



**HAL**  
open science

## **Risks and benefits of oral HIV pre-exposure prophylaxis for people with chronic hepatitis B**

Amir M Mohareb, Joseph Larmarange, Arthur Y Kim, Patrick A Coffie, Menan Gérard Kouamé, Anders Boyd, Kenneth A Freedberg, Emily P Hyle

► **To cite this version:**

Amir M Mohareb, Joseph Larmarange, Arthur Y Kim, Patrick A Coffie, Menan Gérard Kouamé, et al.. Risks and benefits of oral HIV pre-exposure prophylaxis for people with chronic hepatitis B. The Lancet HIV, 2022, Lancet HIV, 9 (8), pp.e585-e594. 10.1016/S2352-3018(22)00123-0 . ird-03879814

**HAL Id: ird-03879814**

**<https://ird.hal.science/ird-03879814v1>**

Submitted on 30 Nov 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



# Risks and benefits of oral HIV pre-exposure prophylaxis for people with chronic hepatitis B

Amir M Mohareb, Joseph Larmarange, Arthur Y Kim, Patrick A Coffie, Menan Gérard Kouamé, Anders Boyd, Kenneth A Freedberg, Emily P Hyle

Individuals with chronic hepatitis B virus (HBV) infection who are at substantial risk of HIV acquisition benefit from pre-exposure prophylaxis (PrEP) with tenofovir-based antiviral therapy. Considering that tenofovir potently inhibits HBV, providing PrEP to individuals with HBV effectively results in treatment of their HBV infection. However, some clinicians might be hesitant to initiate PrEP in people with chronic HBV due to unknown risks of HBV reactivation, hepatitis, and acute liver failure during periods of antiviral cessation. Unfortunately, these knowledge gaps affect scale up of PrEP among people with chronic HBV. Emerging data regarding the risks and benefits of antiviral cessation in people with chronic HBV suggest that PrEP can be safely initiated despite the risks of non-adherence or discontinuation. People with chronic HBV who stop PrEP should be closely monitored for HBV reactivation and hepatitis flares after antiviral cessation.

## Introduction

More than 250 million people live with chronic hepatitis B virus (HBV) worldwide, and over 800 000 people die from HBV-related causes every year.<sup>1,2</sup> HBV is the world's leading cause of chronic liver disease, liver cancer, and liver-related mortality.<sup>3</sup> Because of shared routes of transmission, key populations affected by HBV are also at high risk of HIV infection: the prevalence of HBV among people with HIV approaches 10% worldwide.<sup>4</sup> Co-infection is also common in some HBV-endemic countries with generalised HIV epidemics.<sup>4</sup> In Africa, where over 60 million people have chronic HBV, infection with HBV most often occurs early in childhood.<sup>2</sup> In the WHO Western Pacific region, perinatal transmission accounts for the majority of chronic HBV cases.<sup>2</sup> In all parts of the world, including Europe and the Americas, HBV is prevalent in key populations, including men who have sex with men, sex workers, and people who inject drugs.<sup>2</sup>

In the absence of effective therapy for HBV, people with HBV who are co-infected with HIV will have accelerated liver disease, higher rates of hepatocellular carcinoma, and increased risk of all-cause mortality compared with those who have HIV mono-infection.<sup>5,6</sup> Because greater HIV and HBV replication are associated with higher mortality rates,<sup>7,8</sup> the antiviral activity of dually active antiretroviral therapy (ART), particularly with tenofovir-based regimens, would be expected to reduce mortality to similar rates as those seen in people with HIV mono-infection. However, several studies show that people with HIV and HBV co-infection have higher mortality rates than people with HIV mono-infection, even after immediate initiation of ART and adjustment for HIV-related factors.<sup>9–11</sup> Even under ideal scenarios of linkage to care and retention in care, people with HIV and HBV co-infection could have higher mortality rates than people with HIV mono-infection.<sup>9,11</sup> For these reasons, preventing HIV in individuals with chronic HBV infection is especially important to avoid the harmful consequences of HIV and HBV co-infection.

There is an urgent need to scale up HIV prevention strategies in people with chronic HBV. Since 2015, WHO

has recommended oral tenofovir disoproxil fumarate-based therapy (ie, tenofovir disoproxil fumarate and emtricitabine) as an effective form of HIV pre-exposure prophylaxis (PrEP).<sup>12</sup> Tenofovir disoproxil fumarate is a potent inhibitor of HBV DNA replication; however, because not all people with HBV require antiviral therapy, PrEP initiation in people with HBV introduces additional complexity in medical decision making. Although long-term adherence to tenofovir disoproxil fumarate-based therapy could improve control of HBV DNA replication and minimise the risk of HIV infection,<sup>13,14</sup> abrupt discontinuation of tenofovir disoproxil fumarate can result in HBV DNA reactivation, which is associated with hepatitis flares and acute liver failure.<sup>15,16</sup> Clinical practice guidelines on PrEP currently provide little direction on when and how to safely use PrEP in people with HBV.<sup>12,17</sup> This knowledge gap affects key populations and people in HBV-endemic countries, who are at higher risk of living with chronic HBV yet have the greatest benefits to gain from using tenofovir disoproxil fumarate-based therapy as PrEP to prevent HIV acquisition.

Uncertainty regarding the safety of PrEP in people with HBV and inconsistent antiviral use have probably prevented broader PrEP scale up in this at-risk population. There are currently widespread efforts to scale up PrEP in Africa and Asia.<sup>18</sup> For example, since December, 2021, more than 1·2 million people have initiated PrEP in more than 25 countries across Africa (figure).<sup>18</sup> To scale up PrEP programmes for key populations worldwide, an improved understanding is needed regarding the risks and benefits of PrEP use in people with chronic HBV who are not eligible for antiviral treatment.

## Epidemiology of HBV among people at risk of HIV

HBV is a highly transmissible virus, widely prevalent in some regions and is the world's leading cause of chronic liver disease.<sup>2</sup> Approximately a third of the global population has been exposed to HBV, which is indicated by a positive HBV core antibody. However, a smaller number

Lancet HIV 2022; 9: e585–94

Published Online

July 8, 2022

[https://doi.org/10.1016/S2352-3018\(22\)00123-0](https://doi.org/10.1016/S2352-3018(22)00123-0)

