JOHNS HOPKINS MEDICINE
eLITERATURE REVIEW
eViralHepatitis Review
Jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing
Supported by educational grants from Gilead Sciences, Inc., Merck & Co., Inc., and AbbVie, Inc.

Spring 2017: Advances in HBV Therapies

In this Issue...

As knowledge about the hepatitis B virus expands, clinicians expand their ability to provide better care for more and more patients. However, the same research that provides answers also raises many questions. Who are the patients with indeterminant phenotypes and how should they be managed? How can the risks of vertical transmission be safely reduced? Tenofovir alafenamide (TAF) is a newly FDA approved prodrug of tenofovir — which patients are the most appropriate candidates for switching? What new treatments are on the horizon, and how do they differ from the current options?

In this issue, Dr. Daryl T. Y. Lau from Beth Israel Deaconess Medical Center and Harvard Medical School reviews some of the current investigations seeking to answer these vital questions.

LEARNING OBJECTIVES

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

- Identify patients with chronic hepatitis B for antiviral therapy and evaluate patients with indeterminant HBV phenotypes.
- Describe the efficacy, safety, and limitations of current FDA-approved nucleos(t)ide analogues.
- Discuss how the mechanisms of actions of emerging therapeutic agents affect the HBV life cycle.

GUEST AUTHOR OF THE MONTH

Commentary & Reviews

Daryl T. Y. Lau, MD, MSc, MPH
Associate Professor of Medicine
Beth Israel Deaconess Medical Center Harvard Medical School
Boston, Massachusetts

Guest Faculty Disclosure

Dr. Lau has indicated that she has received research funding from Gilead Sciences, Inc. and Bristol-Myers Squibb and has served as a consultant/advisor to Gilead Sciences, Inc., AbbVie, Inc., and the Asian Health Foundation

Unlabeled/Unapproved uses

Dr. Lau has indicated that she has no financial interests or relationships with a commercial entity whose products or services are relevant to the content of this presentation.

Volume 5
Issue 3

Program Information
CME Information
Accreditation
Credit Designations
Intended Audience
Statement of Need
Internet CME/CE Policy
Faculty Disclosure
Disclaimer Statement

Length of Activity
1.0 hour Physicians
1.0 hour Nurses

Launch Date
April 27, 2017

Expiration Date
April 26, 2019

COMPLETE THE POST-TEST

Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST

IN THIS ISSUE

Program Directors

Mark S. Sulkowski, MD
Professor of Medicine
Medical Director, Viral Hepatitis Center
Divisions of Infectious Diseases and Gastroenterology/Hepatology
Johns Hopkins University School of Medicine
Baltimore, Maryland

Raymond T. Chung, MD
Director of Hepatology and Liver Center
Vice Chief, Gastroenterology
Kevin and Polly Maroni Research Scholar
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

Taryn Haselhuhn, BA, BSN, MSN, CRNP
Nurse Practitioner
Johns Hopkins Hospital
Baltimore, Maryland

COMMENTARY

The natural history of chronic hepatitis B (CHB) is complex and variable. It is associated with serious complications such as hepatocellular carcinoma (HCC) and liver failure.[1] Four clinical phases of chronic HBV infection have traditionally been defined based on HBV DNA and alanine aminotransferases (ALT) levels.[2] The **immune tolerance phase** occurs primarily in patients who have been infected at birth and is characterized by presence of HBeAg, normal ALT, very high HBV DNA levels usually > 1,000,000 IU/mL and no or minimal histological inflammation or fibrosis. The **immune active phase** of HBeAg, positive CHB is characterized by periodic hepatitis flares with fluctuating ALT and HBV DNA levels that can result in liver injury. Eventually, at least 90% of persons with CHB will experience HBeAg seroconversion and develop antibody to HBeAg (anti-HBe). They will go into the **inactive phase**, which is characterized by normal ALT and low levels (usually < 2,000 IU/mL) or undetectable HBV DNA. Approximately 10%-20% of persons in the inactive phase will evolve to a HBeAg **negative immune active phase** with elevated ALT and HBV DNA levels (usually > 2000 IU/mL).

