

## Recent Advances in the Treatment of Chronic Hepatitis B: Highlights from the 2010 AASLD Meeting

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A Review of Selected Presentations from the 2010  
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the Study of Liver Diseases  
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# Recent Advances in the Treatment of Chronic Hepatitis B: Highlights from the 2010 AASLD Meeting

Despite immunization programs and patient education, hepatitis B virus (HBV) infection remains a serious health risk.<sup>1</sup> While acute HBV infection is typically asymptomatic or mild, chronic hepatitis B (CHB) can result in cirrhosis, liver failure, hepatocellular carcinoma, and eventually death.

Fortunately, multiple effective medications are available to treat HBV, including injectable interferon (IFN)-based therapies—both standard IFN  $\alpha$  and pegylated (PEG)-IFN  $\alpha$ —and oral nucleos(t)ide analogues: adefovir dipivoxil (ADV), entecavir (ETV), lamivudine (LAM), telbivudine (LdT), and tenofovir disoproxil fumarate (TDF).<sup>2-4</sup>

Both IFNs and nucleos(t)ide analogues can be effective, but the optimal choice in each case depends on specific patient characteristics. Given that there are differences in the duration of treatment, side effects, treatment costs, and drug resistance, studies are needed to determine the most rapid and effective treatment options for various patients with CHB. Some such studies were presented at the 61st Annual Meeting of the American Association for the Study of Liver Diseases (AASLD), highlights of which are presented in the following pages.

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## Highlights from the 2010 AASLD Meeting

### 476 Continued Efficacy and Safety Through 4 Years of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg-Negative Patients with Chronic Hepatitis B (Study 102)

P Marcellin, M Buti, Z Krastev, S Gurel, AM Di Bisceglie, JA Odin, GM Dusheiko, EJ Heathcote, K Borroto-Esoda, DH Coombs, E Mondou, J Anderson

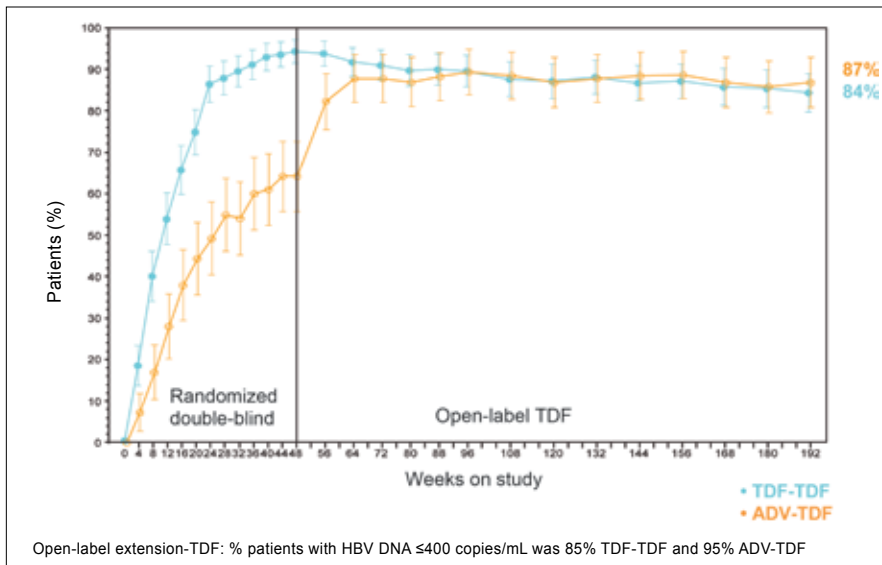
TDF was approved for treatment of CHB in 2008 and is currently under investigation in an 8-year, phase III study of hepatitis B e antigen–negative (HBeAg-) patients (Study 102).<sup>1</sup> This study included LAM-experienced or -naïve patients who had compensated liver disease, HBV DNA levels greater than  $10^5$  copies/mL, alanine aminotransferase (ALT) levels above the upper limit of normal (ULN) but less than 10 times ULN, and a Knodell necroinflammatory score of at least 3. Patients were required to be seronegative for HIV-1, hepatitis D virus (HDV), and hepatitis C virus (HCV). In the double-blind phase of the study, patients were randomized to receive TDF 300 mg (n=250) or ADV 10 mg (n=125) for 1 year. During the open-label phase of the study (Years 1–8), all patients received TDF 300 mg. On or after Week 72, patients with confirmed viral suppression (HBV DNA <400 copies/mL) could add emtricitabine (FTC).

