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Monitoring During and After Antiviral Therapy for Hepatitis B

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Abstract

Recent studies suggest that long-term suppression of viral replication is critical to reducing the complications of chronic hepatitis B virus (HBV) infection. Monitoring for continued virological response during and after treatment is essential because current treatment options have limited success in achieving durable endpoints, and antiviral resistance may emerge during long-term therapy. Methods of monitoring treatment response include tests for serum aminotransferase levels, HBV DNA level, hepatitis B e antigen (HBeAg) and antibody (anti-HBe), hepatitis B surface antigen (HBsAg) or antibody (anti-HBs), and liver histology. Virological suppression and loss of HBeAg or HBsAg with or without seroconversion play a prominent role in decision making regarding the success and duration of antiviral therapy. Guidelines recommend that serum markers be repeated every 12 to 24 weeks during antiviral therapy and every 6 to12 months afterwards. Recent data also suggest that serum HBV DNA levels should be assessed at weeks 12 and 24 of therapy because early viral response may predict the likelihood of sustained response and antiviral resistance. The use of serum HBV DNA levels for this purpose requires an assay with a wide range of quantification, such as real-time polymerase chain reaction assays, which have a 7-8 $\log_{10}$ dynamic range. Newer, investigational methods for monitoring treatment response include quantitative measurement of HBsAg, HBeAg, and intrahepatic covalently closed circular DNA. Better methods for defining durable treatment endpoints are needed. Other areas requiring further research include the optimal treatment duration and the establishment of the optimal use of early viral kinetics for decision-making during antiviral therapy.

Keywords

HBV DNA; Anti-HBe seroconversion; early virological response; treatment endpoints; treatment duration

Introduction

Recent studies suggest that suppression of viral replication is critical to reducing the risk of complications from chronic hepatitis B virus (HBV) infection. In a large-scale, long-term follow up study of a population based cohort of Taiwanese adults with chronic HBV infection, (The REVEAL-HBV study) elevated serum HBV DNA levels were found to be the strongest single risk factors for progression to cirrhosis (1). Active HBV replication also appears to predict the risk of hepatocellular carcinoma in a dose-responsive manner (2). Because current treatment options have limited success in achieving durable endpoints and

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antiviral resistance may emerge during long-term therapy, monitoring for continued virological response during and after treatment is essential.

Periodic serological studies during antiviral therapy are required to assess for adequate primary response to treatment, treatment-related side effects or hepatitis flares, achievement and maintenance of treatment endpoints, and the emergence of antiviral resistance. The optimal frequency and best method of monitoring for these events has not been defined. How to use the available studies to guide decision-making such as treatment duration is also uncertain. The importance of these questions is reflected by the recent publication of several articles specifically addressing this topic (3-5).

Methods of Monitoring Treatment Response

Antiviral therapy for chronic hepatitis B appears to reduce the risk of long-term complications such as cirrhosis and HCC.(6) Because complications tend to occur after decades of infection and often long after treatment has been initiated, clinical trials and practicing clinicians utilize surrogate, short-term markers of risk and treatment benefit. Each of the surrogate markers, including serum aminotransferase levels, serum HBV DNA level, HBeAg or anti-HBe, HBsAg or anti-HBs, and liver histology, has been used as a measure of the response to antiviral therapy. Indeed, several definitions of treatment response have been enumerated at previous NIH conferences and have been used variably in clinical trials of antiviral therapy: *biochemical response* (normalization of serum ALT); *virological response* (decrease in serum HBV DNA or loss of HBeAg with or without the development of anti-HBe); *histological response* (improvement in the histology activity index by at least 2 points without worsening of fibrosis score as compared to pretreatment biopsy); and *complete response* (biochemical and virological response with loss of HBsAg) (7,8). Recent studies favor using durable HBV DNA suppression as the primary measure of therapeutic success.

