South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Obstetrics & Gynaecology
Addendum to the NDoH review: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B

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Prevention of Mother-to-Child Transmission of Hepatitis B by Using Antiviral Prophylaxis - World Health Organization 2024 Updates

Background

In 2023 the Primary Health Care and Adult Hospital Expert Review Committee was tasked with reviewing the use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive (at high risk of vertical transmission (VT), to prevent VT of Hepatitis B.

The following eligibility criteria was approved for the review.

Population	HIV negative pregnant women in third trimester who are at high risk for VT (either HBeAg positive or have a viral load >200 000 IU/ml)
Intervention	Antiviral therapy
Comparator	No treatment/placebo
Outcome	Efficacy outcome: • Vertical transmission of Hepatitis B Safety outcomes: • Adverse events in mother (e.g. Rebound hepatitis) Foetal death
Studies	Guidelines that employed GRADE (and/or have evidence to decision framework).

The GRADE-adolopment approach was used for efficiency purposes.

The 2020 WHO guideline on the Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy guideline was adoloped and in May 2024 NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation of Tenofovir for the

prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are at high risk for VT (either HBeAg positive or have a viral load >200 000 IU/ml).[1]

At that time, in May 2024, a query was raised by NEMLC which was not part of the initial review question:

- How to manage HBsAg-positive pregnant women where HBeAg or viral loads are not available

Additionally following the ratification of the initial review by NEMLC in, May 2024, it was brought to the attention of NEMLC that:

- The WHO in March 2024 released updated guidance for the prevention of vertical transmission of hepatitis B in their guidelines for the prevention, diagnosis, care and treatment for people (including pregnant woman as a key priority topic) with chronic hepatitis B infection[2], including:
    - the use of TDF/3TC and TDF/FTC if TDF monotherapy is not available and
    - the use of TAF to be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis.
- Proposals for advancing triple elimination indicate that relying on the availability of HBeAg testing is no longer recommended; and that HbsAg is a more accurate test to apply.[3]

It should be noted that the NEMLC review considered HBeAg-positive in the eligibility criteria. However in 2019 from the existing recommendation on testing of pregnant women for HIV, syphilis and hepatitis B from the 2019 Consolidated guidelines on HIV testing services[4] and for hepatitis B from the 2017 WHO Guidelines on hepatitis B and C testing[5] WHO had recommended that all pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible during their pregnancy.[1] (HIV standing recommendation since 2007; syphilis: strong recommendation, moderate-quality evidence; HBsAg: strong recommendation, low quality evidence).

In 2020, the WHO recommended that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥5.3 log10 IU/mL (≥200,000 IU/mL) 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). Furthermore, in 2020, the WHO recommended that in settings in which antenatal HBV DNA testing is not available, for example in the public sector in SA, 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 HBV (conditional recommendation, moderate quality of evidence). This is the recommendation that was adoloped by NEMLC in May 2024.

Following the publication of the WHO 2024 guidelines through personal communication by a NEMLC member, with the lead author, it was raised that there is an error in the summary guidance of the 2024 WHO guideline recommendation on page XXXI of the guideline[2] which would have bearing on the following closing statement in the NDOH review: *In March 2024, the WHO released Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection.[2] In this guideline the existing recommendation for use of TDF prophylaxis for HBsAg-positive pregnant women with HBV DNA levels ≥200 000 IU/mL or a positive HBeAg, in settings where there is ready access to these assays, is retained from the 2020 WHO hepatitis B antiviral prophylaxis guidelines for prevention of vertical transmission*. Additionally, the guideline reiterated the 2020 WHO guidance to continue TDF for mothers who meet the criteria for antiviral therapy. The summary guidance, as

included in the narrative of the guideline should have included that in settings where neither HBV DNA nor HBeAg testing is available, prophylaxis with TDF is recommended for all HBV-positive (HBsAg-positive) pregnant women (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV.

Introduction

Historically, the WHO has recommended universal HBsAg screening of pregnant women and using antiviral prophylaxis to prevent vertical transmission of hepatitis B among those pregnant patients with a high HBV DNA (≥200 000 IU/mL) or positive HBeAg test.[6]

In the March 2024 update on guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection[2] the WHO acknowledged the challenges in accessing HBV DNA and/or HBeAg serology testing among HBsAg-positive pregnant women to determine eligibility for antiviral prophylaxis, especially in sub-Saharan Africa. The WHO further acknowledges that as a result, there has been no effective universal HBsAg screening of pregnant women and using antiviral prophylaxis to prevent vertical transmission among those pregnant patients with a high HBV DNA (≥200 000 IU/mL) or positive HBeAg test. Therefore a conditional recommendation to expand TDF prophylaxis to all HBsAg-positive pregnant women was made and based on an overall pragmatic approach.

