© 2026 Journal of Pharmacy & Pharmacognosy Research, 14 (2), 2397, 2026
ISSN 0719-4250
https://jppres.com

DOI: https://doi.org/10.56499/jppres_14.2.2397

Review

Efficacy and safety of tenofovir in preventing hepatitis B mother-to-child transmission: A systematic review and meta-analysis of randomized controlled trials

[Eficacia y seguridad del tenofovir en la prevención de la transmisión de la hepatitis B de madre a hijo: una revisión sistemática y un metanálisis de ensayos controlados aleatorizados]

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Abstract

Context: Hepatitis B virus (HBV) remains a major global health concern, with mother-to-child transmission (MTCT) responsible for one-third of chronic infections. Despite neonatal vaccination and hepatitis B immunoglobulin (HBIG), up to 10% of infants born to HBV-positive mothers remain infected. Tenofovir has emerged as a potential prophylactic therapy.

Aims: To evaluate the efficacy and safety of tenofovir in preventing vertical transmission of hepatitis B during pregnancy.

Methods: This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A comprehensive literature search was conducted using the PubMed and ScienceDirect databases through January 15, 2024, for randomized controlled trials (RCTs) comparing tenofovir with placebo in pregnant women. Eligible studies were systematically analyzed in RStudio 3.5.3 using the metaphor package, and odds and risk ratios were calculated for the outcomes.

Results: A meta-analysis was performed on 4 studies (n = 677). The HBeAg and HBsAg demonstrate a statistically significant reduction in the tenofovir group compared to the control group, with HBeAg (RR = 0.87; 95% CI = 0.8–0.92) showed 13% reduced risk, while HBsAg (RR = 0.7; 95% CI = 0.45–1.08) also showed a reduced risk of 30%. Given its proven efficacy and favorable safety profile, tenofovir should be considered a standard antiviral prophylaxis alongside existing neonatal HBV vaccination and immunoglobulin strategies.

Conclusions: Tenofovir significantly reduces HBV MTCT and is generally well tolerated. But further multicenter trials with larger populations are needed to confirm safety and generalizability.

Keywords: hepatitis B virus; mother-to-child transmission; pregnancy; tenofovir disoproxil fumarate.

Resumen

Contexto: El virus de la hepatitis B (VHB) sigue siendo un importante problema de salud mundial, y la transmisión de madre a hijo (TMH) es responsable de un tercio de las infecciones crónicas. A pesar de la vacunación neonatal y de la inmunoglobulina contra la hepatitis B (HBIG), hasta un 10% de los lactantes nacidos de madres positivas para VHB permanecen infectados. Tenofovir ha surgido como una terapia profiláctica potencial.

Objetivos: Evaluar la eficacia y la seguridad de tenofovir en la prevención de la transmisión vertical de la hepatitis B durante el embarazo.

Métodos: Este estudio se realizó de acuerdo con las directrices de los Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Se llevó a cabo una búsqueda bibliográfica exhaustiva en las bases de datos PubMed y ScienceDirect hasta el 15 de enero de 2024 para identificar ensayos clínicos aleatorizados (ECA) que compararan tenofovir con placebo en mujeres embarazadas. Los estudios elegibles se analizaron sistemáticamente utilizando Rstudio 3.5.3 con el paquete metafor, calculándose los odds ratios y el riesgo relativo para los desenlaces.

Resultados: El metanálisis se realizó sobre 4 estudios (n = 677). El HBeAg y el HBsAg mostraron una reducción estadísticamente significativa en el grupo de tenofovir en comparación con el grupo control, con HBeAg (RR = 0,87; IC 95% = 0,8–0,92) mostrando un riesgo reducido del 13%, mientras que HBsAg (RR = 0,7; IC 95% = 0,45–1,08) mostró también una reducción del riesgo del 30%. Dada su eficacia comprobada y su perfil de seguridad favorable, tenofovir debe considerarse una profilaxis antiviral estándar junto con las estrategias existentes de vacunación neonatal contra el VHB e inmunoglobulina.

Conclusiones: Tenofovir reduce significativamente la TMH del VHB y, en general, es bien tolerado. Sin embargo, se necesitan ensayos multicéntricos adicionales con poblaciones más amplias para confirmar la seguridad y la generalización de los resultados.

Palabras Clave: embarazo; tenofovir disoproxilo fumarato; transmisión madre-hijo; virus de la hepatitis B.

ARTICLE INFO
Received: February 27, 2025.
Accepted: November 25, 2025.
Available Online: February 20, 2026.

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INTRODUCTION

Hepatitis B virus (HBV) infection remains a major global health challenge, with more than 360 million individuals chronically infected worldwide (Tripathi & Mousa, 2023). Mother-to-child transmission (MTCT) is a key route of infection, responsible for over one-third of chronic HBV cases (Matthews et al., 2023). Without intervention, up to 90% of infants infected at birth progress to chronic disease, carrying long-term risks of cirrhosis, hepatocellular carcinoma, and premature mortality (Duberg et al., 2022; WHO, 2020b).

Although neonatal HBV vaccination combined with hepatitis B immunoglobulin (HBIG) significantly reduces MTCT, breakthrough transmission persists in high-risk pregnancies, particularly among mothers with high viral loads, with up to 10% of infants remaining infected despite prophylaxis (Zhang et al., 2021). This highlights the need for maternal antiviral therapy to further suppress maternal HBV DNA levels during pregnancy (Ignat et al., 2024).