A number of guidelines from international liver societies focus on antiviral therapy in chronic hepatitis B. In the United States, the guideline developed by the American Association for the Study of Liver Diseases (AASLD) is most widely used.[3] The AASLD guideline recommends therapy for patients in the immune active phase based on serial HBV and ALT levels. It defined normal ALT as 30 U/L for males and 19 U/L for females. Treatment is recommended for those with persistent elevation of ALT greater than two times the upper limit of normal, plus elevated HBV DNA. Elevated HBV DNA is defined as > 20,000 IU/mL for HBeAg positive immune active patients and > 2,000 IU/mL for HBeAg negative immune active patients. Therapy is also recommended for persons with cirrhosis if HBV DNA > 2,000 IU/mL, regardless of the ALT level.

Additional factors influence the decision to treat patients who do not meet the ALT and HBV DNA treatment criteria. These factors include the presence of significant histological disease, family history of hepatocellular carcinoma (HCC), and presence of extrahepatic manifestations independent of liver disease severity. AASLD also recommends treating pregnant women with HBV DNA > 200,000 IU/mL in the third trimester of pregnancy to

prevent vertical transmission of HBV.[3]

A number of survey results suggest adherence to the AASLD treatment guidelines is suboptimal, with 40%-50% of eligible patients remaining untreated. Besides the lack of awareness or knowledge of the treatment recommendations, the complexity and evolving understanding of hepatitis B likely contribute to the uncertainty of recommending antiviral therapy. The recent study by Di Bisceglie and colleagues, reviewed herein, reported that a large proportion of patients with CHB have indeterminant HBV phenotypes that cannot be classified into the four traditionally defined phases of hepatitis B. AASLD recommends treatment for those with significant histological disease.

Liver biopsy is the most recognized modality to determine degree of hepatic inflammation and fibrosis. It is, however, invasive and is not readily accepted by patients. Major advances have been made in using validated noninvasive serological markers and liver stiffness measurements to determine hepatic fibrosis.[4] The application of these noninvasive modalities to evaluate patients with indeterminant HBV phenotypes will probably increase the number of patients who can benefit from antiviral therapy.

Currently, eight medications for chronic hepatitis B have been FDA approved. In addition to the standard interferon and long-acting pegylated interferon, there are six oral nucleos(t)ide analogues: lamivudine, adefovir, telbivudine, entecavir, and tenofovir, as well as the recently approved tenofovir alafenamide (TAF). Interferon has both antiviral and immunomodulatory activities. Its use has been limited because of its side-effect profile. Nucleos(t)ide analogues are potent antiviral agents that suppress HBV DNA replication by inhibiting the HBV polymerase. Prolonged use of lamivudine, adefovir, and telbivudine, however, has increased the development of drug-associated mutations. Entecavir and tenofovir have been considered the first-line treatment options because of their high barrier to drug-associated mutations. Cumulative evidence suggests that long term use of entecavir and tenofovir can lead to reduced risk of HCC.[5]

TAF is a new prodrug of tenofovir, approved by FDA for treating CHB in November 2016. In clinical trials, TAF 25 mg was found to have similar antiviral potency as tenofovir disoproxil fumarate (TDF) 300 mg. Due to its primary hepatic delivery and metabolism, as described in the 2016 AASLD conference presentation by Seto et al, TAF has demonstrated improved safety relative to TDF in bone mineral density and in multiple renal function parameters.

Even though these highly effective oral antiviral agents have demonstrated reduction in hepatic fibrosis and liver complications[6], indefinite duration of therapy is necessary to maintain prolonged viral suppression in a large proportion of patients. A recent paper by Testoni et al (described herein) details a number of novel therapeutic agents in various phases of clinical development that aim to control viral replication by disrupting targets of the HBV life cycle other than the HBV polymerase. In addition, the authors discuss new immunomodulatory agents being investigated. Hopefully, with the increased knowledge of the HBV disease mechanisms and the advent of novel therapies, finite duration of therapy can be achieved to ultimately control or eradicate HBV.

