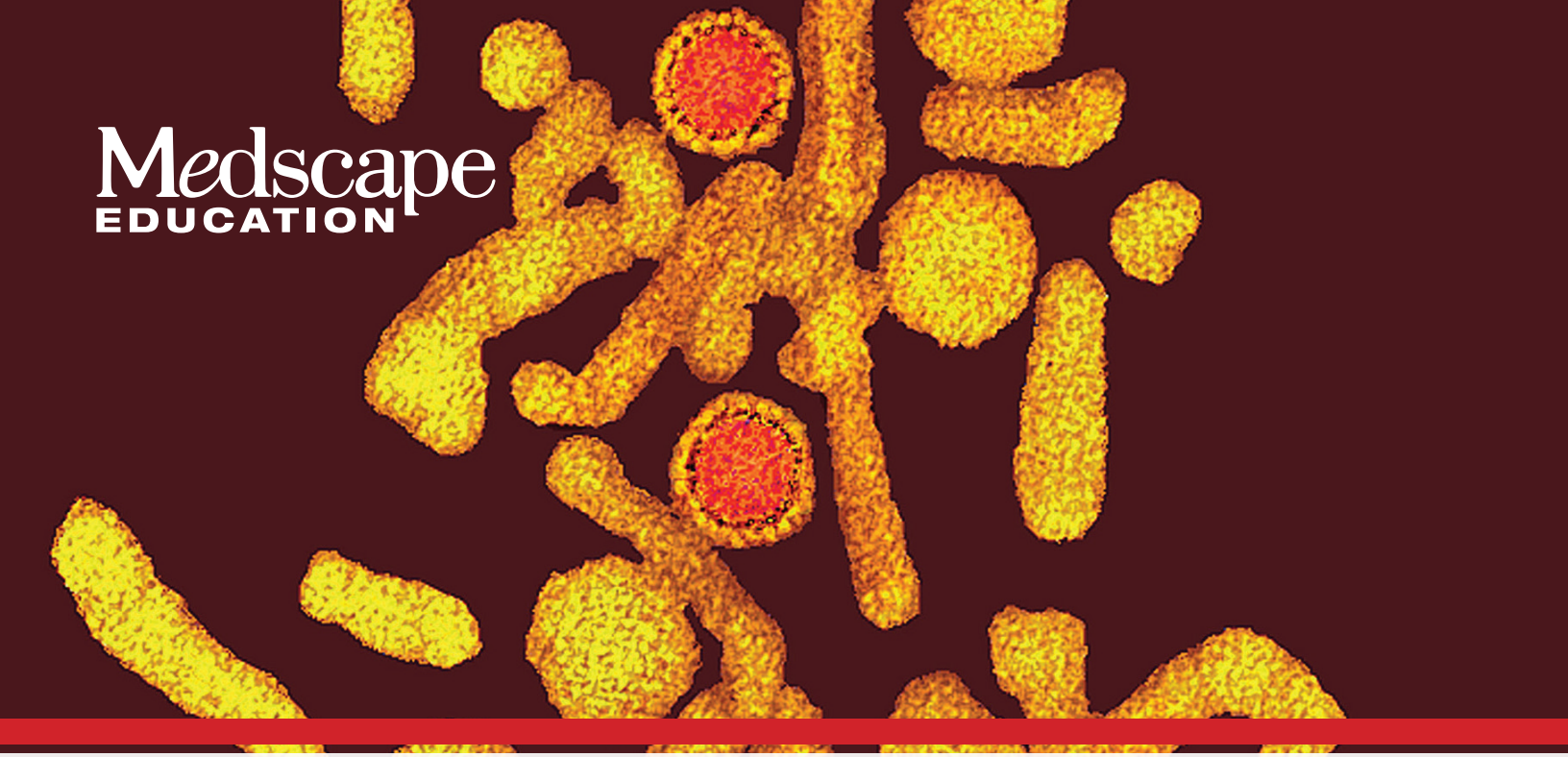

Medscape EDUCATION

# Evaluating Response to Treatment in Patients With Chronic HBV Infection CME


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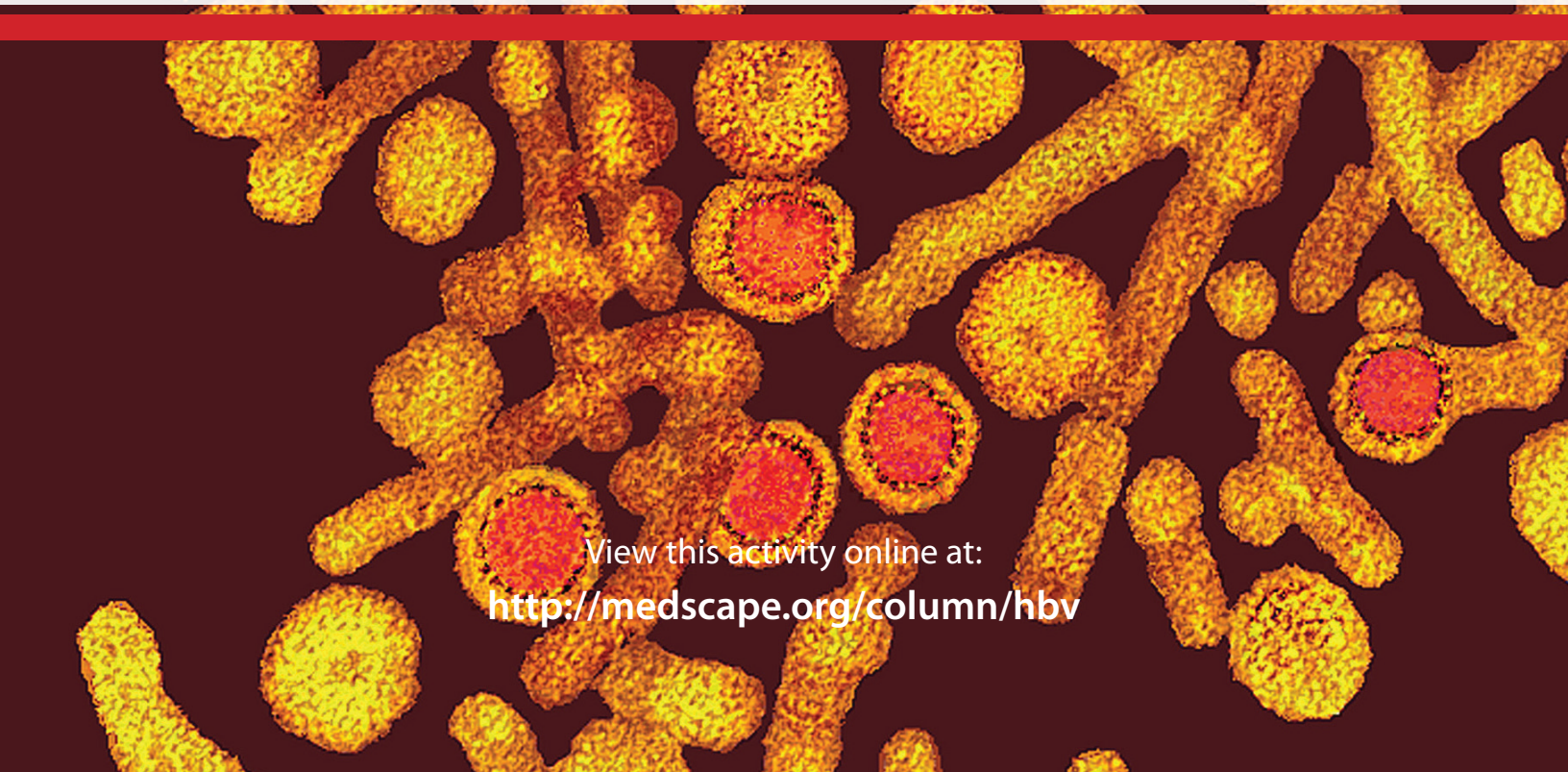

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## Target Audience

This activity is intended for gastroenterologists.

## Goal

The goal of this activity is to further educate physicians who manage hepatitis B virus (HBV) in defining treatment goals, reducing time to appropriate initiation of treatment, and increasing the use of predictors of response and continued monitoring strategies to individualize care within the framework of optimal long-term disease management and reduction of liver-related morbidity and mortality.

## Learning Objectives

Upon completion of this activity, participants will be able to:

1. Summarize the goals of HBV therapy and endpoints for treatment based on patient-specific characteristics
2. Integrate factors involved in disease progression, baseline predictors of treatment response, and on-treatment predictors of treatment response into the development of individualized treatment strategies
3. Differentiate among types of treatment response to actively and effectively care for patients receiving HBV antiviral therapy, including determination of when to stop or alter therapy

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# Evaluating Response to Treatment in Patients With Chronic HBV Infection CME

Kris V. Kowdley, MD

## Introduction

Response to treatment for chronic hepatitis B virus (HBV) infection can be monitored through biochemical, serologic, and virologic measures. Goals of treatment in the past focused on achieving biochemical and serologic response -- with biochemical response indicating a reduction in serum alanine aminotransferase (ALT) level to within the normal range, and serologic response describing outcomes such as loss of hepatitis B e antigen (HBeAg) or hepatitis B surface antigen (HBsAg), or seroconversion from HBeAg- or HBsAg-positive status to hepatitis B e antibody (HBeAb) and hepatitis B surface antibody (HBsAb) status.

