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**eViralHepatitis Review**
**VOLUME 3, ISSUE 5**

## *CURE OF HEPATITIS B: IS IT ACHIEVABLE?*



## In this Issue...

Chronic hepatitis B (CHB) is a major public health problem, affecting more than 400 million people worldwide and greatly increasing their risk of developing liver disease, particularly cirrhosis and hepatocellular carcinoma (HCC). Over the past 15 years, major progress has been made in antiviral therapy of CHB, to the point where it can now be legitimately asked: "Can this disease be cured?"

In this issue, we review recent studies providing evidence that begins to answer that question.

## LEARNING OBJECTIVES

***After participating in this activity, the participant will demonstrate the ability to:***

- Describe current evidence showing that achieving viral suppression can significantly improve fibrosis and decrease the incidence of hepatocellular carcinoma
- Explain how HBsAg loss can be considered a serologic/virologic cure that allows treatment cessation
- Describe how, despite HBsAg clearance, reactivation of HBV and/or development of hepatocellular carcinoma may occur

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**HCV**

- Clinicians do not adequately identify which of their patients are at highest risk for HCV infection or effectively interpret testing results.
- Clinicians need to understand best practices in how to identify and manage HCV treatment-related side effects.
- Clinicians need improved awareness of how newly emerging therapies impact therapeutic decision-making in HCV infected and HIV/HCV co-infected patients.
- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HCV.

**HBV**

- Clinicians do not effectively identify their patients at risk for HBV.

### Program Information

CME Info
Accreditation
Credit Designations
Intended Audience
Learning Objectives
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- Clinicians are unaware of new non-invasive techniques to stage liver disease.
- Clinicians need to understand best practices in identifying cirrhosis and HCC in patients infected with HBV.

## INTENDED AUDIENCE
The target audience (clinicians) for this initiative includes: OB/GYNs, NPs, PAs, hepatologists, gastroenterologists, infectious disease physicians, community gastroenterologists and others who care for patients of Asian and West African descent in areas of high HBV prevalence.

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- **Raymond T. Chung, MD,** discloses that he has served as a consultant for AbbVie, Inc. and Idenix and has received grant/research funding from Gilead and Mass Biologics.

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The authors have indicated that there will be no references to

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## COMMENTARY

Over the past 15 years, the growing efficacy of antiviral strategies to treat chronic hepatitis B (CHB) infection has been remarkable. The use of pegylated interferon alpha has allowed patients to obtain off-treatment responses related to immune control of the infection, primarily in a selected population of patients having favorable predictive factors such as high ALT levels and low HBV DNA levels.[1] Several nucleoside analogues (NA) have been approved over the years. The first generation of NA agents (lamivudine, adefovir dipivoxil, and telbivudine) was associated with a high rate of antiviral drug resistance, which blunted the initial virologic and clinical benefit of therapy. The availability of the second-generation NAs (tenofovir disoproxil fumarate TFV and entecavir) provided both a potent antiviral effect and a high barrier to resistance, which has enabled viral suppression in the majority of patients.[2] This is even true in patients who failed a previous line of antiviral therapy with a low barrier to resistance NA, provided that treatment adaptation is based on the cross-resistance profile of the resistant strain. However, in patients who receive NA-based therapy either de novo or after failure of interferon based therapy, long-term administration of antiviral drug is necessary to avoid viral relapse because of the persistence of HBV cccDNA, ie the viral minichromosome, in the liver of patients infected with HBV.[2]

In contrast to chronic HCV infection, which is a curable infection with a "short" duration of antiviral treatment, the treatment of CHB remains clinically challenging. However, there are several ways to envision how an HBV cure can be achievable.

The first aspect, as shown in some of the investigations reviewed herein, is the evidence that the liver damage associated with CHB can be significantly improved and could be seen as a true endpoint. Indeed, it was shown that with prolonged NA therapy with entecavir or tenofovir, both the necroinflammatory activity and liver fibrosis scores can be improved significantly after several years of therapy. More important, in the study by Heathcote et al,[3] regression of liver cirrhosis was also observed in patients with compensated cirrhosis who received tenofovir (TDF). Clinically, this could be seen as a "cure" of the liver disease, although it remains to be confirmed by extended observations to see if this translates into a reduced incidence of HCC, as suggested by a very recent study presented at the European Association for the Study of the Liver (EASL) conference in Amsterdam.[4]

Another important aspect is that recently published cohort studies suggest that long-term antiviral therapy, when associated with virologic response, is associated with a reduced incidence of HCC. This was well demonstrated in the study by Hosaka et al discussed in this newsletter.

There is now a body of evidence that antiviral therapy, especially when initiated not too late in the natural history of the disease, has a significant impact on HCC development, which can be seen as a big success of these treatments.

