South African National Essential Medicine List
Adult Healthcare Medication Review process
Component: Obstetrics

EVIDENCE REVIEW

Title: 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.

Date: 11 April 2024

Key findings

- The 2022 World Health Organization (WHO) Guideline: "Recommendations for prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy" were informed by a commissioned systematic review and meta-analysis and cost–effectiveness modelling.
- We performed GRADE-adolopment of these WHO guidelines.
- The WHO-commissioned systematic review and meta-analysis identified 129 studies that evaluated the efficacy of antiviral prophylaxis in Hepatitis B virus (HBV)-infected pregnant women to prevent mother-to-child transmission. After removal of duplicate studies n=89 studies were included in a meta-analysis. Most studies were performed in the Western Pacific Region. There were no studies available from the African Region or from the Americas.
- The majority of the 89 studies in the meta-analysis included hepatitis B immunoglobulin (HBIG) in both trial arms (in six studies use of HBIG was not reported). (In SA currently, when a pregnant mother is HepB positive and there is risk for transmission to the baby, HepB vaccine is administered to the baby at birth (instead of the Expanded Programme on Immunisation schedule administration at 6 weeks). Additionally, if HepB Immunoglobulin is available, it is given to the baby after birth.)
- The WHO-approved PICO listed seven antiviral interventions. The WHO systematic review identified studies administering the following antivirals: tenofovir (TDF) 300 mg, lamivudine (3TC) (100–150 mg), telbivudine (LdT) 100 mg and 600 mg, and adefovir dipivoxil (ADV) 10 mg and 500 mg. Neither telbivudine or adefovir are available in South Africa. The WHO review did not find any studies including antiviral treatment with emtricitabine (FTC), entecavir (ETV) or tenofovir alafenamide fumarate (TAF).
- The WHO-approved population of interest was pregnant women with chronic HBV infection. WHO planned subgroup analyses in women coinfected with hepatitis D virus (HDV) and/or human immunodeficiency virus (HIV). However, the WHO reviewers were not able to conduct a subgroup analysis by HIV coinfection status, as there were no eligible studies that reported results for this subgroup separately.
- **For TDF 300mg vs no treatment or placebo:**
  - RCTs and non RCTs showed lower proportion HBsAg positive at 6–12 months in the TDF treatment group
    - 5 RCTs: [(n=1 of 349 (0.3%) vs no treatment/placebo group (n=23 of 337(6.8%)] – ***moderate certainty evidence***.

        - 14 Non RCTs [n=21 of 723 (2.9%) (treatment group) vs n=88 of 499 (17.6%) (no treatment/placebo group [OR 0.17, 95% CI: 0.10–0.29] - ***low certainty evidence***
    - 5 RCTs included in the meta-analysis, moderate certainty evidence, suggests that there will be 80 fewer HBsAg positivity cases at 6–12 months per 1000 in infants whose mothers took TDF prophylaxis versus those who did not; (95% confidence interval 10–140 fewer).
    - HBV flares after treatment discontinuation were reported in six of the 19 included RCT and non RCT studies that administered TDF to mothers. Various definitions were used, including: "postpartum flare", "severe flare", "ALT >5 ULN", "moderate flare" and others. Within these studies, 34 of 418 mothers who were treated with TDF during pregnancy experienced an HBV flare at the time of treatment discontinuation, whereas 20 of 382 mothers who were not treated during pregnancy experienced an HBV flare at a matched time-point. The WHO panel was not able to fully examine the outcome of HBV flare, as standardised information was lacking across studies.
    - 3 RCTs that reported on HBV flares after TDF treatment discontinuation found a higher proportion with hepatitis flares in the TDF treatment groups vs no treatment/placebo [(n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group)] - ***moderate certainty evidence***.
    - Similar results were noted for flare after TDF treatment discontinuation in 3 Non RCTs [(n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group)] ***very low certainty evidence***.
    - For neonatal deaths (death within 28 days of life):
        - 5 RCTs in the meta-analysis reported n=2 deaths of 367 (0.5%) infants (treatment group) vs n=1 death of 350 infants (0.3%) (no treatment/placebo group)- ***moderate certainty evidence***.
        - 14 Non RCTs included in the meta-analysis deaths were reported for n=0 of 712 [(0.0%) (treatment group) vs n=0 of 518 (0.0%) mothers (control group)] - ***low certainty evidence***.

- **For 3TC (100-150mg) no treatment or placebo:**
    - 8 RCTs (***moderate certainty evidence)*** and 32 non RCTs (***low certainty evidence)*** showed lower HBsAg positivity at 6–12 months in the 3TC treatment group respectively ((n=25 of 432 [(5.8%) (treatment group) vs n=105 of 389 (27.0%) (control group) [OR 0.16, 95% CI: 0.10–0.26]] and [(n=41 of 1575 (2.6%) (treatment group) vs n=233 of 1655 (14.1%) (control group) [OR 0.17, 95% CI: 0.12–0.24)]]
    - 1 RCT reported a lower proportion with a HBV flare after 3TC treatment discontinuation (n=16 of 83 (19.3%) (treatment group) vs the control group n= 15 of 46 (32.6%) mothers (control group)) - ***low certainty evidence***
    - Higher proportion for HBV flare up after 3TC treatment discontinuation vs control groups in 5 Non RCTs (n=32 of 287 (12.9%) (treatment group) vs n= 31 of 504 (6.2%) mothers (control group)) – ***low certainty evidence***
    - An equal percentage of neonatal deaths (death within 28 days of life) were noted in 8 RCTs (moderate certainty evidence) (n=1 deaths of 439 (0.2%) infants (treatment group) vs n=1 death of 407 infants (0.2%) (control group) and 31 Non RCTs (***low certainty evidence*** ((n=0 deaths of 1571 (0.0%) infants (treatment group) vs n=0 death of 1686 infants (0.0%) (control group))

- The meta-analysis indicated a protective effect for both TDF and lamivudine in preventing mother-to-child transmission (TDF 300 mg: odds ratio [OR] 0.16, 95% confidence interval [CI]: 0.10–0.26; lamivudine 100 mg: OR 0.17, 95% CI: 0.13–0.22).

- The WHO Guideline was rated as a high-quality clinical practice guideline (AGREE II score of 92% overall and 86% for rigour of development).

➡ To be noted; lamivudine has a low genetic barrier to drug resistance mutations, which may lead to the emergence of drug-resistant strains of HBV while TDF has a higher barrier to drug resistance. WHO recommends nucleos(t)ide analogues with a high barrier to resistance to treat HBV infection Thus, TDF was recommended by WHO as medicine of choice for prevention of vertical transmission of HBV from mother to child.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

PHC/AHL ERC RECOMMENDATON: (11 APRIL 2024)

Recommendation: The committee recommends 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. (moderate CoE, Strong recommendation).

