17. TENOFOVIR DISOPROXIL FUMARATE PRENATAL AS

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TENOFOVIR DISOPROXIL FUMARATE PRENATAL AS A COMPLEMENTARY TREATMENT TO PREVENT VERTICAL TRANSMISSION OF HEPATITIS B VIRUS: A SYSTEMATIC REVIEW

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ABSTRACT Vertical transmission is the dominant transmission method in hepatitis B endemic countries. Immunoprophylactic protocols leave 1% to 4% of infants with a higher risk of immunoprophylactic failure. Within the last ten years, publications regarding the use of prenatal Tenofovir disoproxil fumarate (TDF) have been continuously updated. TDF is preferred because of its potency and lower risk of resistance than lamivudine and telbivudine. The studies analyzed in this systematic review consisted of 2 RCT and 7 NRCT studies, involving 3,765 participants. Six studies described a reduction in viral load HBV DNA levels in the intervention group. Furthermore, five studies reported a decrease in the vertical transmission rate higher than the control group, proven with positive HBsAg parameters at newborns in the intervention group. All studies in this systematic review show a reduced risk of immunoprophylactic failure in the intervention group, proven with negative HBsAg and anti-HBs status when infants were 6-12 months old. There were no significant differences between the intervention and control groups in all studies from a safety point of view. Administration of prenatal TDF and the prophylactic protocol can reduce the vertical transmission rate and the risk of immunoprophylactic failure without causing significant adverse effects both during pregnancy and in infants. Given the consideration, the public health sector and physicians should consider TDF prenatal as a complementary treatment to prevent vertical transmission.

KEYWORDS Hepatitis B, Tenofovir disoproxil fumarate, Vertical transmission

Background

Hepatitis B remains one of the focuses of global health problems, life-threatening if left untreated [1]. In 2015, WHO reported 887,000 deaths caused by long-term complications of hepatitis B, namely cirrhosis and liver cancer [1]. WHO also estimates that at least 257 million people live with chronic hepatitis B infection [1].

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The highest prevalence of hepatitis B is in the Asia Pacific and Africa region [2]. APASL in 2016 reported that Asia Pacific is a region with moderate to high prevalence, which represents three-quarters of the number of chronic hepatitis B (CHB) sufferers worldwide [3]. Indonesia, along with Malaysia, Singapore, and Asian countries, is included in the moderate prevalence category, namely 2-8% [4].

In HBV endemic countries, perinatal transmission is the leading cause of chronic infection [5]. The Indonesian Ministry of Health reports that approximately 2.21% of pregnant women (with early detection coverage of 28.3% out of the total target 100%) are people with hepatitis with a risk of maternal transmission of 95%. Tan et al. (2015) discussed that the likelihood of hepatitis B progression to chronic infection is mainly determined by age at infection [6]. According to WHO, the likelihood

that infection becomes chronic in infants infected during their first year of life is up to 80-90%, and for children infected before 6 years old is 30-50% [1]. Another study in 2015 reports that transmission to newborns from HBeAg-positive mothers results in greater than 90% chronicity while less than 10% of adults with acute HBV progression to chronic infection [7].

Universal HBV vaccination in newborns succeeded in drastically changing the epidemiology of CHB. A systematic review published in 2012 showed a decrease prevalence of CHB from 1990 to 2005 in most countries [8]. WHO states that the proportion of children under five years old who are chronically infected with HBV drops from around 5% in the pre-vaccine era (from the 1980s to the early 2000s) to far less than 1% in 2019 s[1]. This statement is supported by the results of various studies that describe that postnatal active and passive immunoprophylactic combination systems and universal vaccination have effectively suppressed HBV transmission rates from> 90% to only about 10% [9-13]. Nevertheless, immunoprophylaxis failure (IF) can still be found in 1-4% of newborn infants [14-22]. IF significantly happened in infants from mothers with high maternal viral DNA levels (>2×105–107 IU/mL) and/or positive HBeAg [13,15-17,19-29]. In theory, the administration of antivirals during pregnancy can suppress HBV activity and reduce the transmission rate in the uterus and at the time of delivery. Common antiviral medications include lamivudine, telbivudine, and tenofovir disoproxil fumarate (TDF). Majority of worldwide guidelines [2,3,5] preferred TDF for mother to child transmission (MTCT) prevention due to its potency, effectiveness, and low risk of resistance to HBV infection [26,29-35]. However, TDF is still listed in category B of FDA drug for pregnancy. Thus, we conducted a systematic review based on empirical studies to evaluate further oral TDF therapy's efficacy and safety in reducing MTCT rate, focusing on mothers with high viral load.

Methods

Literature Search Strategy

This systematic review is carried out according to the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) guidelines [36]. The Population, Intervention, Comparison, and Outcomes (PICO) for the research questions has been used to break down the clinical questions into searchable keywords (See Table 1) [37]. The literature search was carried out on two electronic databases, namely PubMed and Google Scholar; the precise search terms are available in Table 2. Reference lists of included studies will also be searched. The literature search was carried out from April to July 2020.

Inclusion and Exclusion Criteria

The following guidelines provide a reference to precisely know what the reviewers recommend and, more significantly, a guide for the reviewers to base judgments on the sources used in this analysis. As mentioned above, there has to be strong consistency between the title, aims, question/s, and inclusion parameters of a scoping analysis for the review forms. Studies were included in this systematic review if they met the following inclusion criteria:

1. Studies are published in English and within 2015-2020;
2. Study population: pregnant women with HBsAg positive (preferably with high viral load) and infants born to mothers with positive HBsAg;
3. Comparison intervention: tenofovir as a complementary treatment to active/passive immunoprophylaxis combination system;
4. Outcome measure: the efficacy and safety of using TDF, the efficacy and safety of active and passive hepatitis B immunization, and failure of immunoprophylaxis in the vertical transmission of hepatitis B virus.