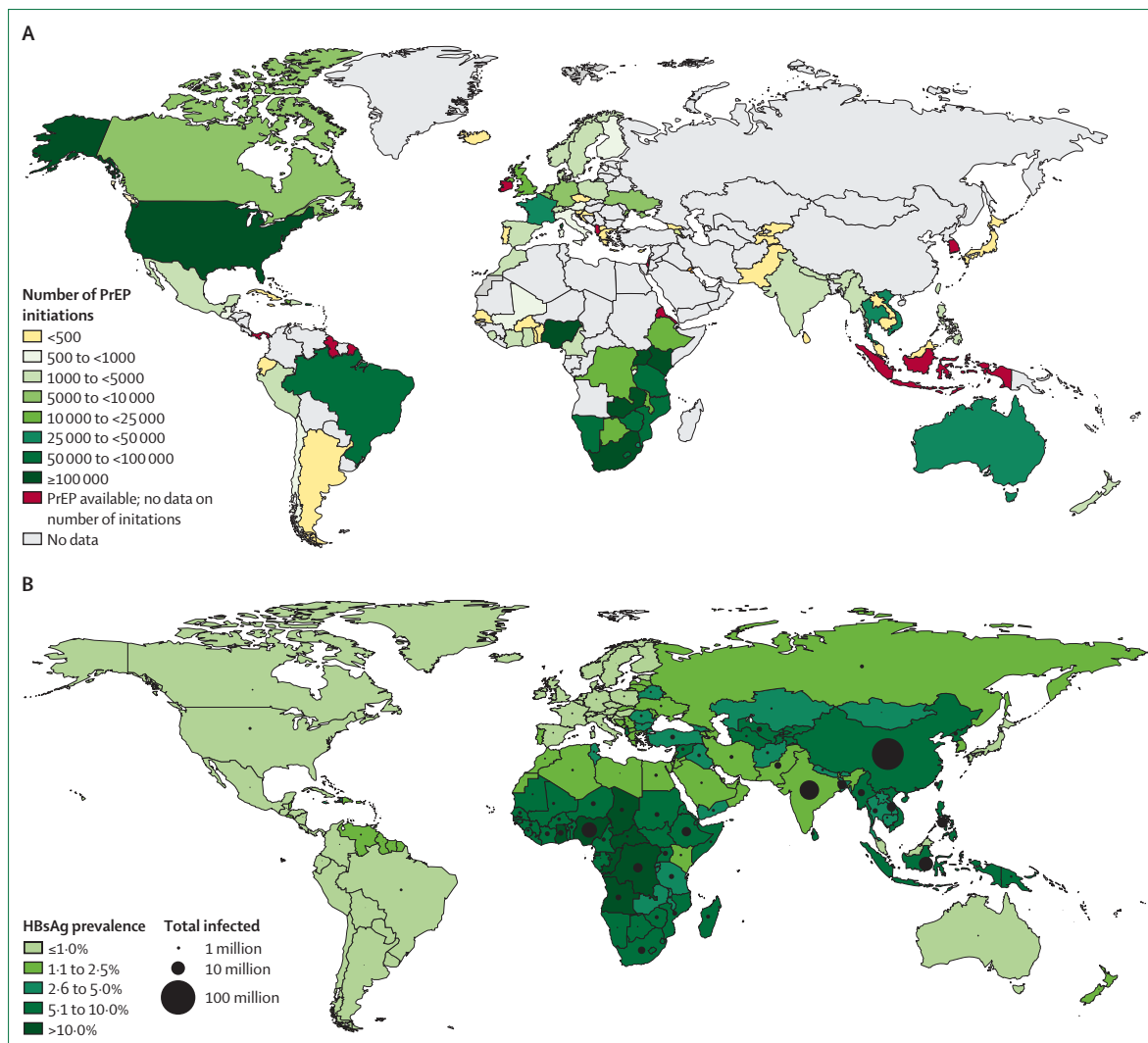
S2352-3018(22)00123-0

Medical Practice Evaluation Center (A M Mohareb MD, K A Freedberg MD, E P Hyle MD), Division of Infectious Diseases (A M Mohareb, A Y Kim MD, K A Freedberg, E P Hyle), and Division of General Internal Medicine (K A Freedberg), Massachusetts General Hospital, Boston, MA, USA; Department of Medicine, Harvard Medical School, Boston, MA, USA

(A M Mohareb, A Y Kim, K A Freedberg, E P Hyle); Centre Population et Développement, Université Paris Cité, IRD, Inserm, Paris, France (J Larmarange PhD); Département de Dermatologie et Infectiologie, Université Félix Houphouët-Boigny, Abidjan, Côte d'Ivoire (P A Coffie MD PhD); Programme PAC-CI, Abidjan, Côte d'Ivoire (P A Coffie, M G Kouamé MD PhD); stichting hiv monitoring, Amsterdam, Netherlands (A Boyd PhD); Department of Infectious Diseases, Public Health Service of Amsterdam, Amsterdam, Netherlands (A Boyd)

Correspondence to:

Dr Amir M Mohareb, Medical Practice Evaluation Center, Massachusetts General Hospital, Boston, MA 02114, USA  
amohareb@mgh.harvard.edu



**Figure: Comparison of global HIV PrEP initiations and HBsAg prevalence, by country**

(A) Countries with some form of PrEP programme as of March, 2022. Source: PrEP Watch (an initiative of AVAC: Global Advocacy for HIV Prevention). (B) Model-estimated global prevalence of HBsAg by country in 2016.<sup>1</sup> HBsAg=hepatitis B surface antigen. PrEP=pre-exposure prophylaxis.

For PrEP Watch see <https://www.prepwatch.org/in-practice/global-prep-tracker/>

go on to have chronic HBV, which describes active or persistent infection marked by a positive HBsAg.<sup>1</sup>

In sub-Saharan Africa, HBV is mainly transmitted through perinatal transmission and horizontal transmission.<sup>2</sup> The risk of HBV infection during adulthood could be elevated for key populations in Africa.<sup>2</sup> In endemic countries in the Western Pacific region, HBV is commonly spread through perinatal transmission.<sup>2,6</sup> HBV is also spread via sexual exposures, needle sharing, health-care exposures, occupational exposures, tattooing, and piercing.<sup>2</sup> Some of these routes of transmission are responsible for the high burden of HBV among key populations. HBV prevalence among key populations in Europe and the Americas could be declining with the scale up of HBV vaccination. HBV prevalence among men who have sex with men in Europe ranges from 0 to 17% depending on the population and year of

study.<sup>19,20</sup> People who inject drugs also have a high risk of HBV infection, with prevalence estimates up to 20% in some studies, and this prevalence is also dependent on the population and the year of evaluation.<sup>20,21</sup> HBV prevalence varies in cohorts of sex workers, ranging from 0 to 6% depending on the setting.<sup>22–24</sup> In these key populations with HBV, the risk of HIV acquisition could be raised, which makes PrEP use a potentially effective, but underutilised, public health strategy.

Although HIV and HBV coinfection is prevalent among key populations in North America and Europe, HBV-endemic countries with generalised HIV epidemics have a higher number of people with co-infection than non-endemic countries.<sup>4</sup> The intersection between the HIV and HBV epidemics is most pronounced in sub-Saharan Africa and among key populations in Asia and other HBV-endemic regions.<sup>4–6</sup> Most HBV infections

in sub-Saharan Africa are acquired at birth or during early childhood, whereas the mean age of HIV infection in sub-Saharan Africa is 20–39 years.<sup>25,26</sup> This difference implies that most people who live with HIV and HBV co-infection in sub-Saharan Africa typically have pre-existing chronic HBV before HIV infection. Therefore, strategies that aim to prevent HIV and HBV coinfection in Africa might be best focused on preventing new HIV infections among people living with chronic HBV. In this setting, the potential for PrEP has not been fully harnessed among people living with HBV.