The serum ALT is the most simple and accessible means of evaluating treatment response. Biochemical response is the most frequently achieved treatment response in clinical trials, occurring in 40 to 70% of patients on antiviral therapy (9). The serum ALT level is commonly used as an indirect marker of histological activity, with normalization of the ALT level during the course of antiviral therapy thought to reflect improvement in hepatic necroinflammation. Serial measurement of ALT levels may reflect treatment-associated hepatitis flares or the emergence of antiviral resistance. Serum ALT is one of the few measures of early treatment response in HBeAg-negative chronic hepatitis B.

The primary drawback of using serum ALT as a marker of treatment response is its limited predictive value. In the early trials of lamivudine therapy not all patients achieving biochemical response (70%) had improvement on histological evaluation (56%)(10). A recent retrospective study of more than one thousand patients with chronic hepatitis B revealed that a substantial proportion of patients with persistently normal ALT levels (<40 U/L) have significant fibrosis or inflammation on biopsy(11). In that study, 40% of patients with HBeAg-positive chronic hepatitis B and 13% of those with HBeAg-negative disease with normal serum ALT had a fibrosis stage greater than 2. The normal range of serum ALT (30-50 U/L) used in clinical trials of antiviral therapy may be too high to identify at-risk patients accurately because the standard reference rates do account for such factors as alcohol habits, diabetes or obesity. Lower thresholds (19 U/L for women and 30 U/L for men) may be more appropriate (12). However, one retrospective study found that the prevalence of advanced histology (defined as stage 2 fibrosis or stage 1 fibrosis with at least grade 2 inflammation) in patients with HBeAg-positive or -negative chronic hepatitis B and an ALT 1-1.5 times the upper limit of the more stringent normal range was 20% and 27%, respectively (13). These data suggest that serum ALT does not alone suffice as a marker of

disease activity and should be interpreted in the context of serum HBV DNA level and histology. The utility of ALT is also limited for patients with a normal ALT level at the start of therapy.

Reduction in the level of serum HBV DNA or *virological response* is the earliest and perhaps most appropriate measure of treatment response. HBV DNA reduction during antiviral therapy appears to be a good surrogate for histological improvement. In a review of 26 prospective studies of treatment of chronic hepatitis B, investigators found a significant correlation between HBV DNA levels and histological grading at the end of treatment in patients with HBeAg-positive chronic hepatitis B treated with nucleoside analogues. Specifically, they noted that a 1 $\log_{10}$ reduction in median serum HBV DNA level corresponded with a 2 point decrease in median histological grading, meeting criteria for histological response (14). Other studies have shown that early reduction in serum HBV DNA predicts the likelihood of sustained virological response to antiviral therapy (15). Of note, maintained HBV DNA suppression is the only reliable measure of ongoing treatment response in the majority of patients who do not achieve durable serological endpoints.

The use of serum HBV DNA level as a method of assessing treatment response has been complicated by a lack of standardization in the unit of measure and in the criteria for treatment response used in clinical trials. To reconcile the heterogeneity in assays, the World Health Organization created the international unit (IU/mL), a standardized unit of measure, (corresponding to approximately 5-6 copies/mL for most amplification assays), which should now be used in all commercial HBV DNA quantitative assays and reported in clinical trials (16).

The commercially available HBV DNA assays differ in their limits of detection and dynamic range, as summarized in Table 1. The use of serum HBV DNA level as a measure of treatment response requires quantification over a wide range, usually at least 5 $\log s_{10}$ (4). Real-time PCR is technique that amplifies and simultaneously quantifies a DNA sample. Current real-time PCR assays possess a 7 or 8 $\log_{10}$ dynamic range, which permits accurate characterization of pretreatment viral loads that may be in the hundreds of millions, as well as the low viral loads (as low as 30 IU/mL) that may be seen in treatment-induced suppression or in inactive carriers (17,18). This wide range of detection allows accurate quantification of the early response to therapy. For assays with more limited range, specimens at the upper end may need to be diluted to extend their range. Consistent use of the same assay is recommended in assessing treatment response. Eventually, the primary goal of therapy will likely be to achieve undetectable serum HBV DNA by the most sensitive assays.