Previous interim results from this study showed that TDF had significantly greater antiviral activity compared to ADV at Week 48, with 93% of TDF-treated patients achieving viral suppression versus 63% of ADV-treated patients.<sup>2</sup> Beyond 48 weeks, both viremic and nonviremic ADV-treated patients who switched to TDF achieved or

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**Figure 1.** Long-term evaluation of patients negative for HBV e antigen who were treated with tenofovir disoproxil fumarate (TDF) only showed that HBV DNA levels remain suppressed with up to 4 years of treatment.  
ADV=adefovir dipivoxil;  
HBV=hepatitis B virus.

maintained viral suppression and normal ALT levels at Week 144. Patients treated with TDF for all 144 weeks also maintained viral suppression and normal ALT levels.

In this interim analysis, Marcellin and associates reported on the 84% of patients who completed treatment at the end of Year 4. In the long-term evaluation of TDF only (LTE-TDF), 87% of patients in the ADV-TDF group and 84% of patients in the TDF-TDF group had maintained viral suppression at Week 192 (Figure 1). In the on-treatment analysis, which excluded patients with missing data, 100% of patients in the ADV-TDF group and 99% of patients in the TDF-TDF group maintained viral suppression at Week 192. At this time point, mean ALT levels were 34 U/L in the TDF-TDF group and 31 U/L in the ADV-TDF group; 80% of TDF-TDF patients and 86% of ADV-TDF patients exhibited normalized ALT levels.

In terms of safety, 3 patients (1%) in the TDF-TDF group and 0 patients in the ADV-TDF group exhibited study-related serious adverse events. Three patients (1%) in the TDF-TDF group and 2 patients (2%) in the ADV-TDF group had confirmed decreased phosphorus (<2 mg/dL) that resolved without intervention. Confirmed increased creatine ( $\geq 0.5$  mg/dL) was observed in 1 patient in each group, and confirmed decreased creatine clearance (<50 mL/min) was observed in 1 patient in the ADV-TDF group. Serum creatine levels remained stable over time; levels at Week 192 were 0.94 mg/dL and 0.92 mg/dL in the TDF-TDF and ADV-TDF groups, respectively. In addition, HBV DNA from 4 viremic patients was genotyped, and no amino acid substitutions were observed at a conserved site.

Based on these results, the investigators concluded that TDF has potent antiviral activity as demonstrated by the high percentage of patients exhibiting viral suppression. Moreover, TDF treatment was well tolerated, serum

creatinine remained stable over time, and no viral resistance was observed during the study period.

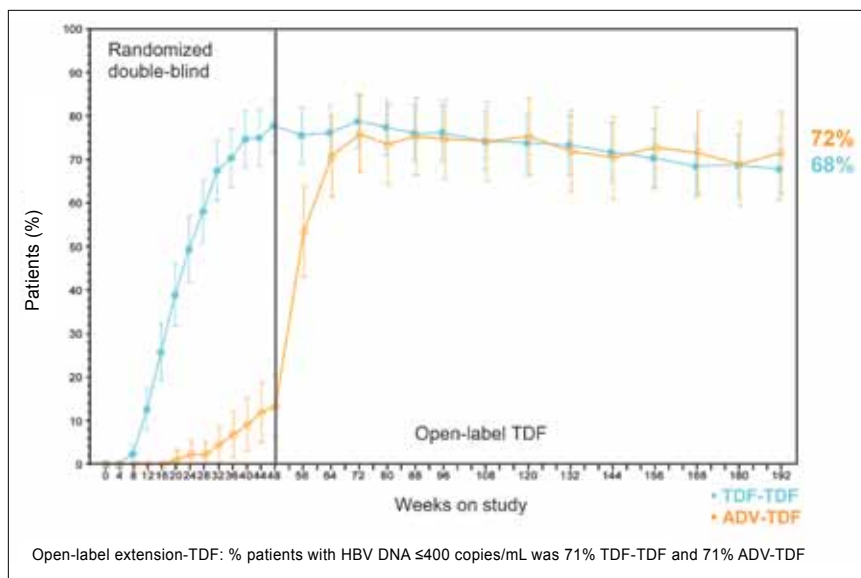
#### 477 Long Term (4 Year) Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) Treatment in HBeAg-Positive Patients (HBeAg+) with Chronic Hepatitis B (Study 103)

