The role of tenofovir disoproxil fumarate for preventing vertical transmission of hepatitis B

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Abstract

Background: Since immunoprophylaxis failure can occur if maternal serum hepatitis B virus (HBV) DNA levels are >200,000 IU/ml, tenofovir disoproxil fumarate (TDF) therapy has been investigated for preventing mother to child transmission (PMTCT).

Methods: A literature search for maternal TDF therapy for PMTCT between 1/1/2015 and 7/1/21 on PUBMED, EMBASE, Cochrane, CNKI, and Wanfang databases was performed. Data from RCTs in English or Chinese were extracted and reviewed. The outcomes of interest included the efficacy and safety of TDF versus placebo for PMTCT.

Results: Among 11 RCTs identified from the databases, the risk-of-bias was low. All studies demonstrated that maternal TDF therapy initiated from the second or third trimester for highly viremic chronic hepatitis B mothers is highly effective and safe in the PMTCT of HBV, except one RCT performed in Thailand which showed no therapeutic advantage on TDF treatment versus placebo for PMTCT (0% vs 3% transmission). Recent emerging data suggest that maternal TDF therapy initiated at the 2nd or early 3rd trimester in mothers with HBV DNA >200,000 IU/ml achieved viremic control before delivery. In the 4-year long follow-up study for maternal TDF therapy, there were no impacts on infants’ physical growth, psychological or mental development, and bone mineral density after fetal exposure to TDF. In the light of updated efficacy and safety data from RCTs, an algorithm was proposed. The approaches in resource-limit areas were discussed.

Conclusions: TDF is safe for both mothers and infants as the preferred therapy for PMTCT in highly viremic mothers. TDF should be initiated at the second or early third trimester in the combination of the appropriate infants’ immunoprophylaxis.

Introduction

Since the 69th World Health Assembly approved the Global Health Sector Strategy to eliminate viral hepatitis by 2030, the global epidemiology of hepatitis B virus (HBV) infection has been estimated at approximately 292 million infections in 2016[1]. Current oral antiviral treatment or interferon therapy can control HBV replication in infected individuals and may reduce the complications of cirrhosis or hepatocellular carcinoma (HCC)[2,3], but cannot cure the existing infection of HBV[4]. Thus, the prevention of new infection becomes the most important step in the process of global elimination of HBV[5]. In the counties or regions with a high prevalence of HBV infection, mother-to-child transmission (MTCT) of HBV is the most common route for individuals who acquired the infection[5–7]. In the past two decades, global efforts have been made to provide infants from HBV-infected mothers with immunoprophylaxis[6]. The method includes the HBV vaccine with hepatitis B immune globulin (HBIG) injection at birth and a series of
two or three doses of HBV vaccine inoculations within the age of 6 months. This method has effectively reduced the MTCT rates from 60 to 90% to approximately 5–10%[5-7]. However, recent studies have indicated that the frequency of MTCT increased to 20% in Asia and 32% in Africa (i.e., immunoprophylaxis failure) among mothers with HBeAg positive or HBV DNA >200,000 IU/ml at delivery[5,6,8-10]. Globally, the HBeAg prevalence was about 20–50% among women of reproductive age in recent years, in which young females in East Asia have the highest prevalence[11] Without further intervention, approximately 3 million infants will be infected with chronic hepatitis B (CHB) globally in the next 10 years[5]. Therefore, management of HBeAg mothers and preventing MTCT (PMTCT) are critical steps in the global elimination of hepatitis B infection[12].

In 2009, Xu et al.[13] performed an RCT to treat 150 highly viremic mothers with either lamivudine 100 mg or placebo from week 32 of gestation to week 4 postpartum. All infants received immunoprophylaxis. At the age of week 52, the study failed to show the effectiveness of PMTCT with maternal lamivudine therapy in subjects who completed the study, although the intention-to-treat (ITT) analysis indicated a reduction of MTCT with lamivudine treatment. The ITT results were challenged by the high drop-out rate in the study (about one-third of study subjects missing outcome data)[13]. In 2011, Han et al. published a prospective cohort study on maternal telbivudine therapy for preventing MTCT in mothers with high levels of HBV viremia[14]. They offered 135 mothers with the third-trimester telbivudine therapy and 94 mothers with no treatment. All infants received immunoprophylaxis. In the telbivudine-treated group, the MTCT rate was significantly lower compared to the control (0% vs. 8%; p = 0.002).