The *serological markers* of treatment response tend to correlate with improvement in other surrogate markers, including serum ALT and HBV DNA levels. For example, anti-HBe seroconversion is more common in patients experiencing full suppression on therapy and rare in those with persistent viremia (19,20). The most durable treatment endpoint is HBsAg loss with or without anti-HBs seroconversion. However, this serological endpoint occurs in less than 2% of patients taking nucleoside analogues for one year and 3 to 8% of patients receiving interferon or peginterferon (7). Unfortunately, in HBeAg-negative disease HBsAg loss is the only meaningful serological endpoint. In HBeAg-positive disease serological markers of treatment response include both HBeAg and HBsAg loss. Treatment cessation is possible after these endpoints occur because they are more durable than HBV DNA suppression alone.

Histological response, defined as an improvement in the histology activity index (HAI) of 2 points or more or improvement in the fibrosis score, has been used as the benchmark for

treatment response in clinical trials. Antiviral therapy has been shown to retard the progression or cause regression of fibrosis in chronic hepatitis B (21,22). The threshold for improvement used in clinical trials has not been demonstrated to be predictive of long-term outcomes prospectively. However, one retrospective study suggests that changes in liver histology of this magnitude may be a valid surrogate endpoint for antiviral therapy. For ten years, investigators followed 89 patients who were treated with interferon alfa and underwent liver biopsies either 6 or 12 months after the completion of therapy. As a group, patients who experienced liver-related complications had a median one-point rise in the modified HAI score, whereas patients without complications had a median reduction of one point in the modified HAI score at the end of therapy (23). Because sampling error, intraobserver variability and discrepancies in pre- and post-therapy biopsy size may account for some of the differences observed in pre- and post-treatment biopsies, a better surrogate for long-term risk reduction is a combination of biochemical, virological and histological improvement. Indeed, in view of the risks of liver biopsy and the demonstrated predictive strength of virological endpoints, histology now appears to be a less useful endpoint in clinical practice.

Treatment Endpoints

Each of the surrogate markers of treatment response can be considered endpoints of therapy, although virological suppression and loss of HBeAg and HBsAg play a more prominent role in decision-making with respect to antiviral therapy.

In HBeAg-positive disease, short-term treatment endpoints include HBeAg loss with or without anti-HBe seroconversion. Seroconversion occurs in approximately 20% of patients in the first year of antiviral therapy and increases with longer duration of therapy. It is sustained in 50% to 90% of treated patients depending on the duration of treatment after seroconversion, patient age and serum HBV DNA level at the end of treatment (24). Treatment-induced seroconversion is associated with suppressed HBV DNA and a reduced risk of cirrhosis (25).

In a small proportion of patients experiencing HBeAg loss, loss of HBsAg or anti-HBs seroconversion also occurs, often after the treatment period. In long-term follow-up of patients who received standard or pegylated interferon, HBsAg loss occurred in 11% of patients over 3-5 years (25,26). In another, smaller study of patients who experienced seroconversion during interferon therapy, HBsAg loss continued after therapy at a rate of approximately 8% per year for a cumulative rate of 86% by 9 years (27). Long-term complications occur at a negligible rate after the development of anti-HBs (28).

For patients with HBeAg-positive chronic hepatitis B in whom seroconversion does not occur but HBV DNA is fully suppressed on therapy, continued normalization of the ALT and sustained HBV DNA suppression are the only markers of successful treatment and the absence of antiviral resistance, as observed in HBeAg-negative hepatitis.

In HBeAg-negative disease, loss of HBsAg is the only clear indication for stopping therapy. It tends to occur after long-term HBV DNA suppression. Among patients receiving adefovir therapy, 5% had HBsAg loss over a five-year period (29). Short of this endpoint, treatment goals in HBeAg-negative chronic hepatitis B include HBV DNA suppression and normalization of ALT levels.