EJ Heathcote, EJ Gane, RA de Man, S Chan, J George, N Tsai, P Marcellin, A Snow-Lampart, DH Coombs, E Mondou, J Anderson

In a related, ongoing study (Study 103), TDF is being tested in HBeAg-positive (HBeAg+), nucleoside-naïve patients with compensated liver disease, HBV DNA levels greater than  $10^6$  copies/mL, ALT levels 2–10 times ULN, and a Knodell necroinflammatory score of at least 3. All patients were seronegative for HIV-1, HDV, and HCV. Patients were randomized to receive TDF 300 mg (n=176) or ADV 10 mg (n=90) during the 1-year, double-blind phase. The protocol for the open-label phase (Years 1–8) was the same as for Study 102.

Previous interim results revealed that TDF exhibited greater antiviral activity than ADV at Week 48.<sup>2</sup> After 48 weeks, nonviremic and viremic ADV-treated patients who switched to TDF achieved or maintained viral suppression and normal ALT levels; they also showed increasing loss of HBeAg and hepatitis B surface antigen (HBsAg) at Week 144. Similar results were observed for patients treated with TDF only.

Heathcote and associates expanded upon previous findings by presenting efficacy and safety data from Year 4. The study achieved 74% retention by the end of Year 4. In the LTE-TDF analysis, 72% of ADV-TDF patients and 68% of TDF-TDF patients maintained viral suppression at Week 192 (Figure 2). The on-treatment analysis reported rates of 99% and 96%, respectively.



**Figure 2.** Long-term evaluation of patients positive for HBV e antigen who were treated with tenofovir disoproxil fumarate (TDF) only showed that HBV DNA levels remain suppressed with up to 4 years of treatment.

ADV=adefovir dipovoxil;  
HBV=hepatitis B virus.

HBeAg loss occurred in 41% of TDF-TDF patients, and HBeAg seroconversion occurred in 29% at Year 4. The cumulative probability of HBsAg loss was 10.8% in TDF-TDF patients and 8.5% in ADV-TDF patients.

Serious drug-related adverse events occurred in 2 TDF-TDF patients (1%) and 2 ADV-TDF patients (2%). Decreased phosphorus was transient and occurred in 1 patient in each group. Creatine levels of at least 0.5 mg/dL occurred in 1 TDF-TDF patient and 2 ADV-TDF patients. No patients exhibited creatine clearance of less than 50 mL/min. Serum creatine also remained stable over time; at Week 192, mean serum creatine levels were 0.91 mg/dL and 0.90 mg/dL in the TDF-TDF and ADV-TDF groups, respectively. No TDF resistance was detected in the 8 viremic (HBV DNA  $\geq$ 400 copies/mL) patient samples that were genotyped.

Based upon the Year 4 data, the authors concluded that TDF achieves viral suppression in almost all HBeAg+ patients studied. TDF is also well tolerated, with stable serum creatine levels and no observed development of resistance.