Despite the encouraging results from several studies on the maternal lamivudine or telbivudine therapy in this population[13-19], the WHO issued the HBV guidelines in 2015 with the position of not recommending maternal antiviral therapy for mothers with HBV infection due to the lower quality of published studies[13-20]. In addition, the development of antiviral resistance during lamivudine or telbivudine therapy increases the risk of persistent viremia throughout the third-trimester treatment, making such intervention less attractive for treatment-experienced HBV patients[21]. Currently, most international guidelines designate these treatments as second-line therapy[4,5,22]. Therefore, the treatment of lamivudine or telbivudine during pregnancy will not be covered in this article. Although one RCT and two cohort studies on maternal tenofovir alafenamide (TAF) therapy for PMTCT have been published[23-25], the quality of the RCT was low due to the small sample size[24]. The current review aimed to highlight the investigational process for tenofovir disoproxil fumarate (TDF) therapy, honor Dr. Martin’s contributions, summarize the updated pieces of evidence, and discuss the advances of maternal TDF therapy for the prevention of HBV transmission. A management algorithm for HBV-infected mothers was also proposed based on the new data. Additionally, future research directions are explored.

**Investigation of maternal tenofovir disoproxil fumarate therapy and support from Dr. Martin**

Since the first study of TDF for preventing MTCT published in 2012[18], investigations for the maternal use of TDF to reduce MTCT have intensified and led to the global acceptance of treating high viremic CHB mothers with TDF during pregnancy[4,5,22,26-35]. Dr. John C. Martin, the former CEO of Gilead Sciences Inc., was one of the strongest supporters and facilitators of studying and implementing TDF as a new treatment option for preventing MTCT on a global scale. His efforts about bringing TDF therapy to help CHB mothers started years before the drug’s approval. In September 2008, Dr. Martin met with me after my presentation; entitled “Controversies in HBV Infection—From Bench to Bedside” at 355 Sandpiper (Brown-Bag Lecture) in Gilead’s headquarters. We discussed the role of TDF in the management of chronic hepatitis B, especially in addressing the unmet needs of treating special populations including pregnant mothers. He had the vision of making the innovation available globally and affordable for patients when TDF got the approval from FDA.

During the AASLD liver meeting in 2009, Dr. Martin briefed me on Gilead’s plan to support post-marketing studies on TDF treatment for CHB. He was interested in my research works and collaborations with the researchers in China to define the maternal viral load for high risk of MTCT and use telbivudine treatment for mothers[9,17,36]. He was extremely enthusiastic about working with investigators, public health administrators, and non-profit organizations in Asia to eliminate HBV infection in the region, where the disease burden was the highest among all continents with over 100 million CHB patients in China[37,38]. Under his leadership, Gilead Sciences provided research funding and medication support to two large studies in China (a cohort study in Taiwan and an RCT in the mainland)[29,35]. The Gilead team was aware that 12 weeks of TDF therapy for mothers during pregnancy would not contribute significantly to the commercial return, but Dr. Martin and his team chose to support the high-quality studies for PMTCT which required big budgets and long durations due to the challenges in enrollment. He explained to the team: “We should do the right things for patients and address the unmet needs.” These studies established the core evidence for
the current WHO and international guidelines on TDF therapy for the PMTCT[29,35].

