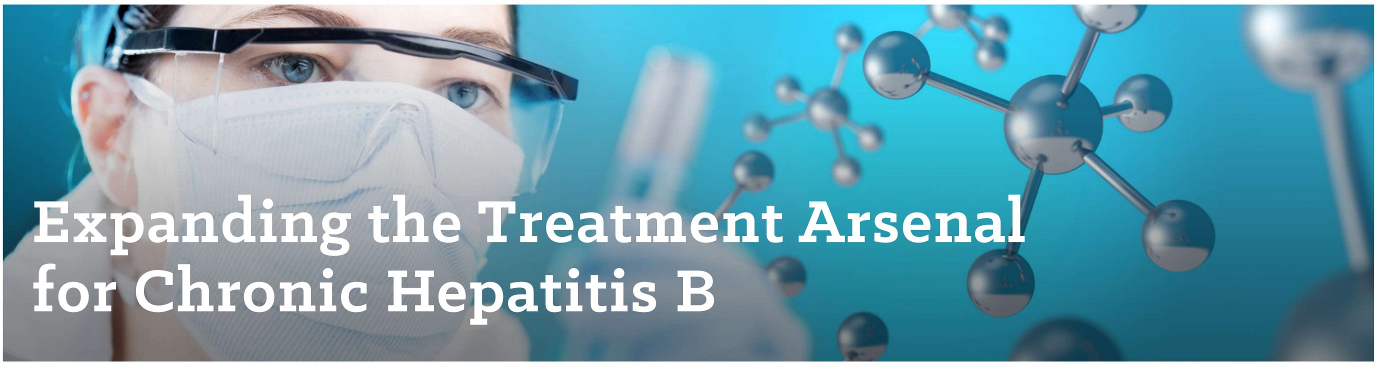


Expanding the Treatment Arsenal for Chronic Hepatitis B

Significant public health issues invariably arise, but the trajectory is not always obvious. Such has been the case for viral hepatitis, which has been called a "silent epidemic." In 2011, the United States (US) Department of Health and Human Services (HHS) published the first US action plan to better focus and coordinate the country's response to the disease. The latest iteration of the plan is effective until 2020.

Issued in January 2017, the current viral hepatitis action plan outlines strategies to achieve four major goals and includes indicators to help track progress. The goals are:

- Goal 1: Prevent new viral hepatitis infections.
- Goal 2: Reduce deaths and improve the health of people living with viral hepatitis.
- Goal 3: Reduce viral hepatitis health disparities.
- Goal 4: Coordinate, monitor, and report on implementation of viral hepatitis activities.

The report notes that, since 2011, federal and non-federal efforts have evolved and advanced in response to the growing threat viral hepatitis poses to public health. Despite this progress, viral hepatitis remains a serious public health threat in the US. The number of new hepatitis C virus (HCV) infections has increased rapidly, prior progress in reducing new hepatitis B virus (HBV) infections has stalled, and hepatitis-related deaths have increased, the report states.

Because chronic HBV and HCV infection can persist for decades without symptoms, about half of those infected remain unaware of their infection status and are not receiving necessary care and treatment. For this reason, the HHS report notes, viral hepatitis is a leading cause of liver disease in the US and the most common reason for liver transplantation. In contrast, hepatitis A virus (HAV) produces a self-limited disease that does not result in chronic infection.

While viral hepatitis can result from infection with any of at least five distinct viruses – HAV, HBV, HCV, hepatitis D virus (HDV), and hepatitis E virus (HEV) – the majority of hepatitis infections in the US are attributable to HAV, HBV, and HCV. The 2017 report mentions that a "major advance" has been the approval and widespread availability of highly effective, all-oral therapies that cure more than 90% of people with chronic HCV infection. Although both hepatitis A and B can be prevented by vaccination, there is no cure for hepatitis B.