References:

1. Chen CJ, Yang HI. Natural history of chronic hepatitis B REVEALed. *J Gastroenterol Hepatol*. 2011 Apr;26(4):628-638.
2. Hoofnagle JH, Doo E, Liang TJ, Fleischer R, Lok ASF. Management of hepatitis B: summary of a clinical research workshop. *Hepatology* 2007;45:1056–1075.
3. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for treatment of chronic hepatitis B. T. *Hepatology*. 2016 Jan;63(1):261-283.
4. Parikh P, Ryan JD, Tsochatzis EA. Fibrosis assessment in patients with chronic hepatitis B virus (HBV) infection. *Ann Transl Med*. 2017 Feb;5(3):40.
5. Papatheodoridis GV, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J Hepatol*. 2015 Apr;62(4):956-967. doi: 10.1016/j.jhep.2015.01.002.

6. Buti M, Fung S, Gane E, et al. Long-term clinical outcomes in cirrhotic chronic hepatitis B patients treated with tenofovir disoproxil fumarate for up to 5 years. *Hepatol Int*. 2015 Apr;9(2):243-250.

Back to top

High Rate of Indeterminant HBV Phenotype

Di Bisceglie AM, Lombardero M, Teckman J, et al; Hepatitis B Research Network (HBRN). Determination of hepatitis B phenotype using biochemical and serological markers. *J Viral Hepat*. 2016 Dec 5.

View Journal Abstract View Full Article

The natural history of hepatitis B is a dynamic process. Attempts have been made to characterize patients into various phases of infection based on serological, virological, and biochemical criteria. This approach has practical implications, in that it could identify patients with active liver disease or increased risk of disease complications.[1] In fact, a number of professional society-published treatment recommendations for chronic hepatitis B are based on the traditional four phases of liver disease. However, it has been increasingly recognized that many patients cannot be classified readily using even serial ALT and HBV DNA levels.

The Hepatitis B Research Network (HBRN) is an NIH-funded clinical network that has enrolled over 2000 CHB patients with various racial backgrounds from North America.[2] DiBisceglie and coworkers, in this study, aimed to determine the distributions of HBV phenotypes in this large cohort of patients. Major exclusion criteria included currently on antiviral therapy, known co-infection with human immunodeficiency (HIV) or hepatitis C virus (HCV), decompensated liver disease, hepatocellular carcinoma, or previous liver transplantation.

In this cross-sectional study including 1390 adult participants, HBV phenotypes were determined using a single ALT and HBV DNA value at the baseline visit. The phenotypes were defined based on modifications of previously published work:

- **Immune tolerant phenotype** — HBeAg positive with normal ALT level (30 U/L for men and 20 U/L for women) and HBV DNA ≥ 10^5 IU/ml
- **HBeAg positive immune active phenotype** — elevated ALT and HBV DNA ≥ 10^5 IU/ml
- **/nactive carrier state** — HBsAg positive, HBeAg negative, normal ALT, HBV DNA ≤ 10^4 IU/ml
- **HBeAg negative immune active phenotype** — elevated ALT and HBV DNA ≥ 10^4 IU/ml

Patients who did not meet the criteria for any one of these four categories were identified as having an “indeterminant” phenotype.

Using this HBV phenotype definition, only 62% of the subjects could be classified into the usual phases of infection; 4% were immune tolerant, 18% had HBeAg positive immune active disease, 23% were inactive carriers, and 17% had HBeAg negative immune active disease. A large proportion of the subjects, 524 (38%), fell into the indeterminant phenotype. Among them, 433 out of 524 (83%) were HBeAg negative with elevated ALT but low HBV DNA level ≤ 10^4 IU/ml. The majority of these patients had no other causes for the elevated serum aminotransferases. Only 19 of 433 (4%) were anti-HDV positive, and 76 (18%) had obvious risk for nonalcoholic fatty liver disease.

