIG.³¹ Although the low-dose administration was indeed successful at <10% of the cost of the high dose, widespread use of HBIG will remain limited in developing countries. Another strategy to reduce the cost of prophylaxis therapy is the use of combination antiviral regimens.^{32,33} Here, a study presented by Gane and colleagues sought to determine whether the combination of two antivirals, lamivudine and adefovir, could sufficiently prevent HBV recurrence in the absence of chronic HBIG administration.²⁶

This was a prospective multicenter study that administered open-label lamivudine (100 mg daily) plus adefovir (10 mg daily) to study participants, who received HBIG (800 IU daily) for only the first week following liver transplantation. A total of 26 adult HBsAg-positive patients who were candidates for liver transplantation were enrolled. All patients had end-stage cirrhosis, and 16 (62%) had HCC. Previous lamivudine exposure was allowed only if patients had not displayed clinical or virologic resistance. Only HBV monoinfected patients were enrolled in the study. At the time of this assessment, 19 patients had undergone liver transplant, whereas 1 remained on the waiting list and 6 were removed from it. Pretransplant antiviral prophylaxis occurred for a median duration of 3.6 months (range: 0–17 months). The baseline (pretreatment) median level of HBV DNA was $3.3 \log_{10}$ IU/mL, and 81% of patients had detectable levels of HBV DNA. HBeAg-positive status was reported in 41% of the candidates.

Pretransplant antiviral administration resulted in viral suppression in some patients. At the time of liver transplant, 50% of the patients had detectable HBV DNA levels (median level: $2.6 \log_{10}$ IU/mL). Importantly, none of the candidates displayed genotypic resistance to either lamivudine or adefovir.

At the time of this report, none of the 19 transplant recipients experienced a recurrence of HBV (median follow-up: 11.7 months; range: 1–40 months). The primary study endpoint was recurrence of HBsAg. HBV recurrence was also assessed by detection of HBV DNA levels. Except for an increase in serum creatinine levels from the baseline of 38 mmol/L, no other treatment-related adverse events were observed.

The authors concluded that the combination of lamivudine and adefovir was a safe and effective prophylactic alternative to the current standard of lamivu-

dine plus HBIG for prevention of HBV recurrence following liver transplantation. This regimen may provide a more cost-effective and convenient choice, leading to increased patient compliance and continued suppression of HBV reemergence.

951 Entecavir: A Rescue Therapy for Chronic Hepatitis B Patients With a Limited Virological Response to Adefovir?³⁴

JG Reijnders, RA De Man, SD Pas, M Schutten, HL Janssen

Entecavir is currently an approved anti-HBV therapy with low rates of drug-induced resistance and potent activity against the virus.^{35,36} In cell culture, entecavir is 100 times more potent than lamivudine and adefovir against HBV.³⁷ This high potency is attributed to the unique mechanism of action of entecavir against HBV,³⁸ which acts by inhibiting the HBV polymerase in three ways: inhibition of the protein-linked priming activity of the enzyme, inhibition of first-strand DNA synthesis activity, and inhibition of second-strand DNA synthesis activity.³⁹ Because of the high activity of entecavir against HBV, entecavir is under investigation for the treatment of patients with resistance to other antiviral agents.^{40,41} One study in patients with lamivudine resistance showed that switching to entecavir produced higher rates of histologic improvement compared with continued lamivudine therapy (55% vs 28%, respectively, $P < .0001$).⁴² An in vitro study of adefovir-resistant HBV found that the virus remained susceptible to entecavir in culture.⁴³ However, there are limited examples of clinical studies evaluating entecavir in the setting of adefovir resistance. In the present study, Reijnders and colleagues describe a small study that tests the efficacy of switching from adefovir to entecavir in CHB patients after they show little response to adefovir.³⁴

This study included 12 patients exhibiting a limited response to adefovir, defined as having HBV DNA levels $>5 \log_{10}$ copies/mL after exposure to 48 weeks of adefovir. The median age of these patients was 44 years (range: 23–73 years), and the majority were men ($n=9$). All but 1 patient were HBeAg-positive, and 3 were classified as cirrhotic. At baseline, the median HBV DNA level was $7.7 \log_{10}$ copies/mL. Half of the participants had previously displayed resistance to lamivudine. Lamivudine-resistant mutations were detected in only 1 patient, and 3 patients exhibited adefovir-resistant mutations.