Through the RCT for TDF therapy on PMTCT in China and other public health projects in Asia, I had the opportunity to work with Dr. Martin. He contributed heavily to the implementation of the prevention of CHB infection on a global scale. During the APASL meeting of 2012 in Taiwan, he organized investigator meetings to discuss HBV prevention and elimination. Later, he teamed up with public health experts and included me to provide updates on data for PMTCT to the WHO team in Geneva and discussed the implementation plan. In many Wilton Park meetings, he moderated and facilitated the discussion of triple elimination including HBV, particularly in meetings in Singapore (in 2015) and Hong Kong (on June 7, 2016) where I also presented the RCT data of PMTCT in mothers with CHB from China (article in press at the New England Journal of Medicine on June 16, 2016) to the WHO team in Asia[35]. The discussion had helped the WHO team to re-examine the approach of not recommending antiviral treatment during pregnancy for PMTCT in the guideline published in 2015. In addition, Dr. Martin’s donation through John C. Martin Foundation contributes heavily to the research and community projects for disease control and elimination. The foundation has funded many projects for viral hepatitis and HIV through the Chinese Hepatitis Foundation and Infectious Disease Hospitals in China, including a large RCT (n = 280) for maternal TDF therapy initiating at gestational week 16 for highly viremic mothers with CHB in a combination of HBV vaccine for infants without HBIG[39]. He preferred to support the aforementioned study on TDF therapy for PMTCT although tenofovir alafenamide TAF is available at that time and TDF had passed the patent period. He emphasized that every patient should benefit from the innovation. It is our responsibility to make that accessible and affordable. TDF treatments for CHB mothers in resource-limited areas are more affordable. The study will provide high-quality evidence and explore the possible solutions for PMTCT of HBV in resource-limited areas.

Updates of maternal tenofovir disoproxil fumarate therapy for the preventing mother-to-child transmission

Data search and selecting criteria

The current review was based on the data from randomized controlled trials that enrolled highly viremic mothers or HBeAg positive pregnant women with CHB who received TDF in a combination of appropriate immunoprophylaxis for their infants reported between Jan 01, 2015 and July 1, 2021. The outcomes of interest were HBV suppression on TDF before delivery, MTCT rates, congenital malformation/defect rates, and adverse outcomes from antiviral therapy in either mothers or infants. Publications were searched and screened by the keywords including “hepatitis B,” “hepatitis B virus infection,” “pregnancy,” “pregnancies,” “gestation,” “pregnant women,” “infants,” “newborns,” “neonate,” “infectious disease transmission,” “vertical,” “transmission,” “maternal-fetal infection transmission,” “mother-to-child transmission,” “hepatitis B virus immunoglobulin,” “HBIG,” “vaccines,” “antiviral,” “antiviral,” “tenofovir,” “tenofovir disoproxil fumarate,” and “fetal exposure.” Data were reviewed after searching from the following databases: PubMed, Embase, Cochrane, and two Chinese-language (CNKI and Wanfang) databases including articles in English or Chinese. Data search strategies are shown in the supplement material (Appendix 1).

Studies were eligible for inclusion when they met all of the following criteria: (1) the study design was classified as an RCT; (2) the study population was CHB mothers with HBV DNA ≥ 200,000 IU/ml during pregnancy or HBeAg positive; (3) at least one study arm (group) had received the TDF intervention during pregnancy and another arm had patients without antiviral treatment (control arm); (4) appropriate immunoprophylaxis was provided to all infants; (5) data were presented as a full publication from 1/1/2015 to 7/1/2021; and (6) Reporting key outcomes of interest (i.e., MTCT rates and congenital malformation/defect rates). The studies were excluded if they met one of the following criteria: (1) Mothers had CHB and co-infected with hepatitis A, C, D, E virus or human immunodeficiency virus; (2) Animal studies or translational studies: (3) mothers received a combination of antiviral therapy for preventing MTCT of HBV during pregnancy. The outcomes of interest assessed by the current review were the MTCT rates in CHB mothers who received TDF therapy during pregnancy when compared to the control group (no maternal antiviral therapy). The MTCT was defined by the infant’s HBsAg seropositivity and/or HBV DNA positivity at the infants’ age of 6–12 months. Secondary outcome assessments were the fetal/infant malformation rates, maternal HBV-DNA reduction at delivery, and adverse events for study subjects (both mothers and infants) reported during the trials.

Data extraction, synthesis, and the risk of bias assessment

After the literature search, a list of eligible studies was generated by screening the titles, abstracts, and keywords of every record. All records that met the inclusion criteria were obtained in full text. Selected studies were further reviewed based on the exclusion criteria. The data were extracted with the pre-specified and itemized data extraction forms designed for the current review. The forms collected the details of the study characteristics, patient
baseline characteristics, intervention details, and outcomes of interest. If further clarifications were needed, the authors of the primary studies were contacted. For outcomes reported with a continuous variable, the mean with standard deviation or median with range, and sample size of each group were extracted. For outcomes with dichotomous variables, the number of events and the total number in each group were extracted. Data were summarized in figures and tables for further presentation in the result section. The risk of bias was assessed with the Cochrane Risk of Bias Assessment Tool. The quality of evidence was evaluated using the Grading of Recommendations Assessment, Development, and Evaluation approach. Criteria used to evaluate the quality of evidence included the risk of bias, indirectness, imprecision, inconsistency, and publication bias.