### 1365 No Resistance to Tenofovir Disoproxil Fumarate (TDF) Detected Following up to 192 Weeks of Treatment in Subjects Mono-Infected with Chronic Hepatitis B Virus

A Snow-Lampart, K Kitrinos, B Chappell, F Myrick, J Schawalder, EJ Heathcote, P Marcellin, K Borroto-Esoda

Examining another facet of the studies described above, Snow-Lampart and colleagues tested whether mono-infected CHB patients develop resistance to TDF. Previous studies by this group found no resistance-associated amino acid substitutions in the reverse transcriptase domain of HBV DNA polymerase (HBV pol/RT) during

144 weeks of TDF treatment in HBeAg- and HBeAg+ patients.<sup>3</sup> In the present study, the authors sought to identify amino acid substitutions in HBV pol/RT following 192 weeks of treatment and determine whether these substitutions impacted clinical response to therapy or TDF susceptibility.

To address these aims, 528 of the HBeAg+ and HBeAg- patients in Study 102 and Study 103 were genotyped by di-deoxy sequencing of serum HBV pol/RT (amino acids 1–344 of pol/RT [amino acids 1–266 of HBsAg]) at baseline and then yearly and/or at discontinuation of TDF monotherapy if HBV DNA was at least 400 copies/mL. After baseline, any patient with conserved site changes in pol/RT, virologic breakthrough (1 log<sub>10</sub> increase in HBV DNA and/or HBV DNA  $\geq$ 400 copies/mL after being  $<$ 400 copies/mL), or polymorphic site changes underwent a phenotypic analysis.

Conserved site changes in HBV pol/RT were not observed in any of the enrolled patients during Year 4. Polymorphic site changes were detected in 4 patients, but the authors noted that these changes were natural polymorphic changes that have been observed in placebo-treated patients. These changes did not impact clinical effectiveness of TDF. At the end of Year 4, only 3 patients had virologic breakthrough; all were HBeAg- patients in the TDF-TDF group and 2 had a documented history of nonadherence. The authors commented that virologic breakthrough was not associated with in vitro resistance to TDF. Persistent viremia was observed in 3 HBeAg+ patients, but conserved site changes were not observed in more than 1 clone.

In conclusion, there was no evidence of resistance in either the TDF monotherapy group or the ADV-TDF group in response to up to 4 years of treatment. Virologic breakthrough was rare ( $<$ 1%) and primarily attributed to

documented nonadherence. Persistent viremia was also rare (<1%); when present, viremia was not associated with TDF resistance.

### 134 HBV rtN236T Mutant Subpopulations Respond Like Wild-type During Tenofovir DF (TDF) Monotherapy or Combination Therapy with Emtricitabine (FTC)

M Curtis, ES Svarovskaia, Y Zhu, K Peschell, MD Miller, K Borroto-Esoda

While long-term data on TDF treatment have found no evidence of HBV pol/RT resistance, *in vitro* studies suggest that the rtN236T ADV-associated resistance mutation may exhibit low levels of cross-resistance to TDF.<sup>4</sup> Curtis and associates therefore aimed to determine clinical response of the rtN236T mutant virus to TDF treatment.

An allele-specific polymerase chain reaction assay was used to scan patient samples for the rtN236T mutant virus before and during treatment with TDF (300 mg) or FTC-TDF (200 mg/300 mg). Patients with the rtN236T mutation at baseline were followed through Week 24 to check for levels of rtN236T and rtN236N. Early viral load decay kinetics through Week 4 were then evaluated.

At baseline, 14 patients (13.3%) were positive for the rtN236T mutation. At Week 4, rtN236T mutant virus and wild-type (WT) virus showed similar rates of early viral load decline during treatment with TDF or FTC-TDF ( $P=.9333$ ). At Week 24, 3 of the 5 patients treated with TDF and 6 of the 9 patients treated with FTC-TDF had HBV DNA levels less than 1,000 copies/mL. The relative proportion of rtN236T to WT virus did not increase in either treatment group.

The authors found that the mutant virus exhibited early viral load decline kinetics similar to WT virus, with no statistical difference observed at Week 4 with either treatment. Thus, it appears that TDF suppressed both rtN236T mutant and WT viruses equally.