The median duration of adefovir treatment was 79 weeks (range: 49–135 weeks). Patients were assessed at baseline for both HBV DNA and ALT levels and were then directly switched from adefovir to entecavir (1 mg

daily), with no drug-free time between agents. Entecavir therapy continued for 24 weeks before re-assessment.

After 24 weeks of entecavir treatment, patients exhibited a median decrease in HBV DNA levels of $-3.7 \log_{10}$ copies/mL. Prior lamivudine resistance did not affect the magnitude of this decrease. No patient achieved undetectable levels of HBV DNA; in fact, 25% of patients had $>5 \log_{10}$ copies/mL, 42% had $3.1-5 \log_{10}$ copies/mL, and the remaining 33% had $\leq 3 \log_{10}$ copies/mL. Only 1 patient exhibited HBeAg seroconversion, which occurred at 12 weeks of entecavir treatment. Importantly, no entecavir-resistant mutations emerged after 24 weeks of treatment. However, the number of patients displaying lamivudine-resistant mutations increased to 2.

According to the study authors, switching patients with poor adefovir response to entecavir produced suboptimal virologic responses. Although patients did experience reductions in HBV DNA viral loads, no patient achieved undetectable HBV DNA levels, a goal of antiviral therapy. These suboptimal responses occurred in treatment-experienced patients regardless of whether they had displayed prior resistance to lamivudine or not. The reductions in HBV DNA levels observed in this study were less robust than previously observed in treatment-naïve individuals, where 83.7% of patients achieved undetectable HBV DNA levels after 24 weeks of treatment.⁴⁴ The authors assert that because HBV DNA levels were not fully suppressed, similar patients should be closely monitored for the emergence of entecavir-resistance mutations after 24 weeks.

938 Four-Year Entecavir Treatment in Nucleoside-Naïve HBeAg(+) Patients: Results From Studies ETV-022 and -901⁴⁵

S Han, T Chang, Y Chao, S Yoon, RG Gish, H Cheinquer, F Carrillho, H Zhang, H Brett-Smith, R Hindes

To evaluate the efficacy of entecavir as front-line therapy in HBeAg-positive CHB patients, a phase III double-blind trial was initiated. The ETV-022 study randomized 715 treatment-naïve individuals to receive either 0.5 mg daily entecavir or 100 mg daily lamivudine for a minimum of 52 weeks. An analysis after the first 48 weeks of therapy, using several parameters as read-outs of efficacy, revealed that entecavir was significantly more active against HBeAg-positive HBV compared to lamivudine.⁴⁶ First, histologic improvement occurred in 72% of the entecavir group compared with 62% of the lamivudine group ($P=.009$). Second, individuals receiving entecavir

compared with those receiving lamivudine were more likely to achieve undetectable HBV DNA levels (67% vs 36%, respectively, $P<.001$) and greater decreases in mean HBV DNA levels (6.9 vs $5.4 \log_{10}$ copies/mL, respectively, $P<.001$). After 52 weeks of randomized treatment, patients with virologic response were allowed to continue blinded therapy for up to 96 weeks, the results of which were recently reported.⁴⁷ Entecavir continued to produce superior responses to lamivudine in this continued assessment, as 74% of entecavir-treated patients and 37% of lamivudine-treated patients exhibited undetectable HBV DNA levels. Subsequent to the ETV-022 study, patients who had received entecavir as part of the study treatment were then allowed to rollover to the ETV-901 trial. The ETV-901 trial then continued to follow these patients who received a total of approximately 4 years of entecavir therapy. The long-term results of the ETV-901 rollover study were presented by Han and colleagues.⁴⁵

The entecavir treatment gap between the two studies was not allowed to exceed 35 days, and the dosage of entecavir was increased to 1 mg daily after rollover. Rollover was permitted for all entecavir-receiving patients from the ETV-022 study, regardless of response to entecavir. A total of 146 patients received the long-term entecavir therapy, and the median follow-up of these patients occurred at 192 weeks.

A large number of these patients (91%) exhibited undetectable HBV DNA levels at the 192-week assessment period. Similarly, most patients (86%) also had normalization of ALT levels. Importantly, 41% of patients showed loss of HBeAg and 16% experienced HBeAg seroconversion, both of which occurred in the rollover study.