Overall assessment of the data selected

Through the keyword search and screening, 11 RCTs were identified from the databases based on the selection criteria (Figure 1). The risk-of-bias assessments of RCTs are shown in the supplement material (Table S1). The majority of RCTs had a low risk of bias and none was classified as at high risk of bias. All studies were conducted in China except one in Thailand. The study courses and key presentations of these studies are summarized in the supplementary material (Appendix 3, Table S2 to S4). All studies enrolled highly viremic mothers (with defined HBV DNA levels in the inclusion criteria) except the study in Thailand by Jourdain et al. which enrolled the HBeAg positive mothers with any levels of viremia. All infants in RCTs received appropriate immunoprophylaxis with the MTCT rates assessed at the age between 6 and 12 months. The MTCT was defined as the HBsAg seropositivity or a detectable level of HBV DNA from the infants’ blood sample at the end of the studies. (Appendix 3, Table S4).

Literature reviews for the preventing mother-to-child transmission with tenofovir disoproxil fumarate therapy

Among 11 RCTs published in the last six years, 1391 mothers enrolled into the RCTs with 698 and 693 in the TDF-treated and the control arms, respectively. The follow-up data for 1357 infants were presented with 689 and 668 in the TDF-exposure and the control group, respectively (supplementary material, Table S3). All RCTs observed a lower frequency of MTCTs in mothers treated with TDF during the second and/or third trimester (0–6%) when compared to that of mothers in the control group (2–30%). The reduction of MTCTs was statistically significant in each RCT except the Thailand study by Jourdain et al. (Table 1). The study design in Jourdain’s study differed from other RCTs and had no HBV DNA inclusion criteria, which had the potential to enroll mothers with HBeAg positive and low levels of HBV DNA. As the result, 11% (35/331) mothers who had HBV DNA load <200,000 IU/ml were enrolled in the study. In addition, the sample size in this study was underestimated. The aforementioned factors in the study design may contribute to the lower transmission rate in the control group and reduce the power to detect the difference between the therapeutic and the control groups for PMTCT. It was not clear if the early use of the birth dose vaccine in Jourdain’s study may reduce the MTCT rates (TDF vs control = 0% vs 3%) in both study arms, because there was a much high MTCT

Figure 1. Data search and selection.
rate (TDF vs control = 0% vs 7%) in Pan’s RCT when the majority of infants had the birth dose of HBV vaccine and HBIG injection within a few minutes of birth.

Other therapeutic assessments in RCTs included maternal viremia reduction before delivery. All RCTs had demonstrated that a significantly lower level of maternal HBV DNA in the TDF group compared to that in the control group (Table 1). However, there was a great discrepancy in the percentage of mothers who could achieve the target levels of HBV DNA <200,000 IU/ml at delivery (TDF-treated ranged from 34 to 90% vs. control ranging from 0 to 15%)[26,27]. The maternal baseline HBV DNA levels and the duration of TDF therapy in different RCTs were likely to affect such outcomes. Other therapeutic assessments included the frequency of HBeAg or HBsAg seronegativity or seroconversion, which did not differ between the two groups in each study. It is expected because mothers received a short duration of TDF during pregnancy (10–16 weeks) and most of them discontinued the treatment within 12 weeks after delivery.