### Benefits and risks of PrEP in people with chronic HBV

The efficacy of tenofovir disoproxil fumarate-based PrEP for preventing HIV infections in people at high risk of HIV acquisition has been shown in several large, randomised controlled trials. People who take tenofovir disoproxil fumarate and emtricitabine as HIV PrEP have up to a 94% lower incidence of HIV acquisition than people who do not take PrEP.<sup>14,27–29</sup> Even when accounting for modest adherence (eg, taking only 74% of prescribed pills<sup>30</sup>), PrEP reduces HIV incidence and has been shown to be cost-effective in a variety of settings, including for men who have sex with men and women who are at high risk of HIV infection in sub-Saharan Africa.<sup>30–32</sup> In the USA, an uninterrupted daily regimen of antiviral therapy (ie, continuous PrEP) is approved by the Food and Drug Administration (FDA) and recommended by the Centers for Disease Control and Prevention for people at high risk of HIV acquisition.<sup>17</sup>

Tenofovir disoproxil fumarate and emtricitabine, which is the most prescribed antiviral regimen for PrEP, potently inhibits HBV DNA replication and functionally serves as

HBV treatment (although it is not FDA-approved as a combination for HBV treatment). Most people with HBV who are treated with tenofovir disoproxil fumarate or tenofovir disoproxil fumarate and emtricitabine eventually have undetectable amounts of HBV DNA. For people with HBeAg—ie, people with an HBeAg-positive infection—tenofovir disoproxil fumarate monotherapy results in a mean reduction in HBV DNA of 3·16 log<sub>10</sub> copies per mL after only four weeks of therapy.<sup>33</sup> Maximum reductions in HBV DNA are typically seen after 18 months of therapy (mean reduction of 6·31 log<sub>10</sub> copies per mL).<sup>33</sup> For people in HBeAg-negative phases of chronic HBV, maximum effects of therapy are typically seen after 1 year of therapy, by which time 93% of participants enrolled in clinical trials have undetectable amounts of HBV DNA.<sup>34</sup> Comparable treatment effects were found in real-world studies of tenofovir disoproxil fumarate monotherapy in people in the HBeAg-negative phases of chronic HBV in Europe (after 1 year, 90% of people had undetectable amounts of HBV DNA),<sup>35</sup> India (after 1 year, 92% of people had undetectable amounts of HBV DNA),<sup>36</sup> and Ethiopia (after 1 year, 85% of people had undetectable amounts of HBV DNA).<sup>37</sup>

Although tenofovir disoproxil fumarate-based therapy is an effective first-line treatment for HBV, not everyone with chronic HBV meets eligibility for treatment according to current international treatment guidelines. Treatment is reserved for people with elevated amounts of HBV DNA and with evidence of hepatic inflammation. Treatment is also prioritised for people who are at high risk of having progressive liver fibrosis and of developing hepatocellular carcinoma.<sup>38,39</sup> Recommendations for HBV treatment eligibility vary between different professional society organisations (table 1) but are generally made on

	European Association for the Study of the Liver	American Association for the Study of Liver Diseases	Asia-Pacific Association for the Study of the Liver
<b>Treatment initiation</b>			
HBeAg-positive	Older than 30 years; family history of hepatocellular carcinoma or cirrhosis; HBV DNA >20 000 IU/mL and ALT >2 times the ULN	Older than 40 years; family history of hepatocellular carcinoma or cirrhosis; HBV DNA >20 000 IU/mL and ALT >2 times the ULN	Older than 35 years; family history of hepatocellular carcinoma or cirrhosis; HBV DNA >20 000 IU/mL and ALT >2 times the ULN; HBV DNA >20 000 IU/mL, ALT 1–2 times the ULN, and moderate inflammation or substantial fibrosis
HBeAg-negative	HBV DNA >2 000 IU/mL, ALT higher than the ULN, and moderate fibrosis or necroinflammation	HBV DNA >2000 IU/mL and ALT >2 times the ULN	HBV DNA >2000 IU/mL and ALT >2 times the ULN; HBV DNA >2000 IU/mL and ALT 1–2 times the ULN and moderate inflammation or significant fibrosis
<b>Treatment cessation</b>			
HBeAg-positive	Seroconversion to anti-HBeAg with normal ALT and undetectable HBV DNA for more than 12 months	Seroconversion to anti-HBeAg with normal ALT and undetectable HBV DNA for more than 12 months	Seroconversion to anti-HBeAg and undetectable HBV DNA for 12 months or more, preferably 3 years
HBeAg-negative	Could be considered if HBV DNA is undetectable for more than 3 years	Continue treatment indefinitely unless there is a compelling rationale for discontinuation	Undetectable HBV DNA on three occasions 6 months apart and treatment for 2 years or more
Abbreviated considerations in treatment initiation and cessation are shown, and full guidelines should be consulted for more details. <sup>38,39,46,58</sup> ALT=alanine aminotransferase. HBV=hepatitis B virus. ULN=upper limit of normal.			
<b>Table 1: HBV treatment initiation and cessation recommendations from professional society organisations</b>			

the basis of serial assessments of viral replication (ie, HBV DNA), hepatic inflammation (ie, aminotransferase elevation), and the presence or risk of liver disease (ie, fibrosis, older age, hepatocellular carcinoma, or a family history of hepatocellular carcinoma). According to these guidelines, an estimated 75–81% of people with chronic HBV are not eligible for antiviral therapy.<sup>40</sup> Many experts have called for expanding HBV treatment eligibility, particularly because emerging data have shown benefits of this treatment for select populations in the so-called grey zone of treatment (ie, modestly elevated HBV DNA without active liver disease or transaminitis) and because population-level HBV elimination campaigns gain momentum.<sup>41,42</sup>

Abrupt cessation of antiviral therapy in people with chronic HBV has been associated with HBV DNA reactivation (ie, an increase in HBV DNA by at least 2.00 log<sub>10</sub> copies per mL from nadir while on treatment) and hepatitis flares (ie, elevations in aminotransferase enzymes).<sup>43,44</sup> Some people can develop acute liver failure.<sup>43</sup> Post-treatment laboratory monitoring in HBV clinical trials of emtricitabine showed that up to 23% of people had aminotransferase levels of more than five times the upper limit of normal (ULN) following discontinuation of emtricitabine.<sup>45</sup> People with HBV who initiate tenofovir disoproxil fumarate-based PrEP but do not fully adhere to a continuous PrEP regimen could be at risk of these HBV-related complications. Furthermore, initiation of tenofovir disoproxil fumarate-based PrEP could lead to the need for lifelong treatment with antiviral therapy.<sup>46</sup> These early concerns probably resulted in the exclusion of people with HBV infection from most of the PrEP clinical trials.<sup>27,47,48</sup> For this reason, PrEP guidelines recommend that people should first be screened for evidence of HBV infection and that those with HBV infection should be referred to a specialist who can assess the risks and benefits of antiviral treatment before starting PrEP.<sup>16</sup>

Event-based PrEP (ie, PrEP on demand) refers to the planned use of antivirals around the time of high-risk exposures and is effective in populations who are at a high risk of infection.<sup>49</sup> However, event-based PrEP introduces additional uncertainties in people with chronic HBV. People who have frequent short courses of tenofovir disoproxil fumarate and emtricitabine might not accrue the benefits of long-term antiviral therapy (ie, HBV DNA suppression), and might still be at risk of HBV reactivation during periods of drug cessation.

There is limited published experience evaluating the risk of HBV reactivation in people with chronic HBV who take PrEP. A phase 2 clinical trial of tenofovir disoproxil fumarate as PrEP among women in sub-Saharan Africa reported no cases of hepatitis flares in 23 participants with HBsAg-positive serology who were followed up for nearly 1 year.<sup>50</sup> Investigators from the FEM-PrEP study, which evaluated tenofovir disoproxil fumarate and emtricitabine as PrEP in sub-Saharan Africa, reported

one participant who was initially HBsAg-negative with suspected resolved HBV infection (ie, anti-HBV surface antibody positive without a history of vaccination) who later developed HBV-related hepatitis with markedly elevated aminotransferases during a period of tenofovir disoproxil fumarate and emtricitabine withdrawal. However, in the absence of HBV sequencing, the investigators could not determine whether this participant had HBV reactivation or reinfection.<sup>16</sup> Most subsequent PrEP clinical trials implemented screening for HBsAg to exclude potential participants with chronic HBV.