For both HBeAg-negative and HBeAg-positive disease, sustained virological suppression is a critical on-treatment endpoint. Indeed, a recent phase III trial comparing telbivudine and lamivudine for the treatment of chronic hepatitis B used reduction in serum HBV DNA as a primary treatment outcome (30). However, questions remain regarding the optimal use of

serum HBV DNA for decision-making during therapy. Clinical trials have used inconsistent target levels for response in part based on the HBV DNA assay utilized and a discriminatory threshold for HBV DNA in predicting risk of progression remains to be established, particularly with the use of highly sensitive assays (4). Evidence-based guidelines for starting and stopping therapy based on serum HBV DNA levels are needed.

The two remaining treatment endpoints, normalization of serum ALT levels and histological improvement, are not particularly helpful for decision-making during antiviral therapy for the reasons discussed already.

On-Treatment Milestones and their Predictive Value

Serum HBV DNA level and its decline at various time points *during* antiviral therapy are likely to play an increasing role in dictating the course of therapy. Because its levels reflect viremia, reduction in HBV DNA is the most direct marker of antiviral effect. Recent studies suggest that early viral kinetics during antiviral therapy may predict the likelihood of sustained virological response in chronic hepatitis B, as it does in chronic hepatitis C (30,31).

The Globe Study Group evaluated 1,370 patients with chronic hepatitis B randomly assigned to receive telbivudine (600 mg daily) or lamivudine (100 mg daily)(30). During therapy, patients were categorized as having undetectable HBV DNA (<300 copies/mL) or having varying degrees of residual viremia. Patients with undetectable serum HBV DNA at 24 weeks had an HBeAg seroconversion rate of 41% at one year, compared to just 4% in those with HBV DNA in excess of 4 $\log_{10}$ copies/mL. Resistance rates for the same groups at one year were 2% and 15%, respectively. In multivariate analysis, undetectable HBV DNA at week 24 was the best predictor of clinical and virological efficacy (independent of HBeAg status).

These findings have been confirmed by several smaller studies, which are summarized in Table 2. In 56 patients receiving adefovir therapy after the development of lamivudine resistance, 87% of patients who experienced a decline in serum HBV DNA by more than 3 $\log_{10}$ at three months lost HBeAg, as compared to only 24% of patients who had less than a 3 $\log_{10}$ decline (32). A study evaluating the predictive value of HBV DNA levels at numerous time points during lamivudine therapy found that HBV DNA levels at weeks 4 (<2000 IU/mL) and 16 (<800 IU/mL) were the best predictors of a combined endpoint of anti-HBe seroconversion, ALT normalization and absence of lamivudine-resistance mutations after five years of treatment (19). All patients with HBV DNA levels lower than these cutoffs achieved the combined endpoint. In contrast, the probability of failing to meet this endpoint at year 5 in patients with HBV DNA levels above these cutoffs were 84% and 88%, respectively. In a study of 66 patients receiving peginterferon and lamivudine (with the majority starting peginterferon 8 weeks prior to lamivudine), 27% had a sustained virological response, defined as loss of HBeAg, anti-HBe seroconversion and HBV DNA less than 10,000 copies/mL at one year (15). Receiver operating characteristic (ROC) curves were used to identify predictors of sustained response. The area under the ROC curve for HBV DNA level was greatest at week 8 and yielded a negative predictive value of 92%, meaning that patients without early virological response were highly unlikely to experience sustained response.

Of great concern, patients who do not experience early and significant HBV DNA suppression are far more likely to develop nucleoside antiviral resistance. In one study, patients with serum HBV DNA levels in excess of 10^3 copies/mL after 6 months of lamivudine therapy had a 63% chance of developing YMDD-resistance mutations (33). While these data do not yet permit definitive decisions regarding treatment duration to be

made based on early virological response, they highlight the importance of assessing early predictors of sustained virological response prospectively in large clinical trials.