### Table 1. Efficacy outcomes of maternal TDF therapy for PMTCT in RCTs.

| Leading investigators (years of the publication) | Maternal efficacy outcomes (antiviral agents vs control) | Infant outcomes and MTCT rates (antiviral agents vs control) |
|--------------------------------------------------|----------------------------------------------------------|-------------------------------------------------------------|
| Pan CQ et al. (2016) | 8.2 ± 0.5 vs 8.0 ± 0.7 | 6.2% (6/97) vs 4.0% (4/100) |
| Liu MH et al. (2017) | 6.5 ± 0.9 vs 6.47 ± 1.00 | NR vs NR |
| Lin Y et al. (2018) | 7.4 ± 0.8 vs 7.7 ± 0.6 | NR |
| Jourdain G et al. (2018) | 7.6 ± 1.5 vs 7.3 ± 1.7 | NR |
| Zhang L et al. (2018) | 7.32 ± 0.35 vs 7.40± 0.37 | 4.04% (4/99) vs 5.05% (5/99) |
| Chen GH et al. (2019) | 7.6 ± 0.51 vs 7.6 ± 0.83 | 25% (1/40) vs 10% (4/40) |
| Bao CQ et al. (2019) | 7.51 ± 0.52 vs 7.53 ± 0.84 | 0 (0/45) vs 13.3% (6/45) |
| Liu JJ et al. (2019) | 7.5 ± 0.5 vs 7.5 ± 0.5 | 2% (1/48) vs 23% (9/39) |
| Yu HP et al. (2020) | 7.28 ± 1.15 vs 7.53 ± 1.09 | NR |
| Zhou J et al. (2020) | 8.2 ± 0.9 vs 8.3 ± 0.7 | 2.4 (1/42) vs 2.4 (1/42) |
| Huang YQ et al. (2021) | 5.7 ± 1.5 vs 5.6 ± 1.6 | 1.7% (1/60) vs 1.7% (1/60) |

*Efficacy outcomes were presented with per-protocol analysis data only.
Abbreviations: TDF, Tenofovir disoproxil fumarate; PMTCT, Preventing mother-to-child transmission; ALT, Alanine aminotransferase; HBsAg/HBeAg, Hepatitis B surface/envelope antigen; NR, not reported.
The key safety assessments for maternal TDF therapy in CHB mothers versus patients in the control group are presented in Tables 2 and 3. Data from RCTs indicated that fetal exposure to TDF during the third trimester did not significantly increase congenital malformation or birth defect rates among infants (Table 2). A large RCT by Pan et al. also had the long-term follow-up data and assessed infants (TDF group: n = 70, control group: n = 75) at the age of 192 weeks[35], which confirmed that birth defect/ malformation rates were similar between groups. There were no negative effects on infants’ physical growth, neurodevelopmental milestones, or bone mineral density weeks (TDF group: 1.37 ± 2.59 vs Control group: 1.36 ± 2.58, p = 0.97) after fetal exposure to TDF[41].

Other safety assessments included maternal and infants’ adverse events or complications. All RCTs reported that TDF therapy was well tolerated during pregnancy and adverse events were captured as grade I to II in severity without serious events. Common maternal adverse events or complications included creatine kinase elevation without significant clinical sequelae during TDF therapy. The frequency of postpartum hemorrhage and prematurity rates did not differ between the two groups (Table 2). Several studies had evaluated the post-partum hepatitis flares after the discontinuation of TDF treatment. However, the definitions of ALT flares differed in the individual trial (Table 3). The frequency of ALT flares was similar between the two groups in each study (TDF 6%, vs. control 3–10%). In addition, none of the flares from TDF cessation had severe clinical consequences. TDF or other antiviral were offered to a few mothers with ALT flares after the cessation of the treatment.

Lastly, there were only a few RCTs that assessed the effect of postpartum maternal antiviral therapy on infants when they received breastmilk. The RCT in Thailand allowed mothers to provide breastfeeding when postpartum TDF therapy was continued for 8 weeks[31]. The investigators observed that infants who received breastmilk in the TDF group had similar physical development when compared to the control group[31]. Breastmilk feeding from CHB mothers did not increase the frequency of HBV infection in

### Table 2. Common adverse events and complications of maternal TDF therapy in RCTs.

| Safety indicators               | Studies that reported the data (n) | Frequency in TDF groups, n (%) | Frequency in the control arms, n (%) | Statistical significance |
|---------------------------------|------------------------------------|--------------------------------|-------------------------------------|--------------------------|
| Maternal safety outcomes        |                                     |                                |                                     |                          |
| Postpartum hemorrhage           | 6                                   | 1.0% (5/487)                   | 0.8% (4/485)                        | p > 0.99                |
| Pregnancy complications         | 5                                   | 10.4% (35/335)                 | 7.3% (24/331)                       | p = 0.22                |
| CK Elevation                    | 4                                   | 2.5% (7/276)                   | 0% (0/279)                          | p = 0.015               |
| Prematurity rate                | 4                                   | 0.93% (3/321)                  | 0.97% (3/307)                       | p > 0.99                |
| Infants’ safety outcomes        |                                     |                                |                                     |                          |
| Malformation rate               | 6                                   | 0.54% (2/368)                  | 0.85% (3/354)                       | p = 0.68                |
| Delay on physical growth (height and weight compared with the national standard) | 7 | 0.20% (1/523) | 0.40% (2/521) | p = 0.62 |
| Breastfeeding                   | 3                                   | 0.3% (1/301)                   | 0% (0/287)                          | p > 0.99                |