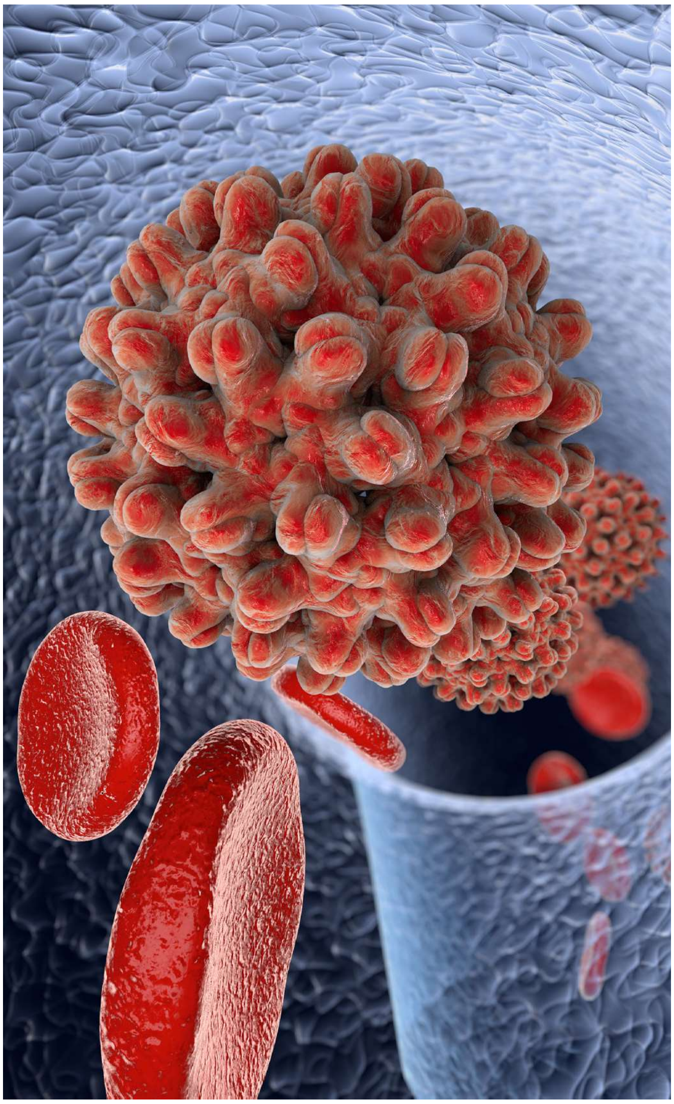
In 2016, a total of 3218 cases of acute HBV infection were reported to the Centers for Disease Control and Prevention (CDC). Since many people may not have symptoms or do not know they are infected, their illness is neither reported nor counted. The CDC estimates the actual number of acute HBV cases was almost 20,900 in 2016.

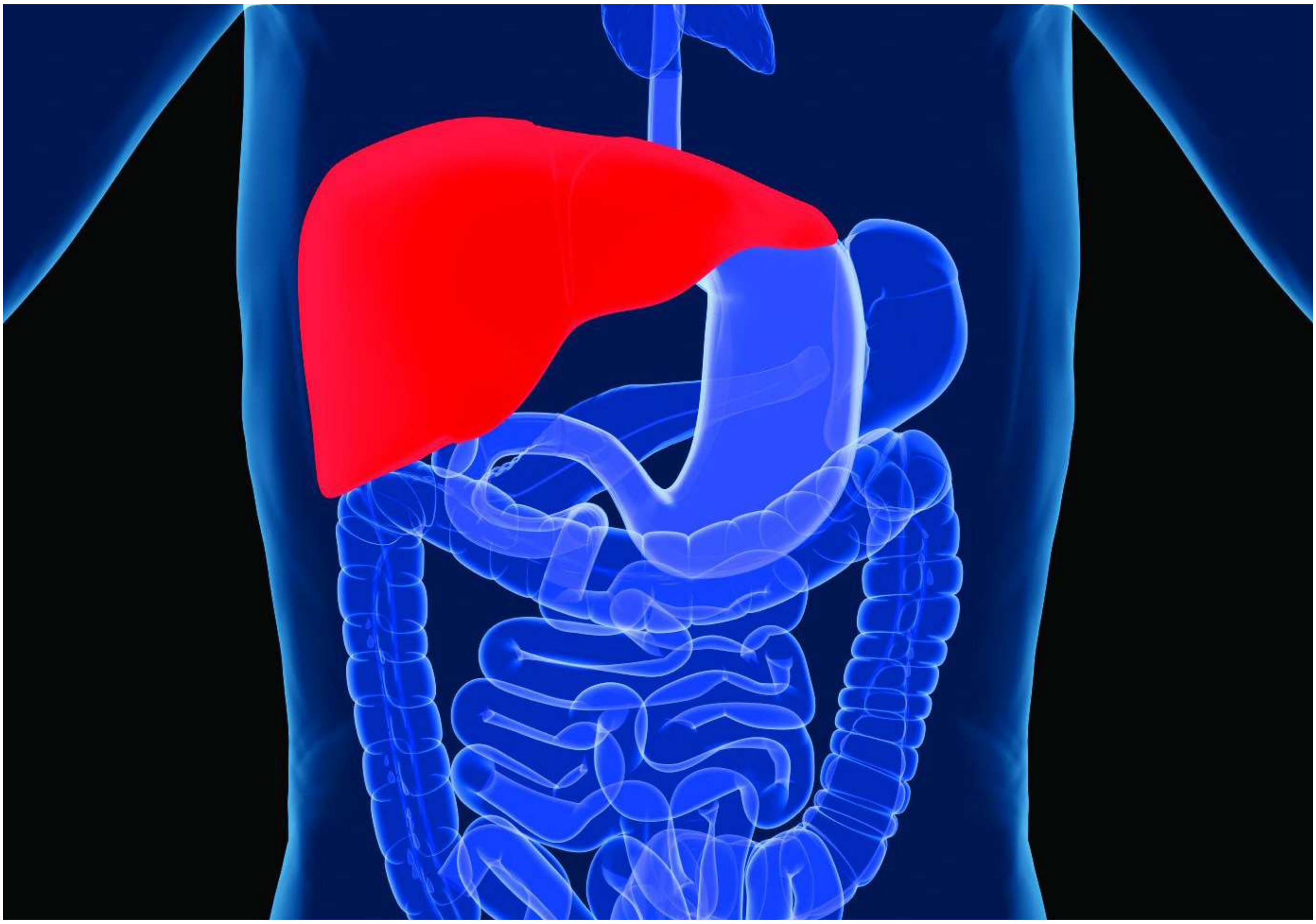
As of May 2018, an estimated 850,000 people in the US have chronic HBV infection, according to the CDC, although that number may be as high as 2.2 million. Globally, approximately 257 million people have chronic HBV infection.