Rationale: There was evidence of moderate benefit and trivial harms, increased equity, and negligible costs. The treatment was found to be feasible and acceptable to implement.

Level of Evidence: Moderate certainty of evidence
Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECOMMENDATION (16 May 2024):

The 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.

Monitoring and evaluation considerations: see review indicators above

Research priorities: see review indicators above

1. Executive Summary

Date: 11 April 2024
Medicine (INN): Tenofovir Antiviral
Medicine (ATC): J05AR12
Indication (ICD10 code): B19.10 – Unspecified viral hepatitis B without hepatic coma
Patient population: Third trimester HBeAG positive, HIV negative pregnant women
Prevalence of condition: 0.67% prevalence of HBsAg in HIV negative pregnant women [Joseph Davey, D., Hsiao, Ny., Wendy Spearman, C. et al. Low prevalence of hepatitis B virus infection in HIV-uninfected pregnant women in Cape Town, South Africa: implications for oral pre-exposure prophylaxis roll out. BMC Infect Dis 22, 719 (2022). https://doi.org/10.1186/s12879-022-07697-5]
Level of Care: Adult Hospital Level
Prescriber Level: Medical Doctor
Motivator/reviewer name(s): n/a
PTC affiliation: n/a

2. Authors, affiliation and conflict of interest details:

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SG, MR, MM & DF have no interests to declare with regard to antivirals in the third trimester of pregnancy in women who are HIV Negative and HBeAG positive.

3. Introduction/ Background

Pregnant women who are hepatitis B virus (HBV) positive have a high risk of transmitting HBV to the baby. Maternal HBV infection may also result in higher rates of preterm births and gestational diabetes.[1]

National Department of Health, updated maternity guidelines (2024)
recommends that all pregnant woman should be offered a test for HBsAg at the first antenatal visit irrespective of gestational age.[2]

The World Health Organization recommends that pregnant women who test positive for HBV infection (HBsAg positive) receive tenofovir (TDF) prophylaxis from the 28th week of pregnancy until at least birth[3]. The Centers for Disease Control advise that all pregnant women should be tested for hepatitis B surface antigen (HBsAg) during each pregnancy and those testing positive should be tested for HBV DNA. Women with HBV DNA >200,000 IU/mL should receive antiviral therapy to prevent perinatal transmission.[4]

The NDOH Guideline for the Prevention of Vertical Transmission of Communicable Infections state that the ART drugs TDF and lamivudine (3TC) treat both HIV and HBV and reduce the risk of vertical transmission by decreasing the viral load of both HIV and Hepatitis B. The guideline recommends that health care workers need to be aware of the required management of a HBV-infected mother and her infant as outlined in the National Maternity Care Guidelines (update published in 2024).[2] The NDOH maternity guidelines (2024) indicate that HBsAg positive pregnant woman (irrespective of HIV status) should be referred to a specialist center for further serological evaluation, where they may be offered TDF. Additionally, PrEP (TDF and emtricitabine) is now routinely available and recommended for all pregnant women including adolescent girls[1]

The NDOH hepatitis guidelines are currently under review for an update for publication. (March 2024 communication from the NDOH program)

The current first line antiretroviral treatment regimen for HIV-positive adults, including pregnant woman, comprises TDF, 3TC and dolutegravir based regimens which provides protection against vertical transmission in HIV positive women who are HBeAG positive.[1, 2]

The WHO Global hepatitis report 2024 which calls for action for access in low- and middle-income countries states that combining routine screening and antiviral prophylaxis for treating pregnant women with hepatitis B, along with the hepatitis B birth-dose vaccination for infants, will be critical to eliminate the mother-to-child transmission of viral hepatitis B, especially in regions such as sub- Saharan Africa with a high disease burden of hepatitis B.[5]

Several local and international guidelines already recommend use of antivirals for HBeAG positive pregnant woman irrespective of HIV status. In order for recommendations to be informed by current evidence in the management of HIV negative and HBeAG positive pregnant woman, the PHC and AHL expert review committee requested a review and adolopment of a good quality guideline recommending management of pregnant woman who are HBeAG positive.

4. Purpose/Objective

Should antivirals be recommended for women in the third trimester of pregnancy who are HIV negative and HBeAG positive?

5. PICO eligibility criteria

Population	HIV negative pregnant women in third trimester who are 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).

6. Methods

The GRADE-adolopment approach was used for efficiency purposes. The choice of source guideline was deliberated and selected by two of the reviewers (SG & MR) and assessed for relevance, credibility (AGREE II) and whether the evidence was sufficiently up-to-date. The GRADE-ADOLOPMENT process was used to adopt, adapt, adopt with minor changes, or exclude recommendations from the source guideline. The GRADE-ADOLOPMENT process briefly, includes 1) selection the guideline topic and question, 2) searching and identifying the source guidelines, 3) matching the source guideline recommendations and underlying evidence, 4) updating and reviewing the underling evidence and 5) populating and/or reassessing the EtD framework to develop recommendations (as either an adopted, adapted or de novo recommendation) [6]. We searched PubMed and google scholar for guidance, in March 2024, on the topic of management of pregnant woman who are HBeAG positive.

An AGREE II (Appraisal of Guidelines, for Research, and Evaluation)[7] assessment was planned in duplicate on the selected guideline to evaluate the process of guideline development and quality of reporting. Two reviewers (MR & DF) independently reviewed the guideline using the online AGREE II assessment tool.

7. Results

We identified the following guidelines: CDC, Australian, Fellow of the Royal College of Obstetricians and Gynecologists (FRCOG), Royal College of Obstetrics & Gynaecology (RCOG) and American College of Obstetricians and Gynecologists; but these focused more on vaccinations and not on our PICO question. We identified one World Health Organization (WHO) guideline addressing our PICO question, that utilised a Grading of Recommendations Assessment, Development and Evaluation (GRADE)[8] framework approach. The source guideline: "Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy (July 2020)" was reviewed for adoption and/ or adaptation.

The WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis In Pregnancy (July 2020) was selected for review for the following reasons:

- Use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods
- Local familiarity
- Applicability
- Rigor as the guideline outlined the evidence and information that guided the recommendations

- Credibility
- Timeliness
- Acceptability
- Trustworthiness (whether it is likely to be up to date)

The AGREE II appraisal outcome is presented in Appendix 2. In summary the WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy (July 2020) guideline can be considered a high-quality clinical practice guideline (AGREE II score of 92% overall and 86% for rigour of development) and was considered up-to-date and relevant to the committee's question.

The applicable WHO review question was posed as follows: Are antiviral therapies efficacious and safe at reducing MTCT of HBV if administered during pregnancy in women with chronic HBV infection?