Throughout both studies, the safety profile of entecavir remained consistently tolerable, with comparable toxicity to lamivudine. In the 96-week analysis of the ETV-022 study, no patient was observed to develop entecavir resistance, measured by the lack of virologic breakthrough while on therapy.⁴⁷ The observed efficacy of entecavir in HBeAg-positive CHB patients through these two studies provides clear evidence for its use as a long-term front-line therapy.

994 Baseline Parameters Predict Both Early Virologic Response and Longer Term Outcomes for Telbivudine-Treated Patients with Chronic Hepatitis B (The GLOBE Study)⁴⁸

S Zeuzem, M Buti, EJ Gane, Y Liaw, AM Di Bisceglie, E Heathcote, NV Naoumov, J Rasenack, S Lim, J Hou, X Qiao, K Galil

995 On-Treatment Virologic Suppression at Week 24 Decreases the Risk of Histologic Progression at 1 Year; Data from the GLOBE Trial⁴⁹

Y Benhamou, AM Di Bisceglie, ZD Goodman, P Lampertico, MP Manns, P Vig, X Qiao, K Galil

Telbivudine is a highly active NRTI that has shown superior efficacy compared with lamivudine against HBV.⁵⁰ It has recently received approval as an anti-HBV antiviral drug.⁵¹ The positive activity of telbivudine in the GLOBE trial was a key factor in determining its approval. The GLOBE trial was a 2-year, phase III, double-blind study that randomized 1,370 HBeAg-positive and -negative patients to receive either 600 mg daily telbivudine or 100 mg daily lamivudine.⁵² After 1 year of therapy, a significantly higher proportion of HBeAg-positive patients in the telbivudine group compared with the lamivudine group experienced therapeutic response (75.3% vs 67.0%, respectively, $P=.005$), defined as a reduction in HBV DNA levels to $<5 \log_{10}$ copies/mL combined with a loss of HBeAg or ALT normalization. Response to telbivudine was not limited to HBeAg-positive patients, as it produced superior reductions in the mean HBV DNA copies/mL from baseline. Here, two retrospective analyses of the GLOBE trial are presented. In the first, authored by Zeuzem and colleagues, baseline parameters are identified that can predict response to telbivudine.⁴⁸ In the second, presented by Benhamou and associates, initial virologic suppression induced by telbivudine decreased the risk of later histologic progression.⁴⁹

In the first analysis, Zeuzem and colleagues used both univariate and multivariate regression analyses to evaluate the influence of certain baseline parameters on response to telbivudine after 2 years (104 weeks).⁴⁸ Baseline HBV DNA levels of $<9 \log_{10}$ copies/mL and ALT levels of ≥ 2 3 ULN were found to significantly predict risk of viral breakthrough at Week 104. In the subset of telbivudine-treated HBeAg-positive patients with these specific baseline characteristics, 47% experienced HBeAg seroconversion whereas 14% experienced viral breakthrough, compared to 30% and 29%, respectively, of all HBeAg-positive patients, regardless of baseline characteristics. Additionally, 71% of this patient subset achieved undetectable levels of HBV DNA after 24 weeks of treatment compared to only 44% of the total population of HBeAg-positive individuals.

Baseline HBV DNA levels of $<7 \log_{10}$ copies/mL in conjunction with elevated ALT levels also had similar predictive effects in HBeAg-negative patients. However, their effect on virologic response was less pronounced,

due to higher rates of viral clearance in the HBeAg-negative group in both arms.

Multivariate analysis revealed that viral load at Week 24 was the most significant predictor of therapeutic outcome at Week 104. In the previously described baseline subset of patients, patients with undetectable HBV DNA levels at Week 24 had a 52% rate of HBeAg seroconversion at 104 weeks, accompanied by a 3.6% risk of virologic breakthrough.

Zeuzem and associates concluded that by identifying patient characteristics that could predict outcome to telbivudine, patients may be more effectively managed while receiving telbivudine therapy.

In the second retrospective analysis by Benhamou and colleagues, on-treatment predictors of liver disease progression were identified.⁴⁹ For this study, patients with progressive liver disease at Week 52 were defined as having either an increase of ≥ 1 point in the Ishak fibrosis score or a ≥ 2 point increase in the Knodell necroinflammatory score. Parameters from both baseline and Week 24 data were used to predict histologic progression.