Advancements for Treating HBV

Research and development for new viral hepatitis treatments are among strategies listed under the goals in the HHS report. The US Food and Drug Administration (FDA), a federal agency of the HHS, seeks to broaden the treatment armamentarium for HBV. It issued a new draft guidance for industry in November 2018, *Chronic Hepatitis B Virus Infection: Developing Drugs for Treatment*, which is intended to assist sponsors in the clinical development of drugs and biologics to treat chronic HBV infection: from the initial investigational new drug application (IND) through the new drug application (NDA)/biologics license application (BLA) and post-marketing phases. This document is the FDA's first version of an indication-specific draft guidance for chronic HBV infection.

As explained in the guidance, currently available therapies for chronic HBV infection achieve sustained suppression of HBV DNA, with low rates of





HBV surface antigen (HBsAg) loss, with or without seroconversion to anti-HBsAg (HBsAb). Sustained HBV DNA suppression is associated with serum alanine aminotransferase (ALT) normalisation and improvement in liver histology, including regression of hepatic fibrosis and cirrhosis. In addition:

- Effective HBV therapy reduces disease-related complications (e.g., hepatic decompensation and liver failure) and decreases risk of hepatocellular carcinoma.
- Clearance of HBsAg is associated with reduced risk of hepatic decompensation and improved survival.

The FDA recommends that therapies should be developed for a wide range of patients with chronic HBV infection, including paediatric populations. Because chronic HBV infection is a global disease, the FDA (under 21 CFR 312.120) will accept a well-designed, well-conducted, non-IND foreign study as support for an IND or application for marketing approval, so long as the trial was conducted in accordance with good clinical practice and the FDA can validate trial data through an onsite inspection, if necessary. The agency suggests that development programmes should include a sufficient number of US patients to ensure applicability of data to the US population.

Due to the heterogeneity of the natural course of chronic HBV infection, sponsors are advised to conduct randomised and well-controlled trials to establish efficacy. In the November 2018 guidance, the FDA details which trial designs are appropriate, depending on whether the therapeutic is intended for chronic suppressive therapy or therapy of finite duration. New therapies could be evaluated in clinical trials using any of the following efficacy endpoints:

- Suppression of HBV DNA (defined as less than the lower limit of quantification [LLOQ], target not detected [TND]) on treatment – similar to currently available chronic nucleoside/nucleotide reverse transcriptase inhibitor (NrtI) therapies.
- Sustained suppression (more than six months) of HBV DNA (less than LLOQ, TND) off treatment, after a finite duration of therapy.
- Sustained suppression (more than six months) of HBV DNA (less than LLOQ, TND) off treatment with HBsAg loss (less than 0.05 international unit/millilitre [IU/mL]), with or without HBsAb seroconversion, after a finite duration of therapy.

The FDA also advises that a limited number of secondary endpoint(s) (e.g., HBeAg loss, ALT normalisation) should be considered for testing using appropriate statistical methods for multiplicity. Biochemical serum markers such as ALT values vary between laboratories, and lack of ALT normalisation may often be confounded by presence of other chronic liver diseases, such as nonalcoholic fatty liver disease (NAFLD). Regarding a type of NAFLD, nonalcoholic steatohepat it is (NASH) the FDA issued a draft guidance for industry in December 2018, *Noncirrhotic Nonalcoholic Steatohepatitis With Liver Fibrosis: Developing Drugs for Treatment.*

The FDA welcomed comments on the HBV draft guidance by January 2, 2019, to Docket No. FDA-2018-D-3903. Comments may be submitted regarding the NASH draft guidance until February 4, 2019, to Docket No. FDA-2018-D-3632.

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