

Reply to: “Does currently recommended maternal antiviral prophylaxis against mother-to-child transmission of hepatitis B virus require enhancement?”



Enhancement of HBV PMTCT is required because the *status quo* fails to protect those at highest risk

To the Editor:

In response to our article,¹ Zhou and Zhao pose the question of whether interventions for prevention-of-mother-to-child-transmission (PMTCT) need to be enhanced.² As MTCT is now the major contributor to new cases of HBV infection, and approaching one million people die of this infection each year, the answer to this question is unequivocally yes – and with urgency.

We tackle specific points raised by Zhou and Zhao in turn.

First, they contend that ‘*most HBV-infected women at child-bearing age are in a immunotolerant phase and do not require antiviral therapy*’. This broad assertion is misleading. The eligibility of pregnant women either for treatment in their own right, or for prophylaxis to reduce transmission, depends on many factors including duration of infection, maternal age and HBV genotype. In most high prevalence settings, determination of a clinical ‘phase’ of infection for risk stratification is difficult or impossible because of lack of access to affordable laboratory testing and/or imaging.^{3,4} It would be a dereliction of public health strategy simply to assume ineligibility for prophylactic interventions on the grounds that we are unable to deliver adequate assessment.

Secondly, they raise the point that ‘*MTCT of HBV can be efficiently prevented by combined immunoprophylaxis with hepatitis B immunoglobulin (HBIG) and hepatitis B vaccine in neonates*’. This statement is biologically true in most cases, although these interventions are not infallible (e.g.⁵). However, the major current weakness of this post-exposure strategy is that it is not possible to deliver in practice, as interventions are not available or cannot be implemented. The barriers are explored in our original paper,¹ and include high costs, lack of policy support and healthcare resources, inconsistent cold-chain, high frequency of births outside clinical settings, and poor education and awareness. These factors have the greatest impact in vulnerable populations with high prevalence of HBV infection.

Since our article was published, the Global Vaccine Alliance (Gavi) has announced that birth dose (BD) HBV vaccination will be formally incorporated into their strategy, which is an important stride forward. However, a clear action plan and funding is yet to be announced, and the latest data suggest that <15% of babies in the WHO Africa region receive timely BD vaccination.⁶ Is it reasonable to accept that these populations cannot currently be reached, or should we use existing interventions that may be more accessible and affordable? We argue that while BD vaccination programmes scale-up, maternal antiviral prophylaxis plays a particularly important role.

Next, we are deeply concerned by the assertion that antiviral exposure during pregnancy is responsible for ‘*severe congenital malformation ... fetal death, stillbirth, infant sudden death ... and premature birth*’. There are no robust data to support these statements, and indeed the references Zhou and Zhao cite universally conclude that there is no significant signal for adverse maternal or foetal outcomes associated with antenatal antiviral HBV prophylaxis (based on comparison with untreated pregnancies or with background population rates), and no evidence to suggest risks associated with either choice or timing of therapeutic regimen. Indeed, there is evidence that earlier prophylaxis can be beneficial.⁷ Case reports are clearly not relevant evidence of drug toxicity, as there is no possible way to determine cause and effect. In addition to being reassured by the findings of individual studies, we should also turn to several rigorous reviews and meta-analyses that assimilate international data for many hundreds of pregnancies, none of which find evidence of safety concerns (e.g.^{7–11}). There are indeed challenges associated with more permissive use of perinatal prophylaxis, but these are primarily associated with implementation (access, infrastructure, monitoring, costs etc).

Finally, Zhou and Zhao claim that ‘*The safety data of maternal ART in HIV-infected pregnant women cannot be directly translated to maternal anti-HBV therapy*.’ While these two viruses have different biological consequences, it would be an oversight not to use the wealth of safety data from the HIV field to help inform HBV interventions. Adverse foetal outcomes in the context of HIV infection are multifactorial, but there are no data to suggest a relationship between tenofovir and elevated risks (in fact, the converse is true). Meanwhile, the Antiretroviral Pregnancy Registry (ClinicalTrials.gov ID NCT00404989) has now collated prospective reports of >5,000 pregnancies exposed to TDF (of whom >3,500 were treated during the first trimester) and found no difference between this population and the US population overall. Reassuring safety data are also accumulating from studies of HIV pre-exposure prophylaxis in which the confounding factor of maternal HIV infection is removed.^{12,13}

