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studies are needed to ascertain the optimal use and curative potential of CpAMs in patients with chronic HBV infection.

We declare no competing interests.

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- 1 European Association for the Study of the Liver. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370–98.
- 2 Berke JM, Dehertogh P, Vergauwen K, et al. Capsid assembly modulators have a dual mechanism of action in primary human hepatocytes infected with hepatitis B virus. *Antimicrob Agents Chemother* 2017; **61**: e00560–17.
- 3 Zhang H, Wang F, Zhu X, et al. Antiviral activity and pharmacokinetics of the HBV capsid assembly modulator GLS4 in patients with chronic HBV infection. *Clin Infect Dis* 2020; published online July 10. <https://doi.org/10.1093/cid/cia961>.
- 4 Yuen MF, Agarwal K, Gane EJ, et al. Safety, pharmacokinetics, and antiviral effects of ABI-H0731, a hepatitis B virus core inhibitor: a randomised, placebo-controlled phase 1 trial. *Lancet Gastroenterol Hepatol* 2020; **5**: 152–66.
- 5 Yuen M-F, Zhou X, Gane E, et al. Safety, pharmacokinetics, and antiviral activity of R07049389, a core protein allosteric modulator, in patients with chronic hepatitis B virus infection: a multicentre, randomised, placebo-controlled, phase 1 trial. *Lancet Gastroenterol Hepatol* 2021; published online July 5. [https://doi.org/10.1016/S2468-1253\(21\)00176-X](https://doi.org/10.1016/S2468-1253(21)00176-X).
- 6 Ligat G, Goto K, Verrier E, Baumert TF. Targeting viral cccDNA for cure of chronic hepatitis B. *Curr Hepatol Rep* 2020; **19**: 235–44.
- 7 Guo YH, Li YN, Zhao JR, Zhang J, Yan Z. HBc binds to the CpG islands of HBV cccDNA and promotes an epigenetic permissive state. *Epigenetics* 2011; **6**: 720–26.
- 8 Lucifora J, Xia Y, Reisinger F, et al. Specific and nonhepatotoxic degradation of nuclear hepatitis B virus cccDNA. *Science* 2014; **343**: 1221–28.
- 9 Ning Q, Han M, Sun Y, et al. Switching from entecavir to PegIFN alfa-2a in patients with HBeAg-positive chronic hepatitis B: a randomised open-label trial (OSST trial). *J Hepatol* 2014; **61**: 777–84.
- 10 Ning Q, Wu D, Wang GQ, et al. Roadmap to functional cure of chronic hepatitis B: an expert consensus. *J Viral Hepat* 2019; **26**: 1146–55.



## The impact of COVID-19 on hepatitis services and civil society organisations

Every 30 seconds, someone dies from viral hepatitis. With the disruptions caused by COVID-19, this health crisis has become even more urgent. We can no longer wait to act on hepatitis. People are dying because they did not receive simple interventions. People who are unaware that they are living with viral hepatitis cannot wait for testing and treatment. Pregnant mothers cannot wait for screening and prophylactic treatment. Newborn babies cannot wait for the hepatitis B birth-dose vaccination.

The COVID-19 pandemic has affected hepatitis prevention, testing, treatment, and vaccination services globally.<sup>1</sup> Even before COVID-19, very few countries were on track to reach the 2030 elimination goals set by WHO.<sup>2</sup> The pandemic has put elimination efforts further behind. Interruptions in the provision of services, coupled with delays in implementing major programmes, such as the anticipated support from Gavi, the Vaccine Alliance, for the hepatitis B birth-dose vaccine, will have dire consequences.<sup>3</sup>

The World Hepatitis Alliance (WHA), a global network of more than 300 community-based organisations across 100 countries, conducted a survey at the onset of the COVID-19 pandemic (March–April, 2020) about the effect of the pandemic on hepatitis services and

on the people and communities that need them.<sup>4</sup> We conducted a follow-up survey a year later to understand how front-line hepatitis services continue to be affected. The survey also sought to assess the effect of COVID-19 on organisation’s planning and finances and the respondent’s country’s progress on hepatitis elimination. The online nine-question questionnaire (appendix pp 1–2) was distributed by email to WHA members between Jan 3 and March 23, 2021. There were 63 respondents from 33 countries representing all WHO global regions (appendix p 3).