Abbreviations: TDF, Tenofovir disoproxil fumarate; CK, Creatine Kinase; Cr, Creatinine; NR, Not reported; * There was only 1 child death occurred at 36 weeks of gestation in TDF groups. The proportion of the studies we included had mentioned relevant safety indicators. NR, Not reported.

### Table 3. Postpartum hepatitis flares with different definitions in the individual study.

| Studies (published years) | Definition of flare | TDF cessation at postpartum weeks | Postpartum flare (TDF vs Control) | Case of hepatic decompensating | Case of death | Clinical course |
|---------------------------|---------------------|----------------------------------|----------------------------------|--------------------------------|---------------|----------------|
| Pan CQ, et al. (2016)     | ALT ≥5 times ULN (=40 UI/l) | 4 weeks                          | 6% vs 9%                         | 0                              | 0             | Women have severe ALT flare restarted the antiviral therapy |
| Jourdain G, et al. (2018) | ALT >300 IU/l in women after trial-regimen discontinuation | 8 weeks                          | 6% vs 3%                         | 0                              | 0             | No women started or restarted TDF after ALT flares |
| Lin Y, et al. (2018)      | ALT 5 > 5 times ULN (=40 UI/l) | 4 weeks                          | 6% vs 10%                        | 1                              | 1             | NR             |

Abbreviations: TDF, Tenofovir disoproxil fumarate; ALT, Alanine aminotransferase; NR, Not reported; ULN, Upper limits of the normal range.
infants\textsuperscript{[31]}. Current international guidelines recommend TDF for nursing mothers if antiviral therapy is needed\textsuperscript{[5,22]}. For mothers who received postpartum antiviral therapy other than TDF, regimens including tenofovir, adefovir, entecavir, or TAF have not been well studied in nursing mothers being treated for HBV. Alternatively, lamivudine may be preferred for nursing mothers if TDF is not tolerated\textsuperscript{[42]}. The timing for initiating maternal tenofovir disoproxil fumarate therapy

Although many RCTs and cohort studies have demonstrated that maternal TDF treatment could be safely discontinued at any time point between postpartum week 4 and week 8 (Table 3)\textsuperscript{[31,35,47–49]}, the timing for initiating maternal TDF remains controversial. WHO and AASLD guidelines recommend initiating TDF therapy during the third trimester\textsuperscript{[4,5]}, whereas EASL guidelines suggested TDF treatment starting at the gestational weeks 24–28 for highly viremic mothers\textsuperscript{[22]}. There is discrepancy among guidelines, which rose in the contexts of fewer safety data at the second-trimester treatment of TDF in RCTs, and the necessity of starting TDF earlier than the third trimester for PMTCT at the time of preparing the guidelines. Recently a large real-world study suggested that providing TDF at the second trimester could be more effective in controlling viremia than that in the third trimester\textsuperscript{[49,50]}. In a viral kinetic study by Pan et al., treatment with 24 weeks of TDF was more effective (97%) in reducing HBV DNA levels to < 200,000 IU/ml versus 12 weeks of TDF therapy (94%) in reproductive-age women\textsuperscript{[51]}. Additionally, a study by Gao et al.\textsuperscript{[52]} demonstrated that TDF therapy initiated at the second-trimester reduced HBV DNA levels more effectively (changes from baseline to delivery at 4.8 ± 1.2 log10 IU/ml) than that initiated during the third-trimester (4.3 ± 1.1 log10 IU/ml, p = 0.041). Because of the emerging data supporting the better control of maternal viremia with a longer duration of therapy, the author of the current review is in favor of the (EASL) position of starting antiviral therapy during the second trimester (gestational weeks of 24–28), particularly in mothers who have HBV DNA levels > 8 log10 IU/ml.

