



## Perspective

## Ultra-long-acting (XLA) antivirals for chronic viral hepatitis

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## ABSTRACT

Viral hepatitis is among the top four causes of mortality globally, causing 1.4 million deaths each year, exceeding tuberculosis, malaria and human immunodeficiency virus. Hepatitis B and C are responsible for 90% of hepatitis deaths, and the remaining 10% are caused by other hepatitis viruses. The annual number of deaths from hepatitis C is declining, whereas the numbers of deaths from hepatitis B and D are increasing. Hepatitis B alone represents the seven highest cause of mortality worldwide. Spurred on by development of curative antivirals for hepatitis C and expanding access to hepatitis B virus (HBV) vaccination, the World Health Organization has committed to eliminating viral hepatitis as a public health threat by 2030.

Like the majority of current antivirals, those available for HBV are virostatic. They are capable of suppressing viral replication but cannot eliminate the virus from infected patients. Therefore, treatment is lifelong. Long-term adherence to medication continues to represent a major challenge. Importantly, HBV often reactivates, leading to potential life-threatening events in immunosuppressed patients. Therapeutic options are limited for hepatitis D; however, promising new, effective antivirals are on the horizon.

Recent advances have emerged in medicinal chemistry and drug delivery approaches to produce ultra-long-acting (XLA) antivirals. These can extend antiviral activity from months to 1 year or even longer. These new formulations can overcome the challenges of daily dosing and maximize drug exposure. The development of XLA antivirals targeting viral hepatitis may also facilitate cure strategies.

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## Chronic viral hepatitis

Chronic viral hepatitis is the leading cause of cirrhosis, hepatocellular carcinoma and liver transplantation worldwide (Cooke et al., 2019; Cox et al., 2020). Three viruses are largely responsible: hepatitis B, C and D. Chronic hepatitis B virus (HBV) infection affects >290 million people (Polaris Observatory HBV Collaborators, 2018), chronic hepatitis C virus (HCV) infection affects 58 million people (Polaris Observatory HCV Collaborators, 2017), and global estimates for chronic hepatitis D virus (HDV) infection range from 12 to 60 million people (Stockdale et al., 2020) (Figure 1).

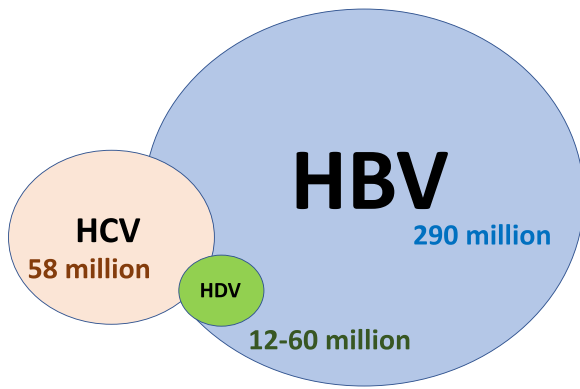
Medical interventions for viral hepatitis rely on both preventative vaccines and antivirals. A vaccine that protects against HBV infection has been available for over 30 years, but no vaccines exist for HCV. Entecavir and tenofovir suppress HBV replication for chronic carriers, but cannot eliminate the virus from infected patients (European Association for the Study of the Liver, 2017). Therefore, treatment is lifelong. For HDV, a viral entry inhibitor, bulevirtide, has been approved recently for treatment, and lonafarnib is now completing phase 3 trials (Urban et al., 2021). Spurred on by recent development of curative drugs for HCV and expanding access to HBV vaccination, the World Health Organization has committed to eliminating viral hepatitis as a public health threat by 2030 (World Health Organization, 2016).

## Hepatitis B virus

HBV is a DNA virus that primarily infects human hepatocytes. Sodium taurocholate cotransporting polypeptide is the cell recep-

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**Figure 1.** Global population with chronic viral hepatitis. HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus.

tor that binds to the HBV surface antigen (HBsAg). Following acute HBV exposure in adults, immunity generally controls viral replication and expression, clearing the virus from the bloodstream and evoking markers of an immune response (anti-HBc and anti-HBs). However, in a small proportion of hepatocytes, the virus is not eliminated and the HBV genome remains. HBV reactivates occasionally, causing viral flare-ups. As the human population is aging, with increasing rates of cancers and use of immunosuppressive therapies, HBV reactivation is emerging as a global health threat (Reddy et al., 2015).

