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# Addressing the global burden of hepatitis B virus while developing long-acting injectables for the prevention and treatment of HIV

**Robert C Bollinger**, **Chloe L Thio**, **Mark S Sulkowski**, **Jane McKenzie-White**, **David L Thomas**, **Charles Flexner**

School of Medicine, Johns Hopkins University, Baltimore, MD, USA (Prof R C Bollinger MD, Prof C L Thio MD, Prof M S Sulkowski MD, J McKenzie-White MAS, Prof D L Thomas MD, Prof C Flexner MD)

## Abstract

The first long-acting formulations of HIV drugs are undergoing regulatory review for use in maintenance of viral suppression in people with HIV. Although these novel drug formulations could contribute greatly to HIV treatment and prevention efforts, their lack of activity against hepatitis B virus (HBV) could limit their global impact, particularly in populations with high burdens of both HIV and HBV. An urgent need for greater investment in research and development of long-acting drugs with dual activity against HIV and HBV exists. Access to long-acting HIV drug formulations with dual activity against HBV would be transformative and have a great impact on efforts to prevent, treat, and eradicate both of these important global epidemics.

## Introduction

Important progress has been achieved in the development of long-acting antiviral formulations for the prevention and treatment of HIV. Replacing daily oral regimens with long-acting ones, administered as infrequent injections or implantable devices, could greatly simplify and improve HIV prevention and treatment.[1–3] The successful uptake of long-acting injectable formulations for treatment of schizophrenia,[4] and the use of implantable formulations of contraceptive medications by millions of women,[5,6] suggests that such formulations would be well accepted. Studies have substantiated that people with HIV and people at risk for HIV infection show strong interest and support for the use of long-acting injectable or implantable versions of their medications.[7–11]

Long-acting formulations of two HIV drugs delivered by intramuscular injection, long-acting cabotegravir and long-acting rilpivirine, have shown promising results in phase 3 trials for HIV treatment.[12,13] Cabotegravir is a potent HIV integrase inhibitor. Rilpivirine is



Correspondence to: Prof Robert C Bollinger, Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA, rcb@jhmi.edu.

Contributors

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a potent second-generation HIV non-nucleoside reverse transcriptase inhibitor with a long half-life and fewer side-effects than other drugs in this class. Multiple studies have shown that people living with HIV who have been taking daily pills that include three or more HIV medications and have achieved viral suppression can stop their pills and safely switch to the two-drug combination of long-acting cabotegravir and long-acting rilpivirine, given as injections every 4 or 8 weeks.[9,12,13]

People who have stopped oral regimens and switched to injections have few side-effects and can maintain effective HIV viral suppression for at least 48 weeks.[12,13] The US Food and Drug Administration (FDA) is reviewing these data and considering approval of injectable formulations of long-acting cabotegravir and rilpivirine for maintenance of viral suppression in HIV-infected people.

## Treatment of hepatitis B and HIV co-infection

Long-acting cabotegravir and rilpivirine represent important new tools to support global HIV prevention and treatment efforts, as well as the ambitious public health goal to end the HIV epidemic in the USA.[14] However, approximately 7·5% of people living with HIV worldwide are co-infected with hepatitis B virus (HBV), and among some populations the prevalence of co-infection is higher. HBV and HIV share the same modes of transmission; thus, many countries have communities with high burdens of both viruses (figure). For individuals co-infected with HIV and HBV, specific antiretroviral nucleoside analogues that are active against both viruses are recommended.[15]

In addition, if those dually active nucleosides are inadvertently discontinued (eg, during a switch to regimens such as long-acting cabotegravir plus long-acting rilpivirine), HBV reactivation and hepatic failure can occur.[16] Because people with HBV infection infrequently accomplish a functional cure with current antivirals drugs, therapy is often lifelong. Thus, HIV–HBV co-infected individuals present an important challenge to the effectiveness of the widespread implementation of long-acting cabotegravir and rilpivirine for HIV treatment, since neither has activity against HBV.

