

## Current and Emerging Therapies for Chronic Hepatitis B

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A Review of Selected Presentations From  
the 2010 Meeting of the European Association  
for the Study of the Liver  
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# Current and Emerging Therapies for Chronic Hepatitis B

The following summary highlights important advances in the treatment of chronic hepatitis B as announced at the European Association for the Study of Liver meeting. This report focuses on long-term follow-up of patients on first-line hepatitis B therapies as well as the outcomes in expanded patient populations.

## 8 Early Prediction of Sustained Response to Peginterferon Alfa-2a in HBeAg-negative Patients

V Rijckborst, BE Hansen, Y Cakaloglu, et al

The majority of hepatitis B e antigen (HBeAg)-negative patients do not attain sustained virologic responses to peginterferon-based treatment. Therefore, it would be useful to be able to identify early those patients who are most likely, or least likely, to benefit from peginterferon. To investigate factors associated with responses to peginterferon, Rijckborst and colleagues<sup>1</sup> assessed hepatitis B surface antigen (HBsAg) and hepatitis B virus (HBV) DNA levels before and during peginterferon-based treatment and correlated them with likelihood of sustained response. The analysis included 107 patients enrolled in an international, multicenter clinical trial who received peginterferon alfa-2a (180 µg weekly) as monotherapy (n=53) or in combination with ribavirin (n=54). There was no significant difference in sustained response rate with monotherapy versus combination therapy (26% vs 19%;  $P=.33$ ). The investigators subsequently conducted a pooled analysis comparing parameters in the 24 patients who attained a sustained response and the 83 patients who did not.

Although there were no significant differences between the groups at baseline, serum HBsAg levels began to decrease substantially at week 8 in only the patients who attained a sustained response. Despite this trend, changes

in HBsAg levels alone were not a strong predictor of sustained response. However, a combination of reductions in HBsAg level and declines in HBV DNA level by week 12 was a better predictor of sustained response. Of the 20 patients who had no decline in serum HBsAg levels and who did not attain an HBV DNA reduction of greater than or equal to  $2 \log_{10}$  copies/mL, none attained a sustained response. Conversely, of the 28 patients with both a decline in serum HBsAg levels and an HBV reduction of greater than or equal to  $2 \log_{10}$  copies/mL, 39% attained a sustained response. The predictive value of these assessments did not improve significantly at week 24 versus week 12. The investigators concluded that this combination of change in HBsAg level and change in HBV DNA level from baseline to week 12 provides a stopping rule for patients with HBeAg-negative chronic hepatitis B (CHB) receiving peginterferon-based therapy.

## 28 Emtricitabine/TDF With or Without HBIG After Orthotopic Liver Transplantation

L Teperman, J Spivey, F Poordad, et al

Study 107 is a randomized trial evaluating fixed-dose emtricitabine (FTC)/tenofovir disoproxil fumarate (TDF) with or without hepatitis B immune globulin (HBIG) for the prevention of hepatitis B recurrence in patients undergoing orthotopic liver transplantation (OLT).<sup>2</sup> The trial enrolled 40 patients with CHB who had undergone OLT and had received at least 12 weeks of prophylactic therapy, including HBIG, after transplantation. Patients had no evidence of CHB recurrence after transplant and had not received TDF or FTC/TDF after transplant. Creatinine clearance of at least 40 mL/min and adequate organ function were required for entry, and coinfection with hepatitis C, hepatitis D, or HIV was not allowed. All patients received FTC/TDF and HBIG for 24 weeks, and