Both the Ishak fibrosis score and the Knodell necroinflammatory score were the only baseline parameters found to significantly predict progression, with an odds ratio of 5.0 and 2.7, respectively ($P<.0001$ for both). The authors found that lower scores were more likely to be predictive of liver disease progression compared with higher scores, and they attributed this difference to the increased likelihood of higher scoring patients responding better to antiviral therapy.

The only on-treatment parameter found to significantly predict liver disease progression was failure to achieve a decline in HBV DNA levels of $>5 \log_{10}$ copies/mL from baseline to Week 24 ($P=.0058$). This was associated with a 57% increased risk of liver disease progression at Week 52.

As liver disease progression was found to be significantly impacted by the magnitude of HBV DNA decline on therapy, the authors suggested that the most potent available antiviral should be used to limit the risk of liver disease progression.

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Commentary

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The growing armamentarium of nucleos(t)ide therapies for chronic hepatitis B, along with steadily accumulating data on strategies for their administration, are allowing for more effective control of disease and, ultimately, better outcomes in our patients. Studies presented at the 2007 AASLD meeting provided information on the potency of novel agents, approaches to therapy in patients who have lost response, and the achievement of meaningful endpoints of therapy, all of which will significantly affect future patient treatment.

The registration studies of tenofovir in HBeAg positive and negative patients by Drs. Marcellin, Heathcote, and associates represent important advances as they are from controlled, blinded, phase III trials with an active comparator that is the current standard of care. The results are remarkable for the huge difference in potency of viral suppression between tenofovir and adefovir, as well as for the lack of impact that this difference in potency has on clinical endpoints of e antigen seroconversion and histologic improvement in the short-term. This is not to say that the increased viral suppression of tenofovir will not ultimately provide greater benefit in the long run. Over time, this may prove to be the case. In addition, the phenomenon of tenofovir patients experiencing hepatitis B surface antigen seroconversion has not been reported in short-term studies of other oral antiviral agents.

Ongoing advances in the potency and resistance profiles of antiviral agents for CHB treatment will encourage a trend toward treatment of patients with higher viral loads earlier in their disease course. However, it is difficult to extrapolate the effect of lifelong therapy from the 5 years of data that could be accrued from a typical study. A patient started on therapy at age 20 is going to need 50 years of therapy, unless they achieve surface antigen loss/seroconversion. Unless the specific endpoint of therapy changes, the starting point for administration of medical therapies will continue to evolve and require case-by-case determination. Further, all of the nucleos(t)ide agents require further study in immune tolerant patients, where we may find lower rates of efficacy and higher

rates of resistance development. The National Institutes of Health is planning a long-term study to determine the histologic benefit and other effects of combination therapy. It is hoped that this study will encompass the treatment of immune tolerant patients as well. It is only through study of treatment in the immune tolerant phase that the question of when to commence therapy will be answered for the majority of our patients.

The outcome of the study of tenofovir by Van Bommel and associates was not particularly surprising, as most of the patients were lamivudine-experienced and it has already been documented that adefovir is equally potent in lamivudine-resistant and lamivudine-naïve patients. Tenofovir would, logically, evince the same efficacy. Despite the high rate of efficacy of tenofovir monotherapy in this study, given the current available data, both adefovir-resistant and lamivudine-resistant patients should receive add-on *combination* therapy, not monotherapy.

Evidence of the benefit of adding on therapy instead of switching in resistant patients is provided by Vassiliadis and associates. These findings confirm those of an earlier study by Lampertico in lamivudine-resistant patients. For patients with lamivudine resistance, combination therapy with lamivudine and, in this study, adefovir, is superior to adefovir monotherapy and the combination-therapy approach for resistant patients should be considered in clinical practice, as a replacement for sequential monotherapy. It is nice to see a second study validating what is currently promoted by many experts as a valid option.

In the transplant setting, it has long been understood that use of HBIG plus lamivudine, with or without adefovir, is very effective in preventing post-transplant recurrence of HBV infection. The problem with this regimen is that HBIG is very expensive and has a number of side effects. Earlier attempts to eliminate HBIG and to prevent recurrence with lamivudine monotherapy, were unsuccessful. More recent trials have attempted to use a short course of HBIG with lamivudine or to use combination nucleos(t)ide therapy. The study by Angus and colleagues was an open-label, pilot study, where patients received lamivudine plus adefovir, with a very short, 7-day course of HBIG. Of the 19 patients who completed the study, none had HBV recurrence at 1-year follow-up and the authors concluded that this method of prophylaxis after liver transplant is safe and effective.