Only four FDA-approved drugs for HIV treatment also have activity against HBV. These are all nucleoside reverse transcriptase inhibitors, including lamivudine, emtricitabine, tenofovir disoproxil fumarate, and tenofovir alafenamide.[17] All four drugs have been used for the treatment of HBV infection, but tenofovir disoproxil fumarate and tenofovir alafenamide are preferred because they have a higher barrier to HBV resistance than lamivudine and emtricitabine.[18–20]

Efforts to develop long-acting versions of antiretrovirals with HBV activity are now underway,[21,22] but lag far behind the development of long-acting cabotegravir and rilpivirine, and it is too early to speculate how those medications might be integrated into a comprehensive antiviral long-acting regimen.

To optimise strategies for use of long-acting injectable drugs to end the HIV epidemic, a greater investment in research and development of long-acting drugs with dual activity against HIV and HBV is urgently needed. Long-acting formulations of medications with

activity against HBV also have great potential to end the HBV epidemic, which is a WHO goal for 2030.[23] Although about 40 million people worldwide have HIV, 257 million people have a chronic HBV infection.[23,24] Of these HBV-infected individuals, only 4·5 million (<2%) are receiving HBV treatment.[25] HBV is the leading global cause of death from chronic liver disease and liver cancer.[26] In addition, by 2040, analyses project that HBV will be responsible for more deaths every year than HIV, tuberculosis, or malaria.[27] Like HIV, HBV can be transmitted through sexual contact, injections, and blood product transfusions, and from mother to child. Between 6% and 10% of people living with HIV in the USA are also infected with HBV,[28] with higher rates among men who have sex with men and people who inject drugs.[29,30]

The burden of HBV infection worldwide, as with HIV, falls on low-income and middle-income countries. Consequently, rates of HBV co-infection are higher than 10% among many populations of people living with HIV in sub-Saharan Africa, west Africa, east Asia, and India, despite the increasing access to HBV vaccination. [28,31–33] Moreover, HIV mono-infected people are at risk for HBV acquisition even with vaccination since they mount poorer and less durable protective responses against HBV than people without HIV.[34,35]

HBV co-infection is associated with much higher rates of liver-related mortality among people living with HIV than among people with either HIV or HBV infection alone.[36,37] Treatment of HIV–HBV co-infected people with HIV medications that do not also have HBV activity is associated with an increased risk for HBV immune reconstitution inflammatory syndrome.[38,39] In addition, discontinuation of HIV medications with anti-HBV activity in co-infected people is associated with HBV reactivation and liver failure.[40] Therefore, current US and international guidelines recommend that all people living with HIV should be screened for HBV infection before starting antiretroviral therapy.[15,41]

HIV drug regimens that include tenofovir disoproxil fumarate or tenofovir alafenamide in combination with emtricitabine or lamivudine are recommended for those with chronic hepatitis B.[15] Unfortunately, in practice, most HIV-infected people globally are not prescreened for HBV infection before initiating HIV treatment.

Prescreening for HBV infection is particularly uncommon in sub-Saharan Africa and Asia, as well as among populations of injection drug users, who have higher HBV co-infection rates than the general population. Failing to account for HBV co-infection has not had major public health implications because more than 60% of drug regimens purchased for people living with HIV in sub-Saharan Africa and Asia contain tenofovir disoproxil fumarate.[42]

However, long-acting cabotegravir and rilpivirine are expected to be available for HIV treatment in high-income countries soon, and could be made available shortly thereafter in low-income and middle-income countries. Given the greater potential adherence, potency, and safety profile of these injectable HIV medications than daily regimens, as well as better protection of health privacy for areas with substantial HIV stigma, many people could benefit from access to these formulations. These medications provide an excellent option for people who have difficulty taking pills every day, including people with injection drug use.

However, people with injection drug use have the greatest risk for HBV co-infection of all people living with HIV.

As noted above, people with HIV–HBV co-infection cannot safely transition to a completely injectable regimen of long-acting cabotegravir and rilpivirine because of the risk of HBV reactivation. The much anticipated switch to the initiation of long-acting cabotegravir and rilpivirine will require a strategy of both testing and switching, since most people in high-income countries will require HBV testing before they can stop tenofovir disoproxil fumarate or tenofovir alafenamide. Therefore, people with HIV–HBV co-infection, especially those in low-income and middle-income countries, might not benefit from the availability of the new long-acting antiviral formulations of cabotegravir and rilpivirine.