The Iniciativa Profilaxis Pre-Exposición (iPrEx) clinical trial, which randomly assigned once daily tenofovir disoproxil fumarate and emtricitabine as PrEP or a placebo to 2499 men who had sex with men, is worthy of special consideration because it did not explicitly exclude people with pre-existing HBV infection.<sup>15</sup> In this trial, six participants with chronic HBV were randomised to receive tenofovir disoproxil fumarate and emtricitabine and had a period of detectable drug concentrations followed by undetectable drug concentrations, potentially from non-adherence. Three of the six participants had HBV DNA reactivation during suspected tenofovir disoproxil fumarate and emtricitabine cessation, which was defined as amounts of HBV DNA greater than 2.00 log<sub>10</sub> copies per mL above nadir while on treatment. Two of the people who had HBV DNA reactivation had transient increases in alanine aminotransferase (ALT) that were two to three times the ULN. Although these people did not meet the study definitions for hepatitis flares, it should be noted that the iPrEx study excluded people with evidence of liver dysfunction. By inadvertently excluding some people at later stages of HBV infection, the study probably put the population at lower risk of developing symptomatic liver disease and acute liver failure in the setting of reactivated hepatitis.

Another potential risk, although perhaps only theoretical, of episodic exposure to tenofovir disoproxil fumarate and emtricitabine is the potential for the development of HBV drug resistance. Compared with older nucleot(s)ide analogues used to treat HBV (ie, lamivudine and adefovir), tenofovir has shown a higher genetic barrier to resistance, and the clinical importance of many resistance-associated mutations to tenofovir remains controversial. It is exceedingly rare for people on long-term tenofovir-based therapy for HBV to have virological failure (ie, HBV DNA reactivation).<sup>51,52</sup> However, some resistance-associated mutations have been identified, and cases of HBV DNA reactivation have been reported in the literature.<sup>53,54</sup> The potential for the development of HBV resistance mutations to tenofovir is low, but it could be higher with PrEP use than with long-term HBV therapy because of the more frequent episodic use expected in people who take PrEP.

The use of non-tenofovir-based regimens as PrEP raises further complexity for HIV prevention among

	Benefits	Risks	Costs
Sustained use of tenofovir-based PrEP in people with HBV	Improved long-term HBV control, lower risk of liver-related complications, and lower risk of HIV infection	Potentially lower likelihood of HBsAg loss compared with people who are untreated	Costs of tenofovir-based PrEP
Cessation of tenofovir-based PrEP in people with HBV	Higher incidence of HBsAg loss (ie, a functional cure of HBV)	HBV DNA reactivation, hepatitis flares, acute liver failure, and risk of acquiring HIV returns to baseline	Laboratory monitoring (eg, HBsAg, ALT, HBV DNA), retreatment costs for those who do not lose HBsAg (ie, tenofovir or tenofovir-based PrEP), and treatment costs for those who have liver-related complications

ALT=alanine aminotransferase. HBsAg=HBV surface antigen. HBV=hepatitis B virus. PrEP=pre-exposure prophylaxis.

**Table 2: Benefits and risks of tenofovir-based PrEP in people with HBV**

people with HBV. Cabotegravir is a long-acting integrase strand-transfer inhibitor that was shown to be superior to daily oral tenofovir disoproxil fumarate and emtricitabine in preventing HIV infection among people who were at risk of not adhering to daily oral PrEP.<sup>55</sup> As cabotegravir becomes more widely used for PrEP, clinicians might favour this long-acting option over oral tenofovir disoproxil fumarate and emtricitabine, particularly for people with chronic HBV who have an elevated risk of clinical hepatitis and acute liver failure following cessation of antiviral therapy. However, long-term use of oral tenofovir disoproxil fumarate and emtricitabine could retain a niche for people with HBV because this antiviral regimen will lead to control of HBV replication, decreasing the risk of liver-related complications and horizontal HBV transmission.

### New insights from HBV treatment cessation studies could guide PrEP use for people with HBV

Long-term use of oral PrEP has clear benefits for people with chronic HBV who are at risk of HIV infection, but PrEP cessation introduces the risks of HBV reactivation and acute liver failure. These unknown risks are one obstacle to scaling up PrEP for people with chronic HBV. In the absence of high-quality data from PrEP clinical trials and observational studies, clinicians could gain new insights into the potential consequences of PrEP cessation from the hepatology literature. An emerging but contested area of HBV research relates to whether it is safe—or even beneficial—to stop antiviral therapy in people who achieve undetectable HBV DNA while on treatment (table 2).<sup>56–58</sup> The risks of continuing antiviral therapy indefinitely in people with chronic HBV infection include drug toxicity, non-adherence to therapy, and the high costs to the person and health-care system.<sup>56,57,59,60</sup> However, cessation of antiviral therapy introduces the risk of HBV DNA reactivation and hepatitis flares, which are often asymptomatic and would require close clinical monitoring to be detected.<sup>56</sup> Some hepatitis flares are induced by the host response to HBV infection (ie, host-dominating), which are effective at ultimately clearing HBsAg and leading to a functional

cure of chronic HBV.<sup>56</sup> In contrast, flares caused by liver dysfunction from extensive viral replication (ie, virus-dominating) do not clear HBsAg and result in elevations of aminotransferases, hepatic necroinflammation, and progressive liver disease.<sup>56</sup> Currently, clinicians cannot predict whether a hepatitis flare following treatment withdrawal will be host-dominating or virus-dominating.

There is no clear consensus in HBV clinical practice guidelines on if, or when, to stop antiviral therapy (table 1), although all practice guidelines recommend monitoring people through an extended period (ie, at least 12 months) of undetectable amounts of HBV DNA while on antiviral therapy before considering treatment cessation.<sup>39,46,58,61</sup> This uncertainty has motivated observational studies and randomised controlled trials to investigate the effects of HBV treatment cessation.<sup>62,63</sup> In a large observational study, investigators in Taiwan found that 80% of 691 participants who stopped antiviral therapy according to clinical society guidelines had HBV DNA reactivation, 61% had HBV DNA reactivation with a rise in ALT (of more than two times the ULN), and 41% required retreatment with antiviral therapy.<sup>64</sup> Investigators also found that 13% of people with treatment cessation had HBsAg loss within 6 years. This loss was higher than in historical on-treatment controls (annual incidence: 1.78% per year for treatment cessation versus 0.15% per year for treatment continuation).<sup>64</sup> Systematic reviews of observational studies found similar estimates for post-withdrawal HBV DNA reactivation and hepatitis flares.<sup>43,65</sup>

These observations motivated three clinical trials on antiviral therapy cessation in people with HBeAg-negative infection. In the FINITE study, 42 people with HBeAg-negative infection and undetectable HBV DNA were randomly assigned to treatment cessation or continuation with strict monitoring and retreatment parameters.<sup>66</sup> This trial found a higher incidence of HBsAg loss in the treatment cessation group than in the continuation group after 144 weeks of observation without major adverse events (19% vs 0%;  $p=0.02$ ).<sup>66</sup> In the Toronto STOP study, 67 people with HBeAg-negative infection and undetectable amounts of HBV DNA were randomly assigned 2:1 to treatment cessation or continuation.<sup>63</sup> After 72 weeks,