However, although these treatments can decrease the incidence of HCC, some cases of HCC still develop during antiviral therapy. These incident cases are usually seen during the first months of therapy and may reflect small HCC undetectable by clinically available imaging techniques present at the beginning of therapy. Furthermore, viral genome integration occurs early during the natural history of infection and may lead to chronic necroinflammatory activity and clonal expansion of hepatocytes that may represent the first step of HCC development. These observations may be an argument for proposing antiviral therapy at earlier stages of the infection to control viral replication and prevent

viral genome integration events and liver damage to occur;[5] this type of strategy would obviously have to be validated with the aim to reduce even further the rate of occurrence of HCC.

The second aspect is related to the virologic cure of HBV infection. The current treatment endpoints of antiviral therapy with interferon or NA are to achieve HBe seroconversion in patients who are HBeAg positive and to achieve viral suppression (undetectable HBV DNA in patients' serum) in all patients. HBsAg loss associated with HBs seroconversion is the next most desirable endpoint. The papers by Lampertico et al and Seto et al discussed in this newsletter provide real-life data on treatment-induced HBsAg loss, which is achieved in only approximately 10% of patients who received a one-year course of interferon when followed for five years after treatment cessation and can be higher in patients with favorable IL28B gene polymorphism. With long-term administration of NA, when associated with virologic response, also approximately 10% of patients lose HBsAg after 5 to 10 years of therapy. HBsAg loss can be seen as a serologic cure of the infection, as it may allow stoppage of treatment and is associated with a decreased incidence of HCC, at least in patients who spontaneously lost HBsAg.

However, this serologic cure does not equate to full eradication of the viral genome. In our experience, as well as in reports from other centers, HBV reactivation may occur despite HBsAg loss. This happens in cases of severe immune depression as seen in patients with AIDS, immune suppressant therapy for organ transplantation, or heavy chemotherapy. This is because viral cccDNA persists in the infected liver, which is responsible for reinitiating active replication when immune control of infection is lost. In these situations, our experience is to recommend antiviral prophylaxis. The other complication that can be seen even in patients with HBsAg loss is the occurrence of HCC as a consequence of long-term infection with viral genome integration and accumulation of liver damage. For this reason, in our institution, we recommend continued ultrasound monitoring of HCC in patients with CHB after HBsAg clearance.

What are the new perspectives about antiviral therapy of CHB? Because of improved clinical endpoints and the possibility to envision finite duration of treatment, HBsAg loss has become the major goal of new antiviral strategies. The aim of future treatments will be to increase the rate of HBsAg clearance. This will require the use of true combination therapy and the identification of new treatment targets. Several lines of research are being explored, with strategies aimed at decreasing the pool of viral cccDNA or silencing its activity, and/or strategies aimed at restoring innate and adaptive immune responses against HBV to clear or cure the remaining infected hepatocytes.[6] Time will be needed to validate these strategies in clinical trials. Meanwhile, there are new trials evaluating the combination of pegylated interferon with NA based on different schedules of administration, which may be the first step for a long-awaited improved (HBsAg loss) success rate of therapy.

**Reference**

1. Lau GK, Piratvisuth T, Luo KX, Marcellin P, Thongsawat S, Cooksley G, Gane E, et al. Peginterferon Alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B . *N Engl J Med*. 2005;352(26):2682-95.
2. Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. Gastroenterology. 2009;137(5):1593-608.
3. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology*. 2011;140(1):132-43.
4. Chan HL, Chan CK, Chan AJ, et al. Tenofovir DF (TDF) compared to emtricitabine (FTC)/TDF in HBeAg-positive, chronic hepatitis B (CNB) virus-infected patients in the immune tolerant (IT) phase. Abstract 101. The International Liver Conference, EASL, Amsterdam, April, 2013.
5. Zoulim F, Mason WS. Reasons to consider earlier treatment of chronic HBV infections. *Gut*. 2012;61(3):333-6..
6. Zoulim F. Are novel combination therapies needed for chronic hepatitis B?*Antiviral research*. 2012;96(2):256-9.

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# REGRESSION OF CIRRHOSIS WITH ANTIVIRAL TREATMENT

Marcellin P, Gane E, Buti M, et al. Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. *Lancet*. 2013 Feb 9;381(9865):468-475. doi: 10.1016/S0140-6736(12)61425-1.



Four hundred million people worldwide are infected with hepatitis B virus, and epidemiologic studies estimate that up to 25% of these die of liver cirrhosis or hepatocellular carcinoma (HCC). None of the currently available treatments can eliminate with certitude the hepatitis B virus. In our clinical practice, therefore, it is important to focus not only on the virus but also on the liver disease itself. This study investigated whether HBV-induced liver disease can be cured or at least significantly improved.

This open label study examined the impact of tenofovir disoproxil fumarate (TDF) on histological liver changes after 240 weeks of treatment. Patients were recruited in 2005-2006 from different hepatology centers worldwide. The study contained a 48 week, randomized, double blind comparison of TDF and adefovir dipivoxil, after which patients were switched to open label TDF treatment. The study enrolled patients who had HBeAg-negative or HBeAg-positive chronic hepatitis B with compensated liver disease and pretreatment liver biopsy specimens that showed a Knodell necroinflammatory score of 3 or more (on a scale of 0 to 18). All patients had been HBsAg-positive for at least 6 months before screening. Patients were HBV mono-infected and had received less than 12 weeks of treatment with any nucleoside or nucleotide for HBeAg-positive patients, but could be pretreated with lamivudine for more than 12 weeks for the HBeAg-negative group. Patients with hepatocellular carcinoma or liver failure were excluded. The liver biopsies were analyzed by an independent pathologist unaware of the treatment outcome.