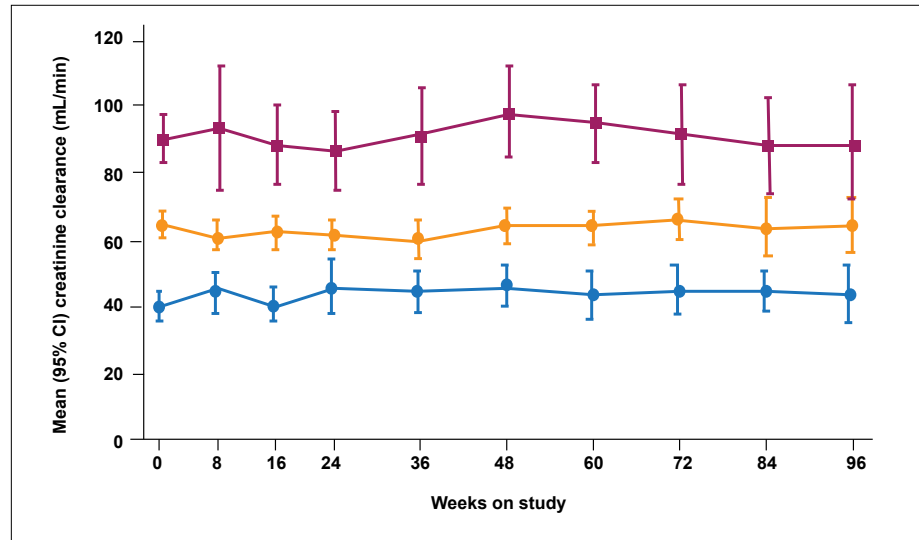
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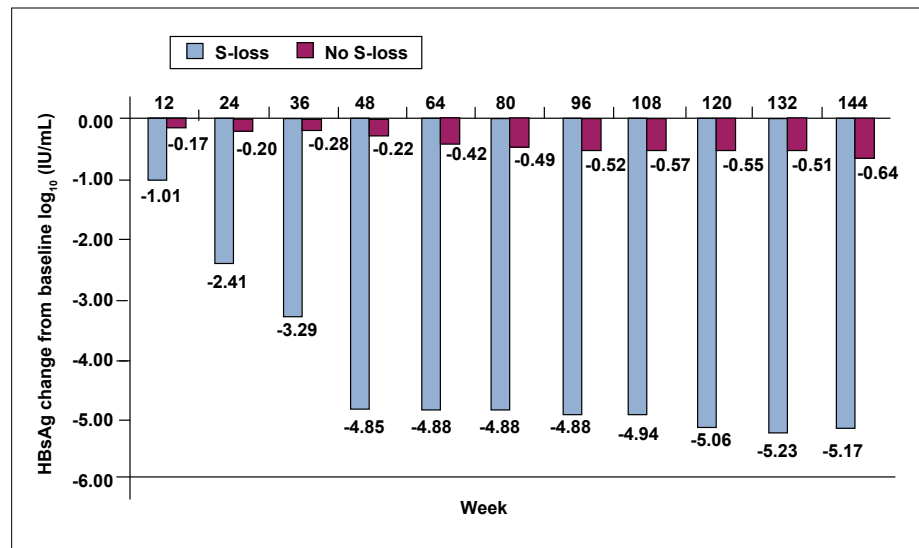
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**Figure 1.** Creatinine clearance over time in patients receiving TDF/FTC with or without HBIG for prevention of hepatitis B recurrence after orthotopic liver transplantation.

FTC=emtricitabine; HBIG=hepatitis B immune globulin; TDF=tenofovir disoproxil fumarate



**Figure 2.** Median decline in hepatitis B surface antigen (HBsAg) according to week 144 HBsAg seroconversion status.



then were randomly assigned to switch to FTC/TDF alone (n=18) or to continue FTC/TDF plus HBIG (n=19) for an additional 72 weeks—a total treatment period of 2 years.

A safety analysis in the 40 enrolled patients revealed no serious or grade 3/4 adverse events considered related to FTC/TDF. Two grade 2–4 adverse events that were considered related to FTC/TDF included 1 patient with a moderate increase in creatinine level/decrease in creatinine clearance and 1 patient with moderate ulcerative colitis. Three patients stopped treatment during the first 24 weeks of therapy: 1 patient discontinued due to an increase in alanine aminotransferase/aspartate aminotransferase (ALT/AST), 1 discontinued due to worsening colitis, and 1 patient died from a stroke.