Earlier agents such as lamivudine and telbivudine demonstrated efficacy but were limited by lower potency and higher resistance rates (Picardi et al., 2018; Wang et al., 2022). Tenofovir disoproxil fumarate (TDF), a potent nucleotide analogue with strong antiviral activity and minimal resistance, has emerged as the preferred candidate for MTCT prevention (Jagarlamudi et al., 2024; Wassner et al., 2020). Randomized controlled trials (RCTs) suggest that TDF significantly reduces maternal HBV DNA and improves neonatal outcomes, including reductions in hepatitis B surface antigen (HBsAg) positivity, hepatitis B e antigen (HBeAg) transmission, and detectable HBV DNA (Han et al., 2024; Lin et al., 2018; Pan et al., 2016; 2024).

However, variations in trial design, inconsistent safety reporting, and limited geographic diversity in studies create uncertainty about the universal applicability of TDF. A systematic review and meta-analysis of RCTs is therefore warranted to clarify its efficacy and safety. This study evaluates four key outcomes: infant HBsAg, infant HBeAg, detectable HBV DNA, and maternal and neonatal adverse events, to determine whether tenofovir should be recommended as standard prophylaxis in HBV-infected pregnant women.

MATERIAL AND METHODS

Review methodology

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (bibliography). To enhance accuracy and minimize bias, the review process involved independent assessment by more than two reviewers, who evaluated the included studies and resolved any discrepancies through discussion and consensus.

Eligibility criteria

During the screening process, studies were selected based on predefined inclusion criteria to ensure methodological rigor and clinical relevance. Only randomized controlled trials (RCTs) were included to provide the highest level of evidence and minimize the risk of bias. Additionally, studies had to be written in English or Indonesian to ensure accessibility and accurate data interpretation.

To refine the selection and maintain the integrity of the meta-analysis, several exclusion criteria were applied. Qualitative studies were excluded as they do not provide numerical data suitable for statistical analysis. Studies lacking essential data for analysis, such as those that did not report neonatal HBsAg positivity, HBeAg positivity, or detectable HBV DNA, were also excluded. Retrospective cohort or observational studies were not considered due to their higher susceptibility to confounding factors and lack of randomization. Furthermore, studies with incomplete intervention details, such as unspecified tenofovir dosage or unclear therapy duration, were excluded to maintain consistency in treatment protocols across the included trials. Lastly, duplicate studies or secondary analyses of previously included trials were removed to prevent over-representation of the same dataset.

During the study selection process, three authors (KRS, RCS, and SDS) independently reviewed the included studies based on the established inclusion and exclusion criteria. Any discrepancies were resolved through consensus discussion. The study selection process is shown in Fig. 1 of the PRISMA flow diagram.

Information sources

A comprehensive literature search was conducted across the PubMed and ScienceDirect databases, covering all relevant studies published through January 15, 2024. To ensure a focused and unbiased selection of studies, references cited in the included study reports were not included in this systematic review. Additionally, references from other systematic reviews on the same or closely related topics were excluded to prevent redundancy and maintain the integrity of the analysis.

Search strategy

The database search used the following keywords: "Tenofovir"[MeSH Terms], "Hepatitis B"[MeSH

Terms], and "Pregnancy"[MeSH Terms]. In ScienceDirect, the search was performed using the keywords ("Tenofovir") AND ("Hepatitis B") AND ("Pregnancy"). These keywords were selected to capture studies relevant to the role of tenofovir in preventing mother-to-child transmission of hepatitis B during pregnancy.

Data collection process

To ensure accuracy and minimize bias, more than two reviewers independently screened each record and assessed every retrieved report. At each stage of the screening process, multiple reviewers worked independently to evaluate studies against predefined criteria. Any discrepancies or disagreements were resolved through thorough discussion and consensus, ensuring a rigorous and objective selection process.

Data items (outcomes)

The primary outcomes for this review were: (1) the presence of HBsAg, (2) the presence of HBeAg, and (3) detectable HBV DNA in infants. These outcomes were selected for their clinical relevance in assessing the efficacy of tenofovir in preventing HBV mother-to-child transmission. Additionally, the secondary outcomes included (1) Adverse effects classified as grade I-II in mothers, (2) Adverse effects classified as grade III-IV in mothers, (3) Adverse effects classified as grade I-II in infants, (4) Adverse effects classified as grade III-IV in infants, and (5) Congenital abnormalities. A meta-analysis was conducted to compare the efficacy of tenofovir against the control group, and the findings were summarized in forest plots to visualize effect size and heterogeneity across studies. The outcome domains were defined based on virological and safety parameters, with data sought within the time frame relevant to perinatal HBV transmission and postnatal monitoring.

Study of risk of bias assessment

The risk of bias assessment was conducted using the Cochrane Risk of Bias 2.0 (RoB 2.0) tool, which is specifically designed for evaluating randomized controlled trials. This tool assesses five key domains: bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. The risk of bias for each domain was classified as low, some concerns, or high, with an overall risk of bias judgment assigned accordingly. Any disagreements between reviewers were resolved through discussion and consensus.