Three hundred forty-eight patients had biopsy at baseline and again at week 240. The results show that 304 patients (87%) had histological improvement of necroinflammatory lesions as defined by a >= 2 point reduction in Knodell necroinflammatory score. In fact, the proportion of patients with mild or no necroinflammation (Knodell 0-3) increased from 8% at baseline to 49% at year 1 ($P < 0.001$) and to 80% at year 5 ($P < 0.001$). One hundred seventy-six patients (51%) had regression of fibrosis, defined by a >= 1 unit regression of Ishak fibrosis score ($P < 0.0001$). At baseline 96 patients had cirrhosis; 71 (74%) of the patients with initial cirrhosis no longer had cirrhosis at week 240 (regression of Ishak score of at least one unit). Only three patients without cirrhosis at baseline progressed to cirrhosis at week 240. The difference between the proportion of patients with cirrhosis regression and those with cirrhosis progression was significant ($P < 0.0001$). Of the 96 patients with cirrhosis at baseline, all but one regressed more than 2 units of Ishak score, and more than half had a decrease of 3 units in Ishak fibrosis score. Patients with the highest liver injury score showed the greatest degree of improvement ($P < 0.0001$).

When comparing the patients who did not show fibrosis regression with those that did in terms of demographic characteristics, the factors differing significantly between the two groups were BMI < 25kg/m2 ($P < 0.01$), history of diabetes mellitus ($P = 0.001$), normal ALT levels under treatment ($P = 0.07$), and Knodell score category 0-3 on biopsy at year 5 ($P = 0.007$).

This is the first large scale study demonstrating the histological benefit of antiviral treatment with the new generation of nucleos(t)ide analogues. While two other studies demonstrated the benefit of long-term entecavir treatment on liver histology,[1,2] they enrolled a smaller number of patients, and neither included equivalent numbers of patients with cirrhosis. Here the regression of fibrosis was considerable, with decrease in Ishak score of three units for more than half of the patients with cirrhosis. Improvement of liver histology was higher when the initial liver injury was greater. Nonregression was shown to be associated with overweight, presence of diabetes mellitus, and continuing liver

inflammation (high ALT and elevated Knodell score after five years of treatment). These factors might be linked and should encourage us to check our patients for metabolic syndrome, because nonalcoholic steatohepatitis is a liver-damaging factor.

This study demonstrates explicitly that effective antiviral treatment can prevent liver fibrosis progression and even revert cirrhotic lesions to noncirrhotic liver. These findings may pave the way toward a cure of HBV-induced liver damage. Further complications, including hepatic decompensation and the development of hepatocellular carcinoma, can therefore be significantly reduced — was previously demonstrated by Liaw et al3 with lamivudine treatment of patients with advanced fibrosis. In the era of powerful nucleos(t)ide analogues, the improvement of the liver damage is one of the main treatment objectives and should be achievable in all patients with CHB.

**References**

1. Schiff ER, Lee SS, Chao YC, et al. Long-term treatment with entecavir induces reversal of advanced fibrosis or cirrhosis in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol*. 2011 Mar;9(3):274-276. doi: 10.1016/j.cgh.2010.11.040. Epub 2010 Dec 8.
2. Chang TT, Liaw YF, Wu SS, et al. Long-term entecavir therapy results in the reversal of fibrosis/cirrhosis and continued histological improvement in patients with chronic hepatitis B. *Hepatology*. 2010 Sep;52(3):886-893. doi: 10.1002/hep.23785.
3. Liaw YF, Sung JJ, Chow WC, et al; Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004 Oct 7;351(15):1521-1531.

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## REDUCING THE INCIDENCE OF HEPATOCELLULAR CARCINOMA WITH ANTIVIRAL TREATMENT

Hosaka T, Suzuki F, Kobayashi M, et al. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology*. 2013 Jul;58(1):98-107.

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The previous article described improvement of liver fibrosis during long-term antiviral treatment with TDF. A previous study by Liaw et al1 suggested a decrease of hepatocellular carcinoma (HCC) incidence in patients treated with lamivudine (LAM); however the long-term benefit was blunted by the emergence of antiviral drug resistance. Potent nucleos(t)ide analogues (NA) with a high barrier to resistance, such as entecavir (ETV) and tenofovir disoproxil fumarate (TDF), have been used more recently, but their benefit for the development of HCC has not been demonstrated. Whether these more potent antiviral treatments can reduce HCC incidence in the long-term is the important clinical issue addressed by these investigators. Four hundred seventy-two patients mono-infected with HBV and treated with ETV were recruited from 2004 to 2010 in Toranomon Hospital in Japan and compared to 1143 patients with HBV mono-infection without treatment. The patients treated with ETV had never been treated by NA before. Patients in the control group were recruited retrospectively between 1973 and 1999 and had not received any antiviral treatment during the observation period. Propensity score matching eliminated the baseline differences, and finally 316 patients per cohort were compared. Three HCC risk scales and risk scores based on recent publications [2-4] were applied to both cohorts and included age, gender, cirrhosis status, levels of alanine aminotransferase, HBeAg, baseline HBV DNA, albumin, and bilirubin.