Serum creatinine and creatinine clearance remained stable; creatinine clearance less than 50 mL/min occurred in 4 of 24 patients (17%) with a baseline

creatinine clearance of 50–80 mL/min (Figure 1). The most common grade 3/4 laboratory abnormalities were hyperglycemia (8%), glycosuria (8%), hypernatremia (5%), leucopenia (5%), hyperbilirubinemia (5%), and creatinine kinase (3%).

Efficacy outcomes were evaluated in 14 patients in the FTC/TDF plus HBIG arm and 12 patients in the FTC/TDF arm at week 72, and in 10 patients in each arm at week 96. No cases of detectable HBV DNA ( $\geq 169$  copies/mL) or HBsAg positivity were detected.

### 1006 Kinetics of HBsAg Loss Following 3 Years of TDF

E Gane, EJ Heathcote, P Marcellin, et al

Gane and colleagues<sup>3</sup> evaluated the kinetics of HBsAg decay in HBeAg-positive patients from Study 103 and studied factors associated with HBsAg loss. Kinetic

analysis showed that in patients who attained an HBsAg loss, HBsAg levels declined rapidly in the first 48 weeks of TDF treatment. The median decline in HBsAg in these patients at weeks 12, 24, and 48 was -1.01, -2.41, and -4.85 log<sub>10</sub> IU/mL, respectively. Median HBsAg decline at the same time points in patients not attaining HBsAg loss was -0.17, -0.20, and -0.28 log<sub>10</sub> IU/mL, respectively (Figure 2).

Several demographic factors and disease characteristics were significantly associated with HBsAg loss. Patients with HBsAg loss had a significantly higher median baseline HBsAg level than those not attaining HBsAg loss (5.11 vs 4.50 log<sub>10</sub> IU/mL;  $P < .001$ ) and were more likely to have a baseline HBsAg of 4.5 log<sub>10</sub> IU/mL or higher (100% vs 48%).

Genotype also was a significant predictor of HBsAg loss ( $P < .001$ ). Genotype A/D was present in 12 of 13 evaluated patients with HBsAg loss versus 82 of 158 patients without HBsAg loss. Baseline median HBV DNA was also significantly higher in patients with HBsAg loss ( $P = .003$ ), as was median ALT ( $P = .043$ ). Finally, there was a trend toward a higher rate of HBsAg loss with a higher baseline Knodell necroinflammatory score. Overall, HBsAg loss was attained by year 3 in 14% of patients with a baseline HBsAg of 4.5 log<sub>10</sub> IU/mL or higher, 13% of patients with genotype A or D, 16% of patients with an HBV DNA of greater than or equal to 9 log<sub>10</sub> copies/mL, and 10% of patients with a Knodell necroinflammatory score of 9 or higher.

### 1009 Entecavir for Nucleos(t)ide-naïve, HBeAg-negative, Chronic Hepatitis B Patients

P Lampertico, M Viganò, F Facchetti, et al

Lampertico and colleagues presented results from a 2-year multicenter cohort study evaluating the effectiveness of entecavir (ETV) in nucleos(t)ide-naïve patients with HBeAg-negative CHB in a clinical practice setting.<sup>4</sup>

A total of 311 patients consecutively enrolled from 17 treatment centers in Italy received ETV 0.5 mg for a mean treatment period of 23 months (range, 8–28 months). The mean age was 58 years, 75% of patients were male, cirrhosis was present in 50%, mean HBV DNA level was 5.7 log<sub>10</sub> IU/mL, and mean ALT was 86 U/L.

ETV was highly effective in these patients, with 94% of patients attaining undetectable HBV DNA (<12 IU/mL). Virologic response rates were 91% at week 48 and 97% at week 96. Only 2 patients (0.6%) had primary nonresponse at week 12. Viral breakthrough was detected in 3 patients (1%) between months 12 and 15, 2 of whom had suboptimal adherence to treatment. Serum from 2 patients was evaluated for ETV resistance, though

no resistance was detected. At week 48, 19 patients (6%) had a partial virologic response; the median HBV DNA level in these patients was 2.8 log<sub>10</sub> IU/mL (range, 1.1–5.5 log<sub>10</sub> U/mL). The investigators concluded that these patients may require rescue therapy.