Using the following eligibility criteria (Table 1) the WHO in March 2024 provide updated recommendations (Table 2 & Figure 1) for the research question: Among HBsAg-positive people, what is the efficacy and safety and cost–effectiveness of antiviral prophylaxis in all HBsAg-positive pregnant women to prevent mother-to-child transmission of HBV compared to those with HBV DNA levels >200 000 IU/mL?

Table 1: WHO Eligibility Criteria

PICO: Use of antiviral prophylaxis for PMTCT of HBV[2]

Population	All pregnant women with chronic HBV infection regardless of HBV DNA level
Intervention	Maternal treatment with antiviral therapy in all HBsAg-positive pregnant women regardless of HBV DNA level
Comparison	Maternal treatment with antiviral therapy in HBsAg-positive pregnant women with HBV DNA level >200 000 IU/mL (current 2020 recommendations)
Outcome	MTCT as indicated by infant HBsAg positivity at 6–12 months of life

Table 2: WHO Recommendations

Taken From: Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024.

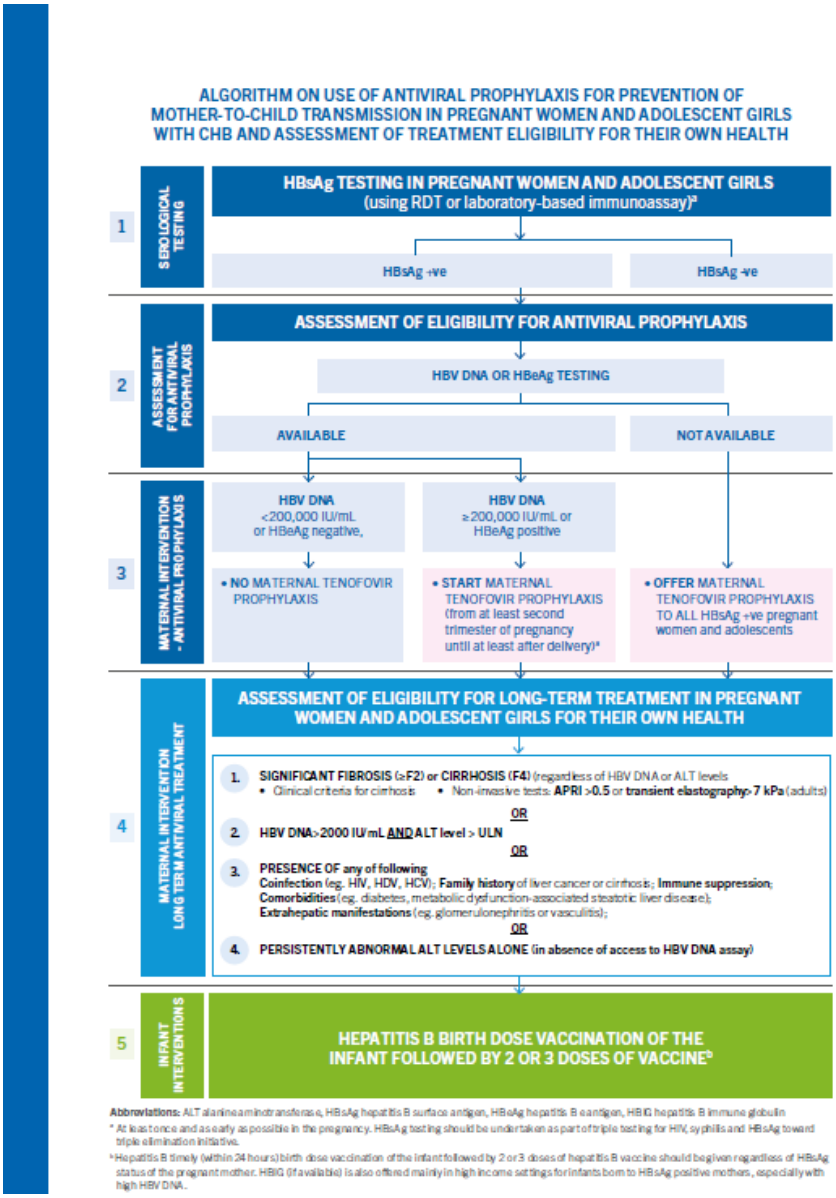
Existing and maintained recommendation (2019 guidelines on HIV testing)	HBsAg testing among pregnant women and adolescent girls	All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible during their pregnancy.	*strong recommendation, low-certainty evidence*
2020 guidelines on antiviral prophylaxis	Antiviral prophylaxis among pregnant women and adolescent girls	In settings where HBV DNA or HBeAg testing is available, prophylaxis with tenofovir disoproxil fumarate (TDF)b is recommended for all HBV-positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg[a] (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV.	*strong recommendation, moderate-certainty evidence*
New recommendation		In settings where neither HBV DNA nor HBeAg testing is available, prophylaxis with TDF[b] is recommended for all HBV-positive (HBsAg-positive) pregnant women (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV. All interventions should be given in addition to at least three doses of hepatitis B vaccination for all infants, including a timely birth dose. Note: All pregnant women and girls of reproductive age should be assessed first for eligibility for long-term treatment for their own health. For women and adolescent girls of childbearing age planning additional pregnancies, TDF prophylaxis can also be maintained after delivery and during subsequent pregnancies, according to women's choice.	*strong recommendation, moderate-certainty evidence*