Globally, more than two billion people have been exposed to HBV and exhibit serological markers of past infection (Polaris Observatory HBV Collaborators, 2018). Up to 290 million people suffer from chronic hepatitis B, defined as persistence of serum HBsAg+ for >6 months (Figure 2). All chronically infected patients are at increased risk for developing cirrhosis and liver cancer (European Association for the Study of the Liver, 2017). The advent of safer and more efficacious HBV antivirals has expanded the indication to treat almost all chronic HBV carriers (McNaughton et al., 2021). A major challenge, however, is keeping patients on daily drug medications for years. Poor adherence to therapy among patients with chronic conditions is amplified during health crises, such as the coronavirus disease 2019 pandemic, when the risk of drug interruption is much greater.

Current treatment for chronic hepatitis B is tenofovir or entecavir, both administered as one oral pill once daily. Both drugs have a high barrier to resistance, although patients who have been exposed to lamivudine may fail more frequently on entecavir (European Association for the Study of the Liver, 2017).

*Antiviral prophylaxis for HBV*

The use of antiviral agents to prevent viral transmission through sexual contact or exchange of body fluids that limit the spread

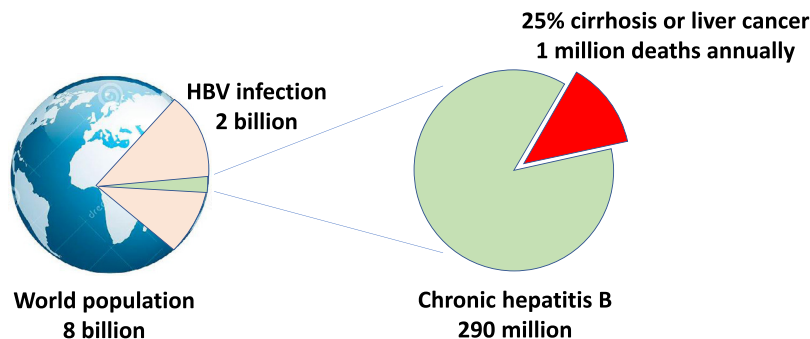
of human immunodeficiency virus (HIV) could have an impact on HBV prevention as both share similar transmission routes. Also, it has been reported that HIV-infected patients receiving antiretroviral therapy (ART) containing dually active HIV–HBV agents (i.e. tenofovir, lamivudine and/or emtricitabine) and engaged in high-risk sexual behaviours experienced a reduction in the incidence of sexually acquired acute hepatitis B (Gatanaga et al., 2013; Heuft et al., 2014). Interestingly, many were men who have sex with men (MSM) who had been vaccinated previously against HBV but failed to develop a protective anti-HBs titre. In the authors’ clinical experience, waning immunity for HBV is presumed for individuals with confirmed full HBV vaccination and current anti-HBs titre <10 mIU/mL. Laboratory evidence of HBV seroconversion following vaccination is lacking for most individuals who received neonatal vaccination. Thus, adult testing is generally undertaken once, and unexpected negative markers of HBV protection are interpreted as waning HBV immunity in those reporting prior vaccination.

*HBV reactivation*

The persistence of HBV cccDNA within the nucleus of infected hepatocytes after initial viral exposure, even in patients who had previously cleared HBsAg from their bloodstream, may account for late HBV rebounds. HBV reactivation may occur under immunosuppression or viral interference (i.e. treating HCV), leading to liver enzyme flares, which can be life-threatening (Reddy et al., 2015; Wang and Hang, 2021). This can be mitigated through antiviral prophylaxis with either entecavir or tenofovir, which should be given before immunosuppression and continued for 12 months after cessation (Reddy et al., 2015).