Many patients in the HBV indeterminant phenotype do not meet treatment criteria, according to the current AASLD treatment guidelines: those with elevated serum ALT and serum HBV DNA values ≤ 2000 IU/mL. While liver biopsy is recommended to determine the severity of liver disease among these patients, biopsy is an invasive procedure with many limitations such as sampling errors, potential risks, cost, and patient acceptance. With the advent of noninvasive serum-based fibrosis markers (ie, APRI, FIB-4 and Fibrotest) and imaging-based technology (ie, transient elastography, MR elastography), clinicians can apply these new modalities to monitor patients with indeterminantte phenotype for disease progression and to make treatment decisions.

References:

1. Martin P, Lau DT, Nguyen MH, et al. A Treatment Algorithm for the Management of Chronic Hepatitis B Virus Infection in the United States: 2015 Update. *Clin Gastroenterol Hepatol*. 2015 Nov;13(12):2071-2087.
2. Ghany MG, Perrillo R, Li R, et al; Hepatitis B Research Network. Characteristics of adults in the hepatitis B research network in North America reflect their country of origin and hepatitis B virus genotype. *Clin Gastroenterol Hepatol*. 2015 Jan;13(1):183-192.

Back to top

Tenofovir to Prevent Vertical Transmission

Pan CQ, Duan Z, Dai E, et al; China Study Group for the Mother-to-Child Transmission of Hepatitis B. Tenofovir to Prevent Hepatitis B Transmission in Mothers with High Viral Load. *N Engl J Med*. 2016 Jun 16;374(24):2324-2334.

View Journal Abstract View Full Article

Before the era of postnatal passive and active immunization, the rate of vertical transmission of HBV to their infants of pregnant women with HBeAg positive chronic hepatitis B was 80%-90%. Standardized HBV vaccine and HBIg administration to newborn babies has reduced the mother-to-child transmission rate from 90% to 10%. However, cumulative reports show that despite immunoprophylaxis, about 10%-30% of the infants born to mothers with HBV DNA levels greater than 1 million copies/ml or 200,000 IU/ml still acquired HBV.[1,2]

There is increasing evidence that vertical transmission of HBV can be further reduced by providing antiviral therapy to pregnant women with high viremia. Most of the previous studies were not conclusive because of small sample size, inadequate study design, and incomplete follow-up of the subjects.[1,2] Pan et al published a high-quality paper in *NEJM* last year that evaluated the role of tenofovir in preventing HBV transmission in mothers with high viral loads.

In that study, 200 HBeAg positive pregnant women with HBV DNA > 200,000 IU/mL were randomized in a 1:1 ratio to either a treatment or a control arm. Patients in the treatment arm received tenofovir 300 mg daily from 30-32 weeks of gestation until week 4 postpartum. Patients in the control arm were provided similar care and frequent clinic visits without antiviral therapy. Mothers in both arms were followed until week 28 postpartum. All the infants received their first dose of HBV vaccine and HBIg shortly after birth.

The two primary outcomes were: 1) the rates of mother- to-child transmission (defined as the proportion of infants with serum HBV DNA > 20 IU/mL or HBsAg positive at 28 weeks); and 2) birth defects with or without TDF exposure. Secondary efficacy outcomes were the percentage of mothers who achieved HBV DNA level < 200,000 IU/mL at delivery, and the rates of HBeAg or HBsAg loss at week 28 postpartum.

The rate of mother-to-child transmission was significantly lower in the TDF-treated group than in the control group. In the intention-to-treat analysis, the transmission rate was 5% with TDF compared to 18% ($P = .007$) with no treatment. In the per-protocol analysis, the rate was 0% with TDF vs 7% ($P = .01$). In both the TDF and control groups, the birth defect rates were low at 2% and 1% respectively ($P = 1.00$). At delivery, 68% of the mothers in the TDF group and 2% in the control group had HBV DNA level < 200,000 IU/mL ($P < .001$). HBeAg and HBsAg loss or seroconversion occurred in five mothers.