## Long-acting pre-exposure prophylaxis

Long-acting antivirals also have a role in the prevention of HIV and HBV infections. Co-formulated tenofovir disoproxil fumarate and emtricitabine taken once daily is highly protective when taken regularly as pre-exposure prophylaxis (PrEP) for individuals at risk for HIV infection.[43,44] However, long-term adherence to oral, daily PrEP is difficult to accomplish and sustain, particularly among women at high risk, injection drug users, and men who have sex with men.[45–47] The uptake and access to oral PrEP is suboptimal in many communities, including in people who inject drugs.[47,48]

The potential of a long-acting injectable formulation of cabotegravir as an alternative to PrEP could be an important new and transformative HIV prevention tool.[49] Two important clinical trials are underway through the HIV Prevention Trials Network, comparing the efficacy of injections of long-acting cabotegravir given every 4 or 8 weeks with a daily oral pill of tenofovir disoproxil fumarate and emtricitabine for the prevention of HIV infection among men and women at high risk.[50,51] Similar concerns with regards to HBV infection apply to PrEP. If long-acting cabotegravir is regarded as effective, switching from the HBV-active tenofovir disoproxil fumarate and emtricitabine might lead to the outbreak of an underlying HBV infection. In addition, even among HIV mono-infected people, it is now well documented that HBV-active antiretrovirals prevent HBV acquisition.[52–54]

Although not as advanced in the drug development pipeline as long-acting cabotegravir and rilpivirine, there is progress in the development of long-acting tenofovir alafenamide injectables and implants, which could be valuable for global prevention of both HIV and HBV. The first human clinical trial of a long-acting tenofovir alafenamide formulation (CAPRISA 018), delivered by a non-degradable implant (similar to those used for long-acting hormonal contraceptives), is about to begin in South Africa.[55] The safety, pharmacokinetic, and efficacy data from this first human study of a long-acting formulation with activity against both HIV and HBV will be highly important to address the challenges and limitations of the current long-acting HIV pipeline.

## Potential applications of long-acting HBV treatments

Many other potentially impactful applications of long-acting HBV treatments also exist. The opportunity to provide pregnant women with a long-acting option for treatment that prevents

mother-to-child transmission of both HIV and HBV could be transformative. 90% of all new chronic HBV infections in the world are due to perinatal transmission.[56] Although more than 90% of individuals who are infected with HBV as adults recover from their HBV infection, more than 90% of perinatally infected infants develop chronic HBV infection.[57] These children contribute to the 700 000 annual deaths from HBV-associated liver disease, cirrhosis, and hepatocellular carcinoma.[23,57] High HBV viral load among HIV–HBV co-infected mothers is associated with lower infant birthweight and increased infant mortality.[58]

Current strategies to prevent perinatal HBV infection include treating pregnant mothers with oral tenofovir disoproxil fumarate, administered daily, and treating their infants at birth with HBV vaccine and immunoglobulin.[23,59] Although these strategies can prevent perinatal HBV transmission, less than 40% of infants born to HBV-infected mothers have access to these prevention methods.[23,56] The main impediment to global elimination of HBV is the inability to deliver these preventive tools to mothers prenatally and to infants immediately after delivery, which in many regions of the world does not occur in a health-care facility.[60] The ability to give long-acting HBV treatment to pregnant women in the second or third trimester could be a major breakthrough in global elimination efforts.

Long-acting HBV treatments could also be used to deliver care to people with chronic hepatitis B without HIV. Approximately 20–30% of the 257 million people with chronic hepatitis B need treatment. However, in 2015, fewer than 9% were diagnosed and less than 10% of those were sustained on treatment.[23] Lack of awareness of HBV infection is even a problem in high-income regions of the world, as shown in a community-based study in the USA.[61] WHO estimated that HBV elimination will require access to diagnosis to be increased to 90%, and the access to treatment to 80%.[23] Long-acting treatments could be very effective in achieving and sustaining this goal.

As we celebrate the inauguration of a generation of long-acting antiviral treatments for HIV, it is essential to consider chronic HBV infection. Governments, industries, and other stakeholders should urgently prioritise the development of long-acting HBV medications, and increase financial support for the necessary additional research and development in accord with the enormous public health potential of such formulations.