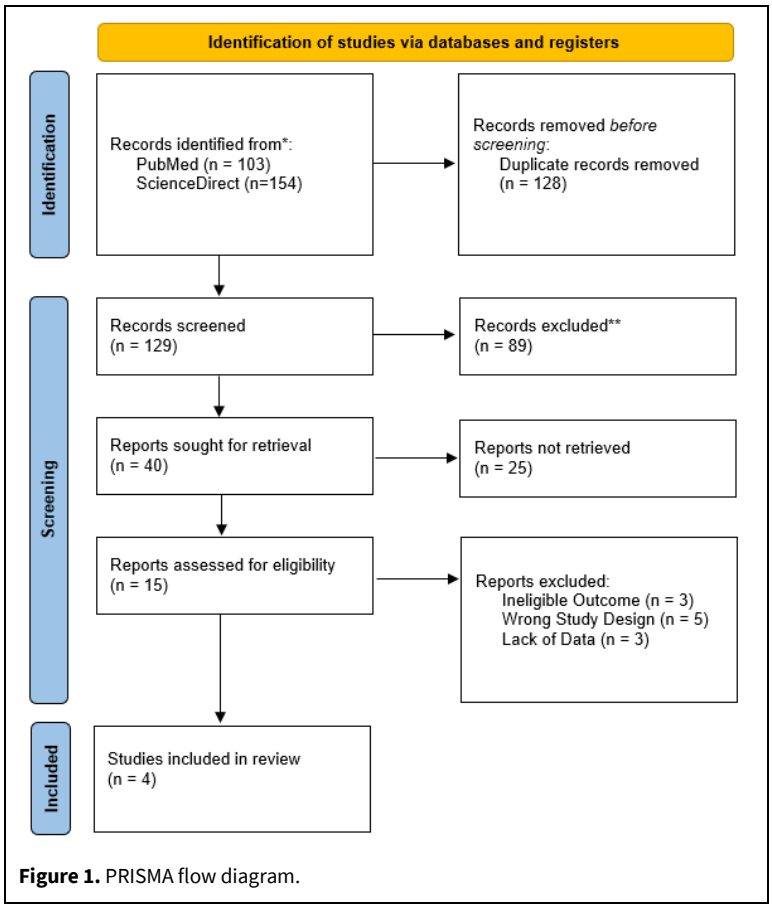

Figure 1. PRISMA flow diagram.

Effect measures

In this systematic review and meta-analysis, different effect measures were used based on the type of outcome being analyzed. The primary outcome was assessed using the risk ratio (RR), which provides a direct measure of the relative probability of an event occurring in the intervention group compared to the control group. Risk ratios are particularly useful when event rates are meaningful and comparable across studies, making them a preferred measure for primary outcomes that assess the impact of an intervention on the likelihood of an event. For the secondary outcome, the odds ratio (OR) was used as the effect measure. Odds ratios are beneficial when analyzing outcomes with low event rates, as they remain stable across different baseline risks and are commonly used in logistic regression models. Although ORs can sometimes overestimate effect sizes relative to RRs, they are particularly useful in retrospective studies or when dealing with rare events.

To interpret the magnitude of the effects, thresholds were defined to categorize the results. A risk ratio close to 1 indicated no difference between groups, while an RR greater than 1 suggested an increased risk, and an RR less than 1 suggested a protective effect. For odds ratios, similar interpretations were applied: values around 1 indicate no association, values above 1 indicate higher odds of the event, and values below 1 indicate reduced odds. If synthesized results were re-expressed into different effect measures, such as converting odds ratios into risk ratios or computing absolute risk reduction based on an assumed comparator risk, appropriate statistical transformations were applied to ensure consistency and comparability.

Synthesis methods

Eligibility for synthesis

All included studies were systematically tabulated based on their key characteristics, including study design, population, intervention details, comparator groups, and measured outcomes. This tabulation allowed for a clear comparison of study interventions against the predefined inclusion criteria and planned synthesis groups. Next, studies were assessed for their suitability for quantitative synthesis (meta-analysis) based on the availability of relevant data and the comparability of study designs. Only studies with sufficiently homogeneous interventions, control groups, and outcome measures were included in the meta-analysis. Heterogeneous studies that differed significantly in methodology or reporting were either synthesized narratively or excluded from pooled analysis. For each outcome, subgroup analyses were considered based on factors such as maternal HBV viral load, timing of tenofovir administration, and follow-up duration. Studies that lacked sufficient data for effect-size estimation or reported outcomes in an incompatible format were excluded from the meta-analysis but were included in the qualitative synthesis.

Statistical synthesis methods

The statistical synthesis for this meta-analysis was conducted using RStudio 3.5.3 with the metaphor package. A random-effect model was employed for the meta-analysis due to the various study durations, treatment start, and endpoints. To assess statistical heterogeneity (I^2), several methods were employed. First, a visual inspection of forest plots was used to assess overlap in confidence intervals across studies, providing a preliminary indication of potential heterogeneity. The I^2 statistic was used to quantify the proportion of total variation attributable to heterogeneity rather than chance. Specific thresholds for I^2 were considered, with values of 25%, 50%, and 75% representing low, moderate, and high levels of heterogeneity, respectively. Prediction intervals were also calculated to estimate the range of true effects in future studies, providing further insight into the potential variability of the treatment effects. Then, a subgroup analysis was conducted to analyze the effects of drug administration when the gestational age is above the third trimester and below it. Furthermore, in outcomes with I^2 scores > 50%, a leave-one-out sensitivity analysis was conducted; however, in outcomes with only one study per subgroup, the sensitivity analysis was not performed.