Another piece of evidence regarding the TDF fetal exposure from the Antiretroviral Pregnancy Registry (APR) suggested that maternal TDF therapy was safe even starting from the first trimester (n = 4483)\textsuperscript{[53]}. The congenital defects/malformation rate was 2.41% (95% CI: 1.98–2.90%), which was comparable to the control population in the Metropolitan Atlanta Congenital Defects Program (2.76%). Considering approximately 13% of deliveries occur before 37 weeks of gestation\textsuperscript{[54]}, starting TDF therapy for high viremic mothers at the second trimester (gestational weeks 24–28) would allow 13–9 weeks of TDF therapy for viremia control, which is supported by the aforementioned recently published data. An updated algorithm for PMTCT of HBV proposed by the author of the current review is presented in Figure 2. Reassessment for the long-term TDF therapy postpartum is needed based on the current treatment guidelines for the management of maternal CHB.

Discussion of current challenges, possible solutions, and research directions

Based on studies on the risk of immunoprophylaxis failure in infants from CHB mothers\textsuperscript{[9,10]}, recent international major guidelines for the management of HBV have recommended that mothers with CHB who have HBV DNA levels above 200,000 IU/ml should receive antiviral during the late trimester\textsuperscript{[4,5,22]}. Current review of RCTs on maternal TDF therapy in these special populations has presented compelling evidence on the efficacy and safety of TDF for the PMTCT. In addition, Funk et al. also confirmed the therapeutic advantage and safety of maternal TDF therapy in a recent meta-analysis when both RCTs and cohort studies were included\textsuperscript{[43]}. Despite the increase in acceptance of treating highly viremic CHB mothers with TDF during pregnancy, data gaps exist for refining the maternal TDF treatment, and challenges remain in the implementation of the therapy on a global scale.

Candidacy for maternal tenofovir disoproxil fumarate therapy

Besides using HBV DNA levels as the major criteria to select CHB mothers for antiviral therapy\textsuperscript{[9,10]}, other viral makers as indicators for maternal therapy have been investigated recently. These markers include HBsAg levels and HBeAg seropositive status\textsuperscript{[5,22]}. HBsAg level >4 log 10 IU/ml was found to be associated with the risk of MTCT in infants with immunoprophylaxis\textsuperscript{[44,45]}. Additionally, Boucheron et al. published a systematic review and meta-analysis and confirmed the accuracy of HBeAg as a maternal indicator of high risk of MTCT. The pooled sensitivity and specificity were 99.5% and 62.2%, respectively\textsuperscript{[46]}. Therefore, in the resource-limited area, the quantitative HBsAg level > 4 Log 10 IU/ml may be considered as the segregate criteria (rather than HBV DNA > 200,000 IU/ml) for maternal antiviral treatment when the HBV DNA tests are not obtainable. Such approaches have been endorsed by the hepatitis B guidelines from EASL and WHO in 2017 and 2020, respectively\textsuperscript{[5,22]}. WHO guidelines also recommend that maternal TDF therapy should be provided to all HBeAg positive mothers if HBV DNA test is not available\textsuperscript{[5]}.
Preventing mother-to-child transmission in areas without birth dose hepatitis B immune globulin and/or vaccine

In resource-limited areas such as most countries in Africa and South Asia, the birth dose of HBIG and/or HBV vaccine are largely unavailable for infants who are born to CHB mothers[^38,55,56]. The universal vaccination program for children in these areas are mainly funded by the Global Vaccine Alliance (GIVA), which includes the second to the fourth dose of HBV vaccine for the prevention of horizontal transmission[^57]. In the author’s opinion, several directions/solutions are worth to be explored for the PMTCT in CHB mothers in this setting, especially for HBeAg positive mothers.

In Jourdains’ RCTs for HBeAg positive mothers, the investigators speculated that their protocol of early use of the first dose of HBV vaccine and HBIG may have contributed to low the transmission rates in the control group, which implied that early birth-dose vaccine with HBIG could potentially replace maternal TDF therapy in lower HBV prevalence area. However, there was still a 3% infection with this approach. More importantly, such an approach will not be practical in resource-limited areas because cold chain storages are unavailable.