Studies were excluded in this systematic review if: (1) study type: editorials, comments, reviews, or letters; (2) study focus: antiviral analogues other than TDF, hepatitis B with co-infection of other diseases such as HIV and HCV.

Data Extraction and Quality Appraisals

Data extracted using an excel form includes study characteristics, participant baseline characteristics, intervention details, and outcomes of interest. The risk of bias of Randomized Controlled Trials (RCTs) and Non-Randomized Controlled Trials (NRCTs) was measured using The Cochrane Collaboration's tool and Newcastle-Ottawa scale, respectively (Table 3) [38,39].

Outcome Measurements

Outcomes of interest in this systematic review include maternal efficacy, MTCT rate, and safety for both maternal and infants. Maternal outcomes included HBV DNA suppression, HBeAg seroconversion, severe flares of ALT levels, cesarean section rates, postpartum haemorrhage, and adverse events grade 3 and 4. Infant outcomes included HBsAg and HBV DNA positive within 24 hours after delivery, vertical transmission (defined as HBsAg positive at 6–12 months or HBV DNA positivity at 6–12 months), titer anti-HBs detected at 6-12 months, and adverse events grade 3 and 4, prematurity, congenital malformations, and infant death.

Results

A PRISMA flow diagram summarizing the study selection process is illustrated in Figure 1. A total of 360 potential studies were identified through May 22, 2020, in the initial search of databases. After eliminating duplicates and initial screening by browsing their titles and abstracts, 55 publications were identified; and we performed further screening by browsing the remaining publications' full texts. Finally, nine studies [13,40-47] that met the inclusion criteria were analyzed in this systematic review. The reasons for excluding each article are shown in Figure 1.

Characteristics of Eligible Studies

Nine studies that fit the inclusion criteria of this systematic review involved 2 RCT studies and 7 NRCT studies, with total participants of 1935 mothers and 1830 infants. Included studies were published from 2015 to 2019. The study sites were located in China (3), Taiwan (2), Thailand (1), Canada (1), Australia (1), and France (1).

In all studies, inclusion subjects' criteria were women with HBV DNA viral load greater than 2x105 IU/mL or women with HBeAg positive. The number of participants in the studies varied from 23 to 474 participants. 7 Study compared an intervention group where pregnant women receive TDF administration with a control group. 2 Study conducted by Wang et al. (2018) and Sellier et al. (2017) is a single-arm design study so that there

Table 1: PICO framework

PICO framework	Keywords / *Evidance Based Practice*
P: *Population*	Mothers with HBsAg positive focusing on those with high viral load, and their infants.
I: *Intervention*	Antiviral prenatal focusing on TDF.
C: *Comparison*	Controls or no intervention in addition to the immunoprophylaxis combination strategy.
O: *Outcomes*	1. Number of immuoprophylaxis failure and MTCT rate. 2. Maternal efficacy with main parameter of HBV DNA suppression 3. Adverse effects and toxicity in both mothers and infants.

Table 2: Keywords search

No.	Keywords / Search strategies	Total
Database: Pubmed		
1	((("hepatitis b"[MeSH Terms] OR "hepatitis b"[All Fields]) AND ((((("infectious disease transmission, vertical"[MeSH Terms] OR ((("infectious"[All Fields] AND "disease"[All Fields]) AND "transmission"[All Fields]) AND "vertical"[All Fields])) OR "vertical infectious disease transmission"[All Fields]) OR ("vertical"[All Fields] AND "transmission"[All Fields])) OR "vertical transmission"[All Fields])) AND ((((((("antiviral agents"[Pharmacological Action] OR "antiviral agents"[MeSH Terms]) OR ("antiviral"[All Fields] AND "agents"[All Fields])) OR "antiviral agents"[All Fields]) OR "antivirals"[All Fields]) OR "antiviral"[All Fields]) OR "antivirally"[All Fields])	220
2	"Hepatitis B Vaccines/therapeutic use"[All Fields] AND ((((((((((((((((((((("infect"[All Fields] OR "infectability"[All Fields]) OR "infectable"[All Fields]) OR "infectant"[All Fields]) OR "infectants"[All Fields]) OR "infected"[All Fields]) OR "infecteds"[All Fields]) OR "infectibility"[All Fields]) OR "infectible"[All Fields]) OR "infecting"[All Fields]) OR "infection s"[All Fields]) OR "infections"[MeSH Terms]) OR "infections"[All Fields]) OR "infection"[All Fields]) OR "infective"[All Fields]) OR "infectiveness"[All Fields]) OR "infectives"[All Fields]) OR "infectivities"[All Fields]) OR "infects"[All Fields]) OR "pathogenicity"[MeSH Subheading]) OR "pathogenicity"[All Fields]) OR "infectivity"[All Fields]) AND (((((("mother s"[All Fields] OR "mothered"[All Fields]) OR "mothers"[MeSH Terms]) OR "mothers"[All Fields]) OR "mother"[All Fields]) OR "mothering"[All Fields]))	37
3	25017181,24560676,25240752,24119736,28231660,28651839,15791611,22993824,7778007,23880364,28198787,8470152, 23571179,17090857,29195717,12117014,8124773,24681228,27539335,22096953,12666586,28199772,26962060,27684874, 2967932,9841230,26600319,23279881,27113166,28320591,27095043,10500670,7874702,28863182,21757978,24370706, 20116181,1362320,2149403,20512395,15809901,27105563,24975813,25149478,10051503,25493019,24216032,1533439, 18208419,23985279,11509998,25252192,9768208,28592091,23625988,27559947,15726538,23533578,26117148,17714836, 15954422,22959987,26447601,27087206,1395837,8938161,9433150,16941267,12148110,1833611,17636112,23422028, 23732904,28859430,8221430,25988560,22210140,7491231,10228050,8906537,17269193,26920790,15864200,9500584, 17875984,26201556,7571846,7571844,7571843,7571815,30506691[UID]	23
4	("hepatitis b"[MeSH Terms] OR "hepatitis b"[All Fields]) AND ((((("infectious disease transmission, vertical"[MeSH Terms] OR ((("infectious"[All Fields] AND "disease"[All Fields]) AND "transmission"[All Fields]) AND "vertical"[All Fields])) OR "vertical infectious disease transmission"[All Fields]) OR ("vertical"[All Fields] AND "transmission"[All Fields])) OR "vertical transmission"[All Fields])	20
Database: Google Scholar		
1	Hepatitis B AND vertical transmission AND Tenofovir "Seropositive mother"	12
2	Hepatitis B AND Vaccination "Seropositive mother"	48