Two significant differences in maternal adverse events between the two study groups were noted. There was a higher frequency of ALT elevation in the TDF group than in the control group between 5 and 28 weeks postpartum (45% in the TDF group vs 30% in the control group, $P = .03$). However, the rates of severe hepatitis flare (5.1-10 times ULN) were low and similar in both groups (5% vs 6%). One patient in the TDF group experienced serious

hepatitis flare (ALT > 10 times ULN) at week 28 postpartum; ALT normalized after resuming antiviral therapy. Three patients in the control group had serious ALT elevation > 10 times ULN within week 4 postpartum, which resolved after the initiation of antiviral therapy. None of the hepatitis flares resulted in HBeAg or HBsAg seroconversion. TDF-treated mothers had higher frequencies of asymptomatic elevation in creatine kinase (7% vs 0%, *P* = .006), although these events were considered not clinically significant.

This study provided solid evidence that supported the AASLD treatment guidelines for pregnancy. The current guideline recommends treating pregnant women who have HBV DNA > 200,000 IU/mL in the third trimester of pregnancy with a pregnancy class B antiviral agent such as tenofovir to prevent vertical transmission of HBV. Since hepatitis flares, especially during early postpartum period, can be serious, pregnant women should continue to be monitored regularly for at least six months postpartum to detect potential hepatitis B reactivation.

References:

1. Cohen E, Tran TT. Hepatitis B in the Female Population. *Gastroenterol Clin North Am*. 2016 Jun;45(2):359-370.
2. Brown RS Jr, McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. *Hepatology*. 2016 Jan;63(1):319-333.

Back to top

Entecavir Reduces HCC Risks among Cirrhotic Patients

Su TH, Hu TH, Chen CY, et al; C-TEAM study group and the Taiwan Liver Diseases Consortium. Four-year entecavir therapy reduces hepatocellular carcinoma, cirrhotic events and mortality in chronic hepatitis B patients. *Liver Int*. 2016 Dec;36(12):1755-1764.

View Journal Abstract View Full Article

Globally, chronic hepatitis B is a major cause of hepatocellular carcinoma (HCC) and liver-related mortality. There is convincing evidence that optimal suppression of HBV DNA with prolonged antiviral therapy, such as entecavir and tenofovir, can reverse hepatic fibrosis. While a number of studies suggest that treated patients also had decreased risk of HCC, the majority of patients in those studies did not have advanced fibrosis or cirrhosis.[1,2]

Current treatment guidelines recommend initiating antiviral therapy for cirrhotic patients with HBV DNA ≥ 2000 IU/mL. In this study, conducted by the C-TEAM (Cirrhosis-Taiwanese EntecAvir Multicenter), Su et al examined the efficacy of long-term entecavir therapy in reducing the risk of HCC in a large cohort of HBV-related cirrhotic patients. They compared the rates of HCC, liver-related complications, and mortality to a historical untreated cohort. Of note, the entecavir-treated patients were older and had higher Child-Pugh scores.

The median entecavir treatment duration was 4 years and the median follow-up for the untreated group was 6 years. HCC was identified in 119 of 1315 (9.0%) of treated patients and in 121 of 503 (24.1%) of the untreated cohort (hazard ratio 0.4). In addition, the treated group had lower rates of other disease complications. The adjusted hazard ratios for variceal bleeding, spontaneous bacterial peritonitis, and liver-related mortality were 0.38, 0.06, and 0.14, respectively. Since this study included a historic cohort for comparison, the improvement in clinical management over time might have influenced some of the study results. However, that should not affect the validity of the HCC trends.