a The use of the HBeAg recommendation represents an additional option for determining eligibility, but HBeAg Rapid Diagnostic Tests have poor diagnostic performance, which limits their routine use in low- and middle-income countries.

b TAF may be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis but is not yet approved for hepatitis B treatment in pregnancy. TAF is not recommended if eGFR is <15 ml/min.

Figure 1: The Algorithm on Use of Antiviral Prophylaxis of Mother to Child Transmission in Pregnant Women and Adolescent Girls with Chronic Hepatitis B and Assessment of Treatment Eligibility for Their Own Health.

Taken From: Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024.



In summary start maternal TDF prophylaxis (from atleast second trimester of pregnancy until at least after delivery) if HBV DNA ≥200 000 IU/mL or HBeAg positive (alongside infant HBV vaccination) and offer maternal TDF prophylaxis to all HBsAg positive pregnant woman and adolescents. Dual therapy is not included in the algorithm for prophylaxis but treatment only.

Summary of Evidence

Existing and Maintained Recommendation

Efficacy and safety of maternal TDF prophylaxis to prevent mother-to-child HBV transmission among those with HBV DNA >200 000 IU/mL or HBeAg positive (alongside infant HBV vaccination)
The maternal and infant efficacy and safety evidence quoted for the retention of the recommendation of TDF prophylaxis to prevent mother-to-child HBV transmission among those with HBV DNA >200 000 IU/mL or HBeAg positive in the WHO 2024 Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection update comes from the WHO Commissioned Systematic review used in the 2020 Guideline for the prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy.

The 2020 WHO guideline for the prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy guideline was adoloped and in May 2024 NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation of Tenofovir for the prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are HBeAG positive.[7]

Additional evidence mentioned in the 2024 guideline for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection

Efficacy and safety of maternal TDF prophylaxis to prevent mother-to-child HBV transmission among those with HBV DNA >200 000 IU/mL or HBeAg positive (alongside infant HBV vaccination)
In the WHO 2024 Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection update, the WHO quote a recent study from the WHO African Region (Democratic Republic of the Congo) demonstrating high protective efficacy of TDF in addition to infant hepatitis B birth dose without hepatitis B immunoglobulin:

- n=0 cases of transmission among babies born to n= 9 treated women.[8]

TAF
In terms of safety WHO also report that the data on the safety of TAF during pregnancy are limited but also suggest an excellent safety profile.[9] However, the WHO 2024 Guideline**Error! Bookmark not defined.** in the narrative of the guideline indicates that TAF has not been approved yet for preventing MTCT of HBV and in a recommendation table (see Table 2 above) that TAF may be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis but is not yet approved for hepatitis B treatment in pregnancy. Refer to the NDOH evidence summary on Tenofovir alafenamide (TAF) for the treatment of chronic hepatitis B (non-HIV co-infection) in patients with renal impairment[10] for additional evidence utilised by NEMLC in recommending TAF in renally impaired patients.

Feasibility of expanding antiviral prophylaxis access to all HBsAg-positive pregnant women
The WHO report that to date, no studies have been undertaken to examine the clinical impact and feasibility of expanding antiviral prophylaxis access to all HBsAg-positive pregnant women. Therefore, the WHO commissioned a modelling study of different scenarios of eligibility for antiviral prophylaxis.[11]

A systematic review and meta-analysis outlined eligibility of pregnant women for antiviral prophylaxis. The study reviewed the proportion of pregnant women with chronic hepatitis that were HBeAG positive with high viraemia (HBV DNA levels ≥200 000 IU/mL). This systematic review also included studies from Africa (while the systematic review commissioned by the WHO in 2020

evidence on TDF efficacy did not). The study concluded: "Approximately 20% of HBV-infected pregnant women are eligible for peripartum antiviral prophylaxis [PAP]".[12] The overall pooled proportion of high viraemia in the WHO Africa region was 12.45%. The study cautions that considering the significant regional variation, each country should define optimal strategies to incorporate HBsAg screening, risk stratification and PAP into routine antenatal care services.[12]