is no control group. All pregnant women in the intervention group were given TDF at a dose of 300 mg daily except for the study by Sellier et al. (2017), the dose of TDF given is 245 mg daily; for research by Thilakanathan et al. (2018), lamivudine 100 mg per day was given to participants recruited from 2008 to 2010. The duration of TDF treatment varied for each study; most studies started treatment from gestational week 24-32 until 4-12 weeks following delivery, whereas for research by Wang et al. (2018), the treatment end at delivery. All infants involved in the inclusion study received HBIg at birth and three doses of hepatitis B vaccine with variable timing according to health protocols for each country or agency involved. Detailed characteristics of each included study are available in Table 4 and Table 5.

Maternal Efficacy and MTCT Rate

Table 6 summarizes the maternal efficacy findings and the MTCT rate of the included studies. Overall, six studies [13,40-43,47] reported that compared to controls, TDF treatment significantly increased HBV DNA suppression at delivery. The parameter of HBV DNA suppression varied for each study (< 200,000 IU/mL for Pan et al. [13], Jourdain et al. [42], and Wang et al. [47]; < 2,000 IU/mL for Lin et al. [43]; and < 1,000,000 IU/mL for Chang et al. [40] and Chen et al. [41]). Three studies reported the HBeAg seroconversion rate under 5% for both study groups [13,41,47]; there was no significant difference between the two groups in this parameter.

Five studies [13,40-42,47] reported infants with HBsAg and HBV DNA positive within 24 hours after delivery. Three out of five studies consistently show that the number of HBsAg seropositivity tended to be lower in the TDF group [40-42]; however, the difference was not significant. This result aligned with a single-arm study by Wang et al. [47], whereas the number of infant HBsAg positive remains under 5%. In the study conducted by Pan et al. [13], the number of HBsAg positive infants tended to be higher in the intervention group, namely 6.2% (6/97) in the TDF group and 4% (4/100) subjects in the control group. These results happened because the data used are intention-to-treat subjects; in other words, subjects who resigned or lost-to-follow-up during the study were categorized as babies born with positive HBsAg. TDF consistently show improvement in reducing infant HBV DNA seropositivity at delivery. All five studies reported that the number of infants with HBV DNA positive at delivery in the TDF group remains under 10% as for the control group, the number varied between 1% to 31%.

All nine studies [13,40-47] reported infants with HBsAg positive within 6-12 months. Overall, the number of infants with HBsAg positive was lower in the TDF group than in the controls. Four studies [13,40,41,43] reported the difference between two groups are significant (P < 0,05). Three studies [42-44] reported zero cases of HBsAg positive infants in the TDF group. Similar results were shown in a single-arm study by Sellier et al. [45], which reported zero cases and Wang et al. [47], which reported the number of infants with HBsAg positive under 1%. Only one study by Thilakanathan et al. [46] show a higher number of HBsAg positive in the TDF group (2%) compared to controls (0%); however, the number did not differ significantly. It was later known that the babies with HBsAg positive were born from mothers with high viral load (>106 IU/mL), and both mothers have a low adherent in carrying out the treatment. These results indicate that prenatal TDF followed by HBIg and vaccination can reduce the rate of vertical transmission and possibly immunoprophylactic failure.

Four studies [42,43,45,47] reported HBV DNA seropositivity of infants within 6-12 months, where the results were consistently lower in the TDF group than controls. All three studies show zero cases in the TDF group, and under 1% for study by Wang et al. [47]. Another parameter to detect immunoprophylaxis failure is detected titer anti-HBs; five studies [40-42,45,46] reported anti-HBs in infants 6-12 months old. The results tended to show a higher scope of anti-HBs positive in the TDF group; however, the number was similar between the two groups.

Safety of Maternal and Fetal

All the included studies reported maternal and infant safety outcomes [13, 40–47]. Compared to controls, TDF therapy did not significantly differ in maternal harm. The number of adverse events occurs in both groups were similar; Jourdain et al. [42] mentioned that at least one adverse event occurred on 24% (41/168) subjects in the TDF group and 27% (44/163) subjects in the control group. One of the most common adverse events is elevated ALT levels. Five studies [13,41-43,47] reported that the number of ALT flare occurrences tended to be higher in the TDF group; however, there were no significant differences. Other than ALT flares, adverse events grade 3 and 4 reported include elevated creatinine serum levels (1 subject) and pre-eclampsia (1 subject); other adverse events reported were categorized as mild or as grade 1 and 2. There were no differences found in both study groups regarding the rates of cesarean section and postpartum haemorrhages. The number of adverse events in grades 3 and 4 in the two groups is similar. According to Jourdain et al., the most common adverse events reported are jaundice and hyperbilirubinemia [42]; other than that, Pan et al. [13] reported that the two adverse events that occur in the TDF group are forceps induced intracranial haemorrhages and pneumonia. The number of congenital malformations between the two groups did not show any significant difference; congenital malformations reported are torticollis, umbilical hernia, hypospadias [13], polydactyly [41], and chromosome abnormality [44]. The number of prematurity and infant death is comparable between the two groups.