Reporting bias assessment

Due to the limited number of studies identified in the comprehensive literature search, a formal assessment of reporting bias was not possible. The small pool of available studies prevented the use of common techniques, such as funnel plots or statistical tests for asymmetry, which are typically employed to detect potential publication or reporting biases. As a result, the conclusions drawn from this review should be interpreted with caution, considering the limitations in the available evidence.

RESULTS

Study selection

Flow of the studies

Comprehensive literature searches using the search strategy described above identified 257 articles from the PubMed and ScienceDirect databases. An automation screening tool was used to eliminate 128

duplicates. After the next assessment, 40 records remained to be screened for title and abstract, of which 25 were excluded for irrelevant titles and abstracts. Full text was retrieved for 15 reports, of which 11 were excluded due to 3 reports with ineligible outcomes, 5 with incorrect study design, and 3 with insufficient data for the meta-analysis. Finally, the search yielded 4 randomized controlled trials, all included in the systematic review and meta-analysis.

Study characteristics

The extracted data and baseline characteristics of the included studies are summarized in Table 1. This systematic review encompasses a total of 677 participants, all of whom were pregnant women diagnosed with hepatitis B. The studies were conducted in China, with participants aged 23 to 31 years. Each study stratified participants into a control group receiving a placebo and a treatment group receiving a fixed oral dose of 300 mg/day of tenofovir disoproxil fumarate (TDF). Variations in treatment duration were observed across studies, ranging from 16 weeks of gestation to 4 weeks postpartum.

Risk of bias in studies

Of the 4 included studies, most had a low risk of bias, with only Pan et al. (2024) and Han et al. (2024) having a high risk of bias in the performance bias and selection bias domains, respectively. The summarized RoB is shown in the traffic light plot in Fig. 2 and in the summary plot in Fig. 3. These visual tools emphasize the importance of critical appraisal in systematic reviews, ensuring that conclusions are drawn with a clear understanding of the limitations of the underlying evidence.

Table 1. Characteristics of selected studies.

Studies, year	Location	Participants		Mean age (years)		Study duration	Outcomes		Adverse events
		C	T	C	T		Maternal	Infants	
Han et al., 2024	China	52	70	27.63 ± 3.21	26.68 ± 2.66	28 weeks of gestation for +/- 5 days	HBV DNA	Positive for HBeAg, positive HBsAg, detectable HBV DNA	Eclampsia, premature rupture of membranes, and premature delivery
Lin et al., 2018	China	60	60	28.06 ± 3.42	28.31 ± 3.56	24 weeks of gestation until 4-weeks postpartum	Adverse events, HBV DNA, ALT	Alanine aminotransferase, positive for HBeAg, positive HBsAg, detectable HBV DNA	Intrahepatic cholestasis of pregnancy, premature delivery, vomiting, itchy skin
Pan et al., 2016	China	100	97	26.8 ± 3.0	27.4 ± 3.0	30 to 32 weeks of gestation until 4-weeks postpartum; followed until 28-weeks postpartum	HBV DNA, alanine aminotransfe rase (ALT)	Alanine aminotransferase, positive for HBeAg, positive HBsAg, detectable HBV DNA	Fatigue, nausea, pruritus, jaundice, upper respiratory infection, preeclampsia
Pan et al., 2024	China	140	140	28.4	28.0	Week 16 of gestation (experimental group) or week 28 (standard care) group) until delivery	Adverse events, HBV DNA <200.000, HBeAg, HBsAg, ALT	Positive for HBeAg, positive HBsAg, detectable HBV DNA	Premature rupture of membranes, intrahepatic cholestasis of pregnancy, threatened preterm labor

C: Control; T: Treatment; HBV DNA: Hepatitis B Virus DNA; HBeAg: Hepatitis B e Antigen; HBsAg: Hepatitis B surface Antigen.

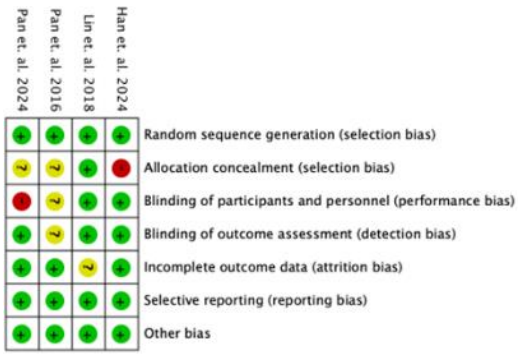

Figure 2. Traffic light plot for risk of bias.

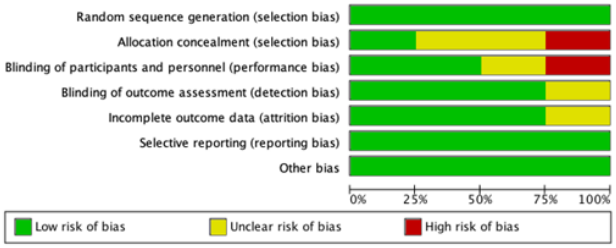

Figure 3. Summary plot for risk of bias.

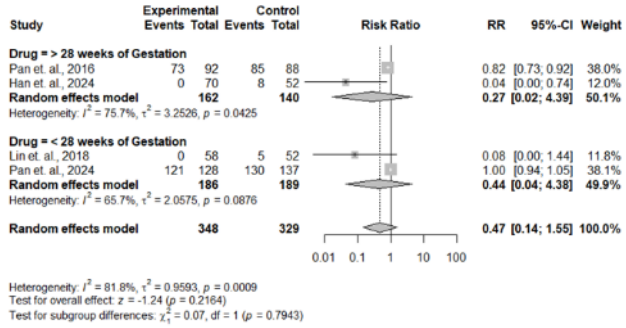

Figure 4. Forest plot of the number of infants who tested positive for HBeAg.