A group of expert hepatologists recently proposed a “roadmap” for antiviral therapy based on early on-treatment response (5). They recommended measurement of HBV DNA at 12 and 24 weeks to predict the likelihood of sustained virological response. The panel recommended that patients with full HBV DNA suppression (<60 IU/mL) at 24 weeks continue the same antiviral agent. They recommended that patients with a partial response to antiviral therapy (60-2,000 IU/mL) have an agent with a different resistance profile added if the initial drug had low genetic barrier to resistance; or undergo further monitoring without a change in therapy until 48 weeks if they were receiving a high genetic barrier agent. For patients with an inadequate response to therapy at 24 weeks, (>2,000 IU/mL), the panel recommended adding a more potent drug. The proposed roadmap applies to patients receiving nucleoside analogues, but an analogous approach may offer a stopping rule for peginterferon. The applicability of the current roadmap to entecavir and tenofovir, which have excellent suppressive efficacy and little long-term resistance to date, is unclear.

Duration of Therapy Based on Treatment Response

Early studies of antiviral therapy in HBeAg-positive chronic hepatitis B suggested that HBeAg loss (or HBeAg seroconversion) was sustained in more than 70% of patients. Later studies showed relapse rates as high as 50% (34,35), which was attributed to duration of therapy after HBeAg loss (24). Subsequently, one group reported results of treating 85 patients with an additional 24 months of lamivudine therapy following HBeAg seroconversion: the rates of relapse following cessation of therapy were 13% at one year and 16% at two years, suggesting that long-term administration of antiviral therapy might enhance the durability of response (36). A second group evaluated patients randomized to 6 or 12 months of lamivudine consolidation therapy following HBeAg seroconversion and reported no difference in relapse rates between the two groups, with a 59% post-treatment virological relapse rate at two years in the 6-month and 50% in the 12-month group (37). The investigators reported that HBV DNA level at the time of treatment cessation was the strongest predictor of relapse: patients with DNA less than 200 copies/mL had a 37% relapse rate compared to 73% in those with HBV DNA levels above 10^3 copies/mL. Guidelines now generally recommend either 6 or 12 months of consolidation therapy following seroconversion.

In HBeAg-negative chronic hepatitis B, the optimal duration of therapy is unknown. Although clinical trials have typically treated patients for 48 weeks, more than 90% of patients with complete HBV DNA suppression on nucleoside therapy relapse within one year after discontinuing therapy (22). As a result, treatment of HBeAg-negative disease with oral antiviral agents is often continued until HBsAg loss occurs or, more commonly, until antiviral resistance and biochemical relapse develops. The duration of interferon therapy in HBeAg-negative disease is typically predetermined rather than based on clinical endpoints. In general, longer duration of therapy appears to be better than shorter duration, but the value of extending therapy from 24 to 48 and to beyond 48 weeks is unknown. The rate of sustained virological response following interferon therapy appears to be better than that of nucleoside therapy, with one study showing 17% of patient having undetectable HBV DNA (<400 copies/mL) after four years of follow-up (38).

Frequency and Timing of Monitoring

The optimal frequency and timing of monitoring during and after antiviral therapy is not known. The American Association for the Study of Liver Disease (AASLD) guidelines recommend that *during* the course of antiviral therapy, patients undergo assessment of liver

tests every 12 weeks and HBV DNA levels every 12 to 24 weeks (9). The guidelines also recommend that HBeAg and anti-HBe testing every 24 weeks in HBeAg-positive chronic hepatitis B, and HBsAg testing every 6 to 12 months in patients who are HBeAg-negative with persistently undetectable levels of HBV DNA. According to the guidelines, patients receiving interferon or peginterferon should have regular assessment for safety with complete blood count checked each month and a thyroid stimulating hormone every 12 weeks. Safety issues also dictate that serum creatinine (with or without phosphate levels) be tested every 12 weeks in patients taking adefovir or tenofovir.