Discussion

One of the biggest challenges in breaking the vertical chain of transmission of the hepatitis B virus is that some pregnant women are in the immunotolerant phase where HBV DNA levels are very high and HBeAg positive [48]. In a study by Alter in 2003, the probability of vertical hepatitis B virus transmission to HBeAg positive mothers is higher than transmission to infants who are not immunoprophylaxis and born to HBeAg negative mothers [49]. Furthermore, there is a correlation between high HBV DNA levels and positive HBeAg during pregnancy and immunoprophylaxis failure. This immunoprophylaxis failure can occur even though the baby has been given HBIg and hepatitis B vaccination. The hepatitis B virus vertical transmission rate also increases significantly at HBV DNA levels 106 to 108 IU / mL, with a vertical transmission rate ratio of 3% at HBV DNA levels <106 IU / mL and 10-30% at HBV DNA levels> 108 IU / mL (Hyun et al., 2017). Besides that, the systematic review by Chen et al. (2017) explained that there was no vertical transmission in pregnant women with HBV DNA levels <2x105 IU / mL. According to several guidelines, such as AASLD [5] and EASL [50], tenofovir disoproxil fumarate (TDF) is a first-line drug for the treatment of CHB. In the last five years, there has

Table 3: Risk of bias assessment 1) For RCTs, risk of bias was assessed with The Cochrane Collaboration's tool. 2) For NRCTs risk of bias was assessed with the Newcastle-Ottawa Scale.

Author (Year)	Country	Study design	Inclusion criteria	Participants		Interventions on Mother			Interventions on Infant
				Mothers	Infants	Dosage	Treatment starts (Gestational weeks)	Treatment discontinuation (Postpartum)	
RCT									
Jourdain et al. (2018)	Thailand	Multicenter trials at 17 public hospitals in Thailand	HBeAg positive; ALT ≤ 30 IU/L at screening and ≤ 60 IU/L at the beginning of trial	168	149	TDF 300mg daily	28	2 months	HBIg + Vaccination
			Same as above	163	147	Control (Immunoprophylaxis only)			HBIg + Vaccination
Pan et al. (2016)	China	Multicenter trials at 5 main regions in China	HBeAg positive; HBV DNA ≥ $2x10^5$ IU/mL	97	95	TDF 300mg daily	30-32	4 weeks	HBIg + Vaccination
			Same as above	100	88	Control (Immunoprophylaxis only)			HBIg + Vaccination
NRCT									
Lin et al. (2015)	China	Multicenter cohort at several hospitals in the Northwest region of China	HBeAg positive; HBV DNA ≥ $2x10^6$ IU/mL	59	58	TDF 300mg daily	24	4 weeks	HBIg + Vaccination
			Same as above	60	52	Control (Immunoprophylaxis only)			HBIg + Vaccination
Chen et al. (2015)	Taiwan	Multicenter prospective cohort at 14 collaborative hospitals in Taiwan	HBeAg positive; HBV DNA ≥ $10^{7.5}$ IU/mL	62	65	TDF 300mg daily	28	4 weeks	HBIg + Vaccination
			Same as above	56	56	Control (Immunoprophylaxis only)			HBIg + Vaccination
Chang et al. (2019)	Taiwan	Multicenter prospective cohort at 14 collaborative hospitals in Taiwan	HBeAg positive; HBV DNA ≥ $10^{7.5}$ IU/mL	110	116	TDF 300mg daily	30-32	4 weeks	HBIg + Vaccination
			Same as above	91	94	Control (Immunoprophylaxis only)			HBIg + Vaccination
Thilakanathan et al. (2018)	Australia	Multicenter prospective cohort at 2 tertiary hospitals in Sydney, Australia	HBV DNA ≥ 10^6 IU/mL on second trimester	168	140	TDF 300mg daily	32	Unclear	HBIg + Vaccination
			HBV DNA < 10^6 IU/mL on second trimester	474	329	Control (Immunoprophylaxis only)			HBIg + Vaccination
Kochaksaraei et al. (2016)	Canada	Single center prospective cohort in Alberta, Canada	HBV DNA ≥ 10^7 IU/mL	23	24	TDF 300mg daily	28-32	12 weeks	HBIg + Vaccination
			HBV DNA < 10^7 IU/mL	138	246	Control (Immunoprophylaxis only)			HBIg + Vaccination
Wang et al. (2018)	China	Single center prospective cohort in Beijing, China	HBeAg positive; HBV DNA > 10^6 IU/mL	143	144	TDF 300mg daily	22-33	Delivery	HBIg + Vaccination
Sellier et al. (2017)	France	Single center prospective cohort in Paris, France	HBV DNA > 10^5 IU/mL on second trimester	23	27	TDF 300mg daily	28	12 weeks	HBIg + Vaccination

Table 4: Characteristics of studies included in the systematic review.

[1]RCT

First author	Selection bias		Performance bias	Detection bias	Attrition bias	Reporting bias	Bias
	Blinding sequence generation	Sequence allocating	Blinding participants	Outcome	Incomplete data outcome	Selective reporting	
Jourdain et al. (2018)	Low (Using permuted blocks and stratified according to trial site.)	Low (Blocks and randomized)	Low (Double-blind, placebo-controlled)	Low (Obtained from lab findings)	Low (Exclusion stated in in fig. 1)	Low (All results in methods are reported)	Low
Pan et al. (2016)	Low (Using randomization table)	Low (Blocks and randomized)	High (No blinding, open label study design)	Low (Obtained from lab findings)	Low (Exclusion data are stated and explained)	Low (All results in methods are reported)	High