The following eligibility criteria was used for the WHO review question above and was in line with the current PHC & AH PICO:

Population: Pregnant women with chronic HBV infection

Intervention: Maternal treatment with antiviral therapy during pregnancy with or without infant birth dose vaccination and/or HBIG. The following antiviral therapies were considered for inclusion:

- adefovir dipivoxil (ADV)
- emtricitabine (FTC)
- entecavir (ETV)
- lamivudine (3TC/LAM)
- telbivudine (LdT)
- tenofovir alafenamide fumarate (TAF)
- TDF.

Comparators: No antiviral therapy or placebo. Timely administration of birth dose vaccine, timely administration of HBIG Completion of three or four doses of infant hepatitis B vaccines also considered in relation to no antiviral therapy or placebo.

Outcomes: The primary outcome of interest was MTCT of HBV, as indicated by infant HBsAg positivity at 6–12 months of life.

Secondary infant outcomes of interest, included:

- Infant HBV DNA positivity at 6–12 months of life
- Any infant adverse event, such as
    - neonatal death (within 28 days of life [WHO, 2006])
    - preterm birth (<37 weeks of gestational age [WHO, 2018])
    - congenital abnormality
    - Apgar score at 1 minute of life
    - measurement of bone density of infants.
- Maternal outcomes of interest, specified in the study protocol, included:
    - any maternal adverse event, including:
        - miscarriage (<28 weeks gestational age,
        - stillbirth (>=28 weeks gestational age,
    - HBV flare after discontinuation of treatment (e.g. elevated HBV DNA and/or elevated ALT)

- postpartum haemorrhage
- Antiviral resistance

The WHO-commissioned systematic review and meta-analysis identified 129 studies that evaluated the efficacy of antiviral prophylaxis in HBV-infected pregnant women to prevent mother-to-child transmission.

The WHO approved PICO included seven different treatments of interest. However, only studies including TDF 300 mg, 3TC (100–150 mg), Telbivudine (LdT) 100 mg and 600 mg, and adefovir dipivoxil (ADV) 10 mg and 500 mg were found eligible. The latter two ARVs are not routinely used in South Africa. No studies investigated any regimens with FTC, ETV, TAF and therefore these treatments were not included.

The WHO approved study population included pregnant women with chronic HBV infection. HIV status was not stipulated. Subgroup analyses were to include coinfection with hepatitis D virus (HDV) or human immunodeficiency virus (HIV). It was not possible to conduct a subgroup analysis by coinfection status, as there were eventually no eligible studies that included coinfected populations. The population studied was applicable to the current review question.

All studies in the meta-analysis (n=89) included HBIG in both trial arms, with the exception of six studies, in which the use of HBIG was not reported.

The systematic review and meta-analysis commissioned by the WHO showed that certain antiviral therapies may be efficacious if used during pregnancy for the prevention of vertical transmission of HBV, as indicated by the proportion of infants with HBsAg detected at 6–12 months of life:

- Meta-analysis of RCTs investigating TDF 300 mg had a protective, pooled OR of 0.10 (95% CI: 0.03–0.35), and
- Meta-analysis of RCTs investigating Lamivudine 100–150 mg had a protective pooled OR of 0.16 (95% CI: 0.10–0.26)

Tenofovir disoproxil fumarate (TDF) 300 mg versus no treatment or placebo

- N=19 studies (n=5 RCTs & n=14 non-randomized trials/observational studies)

Efficacy:

HBsAg positivity at 6–12 months

- 5 RCTs: n=1 of 349 (0.3%) (treatment group) vs n=23 of 337(6.8%) (control group) [OR 0.10, 95% CI: 0.03–0.35] – ***moderate certainty evidence***.
- 14 Non RCTs: n=21 of 723 (2.9%) (treatment group) vs n=88 of 499 (17.6%) (control group [OR 0.17, 95% CI: 0.10–0.29] - **low *certainty evidence.***

Safety:

Postpartum haemorrhage (3 RCTS)

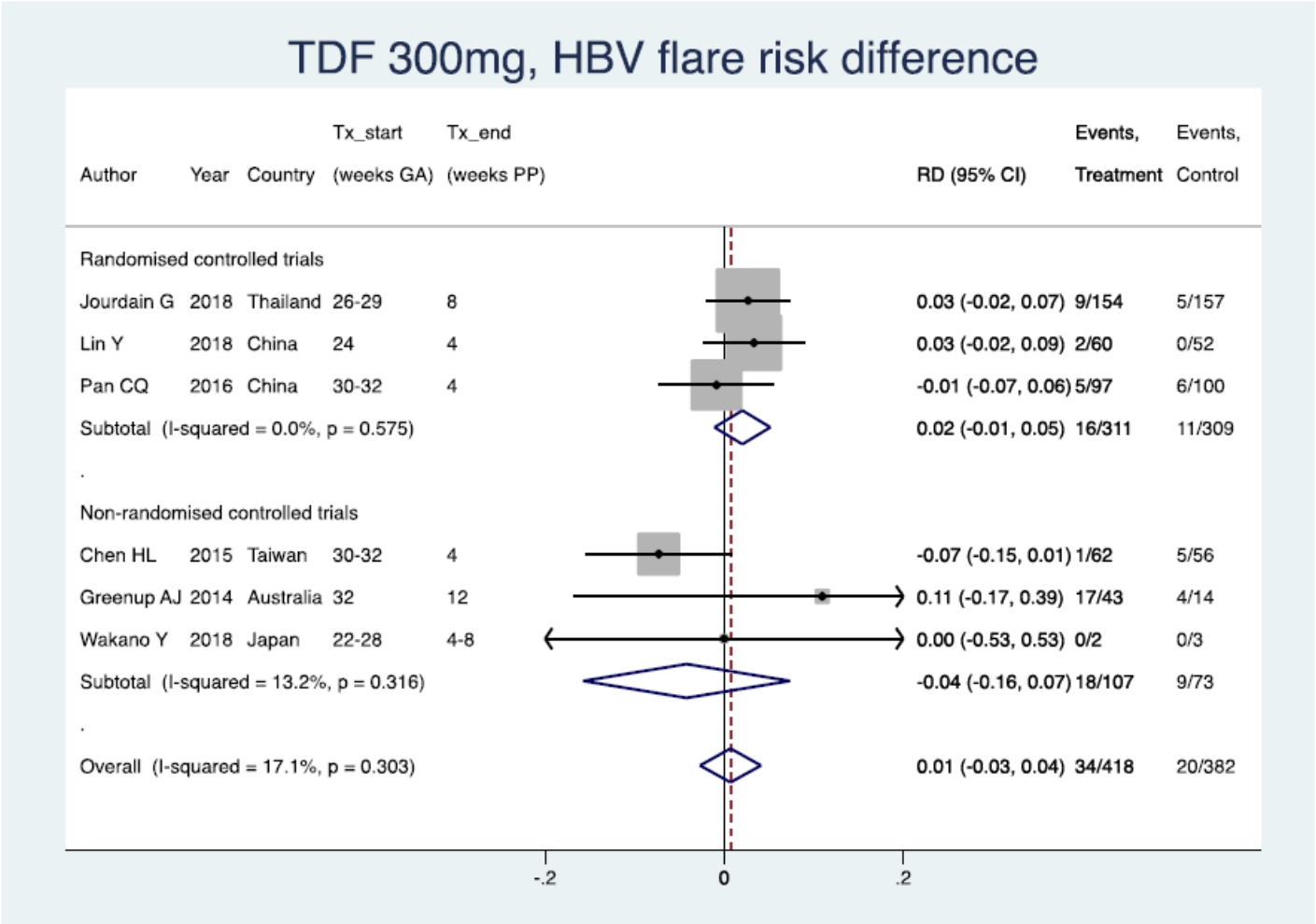
- 3 RCTs: n=4 of 177 (2.3%) (treatment group) vs n=5 of 172 (2.9%) (control group) – ***moderate certainty evidence.***
- 3 Non RCTs: n=5 of 188 (2.7%) (treatment group) vs n=3 of 84(3.6%) (control group) – **low *certainty***