**Hepatitis C virus**

Interest in HCV treatment has resurged over recent years following the advent of new curative antiviral therapies. Combinations of two to three drugs given for 3 months are able to cure almost all patients with good adherence. Increased access to medications globally has led to a significant decline in the number of infections from 70 to 58 million (Polaris Observatory HCV Collaborators, 2017; Samarasekera, 2021). However, the gap remains huge and the speed of cure rates has slowed down. There are several barriers that contribute to treatment gaps which need to be addressed. First, a significant proportion of infected people remain undiagnosed. Second, many asymptomatic carriers do not access health systems and, as such, are precluded from beneficial treatments. Third, a subset of individuals who start to take medications do not adhere and/or fail to complete the planned length of therapy. Finally, individuals engaged in high-risk behaviours, such as injection drug users (IDUs) that share needles or MSM, may be re-infected as there is no protective immunity to HCV.



**Figure 2.** Hepatitis B virus (HBV) – infection and disease globally.

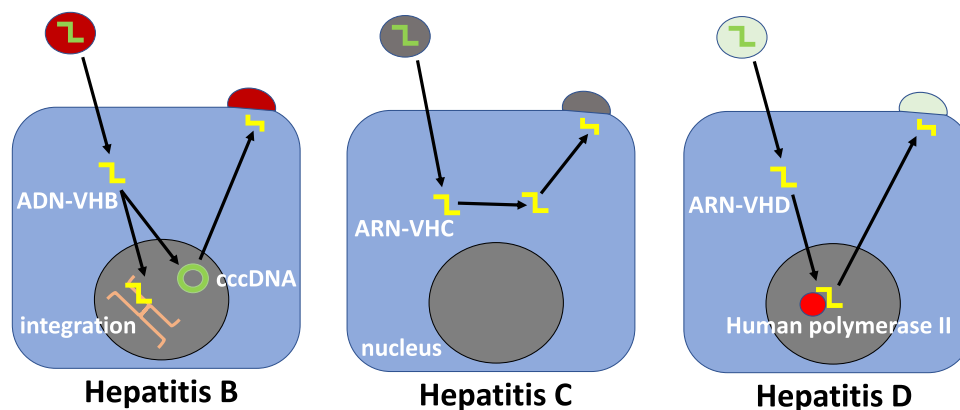


Figure 3. Differences in replication for hepatitis viruses.

In this context, major interventions aimed at individuals unaware of their HCV infection (e.g. promoting point-of-care testing) and the advent of medications with more convenient dosing intervals will be critical (Thomas et al., 2020).

### Hepatitis D virus

HDV is a defective subviral agent with a circular RNA coated by an external lipid layer in which HBsAg is the envelope protein. In contrast to the HBV replication cycle, there is no chromosomal integration and no episomal reservoir for the HDV genome within infected hepatocytes (Urban et al., 2021). In this way, HDV resembles HCV more closely, and stopping replication with drugs could hypothetically be followed by viral extinction within the infected cells (Figure 3).

On average, chronic hepatitis D progresses to liver cirrhosis in 50% of cases within 5 years. This is faster than chronic hepatitis B or C. Accordingly, HDV is associated with a higher incidence of decompensated liver disease, hepatocellular carcinoma and liver-related death (Alfaiate et al., 2020). Globally, HDV contributes to one in six cases of cirrhosis and one in five cases of liver cancer among patients with chronic hepatitis B (Alfaiate et al., 2020). Hepatitis D has become a leading cause of liver transplantation in Europe (Rizzetto et al., 2021).

Recent estimates for global hepatitis D are in the range of 12–60 million people, with large geographical differences (Stockdale et al., 2020). Intravenous drug use and migration from highly endemic regions account for most HDV infections in industrialized countries (Rizzetto et al., 2021).

Until recently, interferon alpha was the only drug used to treat hepatitis D, with poor efficacy (Urban et al., 2021). The shortage of highly effective HDV therapies highlights the urgent need for new treatments. Bulevirtide is a 47-amino-acid peptide that blocks the NCTP receptor that mediates HBV/HDV entry into hepatocytes. It was recently approved as the first treatment for HDV (Asselah et al., 2021). The report of several cases of hepatitis D cured with bulevirtide has revitalized the field (Wedemeyer et al., 2020). Bulevirtide is relatively well tolerated, but needs to be administered subcutaneously. The duration of prescription is not yet clear.

### The HIV paradigm with antiretrovirals: from treatment to prevention

It has been 40 years since the first reports of acquired immunodeficiency syndrome (AIDS). Approximately 80 million people have been infected since then, of whom half have died. The advent of potent ART in the 1990s improved the prognosis of HIV infec-

tion dramatically. Indeed, under good adherence to medications, immunological damage no longer occurs, and the life expectancy of treated HIV-seropositive individuals approaches that seen in the general population (De Cock et al., 2021).