[2]NRCT

First author	Selection				Comparability	Outcome			Final score (Max. 8)
	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcome to occur	Adequacy of follow up of cohorts	
Lin et al. (2018)	Somewhat representative of the community or population (*)	Drawn from the same community as the exposed cohort (*)	Secure record (*)	Yes (*)	Study controls for any additional factors (*)	Record Linkage (*)	Yes (*)	Yes (*)	8
Chen et al. (2015)	Somewhat representative of the community or population (*)	Drawn from the same community as the exposed cohort (*)	Secure record (*)	Yes (*)	Study controls for any additional factors (*)	Record Linkage (*)	Yes (*)	Yes (*)	8
Chang et al. (2019)	Somewhat representative of the community or population (*)	Drawn from the same community as the exposed cohort (*)	Secure record (*)	Yes (*)	Study controls for any additional factors (*)	Record Linkage (*)	Yes (*)	Yes (*)	8
Thilakanathan et al. (2018)	Somewhat representative of the community or population (*)	Drawn from the same community as the exposed cohort (*)	Secure record (*)	Yes (*)	Study controls for any additional factors (*)	Record Linkage (*)	Yes (*)	Yes (*)	8
Kochaksaraei et al. (2015)	Somewhat representative of the community or population (*)	Selection of non exposed differ from exposed cohort	Secure record (*)	Yes (*)	Study controls for any additional factors (*)	Record Linkage (*)	Yes (*)	Yes (*)	7
Wang et al. (2018)	Somewhat representative of the community or population (*)	No control group	Secure record (*)	Yes (*)	No control group	Record Linkage (*)	Yes (*)	Yes (*)	6
Sellier et al. (2017)	Somewhat representative of the community or population (*)	No control group	Secure record (*)	Yes (*)	No control group	Record Linkage (*)	Yes (*)	Yes (*)	6

Table 5: Baseline information of inclusion criteria in each study

Author (Year)	Mother's Age	Gestational weeks on delivery	HBeAg (%)	Baseline of HBV DNA level (log10 IU/mL)
Jourdain et al. (2018)				
TDF	25.5 (22.6-29.1)[a]	39.0 (38.3-39.7)[a]	100%	7.6±1.5
Control	26.7 (23.5-30.5)[a]	38.9 (38.1-40.0)[a]	100%	7.3±1.7
Pan et al. (2016)				
TDF	27.4±3.0	39.2±1.0	100%	8.2±0.5
Control	26.8±3.0	38.9±1.3	100%	8.0±0.7
Lin et al. (2018)				
TDF	28.31±3.56	39.46±1.43	100%	7.44±0.80
Control	28.06±3.42	39.33±1.49	100%	7.66±0.55
Chen et al. (2015)				
TDF	32.5±3.2	NR	100%	8.25±0.45
Control	32.4±3.1	NR	100%	8.24±0.35
Chang et al. (2019)				
TDF	32.84 ± 3.57	NR	100%	8.25±0.48
Control	32.69 ± 3.36	NR	100%	8.29±0.49
Thilakanathan et al. (2018)				
TDF	31	NR	94%	NR
Control	31	NR	7.17%	NR
Kochaksaraei et al. (2016)				
TDF	30 (28-34)[a]	NR	70%	7.7(3.2-8.1)[a]
Control	32 (29-36)[a]	NR	9%	2.3(1.6-3.1)[a]
Wang et al. (2018)				
TDF	29.7 ± 4.2	39.3 ± 1.4	100%	7.6±0.59
Sellier et al. (2017)				
TDF	28.2±4.7	NR	81.50%	NR

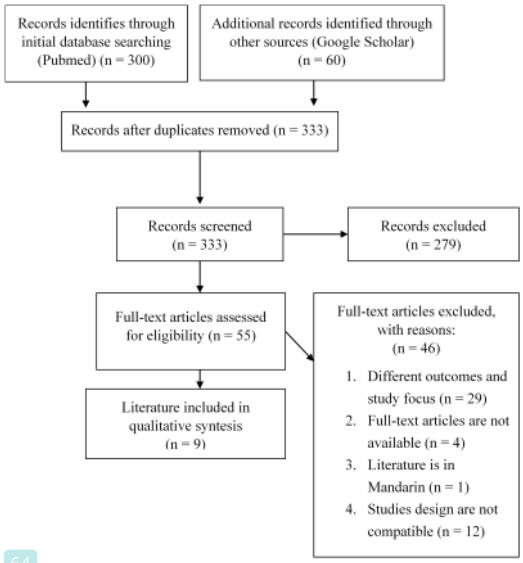

Figure 1:

been an increase in the number of publications that study the efficacy and safety of using TDF as a preventive measure for the vertical transmission of the hepatitis B virus. In determining the efficacy and safety of using TDF and HBIg and vaccination as a preventive measure for vertical transmission, high-quality trials are needed.

Maternal Efficacy of TDF Intervention

Maternal efficacy in this systematic review was seen from 2 parameters: the suppression of viral load HBV DNA and the occurrence of HBeAg seroconversion in the mother. The parameters for HBV DNA suppression themselves varied for each study. According to Lau et al., in a patient with CHB, HBeAg seroconversion was defined as loss of HBeAg in serum and anti-HBe antibodies' progression [51].

Factors that influence immunoprophylaxis failure are HBeAg and HBV DNA seropositivity. This statement is consistently supported by earlier study [18,20,22,52-54]. The HBV DNA cut off as an estimation of immunoprophylactic failure still needs to be explored further. Several studies report risks of immunoprophylactic failure in pregnant women with high levels of viral load HBV DNA such as:

- Zou et al.: Analyzed 27 cases and found that the risk of immunoprophylactic failure was 7.66% for HBV DNA levels above 8log10 IU/mL [22].
- Zhang et al. (2014): Analyzed 28 cases and found a risk of immunoprophylactic failure of 12.1% for HBV DNA levels above 8log10 IU/mL [21].
- Wiseman et al. (2009): As many as 9% (4 of 47 subjects) had a risk of immunoprophylactic failure for HBV DNA levels above 7,2log10 IU/ mL [2009].
- Wen et al. (2013): 27.7% of subjects had a risk of immunoprophylactic failure for HBV DNA levels above 8log10 IU / mL [55].