Results of individual studies

The meta-analysis in this review evaluated three primary outcomes related to perinatal HBV transmission to infants: the number of infants testing positive for HBeAg, HBsAg, and the presence of HBV DNA in infants. HBeAg is a non-structural protein expressed by the hepatitis B virus, commonly used as a clinical marker to assess viral replication, disease severity, and response to related treatment (Padarath et al., 2023). While its expression is not essential for maintaining infection, the presence of HBsAg is strongly associated with hepatitis B, making it a key diagnostic marker since its initial recognition (Lee & Ahn, 2011). Alongside this, HBV DNA also became one of the key markers to look for in infants born to a mother with hepatitis B. The study by Chen et al. (2013) revealed that both HBV DNA and HBsAg levels gradually decreased and eventually became negative in non-infected infants. However, in infected infants, both markers remained persistently positive (Chen et al., 2013; WHO, 2020b).

Tenofovir's safety profile is a critical consideration when using it during pregnancy. The meta-analysis conducted in this review comprehensively divides its adverse effects into five categories: maternal Grade I-II, maternal Grade III-IV, infant Grade I-II, infant Grade III-IV, and infant congenital abnormalities (Pan et al., 2016; 2024). Maternal adverse effects in Grade I-II are mild to moderate effects, such as nausea, fatigue, or mild renal dysfunction, which are generally manageable and reversible (Pan et al., 2016; 2024). Meanwhile, Grade III-IV consists of severe effects, such as significant renal impairment or hepatic toxicity, which are rare but require monitoring (Pan et al., 2016; 2024). Similarly, infant adverse effects from grade I-II also indicate mild to moderate effects, including fever, skin abnormalities such as rash or café-au-lait spots, respiratory symptoms such as cough, and gastrointestinal issues such as diarrhea, vomiting, and jaundice (Pan et al., 2016; 2024). On the other hand, infant adverse effects grade III-IV also stand for severe effects, though rare, including forceps-induced intracranial hemorrhage and pneumonia (Pan et al., 2016; 2024). Finally, evaluation of congenital abnormalities ensures the drug does not adversely affect organ formation or structural development, for example, torticollis, umbilical hernia, and hypospadias (Pan et al., 2016; 2024).

Results of syntheses

Results of statistical syntheses

The results of this meta-analysis demonstrated that tenofovir effectively reduces the risk of perinatal HBV transmission from mothers to infants. The forest plot in Fig. 4 illustrates the proportion of infants who tested positive for HBeAg. The pooled analysis indicates a significant reduction in the tenofovir group (RR = 0.47;

95% CI = 0.14–1.55, p = 0.2164), corresponding to a 53% lower risk of neonatal HBeAg positivity compared to the control group. However, the heterogeneity in this analysis is high (I^2 = 81.8%), which shows a probable difference between studies. The subgroup analysis done, showed that in the gestation age >28 weeks group, the reduction in tenofovir group increased significantly to a 73% lowered risk (RR = 0.27; 95% CI = 0.02–4.39; I^2 = 75.7%), which demonstrated a lower level of heterogeneity compared to the overall results, whereas in the gestation age >28 weeks group, the reduction in tenofovir group increased slightly to a 56% lowered risk (RR = 0.44; 95% CI = 0.04–4.38; I^2 = 65.7%), with a lower heterogeneity level. Due to the high heterogeneity, a leave-one-out analysis (Fig. 5) was performed, revealing that omitting the Pan et al. (2024) study reduced heterogeneity.

The forest plot shown in Fig. 6 demonstrates the number of infants who tested positive for HBsAg. The pooled analysis reveals a 56% reduction in the risk of HBsAg positivity in the tenofovir group (RR = 0.44; 95% CI = 0.09–2.16; I^2 = 63.4%), although the results were not statistically significant (p = 0.3012). Following that, the subgroup analysis revealed that in the group which received tenofovir above 28 weeks of gestation, the positivity levels were further reduced (RR = 0.28; 95% CI = 0.01–10.33; I^2 = 82.1%), but the heterogeneity increased, whereas in the group which received tenofovir below 28 weeks of gestation, the levels of positivity became increased (RR = 0.51; 95% CI = 0.06–4.40; I^2 = 59.8%) revealing an increased positivity levels with lower heterogeneity. Due to the high and persistent heterogeneity, a leave-one-out analysis (Fig. 7) was performed, which revealed that omitting the Han et al. (2024) study reduced heterogeneity to low (I^2 = 28.2%).

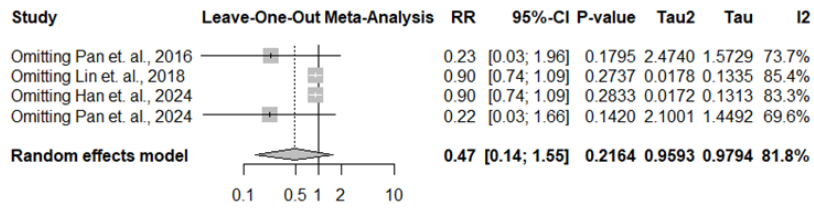

Figure 5. Leave-one-out analysis for the number of infants who tested positive for HBeAg.