Improvements in ART over the last two decades have been significant in terms of potency, safety, and easy to take drug regimens (Saag et al., 2020). Current HIV medications depict unique appealing profiles, often in the form of one single multi-drug pill given once daily. Furthermore, ART is highly efficacious virologically, is well tolerated and safe, generally has few and manageable drug interactions, and has a high barrier to resistance. As result, ART is now recommended for all HIV-positive patients, including those who are asymptomatic and those with normal CD4 counts. Indeed, ‘rapid initiation of ART’ is recommended immediately after HIV diagnosis (Saag et al., 2020).

The widespread use of ART led to the recognition of its power to halt HIV transmission. Infected people treated with ART with undetectable viraemia do not transmit the virus. This effect is known as ‘treatment-as-prevention’ or ‘U=U’ (undetectable equals untransmissible), and has fostered the use of ART globally (Rodger et al., 2016).

Another step forward in the use of ART came from the recognition that HIV-seronegative individuals at risk for viral acquisition could prevent infection by taking antiretrovirals (Figure 4). HIV pre-exposure prophylaxis (PrEP) is currently recommended for uninfected individuals engaged in risky behaviours, such as MSM with multiple partners, sex workers or IDUs who share needles. PrEP is prescribed as one single pill taken either daily, two to three times per week, or on demand. The single pill consists of a combination of one of the two tenofovir prodrugs and emtricitabine, and decreases the acquisition of HIV by >90% (Grant et al., 2010). However, the efficacy of PrEP is reduced when drug adherence is suboptimal, and this frequently diminishes over time.

Efforts towards simplification of ART dosing have resulted in the recent development of long-acting antiretrovirals, such as cabotegravir and rilpivirine, that are administered intramuscularly on a monthly basis (Benitez-Gutierrez et al., 2018). In the clinic, these formulations are considered for HIV patients as an alternative to daily medications, and as PrEP in HIV-negative individuals at risk who may experience pill fatigue and poor drug adherence. It should, however, be noted that non-compliant individuals may still not adhere to long-acting therapies. Sociocultural variables need to be addressed in conjunction with long-term antiviral medications in order to improve and retain treated patients on regular care. Strategies such as linking periodic methadone provision with antiviral administration (and not just handing supply) are working fairly well in IDUs. No doubt this will improve with the advent of long-acting antivirals. Similar healthcare attachments providing

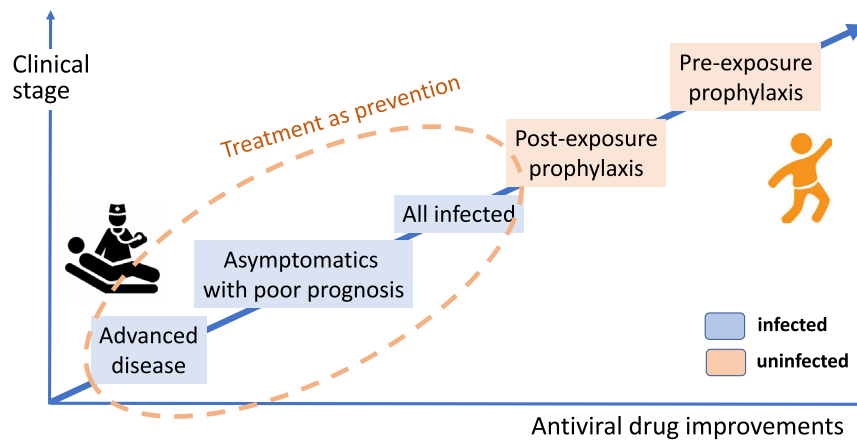


Figure 4. Expanding considerations for using antivirals alongside improvements in drug efficacy, safety and convenience.

periodic testing for sexually transmitted infections could be considered for people with multiple sex partners, including MSM.