## Measures of Success

Today, however, virologic response is considered the best measure of treatment effectiveness. Virologic response, as defined in the American Association for the Study of Liver Diseases (AASLD) Practice Guidelines, indicates complete viral suppression demonstrated by lack of detectable HBV DNA in serum using a sensitive polymerase chain reaction-based assay, and loss of HBeAg in a patient who was previously HBeAg positive. Currently, biochemical response does not carry much clinical relevance; it has been established that the majority of patients who achieve a virologic response also have a biochemical response. Achieving serologic and virologic responses are considered much more important goals of treatment than achieving a biochemical response.

Sustained virologic suppression can now be achieved in most patients with the use of safe and effective antiviral therapies, and the emphasis has now shifted toward achieving and maintaining prolonged suppression of virologic replication. The rationale for prolonged virologic suppression as a goal of treatment is supported by recent studies that demonstrate a clear relationship between viral load and development of both cirrhosis and hepatocellular carcinoma (HCC).[1,2] At least 1 major prospective randomized trial has shown an association between prolonged virologic suppression and reduced rates of liver disease decompensation and HCC.[3]

As with response to therapy, relapse can be defined in biochemical, serologic, or virologic terms, and the term relapse must be distinguished from the terms breakthrough and rebound. Relapse should be restricted to describe recurrent viremia, HBeAg or HBsAg seroreversion, or elevation of serum ALT after discontinuation of treatment. (Virologic breakthrough is defined by the AASLD Practice Guidelines as "increase in serum HBV DNA by > 1 log10 [10-fold] above nadir after achieving virologic response, during continued treatment."[4] Virologic rebound is defined as increase in HBV DNA level to > 20,000 IU/mL or to a level higher than pretreatment.[4])

## Initiating Treatment and Goals

Goals of treatment for chronic HBV infection are to prevent progression of liver disease, reduce the risk for HCC, and achieve normal life expectancy for the patient. To accomplish these goals, we initiate treatment to achieve and maintain complete viral suppression, and seroconversion from HBeAg to HBeAb status. A highly desired, but rarely achieved, endpoint is loss of HBsAg with or without HBsAb seroconversion.

Recommendations for starting and discontinuing treatment differ depending on HBeAg status. For patients with HBeAg-positive chronic HBV infection, the AASLD guidelines recommend treatment for those with HBV DNA > 20,000 IU/mL and elevated serum ALT > 2 times upper limit of normal. By contrast, the European Association for the Study of the Liver (EASL) guidelines recommend treatment for HBeAg-positive patients with serum HBV DNA > 2000 IU/mL.[5] Both EASL and AASLD guidelines recommend that treatment in patients who are HBeAg negative be considered in the presence of HBV DNA > 2000 IU/mL and elevated serum ALT.[4,5]

## What to Monitor During Treatment

AASLD and EASL have published guidelines for monitoring patients undergoing treatment for chronic HBV infection.[4,5] AASLD guidelines recommend that patients undergoing oral antiviral therapy should have serum liver enzymes monitored every 12 weeks during treatment and serum HBV DNA monitored every 12-24 weeks on treatment. HBeAg and HBeAb serologies every 6 months are recommended for patients who are initially HBeAg positive. HBsAg and HBsAb serology should be obtained every 24-48 weeks in HBeAg-negative patients undergoing oral antiviral therapy.[4]

For patients on interferon (IFN) therapy, complete blood count and liver function tests should be obtained every 4 weeks. Serum HBV DNA and thyroid-stimulating hormone (TSH) levels are recommended every 12 weeks, and HBeAg and HBeAb serologies are recommended every 24 weeks. Post-treatment monitoring also is recommended 12 and 24 weeks after treatment, including blood count, TSH, and HBV DNA level, as well as serologies for HBeAg and HBeAb in patients who were HBeAg positive prior to initiation of treatment. (Measurement of HBsAg titer, which has recently been shown to offer important information about treatment response, is discussed below.)