evidence.

HBV Flare after treatment discontinuation (3 RCTs)

Information on HBV Flare after treatment discontinuation was available for six of the 19 included RCT and non RCT studies that administered TDF to mothers. Various definitions were used, including: "postpartum flare", "severe flare", "ALT >5 ULN", "moderate flare" and others. 3 RCTs: n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group) –***moderate certainty evidence.***

- 3 Non RCTs: n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group) – ***very* low *certainty evidence.***



34 of 418 (non-weighted average 8.1%) mothers who were treated with TDF during pregnancy experienced a type of HBV flare at the time of treatment discontinuation, vs 20 of 382 (non-weighted average 5.2%) mothers who were not treated during pregnancy.

The panel was not able to fully examine all important safety outcomes, such as HBV flare, as standardized information was lacking across studies.

- Flares were reported as follows in the six individual RCT and non RCT studies:

- n=1 RCT asymptomatic flares in the alanine aminotransferase level (level of >300 IU per liter) during pregnancy (9 of 154 women (6%; 95% CI, 3 to 11) in the TDF group vs 5 of 157 (3%; 95% CI, 1 to 7) in the placebo group),
- n=1 RCT: digestive tract reaction: vomiting (2 of 60 (3%) TDF group vs 0 of 52 (0%) control group) during pregnancy
- n=1 RCT: severe flare as ALT flare 5.1 to 10 times above the baseline value postpartum (5 of 97 (5%) TDF group vs 6 of 100 (6%) in the control group) & serious alanine aminotransferase flare of an ALT more than 10 times above the upper limit of normal postpartum (1 of 97 (1%) TDF group vs 3 of 100 (3%) in the control group)
- n=1 non RCT: 1 of 62 TDF group (2%) vs 5 of 56 (9%) in the control group
- n=1 non RCT: moderate postpartum flares postpartum (>95 IU/L ALT) (17 of 43 (40%) TDF group vs 4 of 14 (29%) in the control group)
- n=1 RCT: Serum transaminase flares (none reported)

Neonatal deaths (death within 28 days of life) (5 RCTs)

- 5 RCTs: n=2 deaths of 367 (0.5%) infants (treatment group) vs n=1 death of 350 infants (0.3%) (control group) -– ***moderate certainty evidence.***
- 14 Non RCTs: n=0 of 712 (0.0%) (treatment group) vs n=0 of 518 (0.0%) mothers (control group) – ***low certainty evidence.***

Fetal demise (miscarriage [<28 weeks], stillbirth [>=28 weeks]) (5 RCTs)

- 5 RCTs: n=3 cases of 372 (0.8%) (treatment group) vs n=0 of 362 (0.0%) (control group) – ***moderate certainty evidence.***
- 14 Non RCTs: n=0 of 570 (0.0%) (treatment group) vs n=1 of 520 (0.2%) mothers (control group) – ***low certainty evidence.***

Lamivudine (LAM) 100–150 mg versus no treatment or placebo

- n= 40 (n=8 RCTs & n=32 non-randomized trials/observational studies)

Efficacy:

HBsAg positivity at 6–12 months

- 8 RCTs: n=25 of 432 (5.8%) (treatment group) vs n=105of 389 (27.0%) (control group) [OR 0.16, 95% CI: 0.10–0.26] – ***moderate certainty evidence.***
- 32 Non RCTs: n=41 of 1575 (2.6%) (treatment group) vs n=233of 1655 (14.1%) (control group) [OR 0.17, 95%

CI: 0.12–0.24] – ***low certainty evidence.***

Safety

Postpartum haemorrhage

- 1 RCT: n=0 of 53 (2.3%) (treatment group) vs n=0 of 53 (0%) (control group) – ***low certainty evidence.***
- 7 Non RCTs: n=98 of 558 (17.6%) (treatment group) vs n=61 of 699 (8.7%) (control group) – ***low certainty evidence.***

HBV Flare after treatment discontinuation

Various definitions of HBV flare were used in the studies, including: "postpartum flare", "severe flare", "ALT >5 ULN", and others. The WHO panel was not able to fully examine s HBV flare, as standardised information was lacking across studies.

- 1 RCT: n=16 of 83 (19.3%) (treatment group) vs n= 15 of 46 (32.6%) mothers (control group) – ***very low certainty evidence.***
- 5 Non RCTs: n=32 of 287 (12.9%) (treatment group) vs n= 31 of 504 (6.2%) mothers (control group) – **very low *certainty evidence.***

Neonatal deaths (death within 28 days of life)

- 8 RCTs: n=1 deaths of 439 (0.2%) infants (treatment group) vs n=1 death of 407 infants (0.2%) (control group) – moderate ***certainty evidence.***
- 31 Non RCTs: n=0 deaths of 1571 (0.0%) infants (treatment group) vs n=0 death of 1686 infants (0.0%) (control group) – ***moderate certainty evidence.***

Fetal demise (miscarriage [<28 weeks], stillbirth [>=28 weeks])

- 8 RCTSs n=1 cases of 472 (0.2%) (treatment group) vs n=0 of 409 (0.0%) (control group) – ***moderate certainty evidence.***
- 31 Non RCTs n=0 cases of 1531 (0.0%) (treatment group) vs n=9 of 1678 (0.5%) (control group) – low ***moderate certainty evidence.***

Appendix 1 describes the evidence profile (GRADE tables) that informed the WHO Guideline recommendations (for RCTs and non RCTs).