	Potential research methods	Key epidemiological considerations
What is the incidence of acute liver failure among people with HBV who initiate and stop PrEP?	Retrospective cohorts in PrEP clinics or prospective observational cohort studies	Selection could bias estimates towards null; challenges in recruiting patients without HBV-specific indications for treatment; heterogeneous risk between those with and without detectable HBV DNA; and large sample size potentially needed for outcome ascertainment
What is the incidence of HBsAg loss among people who initiate PrEP compared with those who do not?	Randomised clinical trial	Large sample size and long duration of follow-up potentially needed for outcome ascertainment
What is the risk of HBV resistance-associated mutations in intermittent or event-based PrEP?	Prospective observational study with surveillance genetic testing for resistance-associated mutations	Uncertainty in determining the clinical significance of detected mutations
What is the cost-effectiveness of PrEP in people with HBV?	Simulation modelling and cost-effectiveness analysis	Uncertainty about risk of HIV and acute liver failure following PrEP withdrawal and person-level heterogeneity in duration of PrEP use and risk of liver-related complications

HBV=hepatitis B virus. PrEP=pre-exposure prophylaxis.

**Table 3: Research priorities regarding PrEP use in people with chronic HBV**

nearly all people who stopped therapy had HBV DNA reactivation (HBV DNA >20 IU/mL in 98% of participants in the treatment cessation group vs 9% in the treatment continuation group;  $p<0.005$ ), and many had hepatitis flares (ALT rose above the ULN in 24 [53%] of 45 participants in the treatment cessation group vs four [18%] of 22 participants in the treatment continuation group;  $p=0.01$ ).<sup>63</sup> There was no statistically significant difference in HBsAg loss (2% of participants in the treatment cessation group vs 5% in the treatment continuation group;  $p=1.0$ ).<sup>63</sup> In the Stop-NUC trial, 158 people with HBeAg-negative infection and undetectable HBV DNA were randomly assigned to a treatment cessation group or treatment continuation group.<sup>62</sup> In this trial, 22 (14%) of the 158 participants re-initiated treatment, with one participant experiencing acute liver failure.<sup>62</sup> Meanwhile, 16 (10%) of the 158 participants in the treatment cessation group lost HBsAg after 96 weeks, and a low quantitative HBsAg concentration (<1000 IU/mL) before treatment cessation was predictive of HBsAg loss.<sup>62</sup>

Further research and longer follow-up durations are needed to better understand the risks and benefits of treatment cessation in people with HBV infection. The RETRACT-B study, a multicentre observational cohort, constitutes the largest study to date with 1552 participants followed up for up to 4 years (median follow-up was 18 months). In this study, investigators found that 83% of 1552 participants had HBV DNA reactivation, 61% had hepatitis flares with ALT higher than two times the ULN, and 31% had hepatitis flares with ALT higher than five times the ULN. Hepatic decompensation occurred in 19 (1%) participants and hepatocellular carcinoma occurred in 14 (1%) participants during the follow-up period. Death occurred in 7 (37%) of the 19 patients with hepatic decompensation and 2 (14%) of the 14 patients with hepatocellular carcinoma during the follow-up period. The rate of HBsAg loss was approximately 3% per year, and this was higher among people who were White and who had lower quantitative concentrations of HBsAg before treatment withdrawal.<sup>67</sup>

### Recommendations to guide PrEP management in people with HBV

The accumulation of observational and clinical trial data regarding treatment cessation in people with HBV has potential applications to PrEP. However, there are also important differences between controlled treatment cessation and inconsistent or short-term PrEP use that restrict our ability to generalise these data (table 3). In all studied cases of HBV treatment cessation, participants were carefully selected and strictly monitored for complications. All participants had an extended period of observation with undetectable HBV DNA concentrations before treatment cessation. In contrast, some people seeking PrEP could present with elevated HBV DNA and might not remain on PrEP long enough to achieve undetectable HBV DNA. Such a scenario raises the possibility that PrEP use among people with elevated amounts of HBV DNA will result in more severe episodes of reactivation and hepatitis flares than were observed in the clinical studies summarised above. It is unknown if such flares will also be accompanied with a higher likelihood of acute liver failure or HBsAg clearance. However, for people with inactive HBV infection (ie, people with chronic HBeAg-negative infection without indications for treatment), tenofovir disoproxil fumarate and emtricitabine use could result in lower rates of HBV DNA reactivation or hepatitis flares because these people are being exposed to antiviral treatment in a more quiescent disease state compared with people in the clinical trials outlined above.

Furthermore, people often use PrEP during times of high self-perceived HIV risk and stop PrEP when self-perceived risk falls, which typically occurs on shorter time intervals than those studied in HBV treatment cessation studies.<sup>68-70</sup> In many settings, additional challenges make sustained PrEP use difficult, including resource scarcities, unexpected shortages of drug supply, and perceived stigma related to being at risk for HIV.<sup>18</sup> Concerns have also been raised regarding PrEP expansion in countries where people with chronic HBV have sub-optimal access

to affordable HBV monitoring and treatment programmes. In these settings, there could be ethical concerns about providing the same drug (ie, tenofovir disoproxil fumarate) free of charge to people for the purposes of HIV prevention but not for HBV treatment.<sup>71</sup> One potential path forward is to integrate systems for HBV screening, monitoring, and treatment within nascent PrEP programmes in resource-limited settings, particularly where the majority of people with HBV remain undiagnosed and untreated.<sup>71</sup> Although many components of HBV treatment (ie, HBV diagnostic testing, tenofovir disoproxil fumarate-based therapy, and services for adherence counselling) would be integral parts of existing PrEP programmes, other components (ie, HBV DNA monitoring, liver fibrosis screening, and hepatocellular carcinoma screening) would need to be incorporated so that HBV-focused care is also optimised.

With these differences in mind, HBV treatment cessation studies provide important insights for PrEP safety and patient selection (panel). Nearly all people experience reactivation in HBV DNA following treatment cessation after long-term suppression, and some of those people go on to develop clinically apparent hepatitis flares. Acute liver failure, although uncommon, does occur and remains the most feared risk in people with HBV who are being considered for PrEP. Acute liver failure is the major risk that needs to be weighed against the benefits of preventing HIV infection through PrEP. People with pre-existing liver disease appear to be at highest risk for post-cessation liver injury, and we expect this to be the case in PrEP as well.<sup>65</sup> Demographic differences have also been observed in post-cessation hepatitis flares, with higher risk of flares in younger compared with older people and in White compared with Asian people.<sup>65</sup> These observations could be rooted in environmental, immunological, or genotype-related differences in infection. People with low concentrations of quantitative HBsAg before treatment withdrawal are more likely to have HBsAg loss (ie, functional cure of chronic HBV) with hepatitis flares than people with high concentrations of quantitative HBsAg before treatment withdrawal.