The guidelines from European Association for the Study of the Liver (EASL) suggest that *following* antiviral therapy serum studies such as liver biochemistries, HBV DNA level, HBeAg, anti-HBe be checked every 1-3 months for the first 12 months after treatment cessation and then every 6-12 months. They also recommend yearly HBsAg in patients with sustained virological response to monitor for late clearance. In the long-term, the single most important test for demonstrating sustained response is the serum HBV DNA level. The recommendations for the frequency of serum monitoring during and after antiviral therapy are summarized in Table 3.

Monitoring Tools that Require Further Study

Other *serum markers* may eventually prove useful for monitoring the effect of antiviral therapy. Serum hepatitis B core antigen (HBcAg) measurement is less expensive and easier to perform than HBV DNA measurement, and may be a reliable method of predicting treatment response. A recent study compared HBcAg levels in 54 untreated individuals and 39 patients treated with either lamivudine or entecavir for 48 weeks and found that the logarithmic reduction in HBcAg correlated with logarithmic reduction of the serum HBV DNA, total intrahepatic DNA and hepatic covalently closed circular DNA (cccDNA) levels (40). Patients with a baseline HBcAg concentration of less than 40,000 kU/mL or a concentration under 200 kU/mL at week 24 of treatment were more likely to have undetectable HBV DNA at week 48.

Similarly, quantitative measurement of serum HBeAg may be used to predict seroconversion. In 271 patients who received 48 weeks of peginterferon in a phase III trial, HBeAg levels declined consistently throughout the course of therapy in patients who experienced HBeAg seroconversion. After 24 weeks of treatment, patients with the highest HBeAg levels (>100 PEIU/mL) had a 4% chance of seroconversion. The negative predictive value (96%) of high week 24 HBeAg was superior to that of HBV DNA (86%) (41).

HBsAg quantitation may also be a useful method for predicting sustained virological response (40). In 386 patients treated with peginterferon or lamivudine, investigators observed a significant association between on-treatment HBsAg decline (>1 $\log_{10}$) and HBsAg clearance three years after the cessation of therapy (42). Similarly, in another 48 patients receiving peginterferon, a decrease HBsAg levels by 0.5 $\log_{10}$ at 12 weeks had positive and negative predictive values of 89% and 90%, respectively, for sustained response (43). The predictive values of a 1 $\log_{10}$ decline in HBsAg at week 24 were even higher. These findings raise the possibility of using quantitative HBsAg as an alternative to serum HBV DNA as an early on-treatment response predictor.

Intrahepatic cccDNA level may be a superior predictor of treatment response compared to serum HBV DNA level because it accurately reflects viral persistence during antiviral therapy. In 47 patients with HBeAg-positive chronic hepatitis B receiving lamivudine monotherapy or lamivudine and peginterferon combination therapy, the positive and negative predictive values of a -0.8 $\log_{10}$ genome copies/cell decline in cccDNA were 56%

and 86%, respectively, for sustained virological response.(44) Similarly, 32 patients receiving 48 weeks of adefovir therapy experienced a significant decline in cccDNA of -0.8 log genomes/cell.(45) The decline in cccDNA correlated with reduction in the serum HBsAg titer. Prospective studies are needed to define the cccDNA threshold under which host-mediated control of viral replication is possible. Unfortunately, quantitation of cccDNA by real-time PCR is not yet standardized and requires a liver biopsy.