In this systematic review, it was found that TDF could significantly reduce viral load maternal HBV DNA. A recent RCT study by Jourdain et al. explained that giving TDF showed a significant reduction in viral load HBV DNA [42]. Before the start of treatment, levels of viral load HBV DNA were similar in both groups, namely 7.6log10 IU/mL in the intervention group and 7.3log10 IU/mL in the control group. After TDF administration with a median duration of 10.7 weeks, HBV DNA levels in the intervention group were 4log10 IU/mL compared to 7.3log10 IU/mL in the control group (p <0.001). Research by Pan et al. presented similar results where at delivery, HBV DNA levels in the intervention group were 4.7log10 IU/mL (IQR) and in the control group 8log10 IU/mL (IQR) (p <0.001) [13]; these results were consistently aligned with three NRCT studies [40,41,47]. A significant result was also presented in the NRCT study by Lin et al. where 90% of the subjects in the intervention group had HBV DNA levels <4log10 IU/mL and 50% of them had HBV DNA levels <3log10 IU/mL (p <0.001) [43]. In their research, Lin et al. also explained that the reduction in HBV DNA levels occurred rapidly at the start of treatment and slowed down over time, but the reduction in HBV levels was still at the limit of 0.5log10 IU / mL per month. This result indicates that starting therapy at week 24 was able to keep HBV DNA levels lower from gestation to delivery. This condition is ideal for limiting HBV replication for fetal development.

The study conducted by Pan et al. reported that giving TDF to pregnant women with very high HBV DNA levels did not achieve optimal HBV DNA suppression [13]. In the intervention group with HBV DNA levels more than 200,000 IU/mL at delivery, the number of mothers with HBV DNA levels of more than 8log10 IU/mL before starting treatment was more (39%) than the number of mothers with HBV DNA levels less than or equal to 8log10 IU/mL. The number of pregnant women who experienced HBV DNA suppression ranged from 68% to 98.4% and did not reach 100%; this is due to limited intervention time. According to research by Marcellin et al., the number of pregnant women with positive HBeAg who experienced HBV DNA suppression (<400 IU / mL) after 48 weeks of TDF intervention was 76% [56].

According to clinical trials phase 3 conducted by Marcellin et al., the rate of HBeAg seroconversion after TDF intervention for one year was 21% [56]. The study by Pan et al. and Chen et al. showed that the number of mothers who experienced HBeAg seroconversion was not significantly different in the two groups [13,41]. Prenatal TDF was started at 22 to 32 weeks of gestation and was discontinued at four weeks postpartum for the study by Pan et al. and Chen et al. [13,41]; for Wang et al., TDF intervention was stopped at delivery [47]. According to our data and earlier literature, the TDF administration's timing starting from the 3rd trimester is insufficient for HBeAg seroconversion to occur. There is no evidence or clinical trials of TDF administered earlier than the second trimester. Therefore, supervision and monitoring are needed for mothers with high HBV DNA levels to anticipate immunoprophylaxis failure despite TDF intervention.

TDF Intervention to Prevent MTCT Rate

Overall results shown in Table 6 demonstrated a lower risk of MTCT in the intervention group; 5 included studies support this statement [13,40-42,47]. The reduced risk of vertical transmission (judged by HBsAg positive in newborns) in the intervention group was probably due to low viral load HBV DNA levels or HBV DNA suppression at delivery and earlier fetal prophylaxis exposure [42]. However, there were no significant results in

Table 6: Maternal efficacy and MTCT rate

Author (Year)	Maternal Efficacy		MTCT Rate				
			Newborn Infants (24 hours)	Infants (6-12 months old)			
	HBV DNA Suppression	HBeAg Seroconversion	HBsAg Positive	Detectable HBV DNA	HBsAg Positive	Detectable HBV DNA	Anti-HBS Positive
Jourdain et al. (2018)							
TDF	88% (142/161)	NR	0% (0/149)	0% (0/149)	0% (0/149)	0% (0/149)	100% (147/147)
Control	10% (16/159)	NR	1.4% (2/147)	1.4% (2/147)	2.0% (3/147)	2.0% (3/147)	98.6% (145/147)
Pan et al. (2016)							
TDF	68% (66/96)	1% (1/97)	6.2% (6/97)	3.1% (3/97)	5.2% (5/97)	NR	NR
Control	2% (2/100)	3% (3/100)	4.0% (4/100)	15% (15/100)	18% (18/100)	NR	NR
Lin et al. (2018)							
TDF	90% (53/59)	NR	NR	NR	0% (0/58)	0% (0/58)	NR
Control	0% (0/52)	NR	NR	NR	7.7% (4/52)	13.5% (7/52)	NR
Chen et al. (2015)							
TDF	98.4% (61/62)	4.84% (3/62)	10.77% (7/65)	6.15% (4/65)	1.54% (1/65)	NR	96.92% (63/65)
Control	1.79% (1/56)	0% (0/56)	17.86% (10/56)	31.48% (17/56)	10.71% (6/56)	NR	89.29% (50/56)
Chang et al. (2019)							
TDF	96.36% (106/110)	NR	9.56% (11/115)	5.22% (6/115)	1.74% (2/115)	NR	99.12% (112/115)
Control	3.30%(3/91)	NR	16.13% (15/93)	30.11% (28/93)	11.83% (11/93)	NR	97.59% (81/93)
Thilakanathan et al. (2018)							
TDF	NR	NR	NR	NR	2.14% (3/140)	NR	96.4% (135/140)
Control	NR	NR	NR	NR	0% (0/329)	NR	97,8% (322/329)
Kochaksaraei et al. (2016)							
TDF	NR	NR	NR	NR	0% (0/12)	NR	NR
Control	NR	NR	NR	NR	1.3% (1/73)	NR	NR
Wang et al. (2018)							
TDF	93.7% (134/143)	1.4% (2/143)	3.9% (20/144)	0% (0/144)	0.69% (1/144)	0.69% (1/144)	NR
Sellier et al. (2017)							
TDF	NR	NR	NR	NR	0% (0/27)	0% (0/27)	66.67% (18/27)

