

Mother-to-child transmission of hepatitis B virus in sub-Saharan Africa: time to act



What few people thought possible little more than a decade ago is now reality: scientific and operational advances are greatly reducing the number of deaths from HIV. The number of infant infections has decreased by 58% between 2001 and 2013 and mother-to-child transmission (MTCT) of HIV might well be eliminated in the next few years.¹ By contrast, the prevention and management of hepatitis B virus (HBV) infection lags well behind, at least in sub-Saharan Africa.

The Global Burden of Disease Study² highlighted the importance of chronic hepatitis B and its effect on health, which is equivalent to that of tuberculosis or malaria. Worldwide about 240 million people have chronic hepatitis B. In sub-Saharan Africa more than 8% of the population are chronic carriers of HBV,³ the effect of which is compounded by the high HIV prevalence. Hepatocellular carcinoma is the second most common cause of cancer in African men and third most common cause of cancer in African women, with more than 75% of cases being related to chronic hepatitis B, despite the availability of a safe and effective vaccine for more than two decades.

Early HBV transmission is the main route by which HBV infection is perpetuated in high-prevalence communities. About 90% of children infected through vertical transmission develop chronic hepatitis B. By contrast, 96% of adults will clear primary HBV infection. Therefore, interrupting early transmission is the key to breaking the cycle of ongoing HBV infection.

Active immunisation is the cornerstone of preventing HBV MTCT. By 2012, 181 countries had implemented universal HBV vaccination, with global coverage estimated to be greater than 79%,³ leading to a remarkable reduction of chronic viral hepatitis B in high-burden countries in east Asia.⁴ However, sub-Saharan Africa has a low infant HBV vaccine coverage: 72% in 2012.⁵ Although the WHO recommends commencing HBV vaccination at birth,⁶ in much of Africa the first dose is given at about 6 weeks of age (the monovalent HBV vaccine superseded by the pentavalent vaccine DTP-HepB-Hib in many countries). This vaccination regimen is based on the observation that most African adult patients with chronic hepatitis B are of low infectivity and therefore have a low risk of transmitting

perinatally. However, HBV infection in infants who were vaccinated according to this regimen is not uncommon,^{7,9} and studies suggest, although there is a clear regional variation, that up to 38% of pregnant African women with chronic hepatitis B are positive for hepatitis B e antigen (HBeAg) and therefore at high risk of transmitting HBV to their infants.^{7,8} To take full advantage of the benefits of the HBV vaccine, its administration should start at birth. The addition of a birth dose to the current three-dose schedule has been shown to be cost-effective in low-income countries.¹⁰ Further, where HIV infection is prevalent, an additional dose of HBV vaccine in HIV-exposed babies could well be advantageous, since some data suggest poorer antibody responses in HIV-infected and HIV-exposed uninfected babies.¹¹ The use of third-generation vaccines with additional viral epitopes (eg, pre-S domain), showing increased antigenicity, is a strategy that deserves investigation.

In resource-rich settings, giving hepatitis B immunoglobulin to infants born to mothers with high HBV viral loads, in addition to birth dose vaccine, is standard of care to prevent HBV MTCT. However, for most women in sub-Saharan countries, the cost and logistics of HBV diagnosis and administration of hepatitis B immunoglobulin are prohibitive.

The administration of antiviral therapy from the second trimester of pregnancy will reduce maternal HBV viral load and decrease the risk of MTCT.^{12,13} The increased access to tenofovir for the treatment of HIV makes administration of this drug a feasible option for prevention of HBV MTCT. Although drugs such as lamivudine and telbivudine have been shown to reduce MTCT, tenofovir has a high barrier to resistance and has been used extensively in HIV-infected pregnant women. It has a good safety profile in pregnancy, although ongoing vigilance is needed.¹⁴

Rapid immunochromatographic hepatitis B surface antigen (HBsAg) tests with acceptable performance are available to identify HBV-infected pregnant women. Cost-effective point-of-care tests for combined HBsAg and HBeAg detection and determination of HBV viral load are in development.

How can these advances be implemented? Within the constraints of resource-poor settings and in view of their shared approaches, it seems eminently logical to harness the HIV prevention of MTCT infrastructure to address the problem of HBV MTCT. We suggest that identifying women at risk of HBV MTCT with a rapid test, starting and monitoring antiviral therapy in the late second or early third trimester, administering vaccine to the infant at birth, and contact tracing, are all within the expertise of HIV-trained health-care workers. Nevertheless these interventions will require additional resources.

Besides the increase in resources, other hurdles remain. Although tenofovir is available in many countries for HIV therapy, bureaucratic regulations and cost in many areas prevent access for HBV-monoinfected patients. HBV vaccine remains efficacious when exposed to less stringent cold chains¹⁵ yet package inserts have not been modified to reflect these data. Additionally, the rollout of pentavalent vaccine might reduce accessibility to monovalent HBV vaccine.