### 364 A Prospective Open-label Study to Evaluate the Efficacy, Safety and Tolerability of Telbivudine (LdT) in HBeAg + Chronic Hepatitis B (CHB) Pregnant Women

C Pan, GR Han, W Zhao, HX Jiang, MK Cao

Despite preventative measures, HBV is transmitted to 10–30% of infants born to highly viremic mothers.<sup>5</sup> Pan and coworkers therefore sought to evaluate the safety and efficacy of LdT in pregnant women with CHB.

This study enrolled female patients at 12–32 weeks of gestation who were HBeAg+ with HBV DNA above  $6 \log_{10}$  copies/mL and ALT levels above ULN (40 IU/mL) but less than 10 times ULN. Patients received LdT 600 mg/day until postpartum Week 4. At birth, infants received HB immunoglobulin (200 IU) within 24 hours and HBV vaccine at 0, 1, and 6 months.

Fifty-three patients were treated with LdT for a mean duration of 15.5 weeks; 35 untreated patients served as controls. All patients in the LdT group and 92% of patients in the control group completed the study. Complete virologic response (HBV DNA <500 copies/mL) was achieved in 53% of the LdT group and 0% of the control group prior to delivery. At postpartum Week 4, these rates were 62% and 0%, respectively ( $P<.001$ ). In addition, normalized ALT levels were observed in 77% of the LdT group versus 29% of the control group ( $P<.001$ ). Declines in HBeAg titers were observed in 98% of the LdT group and 60% of the control group ( $P<.001$ ). At birth, 4% of the infants from LdT-treated mothers and 23% of the infants from control-group mothers were HBsAg+ ( $P<.001$ ). There were no incidences of congenital deformities and no differences between the 2 groups in terms of postpartum hemorrhage, gestational age, infant height/weight, or Apgar scores. The results of this study led the authors to conclude that LdT treatment during the second and third trimesters was well tolerated and resulted in a significant reduction in HBV infection in newborns.

### 377 Treatment of HBeAg-positive CHB Infection with Peginterferon Alfa-2a [40KD] Plus Lamivudine or Adefovir for 96 Weeks Results in High Rates of HBsAg Clearance/Seroconversion

Z Cao, Y Zhang, L Ma, Y Jin, H Yu, X Zhang, Y Liu, Y Huang, B Ma, S Ren, L Wang, X Chen, L Wei

To assess the benefit of nucleos(t)ide analogues used in conjunction with IFN, Cao and associates reported interim results of a study investigating the safety and efficacy of extended treatment with PEG-IFN  $\alpha$ -2a (40 KD) and LAM or ADV in Chinese patients with HBeAg+ CHB. In this study, 47 consecutive patients were randomized to receive PEG-IFN (135  $\mu$ g/week) in combination with LAM (100 mg/day;  $n=24$ ) or ADV (10 mg/day;  $n=23$ ) for 96 weeks.

Virologic response (defined as HBV DNA <500 copies/mL) was achieved by 96% of patients ( $n=45$ ) by 48 weeks and 100% of patients ( $n=41$ ) by 96 weeks. HBeAg seroconversion rates were 50% in the PEG-IFN plus LAM group and 44% in the PEG-IFN plus ADV group at 48 weeks; these rates rose to 75% and 71%, respectively, at 96 weeks. HBsAg seroconversion rates were 8% in the PEG-IFN plus LAM group versus 4% in the PEG-IFN plus ADV group at 48 weeks; by 96 weeks, these rates were 30% and 24%, respectively. The authors noted that the safety profile for extended treatment was similar to 48-week treatment. Cao and colleagues concluded that use of PEG-IFN in combination with nucleos(t)ide analogues for 96 weeks appears to be a safe and effective treatment option for patients with HBeAg+ CHB, as evidenced by this study's high seroconversion rates.