Table 7: Maternal safety outcomes

Author (Year)	Maternal Safety Parameters					
	Grade 3 and 4 adverse events	Peningkatan Kreatinin Kinase	Peningkatan Kreatinin Serum	ALT *Flare*	Bedah Sesar	Pendarahan *Post-partum*
Jourdain et al. (2018)						
TDF	24.4% (41/168)	NR	NR	5.8% (9/154)	23.5% (38/162)	NR
Control	27.0% (44/163)	NR	NR	5.01% (8/157)	29.4% (47/160)	NR
Pan et al. (2016)						
TDF	7.2% (7/97)	7% (7/97)	0% (0/97)	5.2% (5/97)	48.5% (47/97)	4.1% (4/97)
Control	11% (11/100)	0% (0/97)	1% (1/100)	6.0% (6/100)	50.0% (50/100)	4.0% (4/100)
Lin et al. (2018)						
TDF	0% (0/58)	NR	NR	3.45% (2/59)	36.2% (21/59)	0% (0/59)
Control	0% (0/52)	NR	NR	0% (0/52)	32.7% (17/52)	0% (0/52)
Chen et al. (2015)						
TDF	NR	NR	NR	5.36% (3/62)	41.54% (25/65)	NR
Control	NR	NR	NR	0% (0/56)	30.36% (17/56)	NR
Chang et al. (2019)						
TDF	NR	NR	NR	NR	32.7% (36/110)	NR
Control	NR	NR	NR	NR	29.7% (27/91)	NR
Thilakanathan et al. (2018)						
TDF	NR	NR	NR	NR	16.7% (28/168)	NR
Control	NR	NR	NR	NR	22% (104/474)	NR
Kochaksaraei et al. (2015)						
TDF	NR	NR	NR	NR	33.3% (8/24)	NR
Control	NR	NR	NR	NR	24.7% (36/146)	NR
Wang et al. (2018)						
TDF	0% (0/143)	NR	NR	0% (0/143)	37.5% (54/144)	0% (0/143)
Sellier et al. (2017)						
TDF	NR	NR	NR	NR	NR	NR

Table 8: Infants safety outcomes

Author (Year)	Infants Safety Parameters				
	Grade 3 and 4 adverse events	Congenital malformations	Low birth weight (<2500g)	Prematurity	Infants death
Jourdain et al. (2018)					
TDF	26.7% (43/161)	NR	NR	4.9% (8/162)	1% (1/162)
Control	23.8% (38/160)	NR	NR	8.1% (13/160)	0% (0/160)
Pan et al. (2016)					
TDF	3.2% (3/95)	2.1% (2/95)	NR	2.1% (2/95)	1.1% (1/95)
Control	1.1% (1/88)	1.1% (1/88)	NR	1.1% (1/88)	0% (0/88)
Lin et al. (2018)					
TDF	0% (0/59)	0% (0/59)	NR	1.69% (1/59)	1.69% (1/59)
Control	0% (0/52)	0% (0/52)	NR	3.85% (2/52)	0% (0/52)
Chen et al. (2015)					
TDF	NR	1.5% (1/65)	NR	7.7% (5/65)	0% (0/65)
Control	NR	0% (0/56)	NR	3.6% (2/56)	0% (0/56)
Chang et al. (2019)					
TDF	NR	NR	NR	NR	0% (0/110)
Control	NR	NR	NR	NR	0% (0/91)
Thilakanathan et al. (2018)					
TDF	NR	NR	NR	NR	0.6% (1/168)
Control	NR	NR	NR	NR	0% (0/474)
Kochaksaraei et al. (2015)					
TDF	NR	0% (0/24)	8.3% (2/24)	8.3% (2/24)	0% (0/24)
Control	NR	0.7% (1/146)	NR	2.1% (3/146)	0.7% (1/146)
Wang et al. (2018)					
TDF	0% (0/143)	0% (0/144)	NR	5.6% (8/144)	0% (0/144)
Sellier et al. (2017)					
TDF	NR	NR	NR	NR	NR

terms of positive HBsAg parameters at newborns (P> 0.05).

According to Thilakanathan et al., HBsAg negative and detectable anti-HBs of more than 10 IU/mL are successful vaccination parameters [46]. Results collected in this systematic review show that prenatal TDF can reduce the incidence of vertical transmission and the risk of immunoprophylactic failure. Besides, 4 out of 9 studies showed significant results (P <0.05). Our results also show that prenatal TDF in the intervention group can reduce HBsAg-positive infants by less than 5%. The first RCT study with a research focus on prenatal TDF administration was conducted in 2016 by Pan et al.; the results showed that the use of prenatal TDF significantly reduced the risk of immunoprophylactic failure with a ratio of 18% in the control group and 5% in the intervention group (p = 0.007) [13]. The first NRCT study was conducted by Celen et al. in pregnant women with HBV DNA> 6log10 IU / mL, where the ratio between the intervention group and the control group was 0% and 8% (p = 0.194) [10]. A subsequent NRCT study by Chen et al. demonstrated a significant reduction in vertical transmission and risk of immunoprophylactic failure in the intervention group with a control group comparison of 1.5% and 10.7% (p = 0.048) [41]. This result is consistently supported by Lin et al. with p = 0.004 and Chang et al., where p = 0.003 [40,43]. In another RCT study by Jourdain et al. (2018), the incidence of immunoprophylactic failure in the 2 study groups was not significantly different, namely 0% for the intervention group and 2% for the control group (p = 0.12). The insignificant difference in both groups may be due to this study's inclusion subject that did not have a viral load high enough to be a risk factor for immunoprophylactic failure, so prevention could be carried out by giving active and passive immunizations.

In the study by Jourdain et al., the number of HBsAg-positive infants at six months was 2% (3/147) in the control group; no HBsAg-positive babies were found in the intervention group [42]. The three infants in the infected control group were born to mothers with HBV DNA levels> 7.8log10 IU / mL, and 2 of the three infants were born HBsAg and HBV DNA positive. A similar pattern was found in the study by Pan et al., Where the number of HBsAg positive infants at examination at 28 weeks was 18 (18%) out of 100 subjects in the control group. A total of 6 infants in the infected control group were born to mothers with viral load HBV DNA> 2log10 IU / mL at delivery, 6 of these infants detected HBV DNA at birth, and 4 of the six infants were born HBsAg positive [3]. These results were supported by five other studies [40,41,43-45,47].