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Declaration of interests

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Pharmaceuticals, and ViiV Healthcare, outside the submitted work. In addition, CF has a patent for semi-solid prodrug nanoparticles pending. JM and DLT declare no competing interests.

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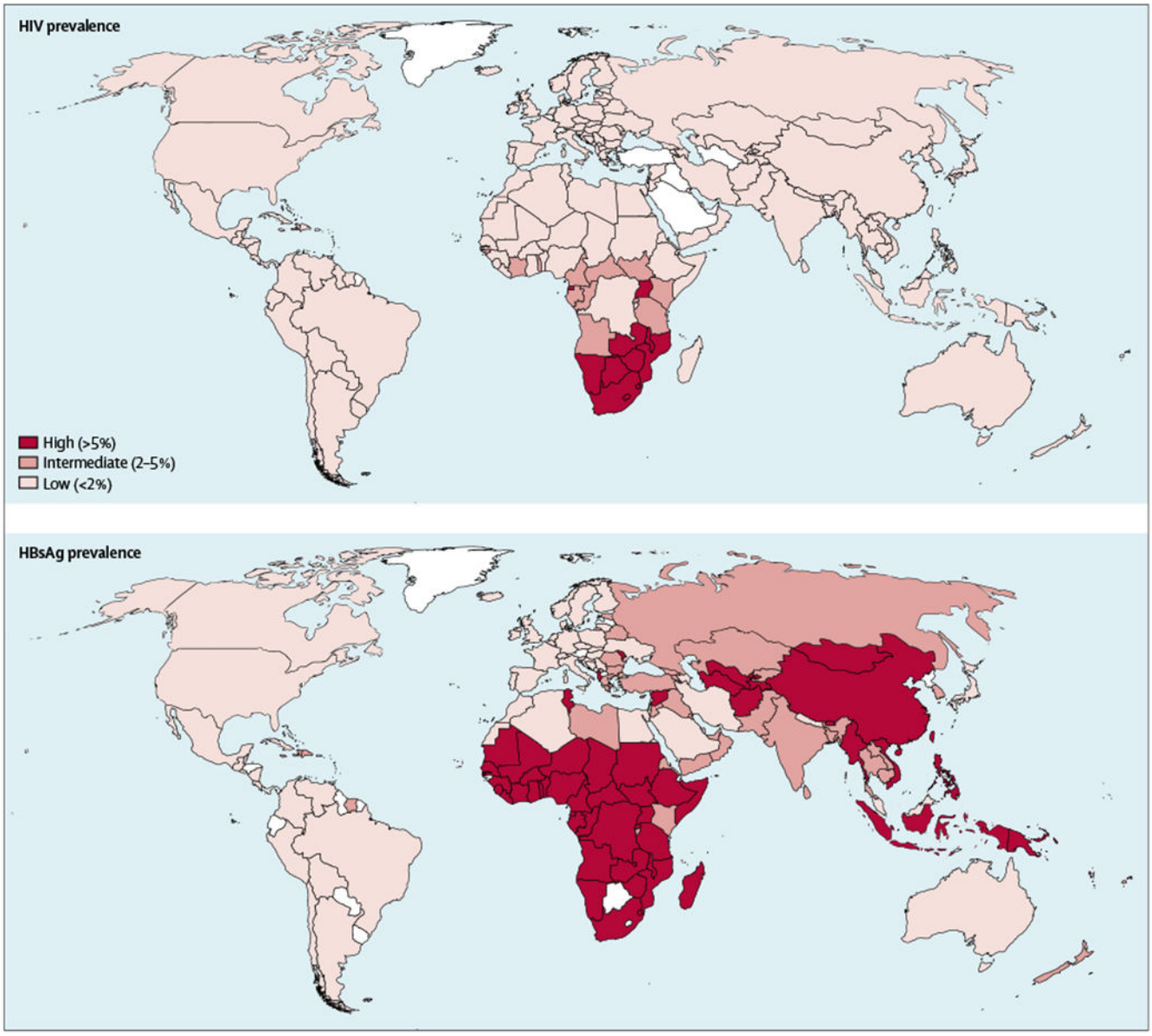


**Figure: HIV and chronic hepatitis B virus infection prevalence**
Data extracted from multiple sources.[62–70]