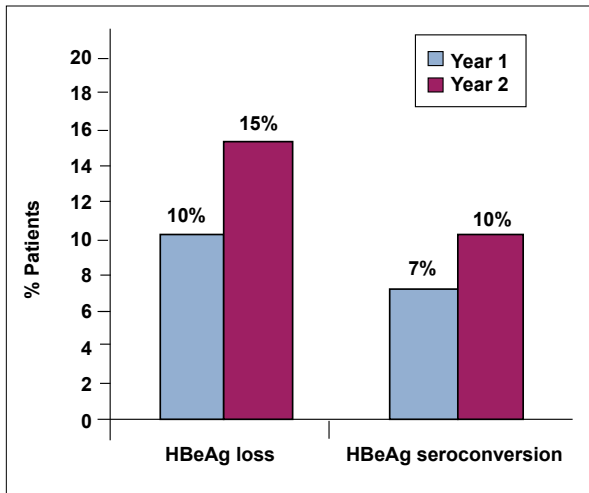
The week 48 partial virologic response rate was significantly higher in patients with a baseline HBV DNA greater than 6 log<sub>10</sub> IU versus less than or equal to 6 log<sub>10</sub> IU (12% vs 2%;  $P < .001$ ). By week 96, ALT levels were within the normal range in 86% of patients. Two patients (0.6%) attained HBsAg clearance and developed protective anti-HBs antibodies, enabling successful treatment cessation. In 58 evaluated patients, only 9% attained a median HBsAg level reduction of at least 0.5 log IU. Five patients with cirrhosis developed hepatocellular carcinoma (HCC) during therapy and 6 patients underwent liver transplantation for existing HCC. Six patients died from liver-related events.

### 1010 Safety and Efficacy of TDF in Patients With Suboptimal Response to ADV or ADV/LAM

M Levrero, L Cimino, P Lampertico, et al

Levrero and colleagues presented results from the OptiB trial, a multicenter, prospective, open-label study evaluating the safety and efficacy of TDF in patients with CHB monoinfection with suboptimal responses to adefovir (ADV) or ADV/lamivudine (LAM).<sup>5</sup> A total of 85 patients were switched from ADV to TDF 300 mg daily as monotherapy (n=13) or in combination with LAM (n=72). The median patient age was 54.8 years (range, 21–75 years), 82.4% were male, and 41.2% were HBeAg-positive. Patients had received ADV for a median of 29.2 months. The baseline median HBV DNA level was 5.7 log<sub>10</sub> IU/mL (range, 2.31–7.3 log<sub>10</sub> IU/mL). Resistance mutations were present in 96% of patients at baseline, including 46.5% with resistance to ADV, 56.3% with resistance to LAM, 9.9% with the multidrug resistance mutation A181T, and 9.9% with ETV resistance mutations.

The efficacy analysis included 78 patients completing 24 weeks of therapy and 70 patients completing 48 weeks of therapy. The proportion of patients with HBV DNA less than 69 IU/mL was 59.6% at week 24 and 71.0% at week 48. HBV DNA less than 12 IU/mL was attained by 44.2% of patients by week 24 and by 51.6% by week 48. There was no correlation between virologic response and HBV genotype, the presence of LAM resistance at baseline, and HBeAg status. However, there was a trend toward lower virologic responses in patients with ADV resistance mutations. Nine patients discontinued treatment due to worsening of liver disease



**Figure 3.** Rates of hepatitis B e antigen (HBeAg) loss and seroconversion over time in HBeAg-positive patients receiving tenofovir disoproxil fumarate.

Combined data from HBeAg-positive patients (N=104) in Studies 103 and 106 (missing=failure).

(n=5), serious adverse events (n=5), lack of response (n=1), and virologic breakthrough (n=5). The investigators reported no clinically significant adverse events associated with TDF.