To conclude, we stand firmly by our original rationale in advocating wider use of antiviral prophylaxis for PMTCT, aiming to provide a safe and pragmatic approach to risk reduction in vulnerable populations in which there is very limited – or absent – access to risk-stratification and to other preventive interventions. Revised WHO guidelines are anticipated, but at present, different strategies may be needed for different settings, recognising that maternal risk stratification, BD-vaccine and HBIG are not widely available. There is an onus of responsibility on clinical and academic communities to promote evidence-based messaging and education, while guidelines and clinical practice must now seek to reduce gross health inequities by making HBV prophylaxis and treatment accessible, acceptable and affordable.

Received 14 July 2023; accepted 18 July 2023; ; available online 7 August 2023

Financial support

PCM is funded by the Wellcome Trust (Grant ref 110110/Z/15/Z), UCLH NIHR Biomedical Research Centre, and receives core funding from the Francis Crick Institute, London.

Conflict of interest

CWS has received speaker fees from GILEAD Sciences and Abbott. CP received research funding and is a speaker for Gilead. PCM supervises a doctoral student with funding support from GSK. SH has received funding from Gilead for HCV Micro-elimination programs. HR has received research funding and speaker's honoraria from Gilead Sciences, AbbVie and Pfizer and is a board member of the CDA foundation. SW has received research funding from Gilead Sciences, and honoraria from Prime Inc, and is on the Board of Directors for the Hepatitis B Foundation, World Hepatitis Alliance, and serves in the patient advisory group and HBV special interest group for the AASLD. FR has received consulting fees from Sanofi Pasteur. GD has received consulting fees and speaker fees from Gilead Sciences, has participated on Data Safety Monitoring Board/Advisory Board for janssen, Glaxo Smith Kline, Arbutus, Aligos, Vir and has roles in the National Medical Research Council Singapore and the World Health Organisation Pediatric Working Group on Viral Hepatitis.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

PCM drafted the initial response. All authors reviewed, edited and endorsed the final manuscript.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhepr.2023.100875>.

References

- [1] Matthews PC, Ocama P, Wang S, El-Sayed M, Turkova A, Ford D, et al. Enhancing interventions for prevention-of-mother-to-child- transmission (PMTCT) of hepatitis B virus (HBV). *JHEP Rep* 2023;100777.
- [2] Zhou Y-H, Zhao H. Does currently recommended maternal antiviral prophylaxis against mother-to-child transmission of hepatitis B virus require enhancement? *J Hepatol Rep* 2023. <https://doi.org/10.1016/j.jhepr.2023.100831>.
- [3] Sonderup MW, Spearman CW. Global disparities in hepatitis B elimination-A focus on Africa. *Viruses* 2022;14. <https://doi.org/10.3390/v14010082>.
- [4] O'Hara GA, McNaughton AL, Maponga T, Jooste P, Ocama P, Chilengi R, et al. Hepatitis B virus infection as a neglected tropical disease. *Plos Negl Trop Dis* 2017;11:e0005842.
- [5] Zou H, Chen Y, Duan Z, Zhang H, Pan C. Virologic factors associated with failure to passive-active immunoprophylaxis in infants born to HBsAg-positive mothers. *J Viral Hepat* 2012;19:e18-e25.
- [6] Coalition for Global Hepatitis Elimination (CGHE) country/Regions data dashboards. [cited 1 Jul 2023]. Available: <https://www.globalhep.org/countryregions-data-dashboards>.
- [7] Song J, Yang F, Wang S, Tikande S, Deng Y, Tang W, et al. Efficacy and safety of antiviral treatment on blocking the mother-to-child transmission of hepatitis B virus: a meta-analysis. *J Viral Hepat* 2019;26:397-406.
- [8] Li W, Jia L, Zhao X, Wu X, Tang H. Efficacy and safety of tenofovir in preventing mother-to-infant transmission of hepatitis B virus: a meta-analysis based on 6 studies from China and 3 studies from other countries. *BMC Gastroenterol* 2018. <https://doi.org/10.1186/s12876-018-0847-2>.
- [9] Funk AL, Lu Y, Yoshida K, Zhao T, Boucheron P, van Holten J, et al. Efficacy and safety of antiviral prophylaxis during pregnancy to prevent mother-to-child transmission of hepatitis B virus: a systematic review and meta-analysis. *Lancet Infect Dis* 2021;21:70-84.
- [10] Chen J-Z, Liao Z-W, Huang F-L, Su R-K, Wang W-B, Cheng X-Y, et al. Efficacy and safety of tenofovir disoproxil fumarate in preventing vertical transmission of hepatitis B in pregnancies with high viral load. *Sci Rep* 2017;7:4132.
- [11] Zhu L, Park J, Deng Y, Pan CQ. The use of tenofovir disoproxil fumarate and tenofovir alafenamide for preventing vertical transmission of hepatitis B. *J Clin Gastroenterol* 2023;57:127-138.
- [12] Moodley D, Lombard C, Govender V, Naidoo M, Desmond AC, Naidoo K, et al. Pregnancy and neonatal safety outcomes of timing of initiation of daily oral tenofovir disoproxil fumarate and emtricitabine pre-exposure prophylaxis for HIV prevention (CAP016): an open-label, randomised, non-inferiority trial. *Lancet HIV* 2023;10:e154-e163.
- [13] Stalter RM, Pintye J, Mugwanya KK. Safety review of tenofovir disoproxil fumarate/emtricitabine pre-exposure prophylaxis for pregnant women at risk of HIV infection. *Expert Opin Drug Saf* 2021;20:1367-1373.