It should, however, be noted that none of the patients in this study had resistance to lamivudine or adefovir, a variable which may be difficult to determine in some patients, particularly those who are lamivudine experienced. As time goes by and more potent agents are available, the proportion of patients with prior lamivudine exposure will decrease. However, the patients who

decompensate and require transplant are generally not those taking more potent agents. They are often patients who experience breakthrough on lamivudine or have been partially noncompliant and developed resistance. Further, in this study, mean follow-up was less than a year and some of the patients were only followed for a month. Before recommending elimination of HBIG from the prophylaxis regimen, I would need to see longer-term data in a larger cohort. However, for patients who cannot afford HBIG or have other issues with its administration, these data offer the likelihood that combination therapy will be reasonably effective in controlling disease.

The study by Reijnders and associates highlights the observation that nucleosides tend to retain activity in nucleotide-resistant patients but with generally suboptimal responses. This again highlights the need for add-on combination therapy in patients who have documented resistance or suboptimal response, rather than sequential monotherapy. For patients who have inadequate response to a nucleoside or a nucleotide, an agent of the other class should be added, not substituted.

The entecavir study ETV-022 with the rollover treatment study ETV-901 followed patients who were maintained on entecavir for up to 4 years. The treatment was associated with a very low resistance rate. The use of an increased entecavir dose (1 mg/day) during the variable period (2-3 years) of the maintenance phase may or may not have affected overall outcomes. What is equally important to note is that the high rate of HBV negativity among these patients did not markedly improve clinical outcomes. The rate of seroconversion is no different from what was seen in prior longterm study of adefovir, despite a higher rate of HBV DNA negativity.

Over its initial 2 years of study, telbivudine has proven itself to be a potent antiviral agent but one marked by unacceptably high rates of resistance development in the overall cohort. In an attempt to better define subgroups of patients in whom telbivudine is a reasonable option for therapy, the GLOBE investigators have conducted subanalyses to refine the agent's administration in specific groups of patients. Most of these substudies have

focused on achieving HBV DNA negativity by week 24 of therapy.

The study by Zeuzem and colleagues selected patients with favorable (low) baseline viral loads and higher ALT levels and showed that these are the patients who are most likely to rapidly (within 24 weeks) achieve HBV DNA negativity on telbivudine. However, these are predictors of response among all HBV therapies including the other available antivirals and interferon. I disagree with the authors' conclusion that the magnitude of HBV decline predicts liver disease progression. Looking back at the previously discussed studies of tenofovir and adefovir, we see that histologic improvement is similar in agents with substantial differences in the rate of complete viral suppression. I believe that a high rate of viral negativity is necessary but more important is a low rate of resistance in order to preserve therapeutic options in the long run.

Based on this profile, telbivudine may ultimately prove useful as an agent for use in combination therapy. The fact that it allows patients to achieve negativity very rapidly may prove an advantage in patients who are critically ill, those who are pregnant, or those requiring chemotherapy prophylaxis. These studies give clinicians a guide in terms of how to best use telbivudine in these scenarios but do not provide compelling evidence to expand its use as a first-line agent.

Suggested Reading

Keeffe EB, Dieterich DT, Pawlotsky JM, Benhamou Y. Chronic hepatitis B: preventing, detecting, and managing viral resistance. *Clin Gastroenterol Hepatol*. 2008;6:268-274.

Lampertico P, Vigano M, Manenti E, Iavarone M, Sablon E, Colombo M. Low resistance to adefovir combined with lamivudine: a 3-year study of 145 lamivudine-resistant hepatitis B patients. *Gastroenterology*. 2007;133:1445-1451.

Weisberg IS, Brown RS Jr, Sigal SH. Hepatitis B and end-stage liver disease. *Clin Liver Dis*. 2007;11:893-916.

Keeffe EB, Dieterich DT, Han SH, Jacobson IM, Martin P, et al. A treatment algorithm for the management of chronic hepatitis B virus infection in the United States: an update. *Clin Gastroenterol Hepatol*. 2006;4:936-962.

Schreiber IR, Schiff ER. Prevention and treatment of recurrent Hepatitis B after liver transplantation: the current role of nucleoside and nucleotide analogues. *Ann Clin Microbiol Antimicrob*. 2006;5:8.