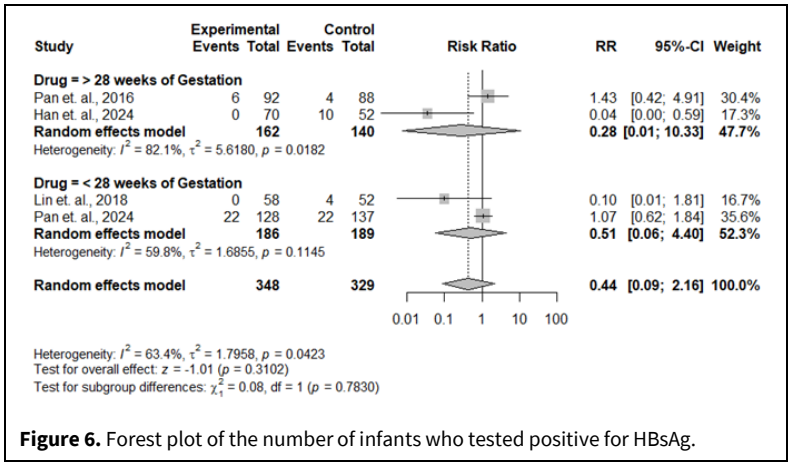

Figure 6. Forest plot of the number of infants who tested positive for HBsAg.

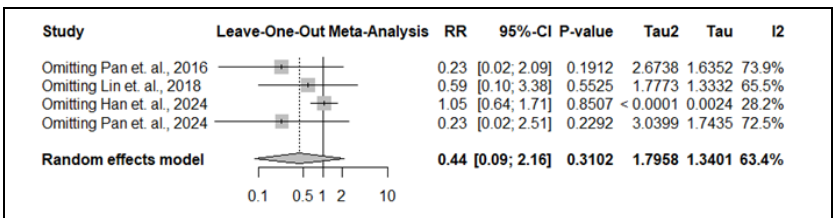

Figure 7. Leave-one-out analysis for the number of infants who tested positive for HBsAg.

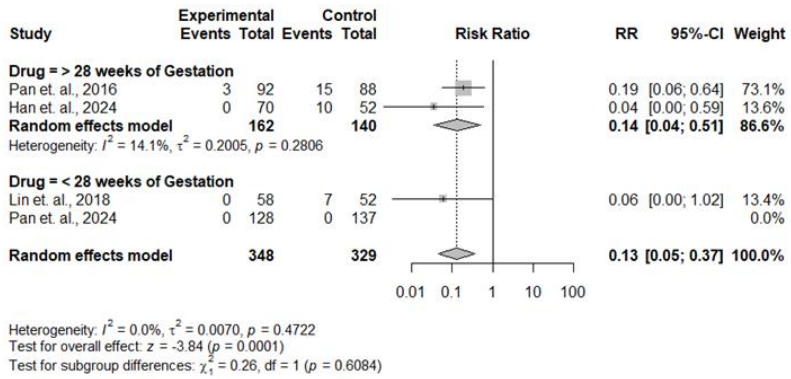

Figure 8. Forest plot of the number of infants with detectable HBV DNA.

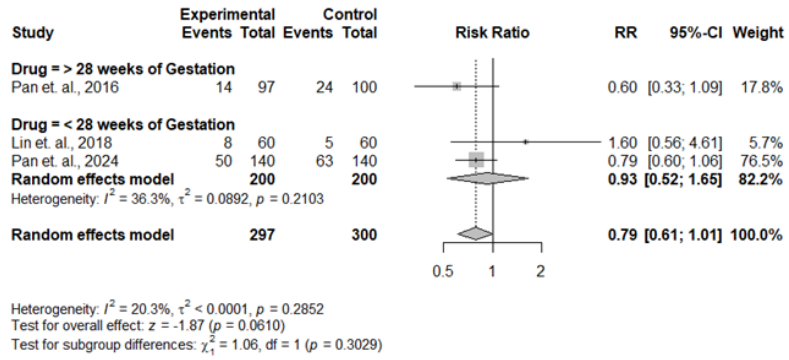

Figure 9. Forest plot of the number of maternal adverse effects Grade I-II.

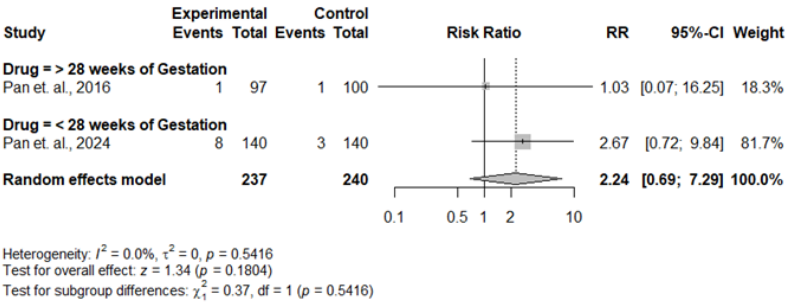

Figure 10. Forest plot illustrating the number of maternal adverse effects Grade III-IV.

The forest plot shown in Fig. 8 reveals the number of infants with detectable HBV DNA. The pooled analysis demonstrates an 87% reduction of detectable HBV DNA in infants in the tenofovir group (RR = 0.13; 95% CI = 0.05–0.37; I^2 = 0%), which was statistically significant (p = 0.0001). Following that, the subgroup analysis shows that in the group that received tenofovir after 28 weeks of gestation, HBV DNA positivity and heterogeneity were slightly increased (RR = 0.14; 95% CI = 0.04–0.51; I^2 = 14.1%).