### 1017 Efficacy of TDF in Patients With Suboptimal Response to ADV

M Manns, J Heathcote, P Marcellin, et al

To evaluate the efficacy of TDF in patients with a suboptimal response to ADV, Manns and colleagues conducted a pooled analysis of 160 patients enrolled across 3 clinical studies, including Study 102 (in HBeAg-negative patients), Study 103 (in HBeAg-positive patients), and Study 106 (in ADV-refractory CHB).<sup>6</sup> The analysis included 160 patients with a suboptimal response to ADV, defined as 48 weeks of ADV exposure prior to entering Studies 102 and 103 with HBV DNA greater than or equal to 69 IU/mL ( $\geq 400$  copies/mL), or 24–96 weeks of ADV exposure in Study 106 with HBV DNA of greater than or equal to 172 IU/mL ( $\geq 1,000$  copies/mL). Prior LAM was allowed in Studies 102 and 106. Overall, 65% of patients were HBeAg-positive, 54% were Caucasian, and 34% were Asian. The mean HBV DNA level was 7.66  $\log_{10}$  copies/mL and the mean ALT was 122.4 U/L. Patients had received an average of 53 weeks of prior ADV (range, 20–131 weeks) and 23% had received prior LAM. ADV resistance was detected in 12 patients (7.5%) and LAM resistance was detected in 7 patients (4.4%).

At week 96 after initiating TDF, the majority of patients had attained viral suppression, including 10 of 12 (83%) with ADV resistance, 6 of 7 (86%) with LAM resistance, and 75% of patients without ADV or LAM resistance, in a missing/switch=failure analysis. At week 96, the mean ALT in these patient subgroups was 31 U/L, 25 U/mL, and 39 U/mL, respectively. Overall, the median HBV DNA level at week 96 was 29 IU/mL (169 copies/mL). Rates of HBeAg loss by years 1 and 2 were 10% and 15%, respectively. Rates of HBeAg seroconversion were 7% and 10%, respectively (Figure 3).

The investigators also noted an excellent safety profile with TDF in these patients. Serious adverse events considered to be related to TDF were reported in 2 patients (1.3%). Grade 3/4 laboratory abnormalities were reported in 13.8% of patients. No patients discontinued due to adverse events. Across the 3 studies, 34 patients receiving up to 96 weeks of TDF had HBV DNA greater than 400 copies/mL ( $>69$  IU/mL), though no TDF-associated resistance was detected in these patients.

### 1022 Development of TDF-Associated Resistance Mutations in Patients With Persistent Viremia

A Snow-Lampart, B Chappell, J Sorbel, K Borroto-Esoda, M Miller

To further characterize the development of TDF-associated mutations, Snow-Lampart and colleagues evaluated serum samples from patients in Studies 102 and 103 with detectable viremia after up to 144 weeks of treatment with TDF.<sup>7</sup> Studies 102 and 103 allowed patients with detectable viremia at week 52 to add FTC 200 mg to open-label TDF 300 mg. Overall, 51 of the 641 (8%) enrolled patients were eligible to add FTC; 17 (33%) patients remained on TDF monotherapy and 34 (67%) patients added FTC. The addition of FTC was not associated with greater virologic responses; HBV DNA of less than 400 copies/mL was attained by week 144 in 65% of patients receiving FTC and TDF and 71% of patients receiving TDF monotherapy.

Population sequencing analyses were performed on samples from all 17 patients with detectable viremia at week 144. Conserved site changes were observed in 1 patient each at rtR51K, rtG152E, rtA181T±rtL180M±rtM204V, rtR192H, and rtN236T±rtR274Q. Non-adherence was reported by 8 of the 17 patients. Clonal analysis was performed in 5 of the 17 patients with persistent viremia and no evidence of viral breakthrough; all were HBeAg-positive. One patient was found to be nonadherent. In the 4 treatment-adherent patients, the median baseline HBV DNA level was 9.84  $\log_{10}$  copies/mL and the median decline in HBV DNA from baseline was 6.1  $\log_{10}$  copies/mL. Clonal analysis showed 17 distinct

conserved site changes. One change, rtF183L, was observed in 2 patients; no other changes were detected in more than 1 patient. However, the presence of rtF183L had no effect on phenotypic susceptibility to TDF in vitro. The investigators concluded that persistent viremia was rare in patients adhering to TDF (0.6%) and was not associated with demonstrable virologic resistance to TDF.

