



PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF
HEPATITIS B VIRUS

GUIDELINES ON ANTIVIRAL PROPHYLAXIS IN PREGNANCY

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Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy.
Policy brief

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POLICY BRIEF

Background

WHO estimates that in 2015, 257 million people were living with chronic hepatitis B virus (HBV) infection worldwide, and that 900 000 died from HBV infection, mostly through the development of cirrhosis and hepatocellular carcinoma (1). Worldwide, the majority of persons with chronic hepatitis B infection and associated deaths in adulthood acquired their infection at birth through mother-to-child perinatal transmission or in early childhood (2). Prevention of perinatal and early childhood transmission of HBV is therefore key to reducing chronic infections that result in the greatest burden of morbidity and mortality. This can be achieved through universal immunization of infants against hepatitis B, birth-dose immunization, and other interventions to prevent mother-to-child transmission of HBV (4). In May 2016, the World Health Assembly endorsed the Global Health Sector Strategy on viral hepatitis 2016-2021, which calls for the elimination of viral hepatitis as a public health threat by 2030 (defined as a 90% reduction in incidence and a 65% reduction in mortality) (3). The prevalence of hepatitis B surface antigen (HBsAg) in children 5 years of age is considered a surrogate indicator of the cumulative incidence of chronic HBV infections (3). The global strategy for elimination includes a prevalence target of HBsAg in children of five years of age of less than 0.1% by 2030 (3).

Rationale for updating the recommendations on prevention of mother-to-child transmission of HBV to include peripartum prophylaxis with antivirals

Immunization against hepatitis B starting at birth is the foundation of the prevention of perinatal and horizontal transmission of HBV. The WHO position papers on immunization recommend that all infants receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours, and that the birth dose be followed by two or three doses of hepatitis B vaccine at least four weeks apart to complete the primary series (5). In 2015, in the WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection, no recommendation was made for the additional use of antiviral therapy to prevent mother-to-child HBV transmission (6). Since then, three key developments prompted the consideration to include the use of peripartum prophylaxis with antivirals as an additional measure to prevent mother-to-child transmission of HBV. First, further evidence has become available on the efficacy and safety of antiviral prophylaxis in pregnant women and their children. Second, WHO has received requests from countries and regions with already high birth dose and infant vaccination coverage for updated guidance on the use of peripartum prophylaxis with antivirals. Third, data from epidemiological studies and modelling suggest that infant vaccination alone would not be sufficient to reach the 0.1% HBsAg prevalence goal in children by 2030 (7), and that peripartum prophylaxis may also be needed (8).

Guidelines methodology

In accordance with the procedures established by its Guidelines Review Committee (GRC), a regionally representative and multidisciplinary Guidelines Development Group (GDG) met in September 2019 to formulate the recommendations using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (9). Evidence to inform the recommendations included two commissioned systematic reviews and meta-analyses, impact and cost-effectiveness modelling, an assessment of the overall balance of benefits and harms (at individual and population levels), patient/health worker values and preferences, resource use, cost-effectiveness, considerations on equity and human rights, and feasibility across the different WHO regions.

Rationale for new recommendations

A WHO-commissioned systematic review and meta-analysis of 129 studies showed a substantial protective effect of using antiviral prophylaxis in preventing mother-to-child transmission in infants born to HBV infected women regardless of the antiviral used. Tenofovir disoproxil fumarate (TDF) has a high genetic barrier to resistance and is the medicine of choice for both PMTCT and treatment of chronic hepatitis B infection. There was a low risk of maternal HBV flare after TDF discontinuation in the studies that reported on this outcome. The Guidelines Development Group also determined a HBV DNA viral load threshold of $\geq 5.3 \log_{10}$ IU/mL ($\geq 200,000$ IU/mL) at which pregnant women are eligible to receive tenofovir prophylaxis. Pregnant woman with a viral load above this level may transmit HBV to their infant even when the infant receives the timely birth dose vaccine, Hepatitis B immune globulin (HBIG) HBIG and completes the hepatitis vaccine series.

Although HBV DNA quantification is the reference method to determine eligibility for tenofovir prophylaxis, the use of HBeAg was recommended as an acceptable alternative test in settings where access to HBV DNA quantification is limited. This was based on a further systematic review that showed the overall sensitivity and specificity of HBeAg for diagnosis of high HBV viral load (defined as $\geq 5.3 \log_{10}$ IU/mL) was 88.2% (95% CI: 83.9–91.5) and 92.6% (95% CI: 90–94.5) respectively. Overall, HBeAg has a high sensitivity but lower specificity for predicting the risk of mother-to-child transmission. A global values and preferences survey showed a broad level of acceptability of HBV testing in pregnant women with use of antivirals in those eligible, but raised concerns about potential costs.