The forest plot shown in Fig. 9 reveals the amount of maternal adverse events Grade I-II. The pooled analysis demonstrates a 21% reduction in maternal adverse events Grade I-II in the tenofovir group (RR = 0.79; 95% CI = 0.61–1.01; I^2 = 20.3%), although the results were not statistically significant (p = 0.061). Following that, the subgroup analysis shows that in the group that received tenofovir below 28 weeks of gestation, the levels of maternal adverse events Grade I-II were increased (RR = 0.93; 95% CI = 0.52–1.65; I^2 = 36.3%), but heterogeneity was greater than in the overall analysis.

The forest plot shown in Fig. 10 reveals the amount of maternal adverse events Grade III-IV. The pooled analysis demonstrates a significant increase in maternal adverse events Grade III-IV in the tenofovir group

(RR = 2.24; 95% CI = 0.69–7.39; I² = 0%), even though the results were not statistically significant (p = 0.1804).

The forest plot shown in Fig. 11 reveals the number of infant adverse events Grade I-II. The pooled analysis demonstrates an increase in infant adverse events Grade I-II in the tenofovir group (RR = 1.27; 95% CI = 0.58–2.79; I² = 84.1%), although the results were not statistically significant (p = 0.5551).

The forest plot shown in Fig. 12 reveals the amount of infant adverse events Grade III-IV. The pooled analysis shows an increase of infant adverse events Grade III-IV in the tenofovir group (RR = 1.20; 95% CI = 0.59–2.45; I² = 0%), which were not statistically significant (p = 0.6098).

The forest plot shown in Fig. 13 reveals the amount of infant congenital abnormalities. The pooled analysis shows a decrease in infant congenital abnormalities in the tenofovir group (RR = 0.62; 95% CI = 0.11–3.38; I² = 42.5%), but the difference was not statistically significant (p = 0.5823).

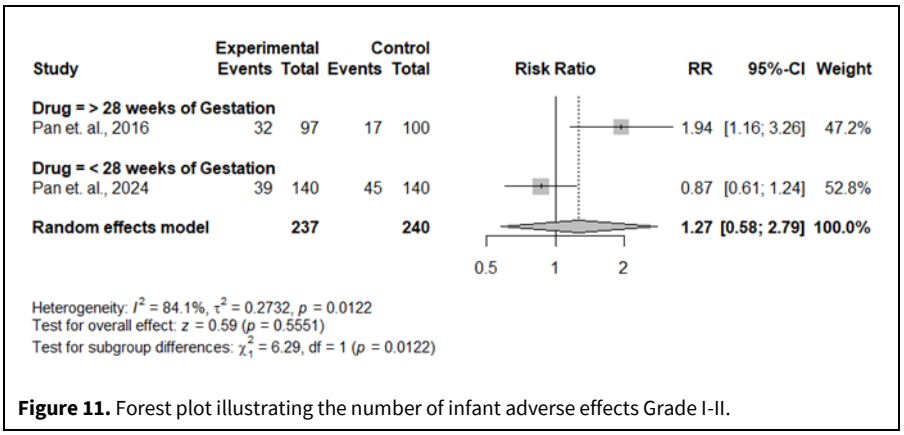

Figure 11. Forest plot illustrating the number of infant adverse effects Grade I-II.

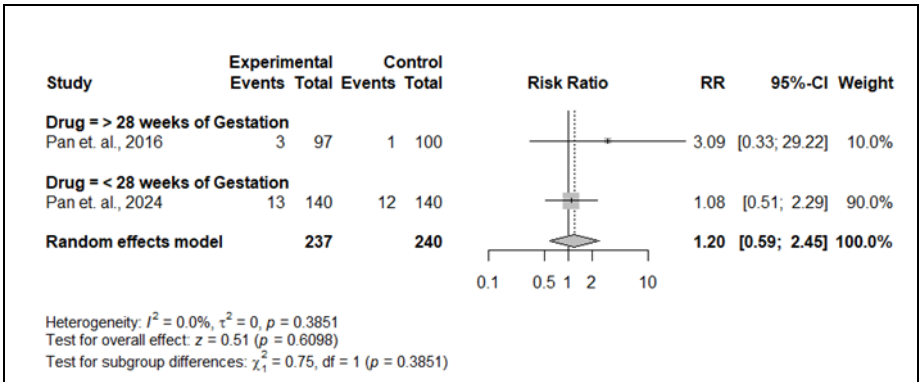

Figure 12. Forest plot illustrating the number of infant adverse effects Grade III-IV.

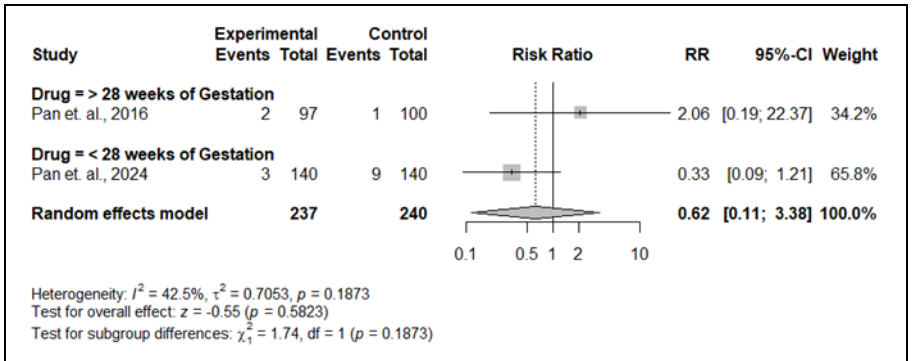

Figure 13. Forest plot of the number of infant congenital abnormalities.