### 1028 Renal Safety and Antiviral Efficacy of TDF in Nucleos(t)ide Analogue-refractory Patients With Hepatitis B Virus Mono-infection

F van Bömmel, RA De Man, P Ferenci, et al

Another analysis of the efficacy and safety of TDF in patients with previous failure on nucleos(t)ide analogs was conducted by van Bömmel and colleagues, who retrospectively analyzed outcomes in all HBV-mono-infected patients who had received TDF in 19 centers in Europe.<sup>8</sup> The analysis was limited to patients who were at least 18 years of age, had HBV DNA of greater than or equal to 10,000 copies/mL, and had received TDF for at least 6 months. To assess renal effects of TDF, the investigators compared mean changes in glomerular filtration rate (eGFR, estimated by Cockcroft-Gault formula) in the evaluated patients versus 89 age-matched asymptomatic HBsAg carriers.

Of the 195 eligible patients evaluated, 75% were male; the mean age was 45 years (range, 18–76 years), 70% were HBeAg-positive, and the mean HBV DNA level was 6.9 log<sub>10</sub> copies/mL (range, 4–10 log<sub>10</sub> copies/mL). Patients had received TDF 300 mg/day for an average of 30 months (range, 6–90 months). Overall, 90% of patients achieved HBV DNA suppression to less than 400 copies/mL, with an estimated 92% achieving viral suppression by 24 months. Although renal function was similar between the patients and the control group at baseline (mean eGFR 114 ± 26 and 102 ± 36 mL/min, respectively), eGFR had decreased significantly more in the TDF-treated patients versus the control patients by month 48 (-16 ± 36 vs -9.6 ± 36 mL/min; *P* = .03). Renal effects did result in a TDF dose reduction after 15 months in 1 patient whose creatinine level rose from 0.8 mg/dL to 1.18 mg/dL.

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8. van Bömmel F, De Man RA, Ferenci P, et al. Renal safety and antiviral efficacy of tenofovir disoproxil fumarate (TDF) monotherapy in nucleos(t)ide analogue refractory patients with hepatitis B virus (HBV) mono-infection. Presented at the 45th Annual Meeting of the European Association for the Study of the Liver; April 14-18, 2010; Vienna, Austria. Abstract 1028.

## Commentary

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This year's European Association of the Study of Liver Disease (EASL) meeting brought new prognostic information and longer-term follow-up of patients on our first-line hepatitis B therapies (pegylated interferon, tenofovir [TDF], entecavir [ETV]) as well as information on treatment outcomes in broader patient populations. In the absence of new therapeutics, research focused on broadening the group of patients that could be studied and novel ways to follow patients on therapy, including early predictors of response. The early predictors of response have largely focused on the use of quantitative hepatitis B surface antigen (HBsAg) levels as these closely reflect the

amount of covalently closed circular DNA (cccDNA) in the liver. The early decline of HBsAg, particularly when accompanied by a decline in HBV DNA levels, is predictive of a sustained response to pegylated interferon in HBe-antigen-negative patients and has also been shown to predict surface antigen loss with TDF therapy. Drops in quantitative surface antigen are more predictive than the decline in HBV DNA, particularly with the oral antivirals, which decrease HBV DNA in the vast majority of patients but have a much lower rate of HBeAg and HBsAg seroconversion. This is due to a potent inhibition of the HBV polymerase, with only a modest effect on the levels of intrahepatic cccDNA. Loss of cccDNA is critical for immune control of HBV, and is required for loss of surface antigen or sustained response in e-negative patients. Declines in HBsAg reflect lower levels of cccDNA and clearance of HBV-infected hepatocytes.