Collected data we analyze in this systematic review shows that prenatal TDF followed by HBIg and vaccination provides more coverage for infants with anti-HBs positivity than the control group. In the study by Jourdain et al., The number of subjects in the intervention group with anti-HBs> 10 IU / mL reached 100% [42]. Furthermore, infants in the control group who had low anti-HBs (<10 IU / mL) were detected positive HBsAg or, in other words, infected with the hepatitis B virus. Research by Sellier et al. coverage of infants with anti-HBs positive and> 10 IU / mL is around 67% (18/27), which is a pretty low number due to the remaining 8 out of 27 subjects aged <9 months and not examined [44]. A similar pattern was found in 3 other studies, and the overall coverage of infants with anti-HBs positive or > 10 IU / mL in the intervention group was over 95% [40,41,46]. The high coverage of anti-HBs detected in the TDF group follows the meta-analysis presented by Li et al., where the provision of TDF can reduce the risk of immunoprophylactic failure.

Maternal and Fetal Safety of TDF Intervention

In addition to the efficacy and advantages of using prenatal TDF, it is necessary to examine further the safety of using prenatal TDF followed by HBIg and vaccination. Overall, there were no significant differences between the TDF and control groups when viewed from several parameters, including adverse effects of grades 3 and 4 in mothers and infants, ALT flares in mothers, cesarean delivery, and postpartum bleeding congenital malformations, prematurity, and fetal death. A study by Jourdain et al. recorded that at least one adverse incident (p=0.62) occurred in 24% of pregnant women in the intervention group and 27% of pregnant women in the control group [42]. Elevated ALT level in the most common adverse event. The findings also showed that pregnant women in the control group appeared to experience adverse reactions before the intervention group. However, there was no substantial difference between the two groups in the postpartum group (p=0.50) [42].

Furthermore, Pan et al. explained two noticeable adverse events in both study groups. The first difference is the finding of more pregnant women who experienced an increase in creatinine kinase levels in the intervention group (7%) compared to the control group (0%) (p = 0.006); however, an increase in creatinine kinase is still categorized as an adverse event grade 1 or 2. [13]. Furthermore, the second difference was that more pregnant women experienced elevated ALT in the intervention group (45%) compared to the control group (30%) (p = 0.03) [13]. Similar results were found in the study by Wang et al. and Lin et al., where no grade adverse events 3 or 4 were found in either study group [43,47]. In 6 studies that described ALT flares in mothers during the duration of the intervention, the results were mixed and inconsistent. The study by Chen et al. reported that the number of elevated ALT> 5 times above normal levels was lower in the intervention group 1-2 months postpartum (p = 0.0218 at month one and p = 0.0135 at month two) [41]. Another study reported that the incidence of ALT flares with telbivudine or lamivudine was 17.1% in the intervention group and 6.3% in the control group [29]. Nguyen et al. described ALT flares' prevalence in pregnant women with lamivudine intervention or prenatal TDF of 40-50% compared to 29% in the control group [58]. This variable rate was due to the different definitions of ALT flares in each study, different protocols for follow-up, and the use of different antiviral agents. According to a study conducted by Jourdain et al., ALT flares that occurred in mothers started at the time of discontinuation of TDF use; in addition to the six months postpartum follow-up, none of the mothers experienced or returned to experiencing ALT flares [42]. Overall, prenatal TDF did not result in a significant increase in ALT. According to Cheung and Lao's review, amniocentesis and delivery path influence immunoprophylactic failure [53]. The study results presented in this inclusion study systematic review indicated no significant difference between the intervention group and the control group in terms of the number of cesarean section deliveries. Our result of the cesarean section is supported by Hyun et al. with a p-value = 0.24 and Chen et al. (2017) with a p=0.521 [34.59]. Furthermore, safety during the maternal period in terms of the rate of postpartum bleeding; the included study results on this systematic review revealed no significant differences between the 2 study groups. A meta-analysis by Hyun et al. supports these findings with p= 0.61 [34].

Research by Jourdain et al. reported that 27% of infants in the intervention group and 24% of infants in the control group experienced at least one adverse event grade 3 or 4(p = 0.61) [42].

The most common adverse events are jaundice or hyperbilirubinemia. In the results of the study by Pan et al., no significant difference was found in the two study groups (p> 0.05) [13]. These study results are consistently supported by Wang et al. and Lin et al., where no infants experienced grade 3 or 4 adverse events in both study groups [43,47].

In terms of the number of congenital malformations in infants, the results of the study by Pan et al. explained that there was no significant difference found in the two study groups (p> 0.05) [13]. Findings on congenital malformations are consistently supported by four other inclusion studies [41,43,44,47]; Hyun et al. showed similar results with a value of p = 0.58 [34]. Furthermore, in terms of the number of preterm births, the study by Chen et al. presented that there was no significant difference between the two study groups (p = 0.4) [41]. A similar pattern was found across all the included studies in this systematic review. Infant safety was also seen in the number of infant deaths, which was not significantly different across the included studies involved (p> 0.05). Overall, there were no significant differences in safety in both maternal and infancy. A meta-analysis by Hyun et al. and Chen et al. supports this statement [34,59]. Further research is needed with more RCT study designs to cover a broader range of safety parameters for using TDF during pregnancy and in infants and long-term monitoring of infant growth and development.

Conclusion

In conclusion, our systematic review suggested that oral TDF therapy starting from the second or third semester reduced HBV DNA levels in infected pregnant women with high viral loads. It also reduces the rates of MTCT defined by HBsAg positivity in infants. Moreover, tenofovir was safe and tolerable for both mothers and their infants; therefore, to prevent MTCT, we recommend TDF administration in pregnant women with CHB and who manifest high HBV DNA levels of > 2×105 IU/mL starting from the third trimester in addition to immunoprophylaxis combination therapy.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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