Antiviral Therapy of Chronic Hepatitis B Infection

CME Post-Test: Circle the correct answer for each question below.

- Progression from phase 2 to phase 3 of CHB infection is marked by seroconversion of circulating _____ antigen to circulating _____ antibodies.
 - HBeAg; anti-HBe
 - HBsAg; anti-HBs
 - HBeAg; anti-HBc
 - HBsAg; anti-HBc
- In a study by Marcellin and colleagues, tenofovir was found to have higher activity in CHB-infected patients compared with _____ in HBeAg-negative patients.
 - entecavir
 - lamivudine
 - adefovir
 - telbivudine
- In a similar study presented by Heathcote and fellow investigators, _____ of tenofovir-treated HBeAg-positive patients achieved HBV DNA levels <400 copies/mL compared to 13% with the control drug.
 - 54%
 - 68%
 - 74%
 - 76%
- In the first multicenter trial to investigate tenofovir activity in monoinfected CHB patients with previous antiviral exposure, ALT levels were normalized in _____ of patients by Week 48 of tenofovir therapy.
 - 76%
 - 78%
 - 80%
 - 90%
- A study presented by Vassiliadis and colleagues showed that ontreatment viral breakthrough occurred in _____ of patients receiving adefovir monotherapy and _____ of patients receiving adefovir combined with lamivudine, causing the investigators to conclude that the combination treatment should be used to prevent the emergence of resistance.
 - 27.3%; 0.0%
 - 0.0%; 27.3%
 - 4.4%; 33.3%
 - 90.0%; 57.1%
- The combination of lamivudine and _____ was found to be an effective prophylactic regimen for prevention of HBV recurrence in liver transplant recipients, as discussed in a study by Gane and colleagues.
 - entecavir
 - tenofovir
 - adefovir
 - telbivudine
- Switching to _____ therapy produced suboptimal virologic responses in patients who exhibited limited response to adefovir, as reported by Reijnders and colleagues.
 - tenofovir
 - entecavir
 - adefovir
 - lamivudine
- A long-term evaluation of entecavir therapy in nucleoside-naïve HBeAg-positive patients found that _____ had undetectable HBV DNA levels at a 192-week assessment.
 - 16%
 - 50%
 - 86%
 - 91%
- A multivariate analysis presented by Zeuzem and fellow investigators found that _____ was the most significant predictor of therapeutic outcome at Week 104.
 - viral load at Week 12
 - viral load at Week 24
 - baseline HBV DNA levels
 - baseline ALT levels
- A retrospective analysis by Benhamou and colleagues found that patients who failed to achieve a decline in HBV DNA levels of >5 log₁₀ copies/mL from baseline to Week 24 of telbivudine treatment had a _____ increased risk of liver disease progression by Week 52.
 - 12%
 - 35%
 - 42%
 - 57%

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Antiviral Therapy of Chronic Hepatitis B Infection

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1. Please rate how effectively you are able to:

- | | | | | | |
|--|---|---|---|---|---|
| a. Discuss the latest data regarding the use of both established and novel nucleos(t)ide agents in the treatment of chronic hepatitis B. | 1 | 2 | 3 | 4 | 5 |
| b. Describe future endpoints of hepatitis B therapy. | 1 | 2 | 3 | 4 | 5 |
| c. Summarize the emerging role of nucleos(t)ide agents in the treatment of post-transplant hepatitis B patients. | 1 | 2 | 3 | 4 | 5 |

2. Activity/Topic:

- | | | | | | |
|--|---|---|---|---|---|
| a. The extent this program met your continuing professional development goals | 1 | 2 | 3 | 4 | 5 |
| b. The overall quality of the activity | 1 | 2 | 3 | 4 | 5 |
| c. The overall format of the activity | 1 | 2 | 3 | 4 | 5 |
| d. The applicability/usefulness of the material to your practice Not in practice ☐ | 1 | 2 | 3 | 4 | 5 |

3. Based on your previous knowledge and experience, this activity was:

Too basic ☐ Appropriate ☐ Too complex ☐

4. Do you feel that the activity was objective, balanced, and free of commercial bias? Yes No

If no, why? _____

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6. Please list any speakers and/or topics you would like in future programs.

7. Would a periodic review of this or related material be appropriate? Yes No

8. We welcome your comments _____



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