A subanalysis of this study compared the incidence of HCC in patients treated with ETV to patients treated with LAM. A cohort of 492 LAM-treated patients were retrospectively recruited from 1995 to 2007. None of these patients had rescue therapy in case of viral resistance. Propensity score matching in these two groups resulted in a matched cohort of 182 patients.

HCC diagnosis was made predominantly by imaging but confirmed by fine-needle aspiration biopsy if imaging was not typical. The cumulative HCC incidence rates at five years were significantly lower in the ETV group (3.7 %) compared to the control group (13.7%; P < 0.001). When adjusting the patients for a number of known HCC risk factors by Cox proportional hazard regression analysis, it turned out that patients in the ETV group were less likely to develop HCC than those in the control group (hazard ratio: 0.37; 95% confidence interval: 0.15-0.91; P = 0.030). The greatest HCC risk reduction occurred in patients scoring higher on the risk scales.

Comparisons of HCC incidence in the ETV-treated group, nonrescued LAM-treated group, and control group showed a significant difference in cirrhotic patients. The HCC incidence reduction effect was the highest in the ETV-treated group compared to the control group (P < 0.001), also present in the LAM-treated group compared to the control group (p = 0.019), and significantly higher in patients treated with ETV compared to patients treated with LAM (P = 0.043).

This study confirms that HCC incidence can be reduced by long-term effective antiviral treatment. It clearly demonstrates that more powerful antiviral treatment with entecavir has a greater impact on HCC incidence than treatment with lamivudine. The beneficial effect of lamivudine is usually blunted by the high incidence of antiviral drug resistance. For instance, Zhang et al5 reported recently on a meta-analysis of 3644 patients which showed that patients who developed antiviral drug resistance had a 2.6 times higher risk of developing long-term complications.

The results of these studies emphasize that, in the future, a major public health challenge will be to expand access to these effective antiviral treatments in high endemic areas where patients are infected at younger age and are thus exposed to a high risk of HCC development.

**Reference**

1. Liaw YF, Sung JJ, Chow WC, et al; Cirrhosis Asian Lamivudine Multicentre Study Group. Lamivudine for patients with chronic hepatitis B and advanced liver disease. *N Engl J Med*. 2004 Oct 7;351)15):152-31.
2. Yang HI, Yuen MF, Chan HL, et al; REACH-B Working Group. Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. *Lancet Oncol*. 2011 Jun;12(6):568-74.
3. Yuen MF, Tanaka Y, Fong DY, et al. Independent risk factors and predictive score for the development of hepatocellular carcinoma in chronic hepatitis B. *J Hepatol*. 2009 Jan; 50(1):80-88. doi: 0.1016/j.jhep.2008.07.023. Epub 2008 Sep 21.
4. Wong VWS, Chan SL, Mo F, et alk. Clinical scoring system to predict hepatocellular carcinoma in chronic hepatitis B carriers . *J Clin Oncol*. 2010 Apr 1;28(10):1660-5.
5. Zhang QQ, An X, Liu YH, et al. Long-term nucleos(t)ide analogues therapy for adults with chronic hepatitis B reduces the risk of long-term complications: a meta-analysis. *Virol J*. 2011 Feb 15;8:72.

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## HBV SURFACE ANTIGEN CLEARANCE BY INTERFERON TREATMENT: ROLE OF IL28B POLYMORPHISMS

Lampertico P, Viganò M, Cheroni C, et al. IL28B polymorphisms predict interferon-related hepatitis B surface antigen seroclearance in genotype D hepatitis B e antigen-negative patients with chronic hepatitis B. *Hepatology.* 2013 Mar;57(3):890-896.

View journal abstract

Achieving HBV surface antigen clearance is the most desirable treatment endpoint leading to a cure of HBV infection. While this goal can sometimes be achieved with interferon treatment, success rates are low and the poor tolerability of interferon still limits its use. The known predictive factors of good response to interferon are often underrepresented in

a particular geographical area (young age, elevated baseline transaminases, low baseline viremia) or vary over time, and are thus difficult to apply. Il28B polymorphism has proved to predict viral clearance during antiviral therapy for chronic hepatitis C. Whether IL28B genotyping is useful in interferon treatment of patients infected with HBV is unknown. This is particularly true in patients who are negative for HBeAg, who are rarely treated with interferon and for whom robust predictive factors of response are lacking. The authors tried to answer to this question in this study.