From these data, we recommend that all people with HBV initiating tenofovir-based PrEP have close follow-up and laboratory monitoring of HBV DNA, aminotransferases, and selected HBV serologies. Because of its dual benefits against HIV acquisition and liver-related complications from HBV, indefinite use of tenofovir-containing PrEP should be considered in people with chronic HBV mono-infection. People who lose HBsAg or who have low concentrations of quantitative HBsAg could be considered for PrEP cessation once the benefits of HIV prevention are no longer indicated. In cases where PrEP is known to be stopped, monitoring practices could be tailored to the person's risk of reactivation and hepatitis. We recommend laboratory testing of HBV DNA and aminotransferases at a minimum frequency of once every 3 months for at least 1 year

#### Panel: Estimated frequency of different events at 12 months post-antiviral cessation

- Hepatitis B virus (HBV) DNA reactivation: 63–83%<sup>65,67</sup>
- Hepatitis flares: 35%<sup>65,67</sup>
- HBeAg reversion: 9%<sup>43,46</sup>
- Acute liver failure: less than 1% (reporting bias due to differing definitions of acute liver failure and low event rates limit the precision of this point estimate)<sup>64,65,67</sup>
- HBsAg loss: 2–4%<sup>46,64,65,67</sup>

following PrEP cessation. Unfortunately, some patients who stop PrEP due to adherence challenges might also experience barriers to engaging with post-cessation follow-up for laboratory monitoring. An observational study in a large PrEP clinic in North America found that only 46% of the PrEP users with documented HBV had any follow-up HBV DNA monitoring.<sup>72</sup> In settings with scarce availability of HBV DNA testing, people could still be safely monitored through serial testing of aminotransferases. In settings with no routine aminotransferase monitoring available, PrEP initiation might still outweigh the potential adverse effects of treatment cessation, particularly if the risk of HIV infection is high. All people with HBV who initiate PrEP should be counselled on the risks of tenofovir disoproxil fumarate and emtricitabine cessation, the need for close laboratory monitoring, and the possibility of needing retreatment (which could be lifelong), for HBV-specific indications if they do have reactivation hepatitis.

#### Conclusion

PrEP scale up in HBV-endemic low-income and middle-income countries and in key populations could markedly decrease the number of people who become co-infected with HIV and HBV.<sup>73</sup> PrEP availability also serves as a unique opportunity to increase the number of people with HBV who are evaluated for treatment. One current challenge in the management of people with chronic HBV is in the long-term retention in care and monitoring of people with inactive disease or who are in the so-called grey zone of treatment initiation.<sup>41</sup> These people could greatly benefit from PrEP use if they can be retained in care for laboratory monitoring while on and off tenofovir disoproxil fumarate and emtricitabine therapy. The risks of acute liver failure among people with HBV who stop PrEP ultimately needs to be weighed against the risks of HIV acquisition in this population. Taken together, the dual benefits in HIV prevention and HBV control make PrEP use with tenofovir-based therapy (or HBV treatment expansion) an attractive public health intervention that has been underutilised to date.

The potent activity of tenofovir disoproxil fumarate and emtricitabine in preventing HIV and treating HBV presents an important opportunity to address both



### Search strategy and selection criteria

We searched PubMed, the Cochrane Database of Systematic Reviews, and Google Scholar with the key term “hepatitis B” combined with “pre-exposure prophylaxis,” “PrEP,” “treatment withdrawal,” “antiviral cessation,” or “finite treatment duration”. We included studies and grey literature in English and French published from Jan 1, 2000, to Oct 1, 2021. We excluded references on non-tenofovir-based regimens for hepatitis B virus therapy or HIV pre-exposure prophylaxis. The final reference list was generated on the basis of relevance to this Review.

public health crises. Tenofovir-based PrEP minimises the risk of HIV infection, but its benefits have not been fully realised in people with chronic HBV, at least partially because of concerns about the risks of HBV DNA reactivation and hepatitis flares following cessation of antiviral therapy. Emerging data from the hepatology literature provides insights to the risks and benefits of antiviral cessation in people with HBV. Although the HBV-specific benefits of initiating PrEP could be greater in people with detectable HBV DNA concentrations than those with undetectable concentrations, the risks of cessation could also be greater, particularly with episodic use of PrEP without laboratory monitoring. It is not possible to determine which people with HBV DNA reactivation following antiviral cessation will also have loss of HBsAg, but data from the ongoing HBV treatment cessation studies could shed more light on this phenomenon. Rigorous studies, including clinical trials, observational studies, and modelling research, are all needed to better weigh the risks and benefits of PrEP in people with different stages of HBV disease.

### Contributors

AMM conducted the literature search, reviewed the results, and drafted the manuscript. All authors critically reviewed and edited the manuscript for important intellectual content and approved the final version to be published.

### Declaration of interests

We declare no competing interests.

### Acknowledgments

AMM is supported by the Massachusetts General Hospital (MGH) Executive Committee on Research Fund for Medical Discovery and the Charles A. King Trust Fellowship Program. AMM is also supported by the Harvard University Center for AIDS Research, a programme funded by the National Institutes of Health (NIH; P30 AI060354), which is supported by the following NIH co-funding and participating institutes and centres: National Institute of Allergy and Infectious Diseases; National Cancer Institute; Eunice Kennedy Shriver National Institute of Child Health and Development; National Institute of Dental and Craniofacial Research; National Heart, Lung, and Blood Institute; National Institute on Drug Abuse; National Institute of Mental Health; National Institute on Aging; National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Nursing Research; National Institute on Minority Health and Health Disparities; Fogarty International Center, and Office of AIDS Research. EPH is supported by the NIH (R37AI058736 and R01AI042006), the Harvard University Center for AIDS Research, and the Jerome and Celia Reich Endowed

Scholar in HIV/AIDS Research at MGH. KAF is supported by the NIH (R37AI058736 and R01AI042006). The MGH Executive Committee on Research, Charles A King Trust Fellowship, Harvard University Center for AIDS Research, and the NIH had no role in the design or authorship of this Review. The article contents are solely the responsibility of the authors and do not necessarily represent the official views of the funders.