From the studies included in the meta-analysis:

- RCTs: moderate certainty evidence suggests that there will be 80 fewer HBsAg positivity cases at 6–12 months per 1000 in infants whose mothers took TDF prophylaxis versus those who did not; (10–140 fewer). From the non RCTs included in the meta-analysis,
- Non RCTs: Low certainty evidence suggests that there will be 140 fewer HBsAg positivity cases at 6–12 months per 1000 in infants whose mothers took TDF prophylaxis versus those who did not; (80–200 fewer).

8. Discussion

The WHO working group made an overall conditional recommendation to use tenofovir prophylaxis to prevent mother-to-child transmission, acknowledging that most clinical trials that evaluated the efficacy of tenofovir prophylaxis had also included the use of HBIG in both arms. The WHO guideline development group set a viral load threshold of HBV DNA ≥5.3 log10 IU/mL (≥ 200,000 IU/mL) at which pregnant women are eligible to receive TDF prophylaxis. Additionally the panel recommended reassessing patients for long-term maternal TDF treatment after delivery.

WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis In Pregnancy (July 2020)

Prophylaxis	Recommendation	Strength of Recommendation
Tenofovir prophylaxis to prevent mother-to-child transmission of HBV	WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥ 5.3 $\log_{10}$ IU/mL (≥ 200,000 IU/mL)[1] 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 hepatitis B vaccination in all infants, including timely birth dose	Conditional recommendation, moderate quality of evidence.

In March 2024, the WHO released Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection.[9] 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.

Conclusion

"The WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy (July 2020)" were suitable for adolopment.

The following recommendations were accepted from the WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy (July 2020):

- Start maternal tenofovir prophylaxis from 28 weeks of Pregnancy until at least birth.
- Reassess for long-term maternal treatment after delivery and monitor (as per WHO HBV guidelines)

Appendix 1: GRADE SUMMARY OF FINDINGS (Taken from: World Health Organisation. 2020. Hepatitis B vaccination and prevention of mother-to-child transmission)

Table 1. GRADE evidence profile – TDF 300 mg during pregnancy to prevent HBV mother-to-child transmission (MTCT)

(Taken from: World Health Organisation. 2020. Hepatitis B vaccination and prevention of mother-to-child transmission)

Number of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	
HBsAg positivity at 6–12 months												
5	*Randomized controlled trials (RCTs)*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	1/349 (0.3)	23/337 (6.8)	**0.10** (0.03–0.35)	**80 fewer** per 1000 (10–140 fewer)	Moderate[a]
14	*Non-RCTs*	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect	21/723 (2.9)	88/499 (17.6)	**0.17** (0.10–0.29)	**140 fewer** per 1000 (80–200 fewer)	Low[b]
HBV DNA positivity at 6–12 months												
4	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	1/319 (0.3)	20/307 (6.5)	**0.11** (0.03–0.43)	**70 fewer** per 1000 (0–150 fewer)	Moderate[c]
7	*Non-RCTs*	No serious	No serious	No serious	No serious	Not able to examine publication bias	Magnitude of the effect	0/451 (0.0)	38/308 (12.3)	**0.06** (0.02–0.19)	**110 fewer** per 1000 (50–170 fewer)	Moderate[d]
Infant safety: neonatal deaths												
5	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	2/367 (0.5)	1/350 (0.3)	-	**0** (10 fewer – 10 more)	Moderate[e]

14	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/712 (0.0)	0/508 (0.0)	-	**0** (10 fewer – 10 more)	Low[f]

Infant safety: prematurity												
4	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	11/337 (3.3)	16/320 (5.0)	-	**10 fewer** (30 fewer – 20 more)	Moderate[g]
4	*Non-RCTs*	No serious	No serious	No serious	No serious	Not able to examine publication bias	None	8/285 (2.8)	6/159 (3.8)	-	**10 more** (30 fewer to 40 more)	Low[h]
Infant safety: congenital abnormalities												
5	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	2/367 (0.5)	3/350 (0.9)	-	**0** (20 fewer – 10 more)	Moderate[i]
9	*Non-RCTs*	No serious	No serious	No serious	No serious	Not able to examine publication bias	None	2/435 (0.5)	2/337 (0.6)	-	**0** (20 fewer – 20 more)	Low[j]
Infant safety: bone mineral density												
1	*RCTs*	No serious	N/A	No serious	Serious	Not able to examine publication bias	N/A	N/A	N/A	-	**−0.006 g/cm²** (−0.019 to 0.007 g/cm²); p=0.38)	Low[k]
Maternal safety: miscarriage and stillbirth												
5	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	3/372 (0.8)	0/362 (0.0)	-	**10 more** (10 fewer – 20 more)	Moderate[l]
14	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/570 (0.0)	1/520 (0.2)	-	**0** (10 fewer – 10 more)	Low[m]
Maternal safety: postpartum haemmorhage												
3	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	4/177 (2.3)	5/172 (2.9)	-	**0** (30 fewer – 30 more)	Moderate[n]
3	*Non-RCTs*	No serious	No serious	No serious	No serious	Not able to examine	None	5/188 (2.7)	3/84 (3.6)	-	**0** (40 fewer	Low[o]

						publication bias					– 40 more)	
Maternal safety: HBV flare after treatment discontinuation												
3	*RCTs*	No serious	No serious	No serious	Serious	Not able to examine publication bias	N/A	16/311 (5.1)	11/309 (3.6)	-	**20 more** (10 fewer – 50 more)	Moderate[p]
3	*Non-RCTs*	No serious	No serious	No serious	Serious	Not able to examine publication bias	None	18/107 (16.8)	9/73 (12.3)	-	**40 fewer** (160 fewer – 70 more)	Very low[q]

[a]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[b]Downgrading due to possible publication bias/small study effects, upgrading due to magnitude of effect.
[c]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[d]Upgrading due to magnitude of effect
[e]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[f]No upgrading or downgrading
[g]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[h]No upgrading or downgrading
[i]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[j]No upgrading or downgrading
[k]Downgrading due to inability to examine certain elements (e.g. inconsistency), and for imprecision due to the fact that there was only one RCT included.
[l]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[m]No upgrading or downgrading
[n]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[o]No upgrading or downgrading [p]Downgrading due to imprecision
[q]Downgrading due to imprecision

Table 2: GRADE evidence profile: Lamivudine 100–150 mg during pregnancy to prevent HBV mother-to-child transmission (MTCT)

(Taken from: World Health Organisation. 2020. Hepatitis B vaccination and prevention of mother-to-child transmission)