This study retrospectively analyzed 110 patients with HBV monoinfection and were negative for HBeAg, most of them infected with genotype D (92%). All patients in this cohort had been treated with standard Interferon or pegylated interferon α2a for 10-48 months (median 23 months), with a follow-up of 1-17 years (median 11 years). The IL28B polymorphism was analyzed for all patients: 48 patients were found to be CC, 42 patients CT, and 11 patients TT. The 3 IL28B groups were comparable in age, gender, serum ALT levels, HBV DNA levels, cirrhosis, type of IFN administered, duration of treatment, and follow-up.

End of treatment response (defined by undetectable HBV DNA or < 2000 IU/ml at end of treatment) and sustained virological response (defined by undetectable HBV DNA or < 2000 IU/ml at six months post-treatment) were significantly higher in patients with CC than those without (end of treatment response was 69% in CC vs 44% in non-CC, P = 0.014 and sustained virological response was 31% in CC vs 13% in non-CC, P = 0.025). During a median follow-up of 11 years post-treatment, 21 patients (21%) cleared HBsAg and 15 developed anti-HBs titers > 10 IU/mL. HBsAg clearance rates were 29% (14 patients) in CC, 7% (3 patients) in CT, and 36% (4 patients) in TT. By univariate analysis, baseline HBV DNA, ALT, duration of treatment, post-treatment follow-up, and IL28B polymorphisms — but not age, gender, cirrhosis, HBV genotype, and type of IFN — were significantly associated with HBsAg clearance. At multivariate analysis, baseline HBV DNA levels (OR, 0.31; 95% CI: 0.15-0.62; P = 0.001), ALT levels (OR, 1.0; 95% CI: 1.0-1.0; P = 0.03), duration of IFN therapy (OR, 1.20; 95% CI: 1.04-1.39; P = 0.012), and genotype CC (OR, 3.6; 95% CI: 1.05-12.5; P = 0.04) predicted HBsAg seroclearance. By combining HBV DNA, ALT, and IL28B genotype, patients were classified into four different groups characterized by increasing rates of HBsAg loss. In the group with low viral DNA (< 6 log cp/mL) and high ALT levels (>136 U/l) and IL 28 B polymorphism CC, the HBsAg clearance rate was as high as 60%.

This study is another step toward HBV treatment optimization and individualization. As the tolerability of interferon is poor, finite duration of treatment and better criteria to accurately identify possibly responders to interferon are needed. In patients positive for HBeAg, the IL28B polymorphism has been described to predict response to pegylated interferon treatment for HBeAg clearance but not HBsAg clearance.[1] To date there have been no data concerning patients who are negative for HBeAg.

The results of this study show that HBsAg clearance in the subgroup of patients with IL28B CC, low HBV DNA levels, and high ALT levels was as high as 60%, indicating that IL28B might therefore be a strong predictor for HBsAg clearance. This predictor is independent of the phase of HBV infection. This study also confirmed the previously known predictive factors of favorable response, ie ALT level and viral load, as demonstrated in other studies [2]. Previous studies attempted to define stopping rules (lack of HBsAg and HBV DNA decline at week 12 compared to baseline) to avoid unnecessarily prolonged interferon treatment in patients who were negative for HBeAg.[3] Gradually, more data are becoming available to optimize our treatment strategies by identifying patients who are negative for

HBeAg, offering a better chance of response to interferon therapy and avoiding useless extension of treatment duration.

One can argue that the study was performed on a small number of patients and the results must be confirmed by larger prospective studies. Furthermore, the restriction of the study population to viral genotype D infection limits its use in clinical practice. Since viral genotype influences the response to interferon treatment, more data are needed to confirm the predictive value of IL28B polymorphism in patients infected with other genotypes.[4]

**Reference**
1. Sonneveld MJ, Wong VW, Woltman AM, et al. Polymorphisms Near IL28B and Serologic Response to Peginterferon in HBeAg-Positive Patients With Chronic Hepatitis B. *Gastroenterology*. 2012 Mar;142(3):513-520.e1. doi: 10.1053/j.gastro.2011.11.025. Epub 2011 Nov 19.
2. Bonino F, Marcellin P, Lau GK, et al. Predicting response to peginterferon alpha-2a, lamivudine and the two combined for HBeAg-negative chronic hepatitis B. *Gut*. 2007 May;56(5):699-705. Epub 2006 Nov 24.
3. Rijckborst V, Hansen BE, Cakaloglu Y, et al. Early on-treatment prediction of response to peginterferon alfa-2a for HBeAg-negative chronic hepatitis B using HBsAg and HBV DNA levels. *Hepatology*. 2010 Aug;52(2):454-461. doi: 10.1002/hep.23722.
4. Moucari R, Martinot-Peignoux M, Mackiewicz V, et al. Influence of genotype on hepatitis B surface antigen kinetics in hepatitis B e antigen-negative patients treated with pegylated interferon-alpha2a. *Antivir Ther*. 2009 14(8):1183-1188. doi: 10.3851/IMP1458.