### References

- Razavi-Shearer D, Gamkrelidze I, Nguyen MH, et al. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018; **3**: 383–403.
- WHO. Global hepatitis report, 2017. <http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1> (accessed Oct 21, 2021).
- Naghavi M, Abajobir AA, Abbafati C, et al. Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017; **390**: 1151–210.
- Leumi S, Bigna JJ, Amougou MA, Ngouo A, Nyaga UF, Noubiap JJ. Global burden of hepatitis B infection in people living with human immunodeficiency virus: a systematic review and meta-analysis. *Clin Infect Dis* 2019; published online Dec 9. <https://doi.org/10.1093/cid/ciz1170>.
- Thio CL. Hepatitis B and human immunodeficiency virus coinfection. *Hepatology* 2009; **49** (suppl): S138–45.
- Hoffmann CJ, Thio CL. Clinical implications of HIV and hepatitis B co-infection in Asia and Africa. *Lancet Infect Dis* 2007; **7**: 402–09.
- Iloje UH, Yang HI, Jen CL, et al. Risk and predictors of mortality associated with chronic hepatitis B infection. *Clin Gastroenterol Hepatol* 2007; **5**: 921–31.
- Mugavero MJ, Napravnik S, Cole SR, et al. Viremia copy-years predicts mortality among treatment-naive HIV-infected patients initiating antiretroviral therapy. *Clin Infect Dis* 2011; **53**: 927–35.
- Kouamé G-M, Boyd A, Moh R, et al. Higher mortality despite early antiretroviral therapy in human immunodeficiency virus and hepatitis B virus (HBV)-coinfected patients with high HBV replication. *Clin Infect Dis* 2018; **66**: 112–20.
- Mbae M, Owen L, Elisha KK, et al. Excess early mortality in HIV/hepatitis B virus co-infected patients initiating antiretroviral therapy in Kenya. *AIDS* 2019; **33**: 1404–06.
- Mohareb AM, Kouamé GM, Gabassi A, et al. Mortality in relation to hepatitis B virus (HBV) infection status among HIV-HBV co-infected patients in sub-Saharan Africa after immediate initiation of antiretroviral therapy. *J Viral Hepat* 2021; **28**: 621–29.
- WHO. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. 2015. [https://apps.who.int/iris/bitstream/handle/10665/186275/9789241509565\\_eng.pdf](https://apps.who.int/iris/bitstream/handle/10665/186275/9789241509565_eng.pdf) (accessed Oct 21, 2021).
- Lok ASF, 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; **63**: 284–306.
- Grant RM, Lama JR, Anderson PL, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010; **363**: 2587–99.
- Solomon MM, Schechter M, Liu AY, et al. The safety of tenofovir-emtricitabine for HIV pre-exposure prophylaxis (PrEP) in individuals with active hepatitis B. *J Acquir Immune Defic Syndr* 2016; **71**: 281–86.
- Malahleha M, Ahmed K, Deese J, et al. Hepatitis B virus reactivation or reinfection in a FEM-PrEP participant: a case report. *J Med Case Reports* 2015; **9**: 207.
- Department of Health & Human Services, Centers for Disease Control and Prevention. Pre-exposure prophylaxis for the prevention of HIV infection in the United States—2017 update. 2017. <https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf> (accessed Oct 21, 2021).
- Were DK, Musau A, Atkins K, et al. Health system adaptations and considerations to facilitate optimal oral pre-exposure prophylaxis scale-up in sub-Saharan Africa. *Lancet HIV* 2021; **8**: e511–20.

- 19 Falla AM, Hofstraat SHI, Duffell E, Hahné SJM, Tavoschi L, Veldhuijzen IK. Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups. *BMC Infect Dis* 2018; **18**: 79.
- 20 Mason LM, Duffell E, Veldhuijzen IK, Petriti U, Bunge EM, Tavoschi L. Hepatitis B and C prevalence and incidence in key population groups with multiple risk factors in the EU/EEA: a systematic review. *Euro Surveill* 2019; **24**: 1800614.
- 21 Gough E, Kempf MC, Graham L, et al. HIV and hepatitis B and C incidence rates in US correctional populations and high risk groups: a systematic review and meta-analysis. *BMC Public Health* 2010; **10**: 777.
- 22 Russi JC, Serra M, Viñoles J, et al. Sexual transmission of hepatitis B virus, hepatitis C virus, and human immunodeficiency virus type 1 infections among male transvestite commercial sex workers in Montevideo, Uruguay. *Am J Trop Med Hyg* 2003; **68**: 716–20.
- 23 Todd CS, Nasir A, Stanekzai MR, et al. HIV, hepatitis B, and hepatitis C prevalence and associated risk behaviors among female sex workers in three Afghan cities. *AIDS* 2010; **24** (suppl 2): S69–75.
- 24 Becquet V, Nouaman M, Plazy M, et al. Sexual health needs of female sex workers in Côte d'Ivoire: a mixed-methods study to prepare the future implementation of pre-exposure prophylaxis (PrEP) for HIV prevention. *BMJ Open* 2020; **10**: e028508.
- 25 Risher KA, Cori A, Reniers G, et al. Age patterns of HIV incidence in eastern and southern Africa: a modelling analysis of observational population-based cohort studies. *Lancet HIV* 2021; **8**: e429–39.
- 26 Akullian A, Bershteyn A, Klein D, Vandormael A, Bärnighausen T, Tanser F. Sexual partnership age pairings and risk of HIV acquisition in rural South Africa. *AIDS* 2017; **31**: 1755–64.
- 27 Thigpen MC, Kebaabetswe PM, Paxton LA, et al. Antiretroviral preexposure prophylaxis for heterosexual HIV transmission in Botswana. *N Engl J Med* 2012; **367**: 423–34.
- 28 Choopanya K, Martin M, Suntharasamaj P, et al. Antiretroviral prophylaxis for HIV infection in injecting drug users in Bangkok, Thailand (the Bangkok Tenofovir Study): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2013; **381**: 2083–90.
- 29 Baeten JM, Donnell D, Ndase P, et al. Antiretroviral prophylaxis for HIV prevention in heterosexual men and women. *N Engl J Med* 2012; **367**: 399–410.
- 30 Luz PM, Osher B, Grinsztejn B, et al. The cost-effectiveness of HIV pre-exposure prophylaxis in men who have sex with men and transgender women at high risk of HIV infection in Brazil. *J Int AIDS Soc* 2018; **21**: e25096.
- 31 Walensky RP, Park J-E, Wood R, et al. The cost-effectiveness of pre-exposure prophylaxis for HIV infection in South African women. *Clin Infect Dis* 2012; **54**: 1504–13.
- 32 Kazemian P, Costantini S, Kumarasamy N, et al. The cost-effectiveness of human immunodeficiency virus (HIV) preexposure prophylaxis and HIV testing strategies in high-risk groups in India. *Clin Infect Dis* 2020; **70**: 633–42.
- 33 Chan HLY, Chan CK, Hui AJ, et al. Effects of tenofovir disoproxil fumarate in hepatitis B e antigen-positive patients with normal levels of alanine aminotransferase and high levels of hepatitis B virus DNA. *Gastroenterology* 2014; **146**: 1240–48.
- 34 Marcellin P, Heathcote EJ, Buti M, et al. Tenofovir disoproxil fumarate versus adefovir dipivoxil for chronic hepatitis B. *N Engl J Med* 2008; **359**: 2442–55.
- 35 Pol S, Lampertico P. First-line treatment of chronic hepatitis B with entecavir or tenofovir in 'real-life' settings: from clinical trials to clinical practice. *J Viral Hepat* 2012; **19**: 377–86.
- 36 Goyal SK, Dixit VK, Shukla SK, et al. Prolonged use of tenofovir and entecavir in hepatitis B virus-related cirrhosis. *Indian J Gastroenterol* 2015; **34**: 286–91.
- 37 Desalegn H, Aberra H, Berhe N, et al. Treatment of chronic hepatitis B in sub-Saharan Africa: 1-year results of a pilot program in Ethiopia. *BMC Med* 2018; **16**: 234.
- 38 Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology* 2018; **67**: 1560–99.
- 39 Lampertico P, Agarwal K, Berg T, et al. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370–98.
- 40 Tan M, Bhadoria AS, Cui F, et al. Estimating the proportion of people with chronic hepatitis B virus infection eligible for hepatitis B antiviral treatment worldwide: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2021; **6**: 106–19.
- 41 Jeng W-J, Lok AS. Should treatment indications for chronic hepatitis B be expanded? *Clin Gastroenterol Hepatol* 2021; **19**: 2006–14.
- 42 McNaughton AL, Lemoine M, van Rensburg C, Matthews PC. Extending treatment eligibility for chronic hepatitis B virus infection. *Nat Rev Gastroenterol Hepatol* 2021; **18**: 146–47.
- 43 Papatheodoridis G, Vlachogiannakos I, Cholongitas E, et al. Discontinuation of oral antivirals in chronic hepatitis B: a systematic review. *Hepatology* 2016; **63**: 1481–92.
- 44 Ghany MG, Feld JJ, Chang K-M, et al. Serum alanine aminotransferase flares in chronic hepatitis B infection: the good and the bad. *Lancet Gastroenterol Hepatol* 2020; **5**: 406–17.
- 45 Mondou E, Sorbel J, Anderson J, Mommeja-Marin H, Rigney A, Rousseau F. Posttreatment exacerbation of hepatitis B virus (HBV) infection in long-term HBV trials of emtricitabine. *Clin Infect Dis* 2005; **41**: e45–47.
- 46 Kao J-H, Jeng W-J, Ning Q, et al. APASL guidance on stopping nucleos(t)ide analogues in chronic hepatitis B patients. *Hepatol Int* 2021; **15**: 833–51.
- 47 Mujugira A, Baeten JM, Donnell D, et al. Characteristics of HIV-1 serodiscordant couples enrolled in a clinical trial of antiretroviral pre-exposure prophylaxis for HIV-1 prevention. *PLoS One* 2011; **6**: e25828.
- 48 Marrazzo JM, Ramjee G, Richardson BA, et al. Tenofovir-based preexposure prophylaxis for HIV infection among African women. *N Engl J Med* 2015; **372**: 509–18.
- 49 Molina J-M, Capitant C, Spire B, et al. On-demand preexposure prophylaxis in men at high risk for HIV-1 infection. *N Engl J Med* 2015; **373**: 2237–46.
- 50 Peterson L, Taylor D, Roddy R, et al. Tenofovir disoproxil fumarate for prevention of HIV infection in women: a phase 2, double-blind, randomized, placebo-controlled trial. *PLoS Clin Trials* 2007; **2**: e27.
- 51 Kitrinos KM, Corsa A, Liu Y, et al. No detectable resistance to tenofovir disoproxil fumarate after 6 years of therapy in patients with chronic hepatitis B. *Hepatology* 2014; **59**: 434–42.
- 52 Liu Y, Corsa AC, Buti M, et al. No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg- patients with chronic hepatitis B after 8 years of treatment. *J Viral Hepat* 2017; **24**: 68–74.
- 53 Mokaya J, McNaughton AL, Bester PA, et al. Hepatitis B virus resistance to tenofovir: fact or fiction? A systematic literature review and structural analysis of drug resistance mechanisms. *Wellcome Open Res* 2020; **5**: 151.
- 54 Cho WH, Lee HJ, Bang KB, Kim SB, Song IH. Development of tenofovir disoproxil fumarate resistance after complete viral suppression in a patient with treatment-naïve chronic hepatitis B: a case report and review of the literature. *World J Gastroenterol* 2018; **24**: 1919–24.
- 55 Landovitz RJ, Donnell D, Clement ME, et al. Cabotegravir for HIV prevention in cisgender men and transgender women. *N Engl J Med* 2021; **385**: 595–608.
- 56 Liaw Y-F. Finite nucleos(t)ide analog therapy in HBeAg-negative chronic hepatitis B: an emerging paradigm shift. *Hepatol Int* 2019; **13**: 665–73.
- 57 Lampertico P, Berg T. Less can be more: a finite treatment approach for HBeAg-negative chronic hepatitis B. *Hepatology* 2018; **68**: 397–400.
- 58 Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int* 2016; **10**: 1–98.
- 59 Ford N, Scourse R, Lemoine M, et al. Adherence to nucleos(t)ide analogue therapies for chronic hepatitis B infection: a systematic review and meta-analysis. *Hepatol Commun* 2018; **2**: 1160–67.
- 60 Lim SG, Aung MO, Chung SWM, Soon CSL, Mak BHN, Lee KH. Patient preferences for hepatitis B therapy. *Antivir Ther* 2013; **18**: 663–70.