DISCUSSION

This meta-analysis found that tenofovir disoproxil fumarate (TDF) significantly reduced maternal HBV DNA levels and lowered the risk of neonatal HBV DNA positivity, confirming its efficacy in preventing mother-to-child transmission (MTCT). Reductions in HBeAg and HBsAg were observed, although not statistically significant, indicating that transmission risk is lowered but not completely eliminated. These results emphasize the continuing importance of neonatal prophylaxis with hepatitis B immunoglobulin (HBIG) and vaccination in combination with maternal antiviral therapy (Aladag & Aladag, 2023). Initiating TDF at 24–27 weeks of gestation has been shown to effectively reduce maternal viral load, while earlier initiation may be beneficial in women with high baseline HBV DNA levels (Ugwu et al., 2023).

The safety profile of TDF was generally favorable. Most reported maternal and infant adverse events were mild, classified as grade I-II, such as nausea, fatigue, fever, or rash, and were usually self-limiting (Pan et al., 2016; 2024). Severe maternal events (grade III–IV), including renal or hepatic impairment, and severe infant events, such as intracranial hemorrhage or pneumonia, were rare (Pan et al., 2016; 2024). Congenital abnormalities were inconsistently reported, with no clear pattern across studies (Pan et al., 2016; 2024). Overall, these findings support the tolerability of TDF in pregnancy, consistent with evidence from larger observational studies (Han et al., 2024; Lin et al., 2018; Pan et al., 2016; 2024).

Pharmacological considerations help to contextualize these outcomes. TDF improves the poor oral bioavailability of tenofovir, which exists as a dianion at physiological pH, by acting as a prodrug that is hydrolyzed after absorption (Lin et al., 2012; Ray et al., 2015; Xiao et al., 2020). Tenofovir is subsequently phosphorylated within hepatocytes to tenofovir diphosphate, the active metabolite. This metabolite competes with deoxyadenosine triphosphate during viral DNA synthesis and, when incorporated into the DNA chain, terminates elongation, thereby inhibiting replication (Buti et al., 2021; Chien et al., 2022; Jenh et al., 2009; Lee et al., 2021). While this mechanism explains its antiviral efficacy, accumulation in non-target tissues has been associated with nephrotoxicity and placental transfer, which may contribute to some reported adverse effects (Best et al., 2015; Mothobi et al., 2018).

Several limitations must be acknowledged. This review included a small number of trials, all conducted in China, restricting generalizability to other populations and HBV genotypes. Adverse event reporting was inconsistent, limiting interpretation of safety. From a clinical perspective, the timing of therapy is important. These findings are consistent with WHO guidance, which recommends TDF as the preferred antiviral for MTCT prophylaxis and chronic HBV management (WHO, 2020a). The demonstrated efficacy, acceptable safety profile, and low risk of HBV flare after discontinuation support its integration into antenatal care.

Limitations of evidence

A comprehensive literature search was conducted; however, this review has several limitations. First, all included studies were conducted in China, which restricts the generalizability of the findings to other populations with different HBV genotypes and healthcare contexts. Second, the limited number of available trials prevented the use of funnel plots to assess publication bias. Third, only a subset of studies reported adverse events, limiting the scope of available safety data for analysis. Finally, the inclusion of only English and Indonesian language studies could have introduced language or publication bias.

Implications

To address limitations in this study, further multicenter, multinational studies with comprehensive adverse event reporting are needed to confirm tenofovir's safety.

CONCLUSION

TDF reduces maternal viral load and lowers neonatal HBV DNA positivity. However, safety data are limited and inconsistently reported. Therefore, the findings should be interpreted cautiously and confirmed in larger multinational trials.

CONFLICT OF INTEREST

The research was conducted entirely free from any involvement in commercial, financial, or personal matters that might be perceived as a possible conflict of interest or that could have influenced the outcomes or interpretation of the study.

ACKNOWLEDGMENTS

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

GENERATIVE ARTIFICIAL INTELLIGENCE (AI)

The authors declare that no generative artificial intelligence (AI) or AI-assisted technologies were used in the preparation, writing, or editing of this manuscript. All content was developed solely by the authors, who take full responsibility for its accuracy and integrity.

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Contribution	Simorangkir KR	Santoso RC	Syofyan SD	Kusmardi K
Concepts or ideas	x	x	x	x
Design			x	x
Definition of intellectual content	x	x	x	x
Literature search	x	x	x	
Experimental studies	x	x	x	x
Data acquisition	x	x	x	x
Data analysis			x	x
Statistical analysis	x	x	x	
Manuscript preparation	x	x	x	
Manuscript editing	x	x	x	x
Manuscript review	x	x	x	x

Citation Format: Simorangkir KR, Santoso RC, Syofyan SD, Kusmardi K (2026) Efficacy and safety of tenofovir in preventing hepatitis B mother-to-child transmission: A systematic review and meta-analysis of randomized controlled trials. J Pharm Pharmacogn Res 14(2): 2397. https://doi.org/10.56499/jppres_14.2.2397

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