SUMMARY OF RECOMMENDATIONS

Existing recommendations on immunization from the Strategic Advisory Group of Experts (SAGE) WHO position paper 2017 (5)

- a) All infants should receive their first dose of hepatitis B vaccine as soon as possible after birth, preferably within 24 hours;
- b) Delivery of hepatitis B vaccine within 24 hours of birth should be a performance indicator for all immunization programmes, and reporting and monitoring systems should be strengthened to improve the quality of data on the birth dose;
- c) The birth dose should be followed by two or three doses to complete the primary series.

Existing recommendation on testing of pregnant women for HIV, syphilis and hepatitis B from the 2019 Consolidated guidelines on HIV testing services (10), and for hepatitis B from the 2017 WHO Guidelines on hepatitis B and C testing (11)

All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg)¹ at least once and as early as possible in the pregnancy (HIV standing recommendation since 2007; syphilis: *strong recommendation, moderate-quality evidence*; HBsAg:¹ *strong recommendation, low-quality evidence*).

Tenofovir prophylaxis to prevent mother-to-child transmission of HBV New recommendation

WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA $\geq 5.3 \log_{10}$ IU/mL ($\geq 200,000$ IU/mL)² receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth to prevent mother-to-child transmission of HBV. This is in addition to three-dose HBV vaccination, including timely birth dose (*conditional recommendation, moderate quality of evidence*).

Use of HBeAg testing (where HBV DNA testing is not available) to determine treatment eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV

New recommendation

WHO recommends that in settings in which antenatal HBV DNA testing is not available, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV³ (*conditional recommendation, moderate quality of evidence*).

¹ Particularly in settings with a $\geq 2\%$ seroprevalence in the general population

² HBV DNA $\geq 5.3 \log_{10}$ copies/mL is equivalent to $\geq 200,000$ IU/mL.

³ The performance of HBeAg testing suggests that it is an acceptable alternative to diagnosing HBV DNA $\geq 5.3 \log_{10}$ IU/mL.