**383 Complete Viral Suppression (CVS) by Entecavir (ETV) in Patients Previously Treated with Adefovir (ADV): Interim Report for a Multicenter Study**

MH Nguyen, HN Trinh, ST Do, PI Tran, T Nguyen, K Nguyen, HA Nguyen, NH Nguyen, RT Garcia

Some studies suggest that ETV may be more potent than ADV in the treatment of HBV.<sup>6</sup> However, it remains unclear whether ETV is effective for patients who were previously treated with ADV. Therefore, Nguyen and colleagues examined whether ETV would result in complete viral suppression (HBV DNA <60–100 IU/mL) and ALT normalization (<40 U/mL) in patients who were switched from ADV due to suboptimal responses, resistance prevention, or other reasons.

CHB patients were enrolled in the study if pretreatment levels of HBV DNA were at least 2,000 IU/mL and if they were previously treated with ADV and then switched to ETV. Exclusion criteria included co-infection with HDV, HCV, or HIV; LAM resistance; and recent or ongoing immunosuppressive therapy. Patients were separated into 2 groups: Group I were ADV partial responders (<2 log<sub>10</sub> reduction in HBV DNA at 6 months or incomplete viral suppression at 12 months of ADV treatment); Group II were ADV responders who achieved complete viral suppression on ADV but were switched to ETV due to physician or patient preference.

The study included 106 patients who completed at least 6 months of ETV therapy (Group I, n=71; Group II, n=35). After 6 months of treatment with ETV, 62% of the ADV partial responders achieved complete viral suppression and 79% achieved normalization of ALT levels (Table 1). By 24 months, these rates were 82% and 87%, respectively. All ADV responders continued to have complete viral suppression

**Table 1.** Treatment Response to Entecavir in Adefovir Partial Responders (Group I)

	ALT normalization % (n/N)	Complete viral suppression % (n/N)
At switch (N=71)	69% (49/71)	0% (0)
6 months after switch (N=71)	79% (56/71)	62% (44/71)
12 months after switch (N=67)	81% (54/67)	70% (47/67)
18 months after switch (N=61)	80% (49/61)	75% (46/61)
24 months after switch (N=45)	87% (39/45)	82% (37/45)

ALT=alanine aminotransferase.

and normalized ALT levels on ETV therapy. The authors indicated that neither side effects nor resistance were issues during ETV treatment.

**LB-3 Controlled Attenuation Parameter: A Novel FibroScan-based Tool to Detect and Quantify Steatosis in Chronic Hepatitis B**

AF Cardoso, MC Sasso, V Miette, C Fournier, L Sandrin, M Beaugrand, C Douvin, V de Ledinghen, R Poupon, M Ziol, P Bedossa, P Marcellin

Steatosis likely contributes to the progression of liver fibrosis in patients with CHB, but detection of steatosis by noninvasive means remains difficult. Cardoso and coworkers therefore developed a novel Controlled Attenuation Parameter (CAP) that was evaluated on signals acquired by FibroScan.

In this prospective study, 133 consecutive patients with CHB (62% male; mean age=39 years) underwent liver biopsy and FibroScan. The authors retrospectively evaluated CAP on the raw data from FibroScan. METAVIR classification was used to stage activity and fibrosis. Steatosis was graded on a S0–S3 scale depending on the percentage of hepatocytes showing steatosis. Area Under the Receiver Operating Characteristic (AUROC) was used to evaluate performance.

A univariate analysis found that liver stiffness correlated to fibrosis, gender, activity, steatosis, age, and sinusoidal fibrosis; multivariate analysis found that liver stiffness correlated only with liver fibrosis (odds ratio=19.9 [6.65–59.8]). A univariate analysis found that CAP was correlated with steatosis, body mass index, presence of nonalcoholic steatohepatitis, and liver fibrosis. Multivariate analysis found that CAP was only associated with steatosis (odds ratio=7e13 [4e8–1e19]). AUROC for liver stiffness was 0.80 (0.72–0.89) for F≥2, 0.91 (0.84–0.99) for F≥3, and 0.91 (0.78–1.00) for F=4. AUROC for CAP was 0.82 (0.74–0.89) for S≥10% and 0.81 (0.72–0.90) for S≥30%. Cardoso and associates concluded that CAP is a novel, noninvasive tool that can effectively detect and quantify steatosis in patients with CHB.