Modelling study of TDF prophylaxis for all HBsAg-positive pregnant women

- Adding HBsAg testing and TDF prophylaxis for eligible pregnant women to the scenario of HepB3 vaccination (three doses of hepatitis B vaccine given in infancy) and hepatitis B birth dose would prevent an additional 2.9–3.0 million neonatal infections over the same period.[12]
- A recent modelling study of 110 countries across all WHO regions assessed the impact and cost–effectiveness of universal TDF prophylaxis among all HBsAg-positive pregnant women regardless of HBV DNA level in settings without access to HBV DNA testing (i.e. excluding the existing recommendation for only those with a high HBV DNA level).[13]
    - **Cost–effectiveness of hepatitis B prophylaxis guided by HBV DNA levels or HBeAg status:**
        - Prophylaxis for HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg strategy would probably be cost-effective in only 28 (26%) of 106 countries analysed, including:
            - China (incremental cost–effectiveness ratio US$ 8131, 95% CI US$ 3958–17 538),
            - South Africa (US$ 1431, 95% CI US$ 943–2494),
            - Vietnam (US$ 1374, 95% CI US$ 960–1832), and
            - Lower diagnostic and monitoring costs would make the strategy cost-effective in 74 (70%) of 106 countries, including 24 in the African Region.
    - **Impact and cost–effectiveness of expanded treatment for all HBsAg-positive pregnant women:**
        - Universal antiviral prophylaxis, regardless of HBV DNA level or HBeAg serostatus, would have great impact on HBV PMTCT, with about 4.9 million (95% CI: 4.7 million–5.1 million) neonatal infections averted. At central cost estimates and compared with hepatitis B birth dose, the universal "prophylaxis for all" strategy would probably only be cost-effective in 42 (40%) of 106 countries.
        - The relative cost–effectiveness of the universal and HBV DNA–driven strategies (each compared with sole hepatitis B birth-dose strategy) depended highly on the relative costs of treatment and diagnostic tests.

Proposal

- Retain the NEMLC ratified recommendation (16 June 2024) of tenofovir monotherapy for the prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are HBeAG positive.
- Additionally, pragmatically, offer maternal TDF prophylaxis to all HBsAg positive pregnant woman even if the HBeAg or viral load result is unavailable.
- Consider TAF for people (including pregnant women) with impaired kidney function and/or osteoporosis noting that TAF is not recommended if eGFR is <15 ml/min).

PHC/Adult ERC Recommendation: 6 June 2024
The PHC /AHL ERC accepted the proposal as stated above.

NEMLC Recommendation: 27 June 2024

NEMLC accepted the proposal as recommended by the PHC/Adult ERC (see above)

[1] National Department of Health: Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B. http://www.health.gov.za/

[2] Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024. Available at: https://www.who.int/publications/i/item/9789240090903, Accessed 2 June 2024).

[3] Chalid MT, Turyadi, Ie SI, Sjahril R, Wahyuni R, Nasrum Massi M, Muljono DH. A cautionary note to hepatitis B e antigen (HBeAg)-negative test results in pregnant women in an area prevalent of HBeAg-negative chronic hepatitis B. J Med Virol. 2023 Jan;95(1):e28125. doi: 10.1002/jmv.28125. Epub 2022 Sep 14. PMID: 36064856; PMCID: PMC10087600.

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[5] Guidelines on hepatitis B and C testing. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/254621/1/9789241549981-eng.pdf?ua=1, accessed 2 April 2020).

[6] Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy. Geneva: World Health Organization; 2020. Available at (https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hepatitis/prevention/mother-to-child-transmission-of-hepatitis-b, accessed 2 June 2024).

[7] National Department of Health: Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B. http://www.health.gov.za/

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[10] TAF – eGFR 15-50: NDoH Evidence Summary: Use of TAF for adults with HIV. V4_14 March 2024.

[11] Nayagam S, de Villiers MJ, Shimakawa Y, Lemoine M, Thursz MR, Walsh N et al. Impact and cost–effectiveness of hepatitis B virus prophylaxis in pregnancy: a dynamic simulation modelling study. Lancet Gastroenterol Hepatol. 2023;8:635–45. doi: 10.1016/S2468-1253(23)00074-2.

12 WHO. Web Annex C. Nayagam S, Hallet T, Schmit N, Shimakawa Y, Lemoine M, Thursz M. Impact and cost–effectiveness of HBV peripartum antiviral therapy. In: Prevention of mother-to-child transmission of hepatitis B virus (HBV): guidelines on antiviral prophylaxis in pregnancy. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

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