The authors found that suppressing HBV DNA to < 20 IU/mL with entecavir in the first year of treatment was associated with a 38% reduction in HCC. However, the annual HCC rate remained significant at 2.4% in the treatment group. Among the treated patients, older age, male gender, HBeAg positivity, and baseline alpha fetoprotein (AFP) ≥ 7 ng/mL were predictors of HCC.

The reduction in HCC risk with long term HBV DNA suppression is encouraging. It is,

however, important to continue regular HCC surveillance with imaging studies, even after prolonged viral suppression, especially for those with baseline cirrhosis.

References:

1. Lok AS, McMahon BJ, Brown RS Jr; et al. Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. *Hepatology.* 2016 Jan;63(1):284-306.
2. Ahn J, Lim JK, Lee HM, et al. Lower Observed Hepatocellular Carcinoma Incidence in Chronic Hepatitis B Patients Treated With Entecavir: Results of the ENUMERATE Study. *Am J Gastroenterol*. 2016 Sep;111(9):1297-304.

Back to top

Safety: Tenofovir Alafenamide (TAF) vs Tenofovir Disoproxil Fumarate (TDF)

Seto W, Asahina Y, Peng C, et al. 2016. Reduced Changes in Bone Mineral Density in Chronic HBV (CHB) Patients Receiving Tenofovir Alafenamide (TAF) Compared with Tenofovir Disoproxil Fumarate (TDF). Presentation. AASLD, Boston, Mass.

View Journal Abstract

Tenofovir alafenamide (TAF) is a novel prodrug of tenofovir that was approved by the Food and Drug Administration (FDA) in November 2016 for chronic hepatitis B. TAF was formulated to deliver the active metabolite directly to the liver cells more effectively (and at a lower dose) than tenofovir disoproxil fumarate (TDF). TAF was proved to have similar efficacy as TDF in HBV DNA suppression at week 48 in two phase 3 clinical trials evaluating patients with HBeAg positive and HBeAg negative chronic hepatitis B (CHB), respectively. By reducing systemic exposure, patients treated with TAF also had lower bone and renal toxic effects.[1,2]

In this study, Seto et al explored factors associated with changes in bone mineral density (BMD) over 48 weeks in patients treated with TAF compared with TDF in these two clinical trials. The study included HBeAg positive (TAF n = 581; TDF n = 292) and HBeAg negative (TAF n = 285; TDF n = 140) CHB patients. At week 72 of continuous therapy, optimal suppression of HBV DNA (< 29 IU/mL) was achieved in over 71% and 92% of the HBeAg positive and HBeAg negative patients, respectively. There was no difference between the TAF and TDF treatment groups.

According to the WHO Scientific Group on the Assessment of Osteoporosis,[3] female gender, age ≥ 50 years, Asian race, and baseline eGFRCG < 90 mL/min were risk factors for osteoporosis. In this study, Asians accounted for 79% (TAF) and 77% (TDF) of the treatment groups. In both the TAF and TDF arms, the mean age was approximately 40 years, 35% were female, fewer than 10% had a BMI over 30, and the median eGFR was 105 mL/min. The average baseline vitamin D levels were 18 ng/ml (TAF) and 19 ng/ml (TDF), respectively.

Prior to therapy, the mean BMD (g/cm^2) at hip (TAF 0.96, TDF 0.95) and spine (TAF 1.06, TDF 1.05) was similar in the two groups. Using the hip T-score, approximately 30% and 1%, respectively, of patients in both groups had osteopenia and osteoporosis. Using the spine T-score, 36% had osteopenia and 7% in both groups had osteoporosis. The Fracture Risk Assessment Tool (FRAX® score) was similar at 2.67% and 2.87%, respectively, in the TAF and TDF arms.

Based on hip BMD at week 48 of therapy, 11% and 3%, respectively, in the TDF and TAF arms developed osteopenia from normal. For those with baseline osteopenia, 3% and 2%, respectively, in the TDF and TAF arms developed osteoporosis. Based on spine BMD at week 48, 13% and 7%, respectively, in the TDF and TAF arms developed osteopenia from normal. For those with baseline osteopenia, 8% in the TDF and 5% in the TAF arms developed osteoporosis.