Number of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	
HBsAg positivity at 6–12 months												
8	*Randomized controlled trials (RCTs)*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	25/432 (5.8)	105/389 (27.0)	**0.16** (0.10–0.26)	**190 fewer** per 1000 (90–280 fewer)	Moderate[a]
32	*Non-RCTs*	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect.	41/1575 (2.6)	233/1655 (14.1)	**0.17** (0.12–0.24)	**140 fewer** per 1000 (110–180 fewer)	Low[b]
HBV DNA positivity at 6–12 months												
5	*RCTs*	Serious	Serious I^2=39.8%	No serious	No serious	Not possible to examine publication bias	N/A	21/312 (6.7)	73/269 (27.1)	**0.22** (0.10–0.47)	**160 fewer** per 1000 (320 fewer to 4 more)	Low[c]
18	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	Magnitude of the effect.	22/1014 (2.2)	137/1057 (13.0)	**0.14** (0.09–0.23)	**140 fewer** per 1000 (90–190 fewer)	Moderate[d]
Infant safety: neonatal deaths												
8	*RCTs*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/439 (0.2)	1/407 (0.2)	-	**0** (10 fewer – 10 more)	Moderate[e]
31	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/1571 (0.0)	0/1686 (0.0)	-	**0** (10 fewer – 10 more)	Low[f]

Infant safety: prematurity												
2	*RCTs*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	0/123 (0.0)	0/93 (0.0)	-	**0** (30 fewer – 30 more)	Moderate[g]
8	*Non-RCTs*	Serious	Serious I^2=55.6%	No serious	No serious	Not possible to examine publication bias	None	14/486 (2.9)	11/306 (3.6)	-	**0** (40 fewer – 40 more)	Very low[h]
Infant safety: congenital abnormalities												
3	*RCTs*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/219 (0.5)	0/222 (0.0)	-	**0** (10 fewer – 20 more)	Moderate[i]
13	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	7/626 (1.1)	5/953 (0.5)	-	**0** (10 fewer – 20 more)	Low[j]
Maternal safety: miscarriage and stillbirth												
8	*RCTs*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/472 (0.2)	0/409 (0.0)	-	**0 more** (10 fewer – 10 more)	Moderate[k]
31	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/1531 (0.0)	9/1678 (0.5)	-	**0** (10 fewer – 10 more)	Low[l]
Maternal safety: postpartum haemmorhage												
1	*RCTs*	Serious	Not applicable	No serious	No serious	Not possible to examine publication bias	N/A	0/53 (0.0)	0/53 (0.0)	-	**0** (40 fewer – 40 more)	Low[m]
7	*Non-RCTs*	No serious	No serious	No serious	No serious	Not possible to examine publication bias	None	98/558 (17.6)	61/699 (8.7)	-	**10 more** (10 less – 40 more)	Low[n]
Maternal safety: HBV flare after treatment discontinuation												

1	*RCTs*	Serious	Not applicable	No serious	Very serious	Not possible to examine publication bias	N/A	16/83 (19.3)	15/46 (32.6)	-	**130 less** (290 fewer – 30 more)	Very low[o]
5	*Non-RCTs*	Serious	Very serious I^2=87.8%	No serious	Very serious	Not possible to examine publication bias	None	37/287 (12.9)	31/504 (6.2)	-	**40 fewer** (200 fewer – 110 more)	Very low[p]

[a]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[b]Downgrading due to evidence of possible publication bias, however, upgrading due to magnitude of effect.
[c]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inconsistency >30%.
[d]Upgrading due to magnitude of effect
[e]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[f]No upgrading or downgrading
[g]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[h]Downgrading due to "serious" study design limitations (the majority of non-RCTs had a score of 6 on the Newcastle–Ottawa scale), downgrading due to inconsistency >30%.
[i]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[j]No upgrading or downgrading
[k]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[l]No upgrading or downgrading
[m]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inability to examine certain elements (e.g. inconsistency) due to the fact that there was only one RCT included
[n]No upgrading or downgrading
[o]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inability to examine certain elements (e.g. inconsistency) due to the fact that there was only one RCT included, downgrading due to serious imprecision.
[p]Downgrading due to "serious" study design limitations (the majority of non-RCTs had a score of 6 on the Newcastle–Ottawa scale), downgrading due to severe inconsistency >30%, downgrading due to imprecision.

Appendix 2: AGREE II Assessment

AGREE II assessment scores																							
WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis In Pregnancy (July 2020)																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	6	6	7	7	7	6	7	7	7	7	7	1	7	7	7	7	7	7	7	4	7	147
Appraiser 2	7	7	7	7	7	4	7	7	7	7	7	6	6	3	7	7	7	6	7	7	6	7	7	150
Item Total	13	13	13	13	14	11	14	13	14	14	14	13	13	4	14	14	14	13	14	14	13	11	14	297
Domain Total	39			38			99								42			54				25		297
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	92%			89%			**86%**								100%			96%				88%		**92%**

Overall assessment: The Guideline is recommened for use in this context

Score: (e.g. domain 1)

$$\frac{\text{Maximum possible score = 7 (highest score) x no. of items x no. of appraisers}}{\text{Minimum possible score = 1 (lowest score) x no. of items x no. of appraisers}}$$

Score for each domain

$$\frac{\text{Obtained score - minimum possible score}}{\text{Maximum possible score - minimum possible score}} \times 100$$

Acknowledgement: Display of the AGREE II assessment taken from developers of the National Department of Health Technology Assessment Methods Guide. 2022-2027.

Appendix 3: Adaptation of the World Health Organisation. 2020. PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS: GUIDELINES ON ANTIVIRAL PROPHYLAXIS IN PREGNANCY

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	• 257 million people were living with chronic hepatitis B virus (HBV) infection worldwide (2015 statistics quoted) • 900 000 had died from HBV infection, mostly as a result of cirrhosis or hepatocellular carcinoma. • Most HBV-associated deaths among adults are secondary to infections acquired at birth or in the first five years of life. • World Health Assembly endorsed the Global Health Sector Strategy on viral hepatitis, which calls for the elimination of viral hepatitis as a public health threat by 2030 (defined as a 90% reduction in incidence of new infections and a 65% reduction in mortality). • Elimination of HBV infection as a public health threat requires a reduction in the prevalence of hepatitis B surface antigen (HBsAg) to below 0.1% in children 5 years of age. • This can be achieved through universal immunization of newborns against hepatitis B and other interventions to prevent mother-to-child transmission of HBV e.g. antiviral prophylaxis.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	In SA, over 1.9 million people are chronically infected with HBV; a significant burden on public health in SA despite the introduction of an infant immunization program implemented in 1995 and the availability of effective treatment for chronic HBV infection. Taken from: Maepa MB, Ely A, Kramvis A, Bloom K, Naidoo K, Simani OE, Maponga TG, Arbuthnot P. Hepatitis B Virus Research in South Africa. Viruses. 2022 Aug 31;14(9):1939. doi: 10.3390/v14091939. PMID: 36146747; PMCID: PMC9503375. The SA Expanded Programme on Immunisation schedule advises HepB vaccination at 6 weeks after birth. The WHO recommends that all babies should receive the hepatitis B vaccine as soon as possible after birth (within 24 hours).	
Desirable effects: How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
WHO Guideline panel		
○ Trivial ○ Small ○ Moderate ○ Large	• Meta-analysis of RCTs investigating TDF 300 mg had a protective, pooled OR of 0.10 (95% CI: 0.03–0.35), and • Meta-analysis of RCTs investigating Lamivudine 100–150 mg had a protective pooled OR of 0.16 (95% CI: 0.10–0.26) **<u>Tenofovir disoproxil fumarate (TDF) 300 mg versus no treatment or placebo</u>**	