Additional information from EASL included expanding the treatment experience of patients with hepatitis B therapy. This included a study of TDF plus emtricitabine alone versus triple combination with emtricitabine, TDF, and hepatitis B immune globulin (HBIG) to prevent recurrent hepatitis B virus (HBV) following liver transplantation. Long-term HBIG has been a mainstay to prevent recurrence of hepatitis B after transplant, and remains the standard of care in combination with nucleos(t)ides monotherapy or in triple combination therapy. The higher cost, particularly with parenteral use, and side effects of HBIG have led to increased interest among transplant professionals in attempting to decrease or stop HBIG now that potent antiviral agents that can suppress HBV viral load are available. In a multicenter randomized trial reported by Teperman and coworkers, HBIG could be stopped safely 24 weeks after transplant in the preliminary results of their study. Additionally, important safety data were obtained for the use of TDF in a group of post-transplant patients with a high prevalence of baseline renal dysfunction and a high risk for renal injury. Though the sample size in this trial was small and the results preliminary, there were no significant increases in creatinine seen in either of the 2 TDF-containing arms.

Additional long-term data on TDF and ETV, the 2 first-line oral therapies, were also prominently presented at EASL. First, Lampertico and colleagues presented long-term data from a large, open-label, cohort study showing prolonged suppression of HBV DNA with ETV in the vast majority of patients in Italy with e-negative chronic hepatitis B. Despite good suppression of HBV DNA, several patients still developed hepatocellular carcinoma (HCC) and required transplant. This highlights that despite the importance of complete suppression of DNA, antiviral therapy will not prevent all adverse clinical outcomes, particularly in the short-term, and close

follow-up of our patients is still required, especially for the development of HCC. Reports on long-term follow-up of the TDF registration trials show excellent suppression at 3 years without any documented resistance to date. Several abstracts reported results of TDF therapy in patients with suboptimal response to adefovir and lamivudine (LAM), including those with documented resistance. Both a nonrandomized trial and a retrospective review of prior studies showed good efficacy for TDF as monotherapy or in combination with LAM. In the abstracts presented by Snow-Lampart and associates and Manns and colleagues, patients had long-term viral suppression without the development of resistance or renal dysfunction, respectively. Although, in these studies, TDF appears to be effective even as a monotherapy for patients with suboptimal response to adefovir and LAM, in my clinical practice, I still use combination therapy for all patients who have had suboptimal response to either a nucleotide or a nucleoside with combination nucleotide plus nucleoside therapy. Van Bömmel and associates also reported the renal effects of long-term use of TDF in a cohort of HBV patients treated with TDF compared to nontreated controls. They saw small changes in GFR over time in the 2 groups, and only 1 of 195 patients required dosage adjustment of TDF for an increase in creatinine from 0.8 mg/dL to 1.18 mg/dL.

The additional data from EASL on long-term therapy with ETV and TDF further strengthen our confidence that long-term monotherapy with the nucleoside ETV or the nucleotide TDF will be successful in most of our patients with close monitoring of HBV DNA levels. Once it becomes available in the United States, measurement of quantitative HBsAg levels will allow early prediction of who will respond optimally to pegylated interferon and oral antiviral therapies. We can reserve early institution of combination therapy for patients who are inadequately suppressed on therapy or who develop viral rebound suggestive of the development of antiviral resistance. The data also highlight the safety of these 2 agents in long-term use without significant resistance, nephrotoxicity, or other toxicity. The renal safety seen with TDF, even in patients who are at higher risk for renal dysfunction, is particularly encouraging.

The information presented at EASL adds to our data and confidence in our first-line agents ETV, TDF, and pegylated interferon in appropriate candidates. Ongoing and future research should further expand and explore broader treatment populations, including immune tolerant patients, pregnant patients, immunosuppressed patients, and patients with decompensated cirrhosis. Additionally, the development of newer therapeutics and improved combinations, which will increase surface antigen clearance and hopefully achieve cure are needed.