However, many injectable medications may produce local injection site reactions and require monthly visits to clinics. In an attempt to overcome this problem, ultra-long-acting (XLA) antivirals are being developed. In one example, when a single-dose intramuscular injection of a cabotegravir prodrug formulation is administered, drug concentrations above the protein-adjusted 90% inhibitory concentration can be sustained for 1 year in animal studies (Kulkarni et al., 2020). The agent exhibits unique properties for prolonged drug release, reflecting a selective depot formation at the injection site and within the reticuloendothelial system. Macrophages are the primary cell depot for drug uptake and wide biodistribution across lymphoid, mucosal, gut and brain tissues (Gautam et al., 2021). Following intramuscular or subcutaneous administration, the drug is absorbed slowly into blood and redistributed into peripheral tissues that serve as secondary drug storage sites. Therefore, unlike orally administered medicines for which clearance rates determine the drug’s half-life, the extended duration of activity for XLA antivirals is dependent on the amount of drug absorbed per day from such injection site depots to collectively enable lower loading doses to last for months (Gautam et al., 2021). Given their nanocrystal formulation, volumes <1 mL are needed for annual administration in humans, reducing the likelihood of local injection site reactions.

Finally, it is worth noting a potential challenge when expanding the use of XLA antivirals, especially as PrEP. In the HIV/AIDS field, compensatory effects as a result of increased risk behaviours taken following a false perception of security have led to increasing numbers of sexually transmitted infections other than HIV, including syphilis, gonorrhoea and even hepatitis C (Fernandez-Montero et al., 2012; Soriano and del Romero, 2018).

### XLA antivirals: a path forward to chronic viral hepatitis elimination

There is growing interest in the development of XLA antivirals to manage chronic viral infections other than HIV, especially viral hepatitis. At first glance, the populations that would gain the greatest benefit from annual injectables are infected prisoners, children and adolescents, homeless people, mentally ill patients and refugees, for whom regular attendance at healthcare sites might be particularly difficult. For similar reasons, infected people in some of the poorest regions would benefit from annual instead of daily medications. Additional advantages include lower risk for selection of drug resistance and increased efficacy.

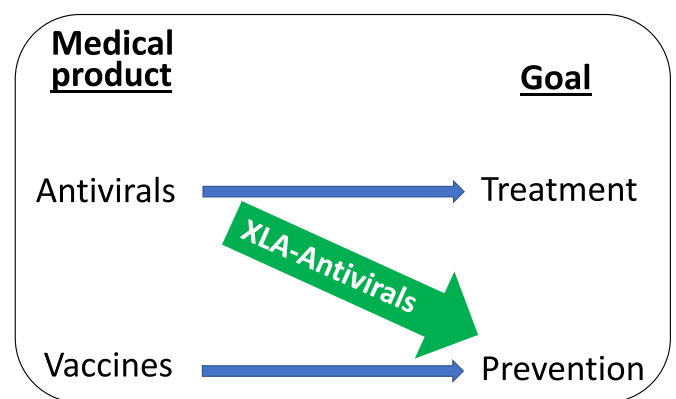


Figure 5. Disruption of classical goals of therapeutic medical strategies using ultra-long-acting (XLA) antivirals.

Development and implementation of XLA antivirals for hepatitis B and D could reduce the infectious burden worldwide. These medications might act as chemical prophylaxis for uninfected people at risk in at least three circumstances: when sustained and universal HBV vaccine coverage is insufficient [only 43% of newborns receive at least one dose of the HBV vaccine worldwide]; when immunity wanes, such as in elderly and immunosuppressed patients (Gu et al., 2017); and when new viral escape mutant variants emerge (Sheldon et al., 2007).

To some extent, XLA antivirals might work as vaccine mimetics, representing a new paradigm for antiviral use, moving from treatment to prevention (Figure 5). Expanding the use of XLA antivirals to the hepatitis field will open up a tremendous opportunity for the elimination of viral hepatitis as a public health threat by 2030.

Three populations would gain the greatest benefit from these new HBV/HDV formulations: patients with chronic hepatitis B needing simplified treatment, as a result of lapses in daily drug adherence; uninfected individuals with high-risk exposure and/or behaviours (e.g. MSM, sex workers and IDUs); and patients at risk for HBV reactivation due to immunosuppression (biological therapies, steroids, chemotherapy, transplantation, malignancies, etc.) (Reddy et al., 2015; Wang and Hang, 2021).