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## PREDICTION OF HBSAG CLEARANCE DURING NUCLEOS(T)IDE ANALOGUE (NA) THERAPY

Seto WK, Wong DK, Fung J, et al. Reduction of hepatitis B surface antigen levels and HBsAg seroclearance in chronic hepatitis B patients receiving 10 years of nucleoside analogue therapy. *Hepatology*. 2013 Mar 6. [Epub ahead of print]

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The Holy Grail of antiviral therapy of chronic hepatitis B (CHB) is to achieve HBsAg loss and seroconversion. In that respect, the quantification of serum HBsAg levels may represent a clinically relevant tool to monitor the effect of antiviral treatment.

Although serum HBsAg levels have been demonstrated to predict sustained viral suppression after pegylated interferon therapy in CHB, the role of serum HBsAg measurement during NA therapy has not been well-defined. Most recent studies have been based on relatively small number of patients and short-term duration of NA administration.

In this study, the authors have investigated the kinetics of HBsAg clearance in patients who received long-term lamivudine therapy with a maintained virologic response (HBV DNA below 2,000 IU/mL). From 1994 to 2002, 322 Chinese patients with CHB were started on lamivudine in their center. Patients were recruited if they had been continuously treated with lamivudine for at least 10 years and maintained favorable virologic responses throughout therapy (HBV DNA < 2,000 IU/mL). HBsAg and HBV DNA levels were measured serially, and the predictability of HBsAg kinetics in determining NA-related HBsAg seroclearance was determined. Seventy patients were recruited for this study, of whom 43 (61.4%) were positive for HBeAg. Fifty-two (74.3%) had undetectable viremia (HBV DNA < 20 IU/mL) during therapy. Fifteen patients (21.4%) were followed up for 15 years. The median rate of HBsAg reduction was 0.104 log IU/mL/year, with no significant difference found when comparing patients who were positive or negative for HBeAg-, genotype B versus C, and detectable versus undetectable viremia during therapy (all $P > 0.05$). Seven patients (10%) achieved HBsAg seroclearance, and when compared with the remaining 63 patients, had a significantly lower median baseline HBsAg levels ($P = 0.012$) and a greater median rate of HBsAg reduction ($P < 0.001$). Baseline HBsAg levels and the rate of HBsAg reduction achieved an AUROC of 0.860 ($P = 0.004$, 95% confidence interval 0.742-0.978) and 0.794 ($P = 0.018$, 95% confidence interval 0.608-0.979), respectively. Baseline HBsAg < 1,000 IU/mL and on-treatment reduction of HBsAg > 0.166 log IU/mL/year were optimal cut-off levels in predicting subsequent HBsAg seroclearance (negative predictive values 98.1% and 97.8% respectively). The authors concluded that low baseline HBsAg levels and greater rate of HBsAg reduction achieved high predictive values for predicting HBsAg seroclearance, strengthening the prognostic role of HBsAg measurements during NA therapy.

This is an interesting study showing the kinetics of HBsAg decay observed in patients receiving long-term lamivudine therapy associated with a good virologic response. It

showed that in the majority of patients, despite viral suppression, the kinetics of HBsAg loss are similar to those observed during the natural history of the disease. The identification of factors predicting HBsAg loss at baseline and during therapy could also be clinically valuable for managing the patients under NA therapy.

However, other studies with tenofovir disoproxil fumarate1 showed that patients who achieved HBsAg loss had a high baseline Knodell necroinflammatory score and higher HBV DNA and HBsAg levels; and were mainly infected with non-Asian viral genotypes (genotype A (60%), D (35%), or F (5%); all were non-Asian; 65% had bridging fibrosis or cirrhosis; and the majority were male.

These different clinical observations may not be contradictory, but may reflect the heterogeneity of patients and viral disease, including host genetic factors, viral factors such as viral genome heterogeneity, liver disease severity, and other unknown factors related to the fine interplay between HBV replication and the host responses. More studies are therefore required to identify clinical predictors of HBsAg loss during NA therapy that would be applicable to different patient populations around the world.

**Reference**

1. Heathcote EJ, Marcellin P, Buti M, et al. Three-year efficacy and safety of tenofovir disoproxil fumarate treatment for chronic hepatitis B. *Gastroenterology.* 2011;140:132-43.

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## HBSAG LEVELS—A SURROGATE MARKER OF cccDNA LOSS DURING NA THERAPY?

Wong DK, Seto WK, Fung J, et al. Reduction of Hepatitis B Surface Antigen and Covalently Closed Circular DNA by Nucleos(t)ide Analogues of Different Potency. *Clin Gastroenterol Hepatol*. 2013 Aug;11(8):1004-1010.

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Wong et al addressed an important question: could the quantification of serum HBsAg be a surrogate marker of intrahepatic cccDNA? The study also tried to obtain information about the magnitude of NUC-induced viral suppression in the liver, as well as the kinetics of clearance of cccDNA and HBsAg during NUC therapy.