Most (55 [90%] of 61 analysable responses) respondents reported that COVID-19 had a negative impact on the hepatitis services available in their country. This finding reflects other global surveys,<sup>5</sup> including one by WHO<sup>6</sup> on the continuity of essential health services in May to July, 2020, with a follow-up survey in 2021. Respondents to the WHO survey were government officials representing more than 100 countries. Of all the communicable diseases measured (including HIV, malaria, and tuberculosis), hepatitis had the highest ranking of disruption. Notably, the proportion of respondents who answered “do not know” for the impact of COVID-19 on the hepatitis response was much higher than for HIV. Thus, the gaps

See Online for appendix

we are seeing might only be a small part of a larger problem.

COVID-19 has potentially jeopardised national elimination planning for viral hepatitis due to diverted resources and attention. 43 (77%) of 56 analysable respondents to our survey reported that their country's progress towards hepatitis elimination has been affected. With governments facing the economic fallout of the COVID-19 pandemic, there is a real risk that funding will be reduced or lost for the foreseeable future. If this is the case, then many of the hard-fought advocacy wins that saw increases in domestic budget allocations would need to start again.

Fear of COVID-19 has been a substantial barrier to hepatitis testing and treatment throughout the crisis. 22 (73%) of 30 respondents reported that people did not have access to their medication because they avoided health-care facilities due to COVID-19. In the 2020 survey, this fear was reported by 50% of respondents.<sup>4</sup>

Fear also affects testing, with 24 (86%) of 28 respondents reporting that the reason for people not accessing testing was avoidance of going to testing facilities due to COVID-19. In our 2020 survey, 65% of respondents cited this fear of attending testing facilities.<sup>4</sup> Throughout the pandemic, civil society organisations have played a key role in overcoming this barrier and evolved their services to provide opportunities to test for hepatitis in settings where the community feels safe and confident during the COVID-19 crisis.

Decentralised, simplified services delivered at the community level are needed more than ever for viral hepatitis. We must innovate and find ways to provide life-giving care to people in locations they trust in a person-centred approach, which might require different approaches. Differentiated care models have been successful for HIV and represent a growing trend in hepatitis C care.

Our survey revealed signs that some services had returned over the pandemic, albeit not to previous levels. 27 (48%) of 56 responses reported community education and awareness raising had stopped but had now resumed at a reduced level. 28 (50%) of 56 responses reported hepatitis B vaccination had stopped but had resumed at a reduced capacity.

Childhood vaccines have been substantially disrupted in many areas, jeopardising children's protection

and leading to the tragic rise in hepatitis B infections in children born during the pandemic.<sup>3</sup> Modelling conducted at Imperial College London showed that in a worst-case scenario, with a 60% reduction in administration of birth dose and a 20% reduction of childhood hepatitis B immunisation at age 1 year, there would be an additional 5.3 million chronic hepatitis B infections in children born between 2020 and 2030, and 1 million additional hepatitis B-related deaths among those children later on in life.<sup>3</sup>

46 (81%) of 57 analysable responses reported that COVID-19 had a negative impact on their organisation's plans in 2021. Respondents reported that the restrictions implemented to tackle the pandemic would affect their ability to deliver services, raise awareness in the community, and fundraise. Most concerning, 45 (79%) of 57 responses reported that the COVID-19 pandemic had a negative effect on their organisation's finances. Although the global health agenda looks at how we can build back better after COVID-19, there is a real danger that many viral hepatitis community organisations might not survive because of substantial financial hardship. Countries must include support of civil society organisations in their elimination planning to ensure that the vital work of community-level awareness and involvement of the affected community continues. If governments do not engage with civil society and the affected community, equity, and the reaching of key populations for viral hepatitis elimination will be at risk.

This World Hepatitis Day, the global viral hepatitis community is calling for urgent action on viral hepatitis to reach elimination. The Hepatitis Can't Wait campaign calls on governments, international donors, decision-makers, and medical professionals to accelerate action to eliminate viral hepatitis and to prevent millions more infections and avoidable deaths.

It is time to act. Hepatitis can't wait.

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1 WHO. Global progress report on HIV, viral hepatitis and sexually transmitted infections, 2021. Accountability for the global health sector strategies 2016-2021: actions for impact. 2021. <https://www.who.int/publications/i/item/9789240027077> (accessed July 15, 2021).