The era of long-acting ART has arrived and pharmacological advances should facilitate the development of XLA antivirals for hepatitis B. Although there have been promising preclinical efforts for long-acting forms of lamivudine and emtricitabine, these agents have a very low barrier to resistance. In contrast, entecavir and, particularly, tenofovir are appealing candidates based on their good safety profile, potent inhibitory activity and high barrier to resis-

tance (European Association for the Study of Liver Diseases, 2017). Recently, a modified ProTide tenofovir formulation has been produced that may provide therapeutic drug exposure for up to 2 months (Cobb et al., 2021). Transformation of such potent long-acting drugs with activity against both HBV and HIV could improve clinical outcomes.

The development of XLA antivirals to treat hepatitis C may overcome the challenge of adherence to daily medication over a treatment course lasting several months (Thomas et al., 2020). Furthermore, if only one subcutaneous or intramuscular shot needs to be given, strategies aimed to facilitate and minimize visits should be encouraged, including ‘test, treat and cure’ strategies. In this way, newly diagnosed individuals are put on treatment the same day, and are hopefully cured with long-acting medications (Thomas et al., 2020).

With respect to HDV, liver transplantation is the only treatment option for patients with end-stage liver disease, hepatocellular carcinoma or fulminant hepatitis HDV superinfection. Given the unmet medical need, new antivirals for patients with HDV, such as bulevirtide and lonafarnib, are being developed under special programmes from the US Food and Drug Administration and European Medicines Agency (breakthrough therapy designation, prime eligibility, orphan drug status). Long-acting forms of bulevirtide will maximize viral entry blocking, and stop further infection of hepatocytes. Lonafarnib is a farnesyl transferase inhibitor that interferes with viral maturation. Developed initially as an anticancer drug that interferes with cell cycle regulation, it also blocks the secretion of HDV virions. Phase 3 clinical trials are being completed with promising results (Yurdaydin et al., 2018; Urban et al., 2021). In addition, lonafarnib has been approved for progeria, a rare genetic disorder.

Two main patient populations would benefit from XLA antivirals for hepatitis D: HBsAg-positive patients engaged in high-risk behaviours, including IDUs and MSM, in order to avoid HDV superinfections; and patients with chronic hepatitis D with difficult daily drug adherence, including homeless people, immigrants, IDUs, etc. As well as the clinical benefit as a result of suppressing viraemia, there would be community benefit derived from treatment as prevention, as undetectability is associated with untransmissibility (U=U) (Rodger et al., 2016; Saag et al., 2020; De Cock et al., 2021).

A last and important caveat for HDV is that virus elimination from infected hepatocytes is feasible, as shown occasionally with interferon (Deterding and Wedemeyer, 2019) or bulevirtide (Wedemeyer et al., 2020) or even spontaneously (Palom et al., 2021). Thus, a promising strategy that should be explored is the combination of bulevirtide and lonafarnib to cure hepatitis D. Since active HBV replication and HBsAg production sustain HDV release, adding anti-HBV agents such as tenofovir or entecavir would be desirable for building any exploratory curative anti-HDV combination (Soriano et al., 2021). In this way and following the steps of HCV, combination therapies (e.g. tenofovir, bulevirtide and lonafarnib) should be tested for eradication of chronic hepatitis D. Hepatitis D is a unique condition, and – hypothetically – HDV could be eliminated from infected hepatocytes despite the persistence of HBV.

## Summary

The development and implementation of long-acting extended-release forms of antivirals that can be given once per year may provide an appealing alternative and/or complementary option to HBV vaccines for preventing HBV and HDV infections. Furthermore, these XLA antivirals will maximize sustained viral suppression in infected and treated patients where long-term drug adherence to daily medications remains a concern. For HCV, the advent of XLA

antivirals may allow expansion of ‘test, treat and cure’ strategies through a single shot shortly after diagnosis. Given that treatment as prevention is a way to advance the elimination of viral hepatitis, diagnosis should be expanded as all carriers must be considered for treatment. Ultimately, this proactive strategy will procure the WHO achievement of viral hepatitis control by 2030.

## Conflict of interest statement

BE and HG hold stocks in EXAVIR, a biotech company. The other authors declare no financial conflict of interests.

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## Ethical approval

All comments and discussions in this article are in accordance with the ethics of human research, as described in the 2020 Declaration of Helsinki.

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