The authors had access to paired liver biopsy samples taken at baseline and after one year of therapy from a group of 124 patients who were treated with one of the five NUCs (lamivudine, adefovir, entecavir, telbivudine, or clevudine). Among the 117 patients who did not develop resistance, the evaluation of viral suppression showed an average reduction of approximately 0.2 log10 IU/mL in HBsAg, 5 log10 IU/mL in serum level of HBV DNA, 2 log10 copies/cell in intrahepatic total HBV DNA, and 1 log10 copy/cell in cccDNA. Although 88/117 patients (75%) had undetectable serum levels of HBV DNA (< 12 IU/mL), all had detectable levels of HBsAg, and only five (4%) had undetectable levels of cccDNA. Patients with greater reductions in levels of cccDNA had greater reductions in HBsAg, but these reductions did not reach statistically significant correlations.

These results are consistent with previous observations that the kinetics of cccDNA clearance are slow, with the same magnitude of reduction as that observed previously in adefovir or lamivudine studies.[1,2] Assuming that the kinetics would be identical beyond one year of therapy, it was predicted that more than 14 years of therapy would be needed to eradicate cccDNA.[1] Interestingly, Wong's group found that the reduction of cccDNA levels after one year of therapy was similar across all five NUCs studied, regardless of their antiviral potencies.[3] This indicates that, despite a different magnitude of inhibition of viral DNA synthesis and virion DNA release, the pool of cccDNA was affected in a similar manner during the observation period. Unfortunately, data are still missing on cccDNA kinetics beyond one year of therapy with entecavir and tenofovir, the two most potent drugs with a high barrier to resistance. One recent study showed that, in a cohort of patients with HIV-HBV coinfection, the decline of cccDNA in liver biopsies obtained three years apart was very slow.[4]

Another important question is whether serum HBsAg quantification could be a surrogate marker of intrahepatic cccDNA levels. A number of studies have analyzed the clinical relevance of HBsAg quantification for monitoring antiviral therapy with interferon alpha or NUCs, as well as for deciding treatment adaptation.[5] Most of these studies have shown that the kinetics of HBsAg decay are very slow in the majority of NUC treated patients;[6,7] the prediction is that more than 50 years of therapy would be needed to obtain HBsAg loss with the currently available treatments.[6] The current analysis by Wong et al is also consistent with those previous observations.[3] The question about using HBsAg quantificatin to predict the levels of intrahepatic cccDNA was also previously addressed. Different results were obtained in different studies when assessing these two parameters on a single time point,[1,8] probably because the regulation of HBsAg expression is complex and includes more parameters than the amount of cccDNA in infected cells. The only trend that has been consistently found is a parallel decrease of serum HBsAg and intrahepatic cccDNA.[1, 9]

The results of all these clinical studies are consistent with the fact that prolonged administration of NUC is required to achieve a significant decrease of serum HBsAg and/or intrahepatic cccDNA levels in the majority of patients.

**Reference**


1. Werle-Lapostolle B, Bowden S, et a;. Persistence of cccDNA during the natural history of chronic hepatitis B and decline during adefovir dipivoxil therapy. *Gastroenterology*. 2004;126:1750-1758.
2. Sung JJ, Wong ML, Bowden S, Let al. Intrahepatic hepatitis B virus covalently closed circular DNA can be a predictor of sustained response to therapy. *Gastroenterology*. 2005;128:1890-1897.
3. Wong DK, Seto WK, Fung J, et al. Reduction of Hepatitis B Surface Antigen and Covalently Closed Circular DNA by Nucleos(t)ide Analogues of Different Potency. *Clinical Gastroenterol Hepatol*. 2013 Aug:11(8):1004-1010.
4. Lacombe K, Boyd A, Lavocat F, et al. High incidence of treatment-induced and vaccine-escape hepatitis B virus mutants among HIV-hepatitis B infected patients. *Hepatology*. 2013 Mar 6 [Epub ahead of print]
5. Janssen HL, Sonneveld MJ, Brunetto MR. Quantification of serum hepatitis B surface antigen: is it useful for the management of chronic hepatitis B? *Gut*. 2012;61:641-5.
6. Chevaliez S, Hezode C, Bahrami S, et al. Long-term hepatitis B surface antigen (HBsAg) kinetics during nucleoside/nucleotide analogue therapy: Finite treatment duration unlikely. *J Hepatol*. 2013 Apr;58(4):676-83. doi: 10.1016/j.jhep.2012.11.039. Epub 2012 Dec 3.
7. Borgniet O, Parvaz P, Bouix C, et al. Clearance of serum HBsAg and anti-HBs seroconversion following antiviral therapy for chronic hepatitis B. *J Med Virol*. 2009;81:1336-1342.
8. Thompson AJ, Nguyen T, Iser D, et al. Serum hepatitis B surface antigen and hepatitis B e antigen titers: disease phase influences correlation with viral load and intrahepatic hepatitis B virus markers. *Hepatology*. 2010;51:1933-44.
9. Wursthorn K, Lutgehetmann M, Dandri M, et al. Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B. *Hepatology*. 2006;44:675-684.