Conclusions and Needs for Future Research

Periodic serum HBV DNA monitoring should now be viewed as the principal means of monitoring therapy and assessing response and will, therefore, play an increasing role in decision-making during antiviral therapy. Serological endpoints are the most desirable durable endpoints. Histological endpoints will likely play a supportive role in management of chronic hepatitis B, although the utility of cccDNA measurement in predicting sustained virological response merits further evaluation. Future research should be aimed at defining criteria for starting and stopping therapy based on HBV DNA level; how to use on-treatment HBV DNA values at defined time points as predictors of therapeutic outcome; and defining threshold levels that predict lack of disease progression and permit rational cessation of therapy. In coming years, the use of standardized measures of HBV DNA is critical, as is the use of consistent measures of outcome in prospective clinical trials so that treatment and monitoring guidelines can be clearly defined and universally applicable. In addition, better methods for defining durable endpoints for antiviral therapy should be explored. The optimal duration of therapy after seroconversion in HBeAg-positive disease, particularly in those with residual viremia, and an appropriate treatment endpoint, short of HBsAg loss, in HBeAg-negative disease must be defined so that indefinite therapy can be averted in large numbers of patients.

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Abbreviations

HBV	hepatitis B virus
HBeAg	hepatitis B e antigen
anti-HBe	antibody to HBeAg
HBsAg	hepatitis B surface antigen
anti-HBs	antibody to HBsAg
HCC	hepatocellular carcinoma
NIH	National Institutes of Health
ALT	alanine aminotransferase
AASLD	American Association for the Study of Liver Diseases
EASL	European Association for the Study of the Liver
ROC	receiver operating characteristics
ccc	covalently closed circular

Table 1
Dynamic ranges of some commercially available HBV DNA assays

Detection method	Approx. range of quantification	Commercially available assays
Signal Amplification	1.4×10^5 to 1.7×10^9 copies/mL	Digene Hybrid Capture II
	2×10^3 to 10^8 copies/mL	Bayer Versant HBV 3.0
Target Amplification	2×10^2 to 2×10^5 copies/mL	Roche Cobas Amplicor HBV
	2×10^2 to 10^9 IU/mL	Artus-Biotech Real Art HBV PCR
	30 to 1.1×10^8 IU/mL	Roche Cobas Taqman
	10 to 10^9 IU/mL	Abbott Realtime PCR (not yet available.)

Table 2
Predictive value for outcomes of early HBV DNA measurements during antiviral therapy

Time	Antiviral	Predictive level	Seroconversion	Resistance Rate
Week 4	LMV	HBV DNA <2000 IU/mL	100% PPV for HBeAg seroconversion	-
Week 8	PEG/LMV	HBV DNA > 10^4 copies/mL	92% NPV for HBeAg seroconversion	-
Week 12	ADV	>3 $\log_{10}$ decline in HBV DNA	87% HBeAg seroconversion (vs 24% if <3 $\log_{10}$)	-
Week 24	TEL/LMV	HBV DNA <300 copies/mL	41% HBeAg seroconversion (vs 4% if >10^4 copies/mL)	2% (vs 15% if HBV DNA >10^4 copies/mL)
Week 24	LMV	HBV DNA <200 copies/mL	-	8% (vs 64% if HBV DNA >10^4 copies/mL)

Abbreviations: SC, seroconversion; PPV, positive predictive value; NPV, negative predictive value, TEL, telbivudine, LMV, Lamivudine; PEG, pegylated interferon; ADV, adefovir; IU, international units;

Table 3
Suggested frequency of monitoring during and after antiviral therapy

Serum marker	On therapy	After therapy
HBV DNA	Every 12 weeks (every 24 weeks after one year)	Every 4 to12 weeks (every 24 to 48 weeks after one year)
HBeAg, anti-HBe	Every 24 weeks (If HBeAg positive)	Every 4 to 12 weeks (every 24 to 48 weeks after one year)
HBsAg	Every 24 to 48 weeks (If HBeAg negative)	Every 48 weeks
ALT	Every 12 weeks	Every 12 weeks
Liver biopsy	Not Needed	Individualized
Creatinine/Phosphate (ADV/TDF)	Every 12 weeks	Not needed
CBC (Interferon)	Every 4 weeks	Not Needed
TSH (Interferon)	Every 12 weeks	Not needed

Abbreviations: ADV, adefovir; TDF, tenofovir; CBC, complete blood count; TSH, thyroid stimulating hormone