- 61 Terrault NA, Bzowej NH, Chang K-M, Hwang JP, Jonas MM, Murad MH. AASLD guidelines for treatment of chronic hepatitis B. *Hepatology* 2016; **63**: 261–83.
- 62 Van Bömmel F. Response to discontinuation of long-term nucleos(t)ide analogue treatment in HBeAg negative patients: results of the Stop-NUC trial. International Liver Congress; August 29, 2021 (abstr LBO-06).
- 63 Liem KS, Fung S, Wong DK, et al. Limited sustained response after stopping nucleos(t)ide analogues in patients with chronic hepatitis B: results from a randomised controlled trial (Toronto STOP study). *Gut* 2019; **68**: 2206–13.
- 64 Jeng W-J, Chen Y-C, Chien R-N, Sheen I-S, Liaw Y-F. Incidence and predictors of hepatitis B surface antigen seroclearance after cessation of nucleos(t)ide analogue therapy in hepatitis B e antigen-negative chronic hepatitis B. *Hepatology* 2018; **68**: 425–34.
- 65 Hall SAL, Vogrin S, Wawryk O, et al. Discontinuation of nucleos(t)ide analogue therapy in HBeAg-negative chronic hepatitis B: a meta-analysis. *Gut* 2021; **86**: 201–07.
- 66 Berg T, Simon K-G, Mauss S, et al. Long-term response after stopping tenofovir disoproxil fumarate in non-cirrhotic HBeAg-negative patients—FINITE study. *J Hepatol* 2017; **67**: 918–24.
- 67 Hirode G, Choi H, Chen CH, et al. Off-therapy response after nucleos(t)ide analogue withdrawal in patients with chronic hepatitis B: an international, multicenter, multiethnic cohort (RETRACT-B study). *Gastroenterology* 2021; **162**: 757–71.
- 68 Coyer L, van den Elshout MAM, Achterbergh RCA, et al. Understanding pre-exposure prophylaxis (PrEP) regimen use: switching and discontinuing daily and event-driven PrEP among men who have sex with men. *EClinicalMedicine* 2020; **29**: 100650.
- 69 Jongen VW, Hoornborg E, van den Elshout MA, et al. Adherence to event-driven HIV PrEP among men who have sex with men in Amsterdam, the Netherlands: analysis based on online diary data, 3-monthly questionnaires and intracellular TFV-DP. *J Int AIDS Soc* 2021; **24**: e25708.
- 70 Vuylsteke B, Reyniers T, De Baetselier I, et al. Daily and event-driven pre-exposure prophylaxis for men who have sex with men in Belgium: results of a prospective cohort measuring adherence, sexual behaviour and STI incidence. *J Int AIDS Soc* 2019; **22**: e25407.
- 71 Larmarange J, Becquet V, Masumbuko J-M, et al. Implementing preexposure prophylaxis among key populations: an opportunity for patient-centered services and management of hepatitis B. *AIDS* 2018; **32**: 829–30.
- 72 Thompson KA, Blank G, Toy J, et al. Chronic hepatitis b infection among preexposure prophylaxis users enrolled in a population-based program in British Columbia, Canada. *Open Forum Infect Dis* 2021; **8**: ofab492.
- 73 Laurent C, Dembélé Keita B, Yaya I, et al. HIV pre-exposure prophylaxis for men who have sex with men in west Africa: a multicountry demonstration study. *Lancet HIV* 2021; **8**: e420–28.

Copyright © 2022 Elsevier Ltd. All rights reserved