Side effects are rare with entecavir and tenofovir. Fanconi syndrome, osteomalacia, and renal phosphate wasting have been reported with tenofovir and adefovir, and the AASLD guidelines recommend monitoring serum creatinine every 3 months in patients receiving these agents. (Renal complications with tenofovir have, however, been reported mainly in patients undergoing treatment for HIV, not HBV.[4,5]) Lactic acidosis, a rare side effect associated with this class of antiviral agents, has been reported with entecavir and tenofovir in patients with advanced liver disease or HIV infection.[6] Lactic acidosis and mitochondrial toxicity are rare in patients undergoing monotherapy for HBV with entecavir and tenofovir.[7,8] Myopathy and peripheral neuropathy have been reported with telbivudine as well as clevudine.[7,9]

IFN-alpha is associated with different side effects than those seen with oral agents, including flu-like symptoms, cytopenias, exacerbation or development of autoimmune conditions, injection site reactions, and neuropsychiatric symptoms.[4] In addition, IFN-alpha also has been associated with the risk for a flare of liver disease during treatment. Some guidelines, such as those from AASLD suggest that IFN-based therapy is not ideal for patients who have cirrhosis, with the AASLD suggesting that patients with compensated cirrhosis "are best treated with NAs [nucleos(t)ide analogs] because of the risk of hepatic decompensation associated with IFN-related flares of hepatitis." In contrast, the EASL HBV treatment guidelines support the use of IFN-alpha for patients with "well-compensated cirrhosis."[5] Therefore, patients undergoing treatment with IFN-alpha require more frequent monitoring.

## Monitoring Response to Treatment: HBV DNA Level Tells the Story

The main goal of treatment for chronic HBV infection is suppression of viral replication without virologic breakthrough or rebound (either of which suggest nonadherence to treatment or emergence of antiviral resistance). As noted above, it is important that serum HBV DNA level be monitored after 12 weeks of treatment and then at least every 24 weeks; both the AASLD and EASL guidelines recommend that HBV DNA level be monitored every 12-24 weeks throughout the course of treatment.

Treatment with entecavir and tenofovir is associated with rapid reduction in serum HBV DNA level. The majority of treatment-naive HBeAg-positive patients have undetectable HBV DNA levels after 1 year of treatment (67%-76%)[4] and most achieve undetectable HBV DNA after 2 or more years of treatment. HBeAg seroconversion occurs in 21% of patients after 1 year of treatment with entecavir and tenofovir.[4] HBeAg seroconversion identifies patients in whom treatment can be discontinued; a low relapse rate is seen in patients who achieve complete suppression of HBV DNA and HBeAg seroconversion, and they are given an additional 6-12 months of treatment after HBeAg seroconversion and undetectable HBV DNA.[10,11]

The goal of treatment in a patient who has HBeAg-negative chronic HBV infection (prolonged viral suppression) generally requires long-term treatment. HBV DNA levels tend to be lower among patients with HBeAg-negative disease, and therefore a high proportion of these patients (80%-90%) achieve undetectable serum HBV DNA levels after 1 year of treatment. Relapse is common, however, if treatment is discontinued after 1 or 2 years of treatment, and patients with HBeAg-negative chronic HBV infection generally require a longer duration of treatment. In the rare event of HBsAg loss associated with viral suppression, treatment discontinuation may be considered in patients without cirrhosis. (Note that close monitoring of serum HBV DNA at least every 3 months is indicated if treatment is discontinued.)

The rate of HBsAg loss with oral agents is negligible, although it may approach 7%-9% with pegylated IFN (PEG-IFN) therapy.[12] Recent data suggest that quantitative HBsAg titers may help predict off-treatment sustained response in HBeAg-negative disease treated with PEG-IFN.[11] Similarly, the decline in HBsAg titers has also been found to predict HBeAg loss among HBeAg-positive patients treated with both PEG-IFN and entecavir, and it may be useful in the future in predicting treatment response.[13,14]

## Decision Points During Treatment

The choice of therapeutic agent should be revisited if no progressive decline is seen in serum HBV DNA level during treatment. Adherence to the drug regimen should be reviewed with the patient, and alternative treatment strategies should be considered as appropriate. Resistance testing can be helpful in patients who have previously received adefovir or lamivudine. There is growing consensus that sequential monotherapy is not the best approach, given the higher risk for resistance.[15] Multidrug resistance has been reported, and may pose a serious challenge because nucleos(t)ide analogs are the only oral drugs available to treat chronic HBV infection.[16]

## Summary

All patients undergoing treatment for chronic HBV infection should be monitored with periodic measurement of serum HBV DNA levels to assess treatment success, detect suboptimal responders, and identify early those patients at risk for resistance to treatment. Treatment endpoints include disappearance of HBV DNA from serum, HBeAg loss and seroconversion, and HBsAg loss. Treatment should be continued indefinitely in patients who have cirrhosis but may be discontinued among HBeAg-positive patients who achieve a 3-point seroconversion. The minimum duration of treatment in HBeAg-negative patients is not known, and it is likely that several years of treatment may be required. Discontinuation may be considered with HBsAg loss or seroconversion.

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