Patients treated with TDF had a positive relationship between the number of risk factors for osteoporosis and BMD decline. The percentages of subjects with > 3% BMD reduction at 48 weeks of therapy were 20% with two or fewer risk factors, 40% with three risk factors, and 58% for those with all four risk factors. In contrast, among patients treated with TAF, the proportion with > 3% BMD reduction was relatively constant at 8% to 10%, regardless the number of risk factors.

In summary, TAF has significantly less impact on decline in hip and spine BMD compared to TDF among patients with chronic hepatitis B. While this favorable trend does not appear to be influenced by the number of known risk factors for osteoporosis, longer observation (beyond 48 weeks) is necessary to draw firm conclusions.

References:

1. Chan H, Fung S, Seto WK, et al; the GS-US-320-0110 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*; 2016; 1:185-195
2. Buti M, Gane E, Seto WK, et al; the GS-US-320-0108 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of patients with HBeAg-negative chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol*; 2016; 1:196-206
3. WHO scientific group on the assessment of osteoporosis at primary health care level. Summary meeting report. Brussels, Belgium 5-7 May, 2004. Available at: www.who.int/chp/topics/Osteoporosis.pdf

Back to top

Emerging New Therapies for Hepatitis B

Testoni B, Durantel D, Zoulim F. Novel targets for hepatitis B virus therapy. *Liver Int*. 2017 Jan;37 Suppl 1:33-39. PMID: 28052622

View Journal Abstract View Full Article

HBV is a DNA virus belonging to the family of Hepadnaviridae. The compact genome of HBV consists of four partially overlapping, open-reading frames encoding for the envelope (pre-S/S), core (precore/core), polymerase, and X proteins. Through the newly identified HBV entry receptor, human sodium taurocholate cotransporting polypeptide (hNTCP), HBV gains entry into the hepatocyte. After uncoating, the relaxed circular genome is converted to a covalently closed circular (ccc) DNA in the nucleus. The cccDNA serves as the template for viral replication by transcribing into subgenomic RNA (sgRNA) and pregenomic RNA (pgRNA). Inside the nucleocapsid (HBV Core), the pgRNA is first reverse transcribed into negative-strand DNA, then forms plus-strand from the negative strand by the HBV polymerase. The nucleocapsid either reenters the nucleus for cccDNA amplification or is enveloped by HBsAg and subsequently released as mature virion via the endoplasmic reticulum.[1]
The persistence of HBV in the liver is caused by the maintenance of cccDNA in the infected cells, despite prolonged viral suppression. The currently approved nucleos(t)ide analogues inhibit HBV polymerase but cannot eradicate the cccDNA from the infected hepatocytes. Thus, the HBsAg clearance is only achieved in approximately 10% of patients who have had over five years of nucleos(t)ide analogue therapy.

With the recent identification of the HBV entry receptor and increased understanding of the molecular and immunological disease mechanisms, many new therapeutic agents are in various clinical phases of development. These new agents either directly inhibit viral replication by targeting steps of viral life cycles such as entry, cccDNA formation, capsid assembly, and viral secretion, or indirectly enhance the host immune system to for effective viral clearance.

Among the *direct antiviral* therapeutic agents in development at the time of this publication are:

· **Entry inhibitors** (inhibit hNTCP function): Myristoylated preS-peptide (myrcludex-B), a

lipopeptide derived from the pre- S1 domain of the HBV envelope, was found to prevent HBV and HDV infection by preventing interaction between virions and the receptor (phase 2 clinical trials)

· **HBV mRNAs:** ARC-520 produced durable suppression of viral antigens and DNA in a phase 2 study, providing the first proof of concept for siRNAs as therapeutic molecules in CHB.