The issue of HBV MTCT deserves our full attention. Screening women for HBV infection and starting antiviral therapy for those who need it, introducing HBV birth dose vaccine, and increasing overall coverage of vaccine are all feasible. What is needed now is strategic political and financial investment that could lead to the elimination of HBV MTCT in sub-Saharan Africa in our lifetime, and in so doing greatly reduce the global burden of this important public health problem.

**Monique I Andersson, Ruma Rajbhandari, Michael C Kew, Sandro Vento, Wolfgang Preiser, Andy I M Hoepelman, Gerhard Theron, Mark Cotton, Jennifer Cohn, Dieter Glebe, Olufunmilayo Lesi, Mark Thursz, Marion Peters, Raymond Chung, Charles Wiysonge*
 University of Stellenbosch, Division of Medical Virology, Francie van Zijl Ave, Cape Town 7505, South Africa (MIA); Department of Hepatology, Massachusetts General Hospital and Harvard University, Boston, MA, USA (RR, RC); Department of Medicine, University of Cape Town, South Africa (MCK); University of Botswana, Botswana (SV); Division of Medical Virology (WP), Department of Obstetrics and Gynaecology (GT), Department of Child Health (MC) and Department of Evidence based Medicine

(CW), University of Stellenbosch, Stellenbosch, South Africa; Department of Medicine, University of Pennsylvania, Philadelphia, PA, USA; Department of Medicine, Utrecht University, Utrecht, Netherlands (AIMH); Institute of Medical Virology, Justus-Liebig University Giessen, Giessen, Germany (DG); Department of Hepatology, University of Lagos, Lagos, Nigeria (OL); Department of Hepatology, Imperial College, London, UK (MT); and Department of Hepatology, University of California San Francisco, San Francisco, CA, USA (MP)
 andersson_m@sun.ac.za

We declare no competing interests. We acknowledge funding from the Poliomyelitis Research Foundation and National Health Laboratory Service Research Trust.

Copyright © Andersson et al. Open Access article distributed under the terms of CC BY.

- 1 UNAIDS. 2013 Progress Report. 2013. http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2013/20130625_progress_global_plan_en.pdf.
- 2 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095–128.
- 3 WHO. Global policy report on the prevention and control of viral hepatitis in WHO member states. Geneva: World Health Organisation, 2013.
- 4 Chiang C-J, Yang Y-W, You S-L, Lai M-S, Chen C-J. Thirty-year outcomes of the national hepatitis B immunization program in Taiwan. *JAMA* 2013; **310**: 974–76.
- 5 WHO. Atlas of African Health Statistics 2014. Geneva: World Health Organisation, Regional Office for Africa, 2014.
- 6 Botha JF, Ritchie MJ, Dusheiko GM, Mouton HW, Kew MC. Hepatitis B virus carrier state in black children in Ovamboland: role of perinatal and horizontal infection. *Lancet* 1984; **1**: 1210–12.
- 7 Chasela CS, Kourtis AP, Wall P, et al. Hepatitis B virus infection among HIV-infected pregnant women in Malawi and transmission to infants. *J Hepatol* 2014; **60**: 508–14.
- 8 Andersson MI, Maponga TG, Ijaz S, et al. The epidemiology of hepatitis B virus infection in HIV-infected and HIV-uninfected pregnant women in the Western Cape, South Africa. *Vaccine* 2013; **31**: 5579–84.
- 9 Ekra D, Herbinger K-H, Konate S, et al. A non-randomized vaccine effectiveness trial of accelerated infant hepatitis B immunization schedules with a first dose at birth or age 6 weeks in Côte d'Ivoire. *Vaccine* 2008; **26**: 2753–61.
- 10 Klingler C, Thoumi AI, Mrithinjayam VS. Cost-effectiveness analysis of an additional birth dose of Hepatitis B vaccine to prevent perinatal transmission in a medical setting in Mozambique. *Vaccine* 2012; **31**: 252–59.
- 11 Rutstein RM, Rudy B, Codispoti C, Watson B. Response to hepatitis B immunization by infants exposed to HIV. *AIDS* 1994; **8**: 1281–84.
- 12 Greenup A-J, Tan PK, Nguyen V, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy to prevent perinatal transmission of hepatitis B virus. *J Hepatol* 2014; **61**: 502–07.
- 13 Celen MK, Mert D, Ay M, et al. Efficacy and safety of tenofovir disoproxil fumarate in pregnancy for the prevention of vertical transmission of HBV infection. *World J Gastroenterol* 2013; **19**: 9377–82.
- 14 Fowler MG, Qin M, Shapiro D, et al. PROMISE: efficacy and safety of 2 strategies to prevent perinatal HIV transmission. CROI Conference; Seattle, WA, USA; Feb 23–26, 2015. Abstr 311B.
- 15 Wang L, Li J, Chen H, et al. Hepatitis B vaccination of newborn infants in rural China: evaluation of a village-based, out-of-cold-chain delivery strategy. *Bull World Health Organ.* 2007; **85**: 688–94.