○ Varies ○ Don't know	• N=19 studies (n=5 RCTs & n=14 non-randomized trials/observational studies) **Efficacy:** *HBsAg positivity at 6–12 months* • 5 RCTs: n=1 of 349 (0.3%) (treatment group) vs n=23 of 337(6.8%) (control group) [OR 0.10, 95% CI: 0.03–0.35] – ***moderate certainty evidence***. • 14 Non RCTs: n=21 of 723 (2.9%) (treatment group) vs n=88 of 499 (17.6%) (control group [OR 0.17, 95% CI: 0.10–0.29] - **low *certainty evidence.*** **Lamivudine (3TC) 100–150 mg versus no treatment or placebo** • n= 40 (n=8 RCTs & n=32 non-randomized trials/observational studies) **Efficacy:** *HBsAg positivity at 6–12 months (8 RCTS)* • 8 RCTs: n=25 of 432 (5.8%) (treatment group) vs n=105of 389 (27.0%) (control group) [OR 0.16, 95% CI: 0.10–0.26] – ***moderate certainty evidence.*** • 32 Non RCTs: n=41 of 1575 (2.6%) (treatment group) vs n=233of 1655 (14.1%) (control group) [OR 0.17, 95% CI: 0.12–0.24] – ***low certainty evidence.***	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		
Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Panel was confident that the desirable effects of the intervention outweighed the undesirable effects and most or all patients would benefit from antiviral prophylaxis. **Tenofovir disoproxil fumarate (TDF) 300 mg versus no treatment or placebo** • N=19 studies (n=5 RCTs & n=14 non-randomized trials/observational studies) **Safety** *Postpartum haemorrhage (3 RCTS)*	

- 3 RCTs: n=4 of 177 (2.3%) (treatment group) vs n=5 of 172 (2.9%) (control group) – ***moderate certainty evidence.***
- 3 Non RCTs: n=5 of 188 (2.7%) (treatment group) vs n=3 of 84(3.6%) (control group) – **low *certainty evidence.***

HBV Flare after treatment discontinuation (3 RCTs)

- 3 RCTs: n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group) –***moderate certainty evidence.***
- 3 Non RCTs: n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group) – ***very* low *certainty evidence.***

Neonatal deaths (death within 28 days of life) (5 RCTs)

- 5 RCTs: n=2 deaths of 367 (0.5%) infants (treatment group) vs n=1 death of 350 infants (0.3%) (control group) -– ***moderate certainty evidence.***
- 14 Non RCTs: n=0 of 712 (0.0%) (treatment group) vs n=0 of 518 (0.0%) mothers (control group) – ***low certainty evidence.***

Fetal demise (miscarriage [<28 weeks], stillbirth [>=28 weeks]) (5 RCTs)

- 5 RCTs: n=3 cases of 372 (0.8%) (treatment group) vs n=0 of 362 (0.0%) (control group) – ***moderate certainty evidence.***
- 14 Non RCTs: n=0 of 570 (0.0%) (treatment group) vs n=1 of 520 (0.2%) mothers (control group) – ***low certainty evidence.***

Lamivudine (3TC) 100–150 mg versus no treatment or placebo

- n= 40 (n=8 RCTs & n=32 non-randomized trials/observational studies)

Safety

Postpartum haemorrhage

- 1 RCT: n=0 of 53 (2.3%) (treatment group) vs n=0 of 53 (0%) (control group) – ***low certainty evidence.***
- 7 Non RCTs: n=98 of 558 (17.6%) (treatment group) vs n=61 of 699 (8.7%) (control group) – ***low certainty evidence.***

HBV Flare after treatment discontinuation

- 1 RCT: n=16 of 83 (19.3%) (treatment group) vs n= 15 of 46 (32.6%) mothers (control group) – ***very low certainty evidence.***
- 5 Non RCTs: n=32 of 287 (12.9%) (treatment group) vs n= 31 of 504 (6.2%) mothers (control group) – **very low *certainty evidence.***

Neonatal deaths (death within 28 days of life)

- 8 RCTs: n=1 deaths of 439 (0.2%) infants (treatment group) vs n=1 death of 407 infants (0.2%) (control group) – moderate

	certainty evidence. • 31 Non RCTs: n=0 deaths of 1571 (0.0%) infants (treatment group) vs n=0 death of 1686 infants (0.0%) (control group) – ***moderate certainty evidence.*** <u>*Fetal demise (miscarriage [<28 weeks], stillbirth [>=28 weeks])*</u> • 8 RCTSs n=1 cases of 472 (0.2%) (treatment group) vs n=0 of 409 (0.0%) (control group) – ***moderate certainty evidence.*** • 31 Non RCTs n=0 cases of 1531 (0.0%) (treatment group) vs n=9 of 1678 (0.5%) (control group) – low ***moderate certainty evidence.***	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
o Large o Moderate o Small o Trivial o Varies o Don't know	○ 3 RCTs that reported on HBV flare after TDF treatment discontinuation showed a higher proportion with hepatitis flare-ups in the TDF treatment groups vs no treatment/placebo [(n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group)] - ***moderate certainty evidence.*** ○ Similar results were noted for flare after TDF treatment discontinuation in 3 Non RCTs [(n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group)] ***very low certainty evidence.***	
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
o Very low o Low o Moderate o High o No included studies	•Moderate certainty evidence	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
o Very low o Low o Moderate o High o No included studies		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Guideline indicated that n=3 published studies and n=2 unpublished studies were identified that assessed the preferences of pregnant women related to interventions to prevent mother-to-child transmission. These studies indicated that most women were willing to have their infant given a timely birth dose, varying from 66% (251/380) of women in Vietnam, to 93% (195/209) in Ghana. • In Ghana, 93% of the surveyed women were willing to take antiviral prophylaxis. In a study in Burkina Faso, 100% of eligible women agreed to take antiviral prophylaxis (A. Guingane, unpublished data). • In China (the SHIELD project), 97% of women eligible for prophylaxis were willing to receive it (Dr Hou, unpublished data). However, one study conducted in Guangdong China found that only 17% (125/737) of women surveyed were willing to take antiviral prophylaxis).	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Maternal tenofovir prophylaxis may prevent HBV infection in infants born to HBV infected women. This may protect these children from the risk of developing serious disease complications later in life. On a population level, prevention of transmission of HBV may reduce the reservoir for further transmission. The main potential harm is the risk of liver flare after discontinuation of prophylaxis. Although the risk of flare is low, reactivation has been reported in patients treated for hepatitis B after antiviral prophylaxis had been withdrawn. There is also the risk that a recommendation could lead to the false perception that tenofovir prophylaxis in HBV-infected pregnant women could replace the use of timely birth dose vaccination. ○ 3 RCTs that reported on HBV flare after TDF treatment discontinuation showed a higher proportion with hepatitis flare-ups in the TDF treatment groups vs no treatment/placebo [(n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group)] - ***moderate certainty evidence.***	