· **pgRNA packaging inhibitors:** These molecules either inhibit pgRNA encapsidation or alter HBV core (HBc) capsid formation, leading to arrest in neosynthesis of DNA. Besides disrupting the cytoplasmic encapsidation process, the HBc allosteric modulators (CpAMs) may interfere with the cccDNA regulation via epigenetic mechanisms. A number of CpAms are in early-phase trials.

· **Virion secretion inhibitors:** Rep2139, a nucleic acid polymer (NAP), has been reported to inhibit the secretion of HBsAg. In combination with pegIFN-α, it has been shown to result in a significant reduction in circulating HBsAg levels and viremia. Further data is necessary to confirm these preliminary results.

· **cccDNA inhibitor:** Several cytokines including interferon could lead to the upregulation of APOBEC3A/B deminases, which in turn induce nonhepatotoxic degradation of cccDNA. APOBEC3A/B, therefore, is an attractive therapeutic target.Immune modulators in development include:

· **Toll-like receptor (TLR) agonists:** Stimulate interferon (IFN) production by intrahepatic plasmacytoid dendritic cells (pDC). GS-9620, an oral TLR7 agonist in phase 1b study, was associated with induction of peripheral ISG15 production in the absence of significant systemic IFN related symptoms. It will be interesting to follow the phase 2 trial comparing the combination of tenofovir and GS- 9620 with tenofovir monotherapy.

· **Checkpoint inhibitors:** The HBV-specific T-cell exhausted phenotype is particularly associated with the overexpression of coinhibitory receptors such as programmed cell death (PD-1). In a study of chronically infected woodchucks, inhibition of PD- L1 was shown to enhance the antiviral effect of the combination of entecavir and therapeutic vaccination and restore T- cell responses.

With the advent of novel therapeutic targets, this is an exciting time for exploring new therapies for chronic hepatitis B. The new approaches, singly or in combination, raise hopes for functional cure with HBsAg clearance, and perhaps even complete cure with eradication of cccDNA. As Testoni et al note, carefully designed clinical trials are essential to determine both the efficacy and potential side-effects of the currently available therapy.

References:

1. Seeger C, Mason WS. Hepatitis B virus biology. *Microbiol Mol Biol Rev*. 2000 Mar;64(1):51-68

Back to top

KEY TAKEAWAYS

- Nucleos(t)ide analogues, by long-term viral suppression, can regress hepatic fibrosis, prevent liver failure, and reduce HCC risk.
- Tenofovir reduces risk of vertical transmission of HBV in pregnant women with high viremia.
- Patients with reduced BMD and renal dysfunction are candidates for tenofovir alafenamide (TAF).
- Functional cure of hepatitis B may be possible with novel therapeutic agents that inhibit different targets of the HBV life cycle.

Back to top

IMPORTANT CME/CE INFORMATION

ACCREDITATION STATEMENTS

Physicians

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing

INTERNET CME/CE POLICY

DISCLAIMER STATEMENT

STATEMENT OF RESPONSIBILITY

Medical Education (ACCME) through the joint providership of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. The Johns Hopkins University School of Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Nurses
The Institute for Johns Hopkins Nursing is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation.

CREDIT DESIGNATION STATEMENT

Physicians
eNewsletter: The Johns Hopkins University School of Medicine designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nurses
eNewsletter: This 1.0 contact hour Educational Activity is provided by the Institute for Johns Hopkins Nursing. Each Newsletter carries a maximum of 0.5 contact hour, or a total of 3 contact hours for the 6 newsletters in this program.

POLICY ON SPEAKER AND PROVIDER DISCLOSURE

It is the policy of the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing that the speaker and provider globally disclose conflicts of interest. The Johns Hopkins University School of Medicine OCME has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Detailed disclosure will be made in the instructional materials.

COMPLETE THE POST-TEST

Click on link to download instructions for the post-test and evaluation

PHYSICIAN POST-TEST

NURSE POST-TEST

This activity was developed in collaboration with DKBmed.