For more on the **Hepatitis Can't Wait** campaign see <https://www.worldhepatitisday.org/>

- 2 WHO. Global health sector strategy on viral hepatitis 2016–2021. 2016. <https://apps.who.int/iris/handle/10665/246177> (accessed July 15, 2021).
- 3 WHO. Fast-tracking the elimination of hepatitis B among mothers and children. 2020. <https://www.who.int/news/item/27-07-2020-world-hepatitis-day-fast-tracking-the-elimination-of-hepatitis-b-among-mothers-and-children> (accessed July 15, 2021).
- 4 Wingrove C, Ferrier L, James C, Wang S. The impact of COVID-19 on hepatitis elimination. *Lancet Gastroenterol Hepatol* 2020; 5: 792–94.
- 5 Laury J, Hiebert L, Ward JW. Impact of COVID-19 response on hepatitis prevention care and treatment: results from global survey of providers and program managers. *Clin Liver Dis* 2021; 17: 41–46.
- 6 WHO. Pulse survey on continuity of essential health services during the COVID-19 pandemic. 2021. [https://www.who.int/docs/default-source/coronaviruse/finalupdate\\_22-april-2021\\_summary-ppt\\_ehs-pulse-survey-second-round.pdf?sfvrsn=a965e121\\_8](https://www.who.int/docs/default-source/coronaviruse/finalupdate_22-april-2021_summary-ppt_ehs-pulse-survey-second-round.pdf?sfvrsn=a965e121_8) (accessed July 15, 2021).



## Gastrointestinal bleeding in patients with *Helicobacter pylori* and dual platelet inhibition after myocardial infarction

In patients with ST-elevation myocardial infarction (STEMI) receiving dual antiplatelet therapy (DAPT), proton pump inhibitors are recommended for those at risk of upper gastrointestinal bleeding.<sup>1,2</sup> The question of whether concurrent *Helicobacter pylori* infection increases the risk of upper gastrointestinal bleeding in this scenario is of major concern and has not been properly resolved.

Treatment of STEMI with early revascularisation and DAPT demands a fundamental trade-off between decreasing the risk of ischaemia and increasing the risk of bleeding. Secondary prevention with potent DAPT, combining aspirin with P2Y12 inhibitors (eg, prasugrel, ticagrelor, and clopidogrel), reduces the risk of further cardiovascular events.<sup>1,2</sup> The 1-year cumulative incidence of upper gastrointestinal bleeding in these patients is estimated to be 1.7–4.5% depending on the background population.<sup>3,4</sup> Upper gastrointestinal bleeding leads to increased morbidity, mortality, and discontinuation of DAPT with consequent failure of adequate secondary prevention of cardiovascular complications.

European cardiology guidelines (2017) for management of acute myocardial infarction in patients with STEMI suggest that proton pump inhibitors should be used in patients at risk of upper gastrointestinal bleeding.<sup>1</sup> American cardiology guidelines, presented in a 2008 expert consensus document,<sup>2</sup> with an update in 2016, recommended not only acid suppressant therapy to reduce the risk of upper gastrointestinal bleeding associated with antiplatelet and non-steroidal anti-inflammatory drug (NSAID) therapy, but also testing and curing of *H pylori* in patients with a history of peptic ulcer disease before starting long-term antiplatelet therapy. Although the 2016 update of the American guidelines provided further evidence that *H pylori*

infection (by itself) is a risk factor of a similar magnitude to anticoagulants, steroids, and NSAIDs for upper gastrointestinal bleeding, they again recommend only prophylactic proton pump inhibitors for patients at risk.<sup>5</sup>

Known risk factors for upper gastrointestinal bleeding include advanced age, female sex, diabetes, renal failure, and anaemia, as well as infection with *H pylori*, the latter of which can be cured. Data indicate that *H pylori* prevalence is 20% among Swedish patients with acute myocardial infarction, and that *H pylori* infection is more common in patients with STEMI (26%) than in those without STEMI (15%).<sup>6</sup>

Concomitant *H pylori* infection and antithrombotic therapy substantially increase the risk of upper gastrointestinal bleeding by 1.8 times (95% CI 1.5–2.1) with low-dose aspirin alone, and by 7.4 times (3.5–15) with DAPT.<sup>7</sup> Studies show that the odds ratio (OR) for the risk of upper gastrointestinal bleeding in patients on non-aspirin antiplatelet agents is 4.37 (95% CI 1.28–14.99), whereas concomitant aspirin plus NSAID drug intake raises the OR to 5.85 (1.68–20.36), and DAPT raises the OR even further to 8.43 (1.09–65.17).<sup>8</sup> *H pylori* seems to play a more important role in upper gastrointestinal bleeding with low-dose aspirin than with NSAIDs because, although low-dose aspirin is not as ulcerogenic as NSAIDs, it still has a high risk of provoking bleeding from pre-existing *H pylori* ulcers.<sup>9</sup> Eradication of *H pylori* heals ulcers and, therefore, resumption of low-dose aspirin does not induce recurrent gastroduodenal ulceration and bleeding. This explanation finds support in the low incidence of recurrent upper gastrointestinal bleeding in patients taking long-term aspirin after eradication of *H pylori* without prophylactic proton pump inhibitors.<sup>9</sup> In this context, and in patients taking aspirin in particular,