	○ Similar results were noted for flare after TDF treatment discontinuation in 3 Non RCTs [(n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group)] ***very low certainty evidence.***	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention (compared to placebo) ○ Favors the intervention ○ Varies ○ Don't know		
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The global cost of adding antenatal testing of pregnant women for HBsAg and providing tenofovir prophylaxis for those at increased risk of mother-to-child transmission (over scaled up timely birth dose) would be an extra US$ 2.2–2.7 billion over 10 years. The ICERs of this testing and prophylaxis strategy guided by HBV DNA, in addition to timely birth dose, varies between US$ 890 and US$ 7355 per DALY averted, depending on the world region. The regions with the lowest ICERs for antiviral scale up are East Asia, West Africa, Central Europe, Central Africa and East Africa with ICERs of US$ 890, US$ 1066, US$ 1069, US$ 1106 and US$ 1250 per DALY averted, respectively.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	TDF – 300MG – 28 Tablets – R 41.01 (March 2024 MHPL) i.e. R1.46 per tablet	Prevalence of condition: 0.67% prevalence of HBsAg in HIV negative pregnant women [Joseph Davey, D., Hsiao, Ny., Wendy Spearman, C. et al. Low prevalence of hepatitis B virus infection in HIV-uninfected pregnant women in Cape Town, South Africa: implications for oral pre-exposure prophylaxis roll out. BMC Infect Dis 22, 719 (2022). https://doi.org/10.1186/s12879-022-07697-5]
Certainty of evidence of required resources: What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

• **WHO Guideline panel**		
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	Compared to the status quo, scaling up timely birth dose was reported as the most cost-effective option that delivers the most health benefit for the lowest cost. However, in countries that have already scaled up the timely birth dose, adding antenatal testing of pregnant women and tenofovir prophylaxis is an additional opportunity to prevent perinatal infections and may be cost effective in some regions, depending on diagnostic costs and how such a strategy is implemented.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	It is noted that in South Africa, universal Hepatitis B antenatal testing is planned and underway. SA NDOH advises routine testing during antenatal care, but provinces have not started to implement this yet due to logistical and budgetary challenges.	
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Testing of pregnant women and tenofovir prophylaxis is an additional opportunity to prevent perinatal infections and may be cost effective in some regions, depending on diagnostic costs and how such a strategy is implemented.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		

Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Increased equity for disadvantaged groups Emphasizing the need to increase access to cheaper HBV DNA tests and endorsement of HBeAg as an alternative marker for HBV DNA quantification could result in increased availability of affordable testing and subsequent access to tenofovir prophylaxis. This would reduce inequities in access for pregnant women in settings with poor access to testing and prophylaxis	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Global Hepatitis Programme conducted an online stakeholder consultation to gather the perspectives of programme managers, health-care workers and civil society organizations on introducing antiviral prophylaxis to prevent mother-to-child transmission of HBV. • Tenofovir prophylaxis is acceptable and feasible to implement according to the majority of respondents who answered the questionnaires. • Tenofovir prophylaxis is an opportunity to prevent HBV infection and integrate with and strengthen HIV and syphilis PMTCT services. • Reported concerns are availability and costs of diagnostics. Therefore, costs, cost–effectiveness and availability of tests will need to be taken into account. • Other perceived concerns are the safety of the mother and infant. Safety monitoring will need to be provided to address these concerns. • Confidentiality, stigma and discrimination remain a source of concern when pregnant women are routinely tested. Safeguards will need to be provided to address these issues.	.

• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no ○ Possibly/Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Global Hepatitis Programme conducted an online stakeholder consultation to gather the perspectives of programme managers, health-care workers and civil society organizations on introducing antiviral prophylaxis to prevent mother-to-child transmission of HBV. • Respondents were consulted to determine their views on the acceptability and feasibility of a policy to use tenofovir prophylaxis in eligible pregnant women to prevent mother-to-child transmission of HBV infection. Around 30% of respondents in the African Region. • 77% of respondents felt that it is feasible to implement tenofovir prophylaxis in eligible pregnant women. Perceived challenges to implementation were cost and availability of HBV DNA tests and tenofovir, education of health-care workers and women living with HBV infection, and the lack of infrastructure to test and treat pregnant women.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	11 April 2024	SG, MR, MM	The committee suggests 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. (moderate CoE, Strong recommendation).

1 NDOH. Guideline for the Prevention of Vertical Transmission of Communicable Infections August 2023.

2 NDOH. National Maternity Care Guidelines. Updated 2024.

3 World Health Organisation. 2020. Hepatitis B vaccination and prevention of mother-to-child transmission. Available at: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hepatitis/prevention/mother-to-child-transmission-of-hepatitis-b. Accessed 27 March 2024.

4 Centers for Disease Control. Hepatitis B Virus (HBV) infection. Available at: https://www.cdc.gov/nchhstp/pregnancy/overview.html

5 WHO. Global hepatitis report.2024.Available at: https://www.who.int/publications/i/item/9789240091672. Accessed 25 April 2024.

6 Martins RS, Hussain H, Chaudry M, Rizvi NA, Mustafa MA, Ayub B, Aamdani SS, Rehman AA, Pervez A, Nadeem S, Khalid R, Ali AS, Shahid S, Zubairi ABS, Haider AH, Irfan M. GRADE-ADOLOPMENT of clinical practice guidelines and creation of clinical pathways for the primary care management of chronic respiratory conditions in Pakistan. BMC Pulm Med. 2023 Apr 17;23(1):123. doi: 10.1186/s12890-023-02409-4. PMID: 37069600; PMCID: PMC10111762.

7 Appraisal Of Guidelines For Research & Evaluation II. Available at: https://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf. Accessed 19 April 2024.

8 Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.

9 World Health Organisation. 2024. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Available at: https://www.who.int/publications/i/item/9789240090903. Accessed 25 April 2024