Philippa C. Matthews^{1,2,3,*}

Ponsiano Ocama⁴

Su Wang^{5,6}

Manal El-Sayed⁷

Anna Turkova⁸

Deborah Ford⁸

Judith Torimiro^{9,10}

Ana Cristina Garcia Ferreira¹¹

Angélica Espinosa Miranda¹¹

Fernando Pio De La Hoz Restrepo¹²

Emmanuel Seremba⁴

Robinson Mbu¹⁰

Calvin Q. Pan¹³

Homie Razavi¹⁴

Geoffrey Dusheiko¹⁵

C. Wendy Spearman^{16,†}

Saeed Hamid^{17,†}

¹The Francis Crick Institute, 1 Midland Road, London, NW1 1AT, UK;

²Division of Infection and Immunity, University College London, Gower St, London WC1E 6BT, UK;

³Department of Infection, University College London Hospitals, 235 Euston Rd, London NW1 2BU, UK;

⁴Department of Medicine, Makerere University College of Health Sciences, Kampala, Uganda;

⁵Cooperman Barnabas Medical Center, Florham Park, NJ, USA;

⁶Hepatitis B Foundation, Doylestown, PA, USA;

⁷Department of Paediatrics, Faculty of Medicine, Ain Shams University, Cairo, Egypt;

⁸Medical Research Council Clinical Trials Unit, University College London, 90 High Holborn London WC1V 6LJ, UK;

⁹Chantal Biya International Reference Centre for Research on Prevention and Management of HIV/AIDS (CIRCB), Yaounde, Cameroon;

¹⁰Faculty of Medicine and Biomedical Sciences, University of Yaounde, Yaounde, Cameroon;

¹¹Ministry of Health, Health Surveillance Department, Department of Chronic Diseases and Sexually Transmitted Infections, SRTVN Quadra 701, Lote D, PO700 Building, CEP: 70719040, Brasília/DF, Brazil;

¹²Universidad Nacional de Colombia, Bogotá, Colombia;

¹³Division of Gastroenterology and Hepatology, NYU Langone Health, NYU Grossman School of Medicine, NY, USA;

¹⁴Center for Disease Analysis Foundation, 1120 W South Boulder Rd Suite 102, Lafayette, CO 80026, USA;

¹⁵Liver Unit, King's College Hospital, Denmark Hill, London SE5 9RS, UK;

¹⁶Division of Hepatology, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa;

¹⁷Department of Medicine, Aga Khan University, Karachi, Pakistan

x8E†x90 Joint senior author.

*Corresponding author. Address: The Francis Crick Institute, 1 Midland Road, London, NW1 1AT, UK.

E-mail address: philippa.matthews@crick.ac.uk (P.C. Matthews).