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## Commentary

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One of the key messages from the studies presented in this monograph is that long-term use of TDF and ETV is quite effective, with patients showing very high rates of virologic response—approaching 100% among compliant patients. Currently, we have 4 years of follow-up data on TDF and at least 4 years of follow-up data on ETV, and to date these studies have not shown significant virologic breakthrough. When breakthrough occurs, it is usually related to patient noncompliance and not to resistance; at 4 years, rates of resistance were reported to be 0% for TDF and 1.2% for ETV.

A second key finding from these studies is that control of viral replication is associated with biochemical response (ie, normalization of ALT levels) and improvement of liver disease. Studies suggest that long-term treatment with TDF or ETV can stop or even reverse fibrosis and may also reverse cirrhosis. In addition, treatment of HBeAg+ patients can trigger a decrease in HBsAg levels and a non-negligible rate of antigen loss. The loss of HBsAg is a good marker of sustained response—effectively a “cure”—and achieving HBsAg loss means that clinicians can consider stopping treatment in these patients. With previous drugs, loss of HBsAg was exceptional; with today’s more potent drugs, however, a decrease in antigen levels is more common, and loss of antigen can be achieved.

In addition to demonstrating efficacy, the studies in this monograph also show that TDF and ETV are safe for long-term use. While a few patients treated with TDF have shown an increase in creatine, this increase was usually modest and reversible. There have also been no cases of serious kidney problems in the TDF studies. Overall, safety data from these studies are reassuring,

with no interruptions of treatment due to severe adverse events. Because clinicians typically treat HBV patients for extended periods, we are naturally concerned about long-term safety and efficacy when prescribing antiviral agents. Given the encouraging data presented here, however, clinicians can feel confident that long-term administration of TDF or ETV will prove effective and is unlikely to cause serious side effects.

While these studies provide 4-year outcome data, treatment of HBV patients may exceed 4 years in clinical practice, so additional follow-up analyses are necessary. Follow-up analysis is planned out to 8 years for the TDF studies, and long-term follow-up is also ongoing in the ETV studies, but clinicians must wait several years before these data become available. Another limitation of the studies discussed in this monograph is that they included only carefully selected patients, who may have had more moderate CHB, a better chance of response, and a lower risk of side effects than patients seen in clinical practice. For example, the proportion of patients with cirrhosis is relatively low in these studies, and those patients who had cirrhosis had compensated cirrhosis. Because the extent to which we can extrapolate from these study cohorts to a broader patient population may be limited, observational follow-up studies are needed to assess real-world drug performance.

Other studies are needed to define the characteristics of patients in whom HBsAg decline is achieved. Since antigen loss is effectively a cure for patients with HBV infection, we need to determine the factors associated with this outcome, particularly the role of viral genotype in HBsAg loss. In terms of virology, we would also like to better understand the impact of long-term treatment on intrahepatic viral status. Even if treatment halts viral replication and HBV DNA levels in patients’ serum are undetectable, the liver can still contain viral DNA—particularly a very robust and resistant form called ccc DNA—but few studies have looked at the impact of treatment on intrahepatic HBV DNA. We also need more studies examining the impact of treatment on fibrosis stage; the risk of cirrhosis, hepatocellular carcinoma, and other complications; and survival.

Finally, we need to learn more about the immunologic response in patients treated with TDF or ETV. To achieve a good virologic response, clinicians need effective antiviral drugs, but these drugs are probably not enough in some patients. Often, a good immune response is also necessary, so studies are examining its role in triggering antigen decline and HBsAg loss. Some studies suggest that combining an antiviral drug such as TDF or ETV with an immunomodulator such as PEG-IFN could increase the rate of HBsAg loss, at least in some patients, and this approach needs to be explored further.