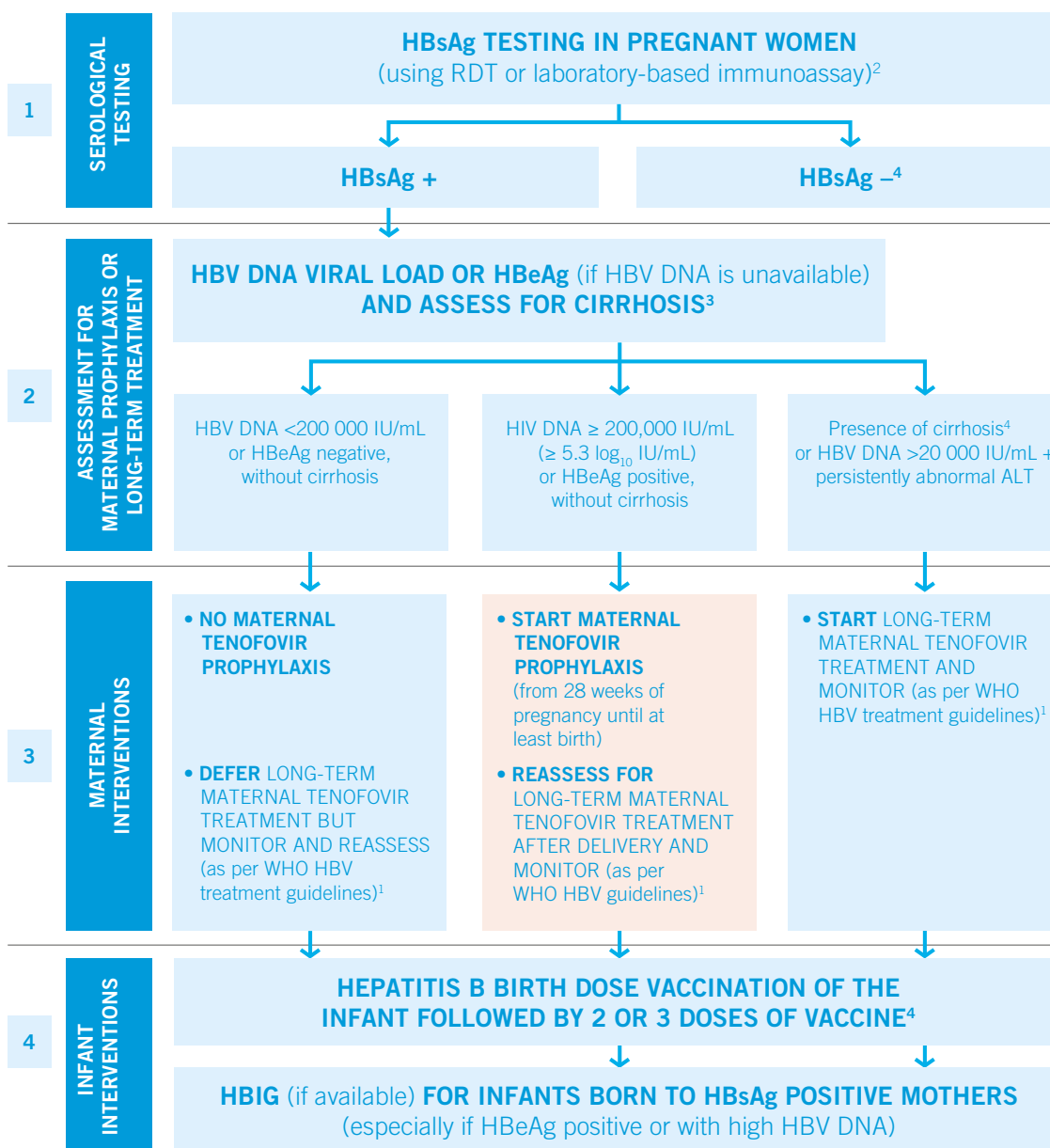
IMPLEMENTATION CONSIDERATIONS

- Universal immunization of infants with hepatitis B vaccine, including a timely birth dose, is the foundation of programmes to prevent HBV infection at birth and in the first years of life. Countries that have not yet reached the 2020 goal of 1% HBsAg prevalence among children aged 5 years through vaccination need to focus their efforts on increasing their vaccination coverage, including timely birth dose.
- Clinical trials that evaluated the efficacy and safety of tenofovir prophylaxis also included hepatitis B immune globulin (HBIG) as an additional preventive strategy in both trial arms. In a number of settings (mostly in high-income countries) where it is available, HBIG is used in addition to hepatitis B vaccination, including birth dose, to reduce the risk of mother-to-child transmission of HBV. HBIG is a blood product that has to be screened for infectious diseases. The costs are high, a cold chain is required and HBIG can be in short supply. In low and middle-income setting, it may only be available when purchased by individuals.
- As many countries are working towards the dual elimination of perinatal HIV and syphilis infection, there are opportunities for efficiency gains and integration of elimination of mother-to-child transmission of HBV. Two WHO regions (Region of the Americas and the Western Pacific Region) already have plans and a framework for triple elimination.
- Programmes to test and treat all eligible pregnant women for HBV infection need to be implemented in the context of universal health coverage, aiming for covering the highest proportion of women while reducing financial hardship.
- Testing of pregnant women needs to take place under circumstances that prevent stigma and discrimination and provides post-test counselling and education on measures to reduce the risk of transmitting HBV to the infant, encourage partner testing and ensure linkage to care of HBsAg positive women.
- Clinical assessment should include an evaluation of whether an HBsAg-positive pregnant woman would be eligible for antiviral treatment for their own health. However, in accordance with criteria in the 2015 WHO Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection, only a small proportion of women of childbearing age would be eligible for long-term treatment (6).
- HBV DNA quantification is the reference method to identify those HBsAg-positive pregnant women with a high viral load most at risk of transmitting HBV to their infants. Access to HBV DNA quantification (in terms of cost and availability of testing platforms) remains limited in low-income settings. Continuing efforts are needed to increase access to HBV DNA testing and reduce costs.
- Diagnostic tests used need to meet quality, safety and performance standards (with regard to analytical, diagnostic and clinical sensitivity and specificity)¹

¹ Assays should meet minimum acceptance criteria of either WHO prequalification of in vitro diagnostics (IVDs) or a stringent regulatory review for IVDs. All IVDs should be used in accordance with manufacturers' instructions for use and, where possible, at testing sites enrolled in a national or international external quality assessment scheme.

FIGURE 1 Summary algorithm on HBV testing of pregnant women to prevent mother-to-child transmission of HBV and refer eligible women to treatment¹

(Based on these guidelines and the 2017 WHO HBV and HCV testing guidelines)²



Abbreviations: ALT: alanine aminotransferase; HBV: hepatitis B virus; HCC: hepatocellular carcinoma; HBeAg: hepatitis B e antigen; HBIG: hepatitis B immune globulin; HBsAg: hepatitis B surface antigen; RDT: rapid diagnostic test

¹ HBV birth dose vaccination of the infant followed by 2 or 3 doses of HBV vaccination should be given regardless of testing of pregnant women.

² Guidelines for the prevention, care and treatment of persons with chronic hepatitis B infection; https://apps.who.int/iris/bitstream/handle/10665/154590/9789241549059_eng.pdf;jsessionid=F81A4051291A7F1C73BD14BC49E37E27?sequence=1

³ At least once and as early as possible in the pregnancy

⁴ Monitor toxicity (every 12 months), treatment response and detection of HCC (every 6 months) of mother.

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