Another approach is the use of maternal TDF therapy in HBeAg-positive mothers with the omission of the birth dose of HBV vaccine and/or HBIG, which is more practical in areas without cold chain storage. In a nonrandomized cohort study,

[^38]: [Source of reference 38]
[^55]: [Source of reference 55]
[^56]: [Source of reference 56]
[^57]: [Source of reference 57]
study by Segeral et al. in Cambodia [58], 318 HBeAg positive mothers (median HBV DNA levels 7.91 log10 IU/ml) received TDF therapy from gestational week 24 to postpartum week 6 and their infants received birth dose of HBV vaccine within 2 h of birth (median time 15 min from birth) without HBIG. The subsequent HBV vaccines were provided at weeks 6, 10, and 14. Although the appropriate control group was not selected (mothers with lower levels of HBV DNA were in the non-TDF treated group), data were available in 324 infants at the age of 6 months, which showed 6.52% MTCT (defined by HBsAg positive and confirmed with HBV DNA test) in those whose mothers received TDF for 4 weeks or less and at 0% in those whose mothers received TDF longer. Overall proportions of infants positive for HBsAg at 6 months were 1.26% in the TDF-treated group (95% confidence interval [CI] 0.34–3.20). TDF therapy was well tolerated and Grade 3 or 4 adverse events affected 10% of TDF-treated women (95% CI 7.1–13.8). The researchers stressed that maternal TDF therapy with an HBIG-free strategy could reduce perinatal HBV transmission if mothers take TDF for more than 1 month before delivery.

In addition, an ongoing RCTs supported by Dr. John C. Martin Foundation will be completed in the first quarter of 2022 [39], which enrolled 280 highly viremic mothers to receive TDF from gestational weeks 14–16 to delivery in a combination of HBV vaccination for infants (omission of HBIG) or receive TDF from gestational week 28 to delivery in the combination of infants’ standard immunoprophylaxis (vaccine plus HBIG). At the time of completing the current review (September 2021), 103/140 infants had completed the study at the age of 28 weeks in the group without HBIG and none of them had HBV infection (unpublished data, personal communications). In light of the aforementioned study results, the author

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**Figure 3.** Modified Algorithm for CHB mothers in resource-limited areas without cold chain storage.
proposed a management algorithm for mothers with a high risk of HBV vertical transmission in the setting of a birth dose of HBIG unavailable for infants (Figure 3). The proposal should be further confirmed with ongoing investigations and modified as data emerges.

Conclusion

Accumulating pieces of high-quality evidence confirmed that maternal TDF therapy initiated from the second or third trimester for highly viremic CHB mothers is highly effective and safe in the PMTCT of HBV. Recent long-term data also confirmed that there were no safety concerns in infants’ psychological and physical developments including bone mineral density parameters after fetal exposure to TDF\(^{[41,59–61]}\). Emerging data suggested that maternal TDF therapy initiated at the second trimester achieved a better viremic control before delivery when compared to the third trimester TDF treatment\(^{[49,51,52]}\). However, further studies are needed to explore if the early treatment during the second trimester translated to better outcomes of PMTCT, particularly in mothers with HBV DNA levels >8 log10 IU/ml. In resource-limit areas without cold chain storage, preliminary evidence pointed to the direction that initiating maternal TDF during the second or third trimester may overcome the shortage of the birth dose of HBIG\(^{[38,58]}\). The ongoing RCTs with the final results available next year are likely to confirm the efficacy and safety of TDF therapy in these settings.

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Supplemental Material

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Appendix

**Abbreviations**

APR antiretroviral pregnancy registry  
ALP alkaline phosphatase  
ALT alanine aminotransferase  
AST aspartate aminotransferase  
CG Cockcroft–Gault  
CHB chronic hepatitis B  
CI confidence interval  
CrCl creatinine clearance  
DNA deoxyribonucleic acid  
eGFR estimated glomerular filtration rate  
HBcAg hepatitis B core antigen  
HBeAg hepatitis B e antigen  
HBigB hepatitis B immunoglobulin  
HBsAg hepatitis B surface antigen  
HBV hepatitis B virus  
HCV hepatitis C virus  
HDV hepatitis D (delta) virus  
HIV human immunodeficiency virus  
MTCT mother to child transmission  
PCR polymerase chain reaction  
PMTCT prevention of mother-to-child transmission  
TDF tenofovir disoproxil fumarate

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