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## KINETICS OF cccDNA AND HBSAG DECLINE DURING COMBINATION THERAPY FOR CHB

Lutgehetmann M, Volzt T, Quaas A, et al. Sequential combination therapy leads to biochemical and histological improvement despite low ongoing intrahepatic hepatitis B virus replication. *Antivir Ther*. 2008;13(1):57-66.

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In this paper, the authors sought to determine whether sequential combination therapy of pegylated interferon (peg-IFN) with adefovir dipivoxil (ADV) followed by ADV monotherapy could lead to improved virologic and clinical efficacy. This was an important study because previous clinical trials of de novo combination therapy of lamivudine with pegylated interferon did not show a benefit in terms of virologic or clinical off-treatment responses. It was therefore clinically relevant to evaluate new schedules of administration of a NUC with peg-IFN.

The design of this pilot study was to administer 48 weeks of combination therapy with pegylated interferon-alpha2b and adefovr dipivoxil, followed by 96 weeks of ADV monotherapy in 24 patients with chronic hepatitis B. In a previous paper, these authors observed marked decreases of HBV covalently closed circular DNA (cccDNA) (-2.4 log10 copies/ml) during the phase of combination therapy. They now report the final outcome after 144 weeks of sequential antiviral treatment.

At week 144, 12 of 15 patients positive for HBeAg had lost HBeAg; ALT levels were normal in 23 patients (96%); and median serum HBV DNA had decreased by -4.9 log10 copies/ml and was undetectable (<100 copies/ml) in 11 of 24 patients (46%). Median total intrahepatic HBV DNA had decreased by -2.2 log. Overall, four of the 24 patients achieved HBsAg loss. Although no further significant cccDNA changes occurred between week 48 and week 144, two years of ADV monotherapy proved capable of controlling cccDNA levels in most patients. Analysis of intrahepatic HBV DNA species demonstrated that combination therapy with PEG-IFN and ADV inhibited viral productivity by 99% and subsequent ADV monotherapy by 76%, respectively. Virus suppression to undetectability within the first 12 weeks of treatment was strongly associated with long-term virological response and HBeAg and HBsAg seroconversion. Histological improvement was determined in 11 of 16 patients at week 144. Two patients developed ADV resistance during the third year of treatment. The authors concluded that reduction of intrahepatic viral load achieved after 48 weeks of combination therapy with PEG-IFN and ADV was maintained at 96 weeks of ADV monotherapy and translated into long-term clinical benefit for most of the treated patients.

The results of this study are interesting in that they show that maximal viral suppression—evaluated by intrahepatic viral DNA, including cccDNA, and serum markers including quantification of HBV DNA and HBsAg — was observed during the first phase of combination therapy. The magnitude of viral suppression was maintained in most patients during the second phase of ADV monotherapy. These findings may reflect the combined action of ADV on the intracellular recycling pathway of cccDNA2 and that of peg-IFN on the inhibition of the transcriptional activity of cccDNA.

On the other hand, other recent studies[1-4] have shown that restoration of specific CD4/CD8 T cell responses are observed after several years of NUC-induced viral suppression. This may open the possibility to study other regimens of combination based on peg-IFN add-on after obtaining viral suppression and restoration of cellular immune responses with long-term NUC administration.

These clinical data suggest a potential benefit for a combination of peg-IFN and NUC to enhance viral suppression and eventually achieve HBsAg loss; however, they also point out that the optimal schedule of administration might depend on each individual patient situation.

**Reference**


1. Wursthorn K, Lutgehetmann M, Dandri M, Volz T, Buggisch P, Zollner B, Longerich T, Schirmacher P, Metzler F, Zankel M, Fischer C, Currie G, Brosgart C, Petersen J. Peginterferon alpha-2b plus adefovir induce strong cccDNA decline and HBsAg reduction in patients with chronic hepatitis B. *Hepatology*. 2006 Sep;44(3):675-684.
2. Werle-Lapostolle B, Bowden S, Locarnini S, Wursthorn K, Petersen J, Lau G, Trepo C, Marcellin P, Goodman Z, Delaney WEt, Xiong S, Brosgart CL, Chen SS, Gibbs CS, Zoulim F. Persistence of cccDNA during the natural history of chronic hepatitis B and decline during adefovir dipivoxil therapy. *Gastroenterology* 2004;126:1750-1758.
3. Belloni L, Allweiss L, Guerrieri F, Pediconi N, Volz T, Pollicino T, Petersen J, Raimondo G, Dandri M, Levrero M. IFN-alpha inhibits HBV transcription and replication in cell culture and in humanized mice by targeting the epigenetic regulation of the nuclear cccDNA minichromosome. *J Clin Invest*. 2012;122:529-537.
4. Boni C, Laccabue D, Lampertico P, Giuberti T, Vigano M, Schivazappa S, Alfieri A, Pesci M, Gaeta GB, Brancaccio G, Colombo M, Missale G, Ferrari C. Restored function of HBV-specific T cells after long-term effective therapy with nucleos(t)ide analogues. *Gastroenterology*. 2012;143:963-973 e9.


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