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Review

Tenofovir disoproxil fumarate for preventing mother-to-child transmission of hepatitis B: a literature review

Iulia Baciu[1], Dalila-Ana Domuncu[2], Tiberiu Domuncu[3], Anca Marina Ciobanu[1], Theodor Voiosu[4,5], Gheorghe Peltecu[1,5], Anca Maria Panaitescu[1,5,*]

[1]*Obstetrics-Gynecology, Filantropia Clinical Hospital, 010082 Bucharest, Romania*

[2]*Intensive Care Department, National Institute for Infectious Diseases "Prof. dr. Matei Balș", 010082 Bucharest, Romania*

[3]*Department of Nephrology, "Dr. Carol Davila" Clinical Nephrology Hospital, 010082 Bucharest, Romania*

[4]*Department of Gastroneterology, Colentina Hospital, 010082 Bucharest, Romania*

[5]*Carol Davila University of Medicine and Pharmacy Bucharest, 010082 Bucharest, Romania*

*Correspondence: anca.panaitescu@umfcd.ro (Anca Maria Panaitescu)

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Infection with the hepatitis B virus (HBV) is one of the leading global public health issues. Over 250 million people worldwide have chronic HBV infection, out of which roughly 65 million are women in their reproductive age. The most common route of passing the infection in areas of high endemicity is by mother-to-child transmission (MTCT). In children the infection may still occur despite adequate immunoprophylaxis, however, antiviral medication, such as Tenofovir disoproxil fumarate (TDF), may be helpful in reducing the risk of MTCT. A literature review was conducted concerning TDF's role in preventing MTCT and its safety in pregnancy. Studies were identified by researching various databases up to 2020 for variations of the following sentence: "Tenofovir disoproxil fumarate and Lamivudine and Telbivudine and Entecavir and pregnancy and transmission and safety and HBV". Prenatal and perinatal adequate management of maternal HBV infection is of utmost importance, with focus on prevention of MTCT as the key strategy to reduce the global HBV infection burden. This review discusses the most up-to-date evidence from a multidisciplinary perspective of using TDF to reduce MTCT of HBV infection as well as its safety profile for pregnant women.

Keywords

Tenofovir; Hepatitis B; Transmission; Mother to child; Fetal infection; Prevention

1. Introduction

Infection with the hepatitis B virus (HBV) is a major cause of global health concern especially because of its chronic persistence and potential evolution to cirrhosis and hepatocellular carcinoma. Prevalence of HVB varies worldwide - it reported as high as 12% in countries in East Africa, as less than 1% in most European countries and the United States and around 4% in Romania [1, 2]. For all countries, more than 250 million individuals are thought to be chronically infected, with approximately 65 million being women of reproductive age [3]. HBV infection during pregnancy unfolds similarly to what we would expect for the general adult population; it does not specifically increase maternal mortality, nor does it have teratogenic effects [4]. However, it does pose a significant risk for mother-to-child-transmission (MTCT) and the earlier in life the infection is acquired, the greater its likelihood of persisting as chronic. Up to 90% of those infected perinatally may develop chronic infection, and almost 30% will end up with cirrhosis [5]. In areas with a high HVB prevalence, MTCT is the primary source of infection. MTCT occurs most commonly around the time of delivery but may also occur during the intrauterine period or the postpartum period [6].

Screening for HBV in pregnancy is recommended worldwide, and all newborn infants should be vaccinated within the first 24 hours after birth, and thereafter receive at least two additional doses at later times [7]. Newborns of HBsAg-positive mothers also receive within the first 24 hours, hepatitis B immune globulin (HBIG) (known as passive immunoprophylaxis) in addition to their first vaccination dose (active immunoprophylaxis) [8]. With this approach, there is a reported reduction of 95 to 97% in MTCT rates [8]. MTCT during pregnancy and delivery is associated with blood levels of maternal HBV DNA [9]. The rate of MTCT at a maternal HBV DNA level of 5 log10 was estimated at 0.9%, and it seems to increase significantly for every log increase as demonstrated in a study by Wen *et al.* [10]. The main risk factors for MTCT are the maternal high HBV DNA (HBV DNA $>$ 200.000 IU/mL) [11] and the HBeAg-positivity [12]. In women with chronic HBV infection, the risk of MTCT without prophylaxis is different according to the HBeAg/anti-hepatitis B-antibodies (HBeAb) status of the mothers, varying from 12% for HBeAg-negative/HBeAb-positive mothers, to 25% for HBeAg-negative/HBeAb-negative mothers and being as high as 70%-90% for HBeAg-positive/HBeAb-negative mothers [13].

Given the fact that 70% of those infected with HBV are in high endemic countries (Asia and Africa), most of chronic

HBV infections result because of acquiring the virus around birth or during early childhood [14]. In 2019, WHO estimated that the complete vaccination schedule (the three doses of the hepatitis B vaccine) reached an 85% global-wide coverage, but only 43% of infants received their first dose in the 24 hours after birth, the coverage being as high as 84% in Western Pacific Region and as low as 6% in the African region [15]. This difference shows the importance of implementing efficient vaccination strategies in resource-limited countries, taking into account that around 50 million new cases of hepatitis B are still being diagnosed each year, mostly in relation to MTCT [16].

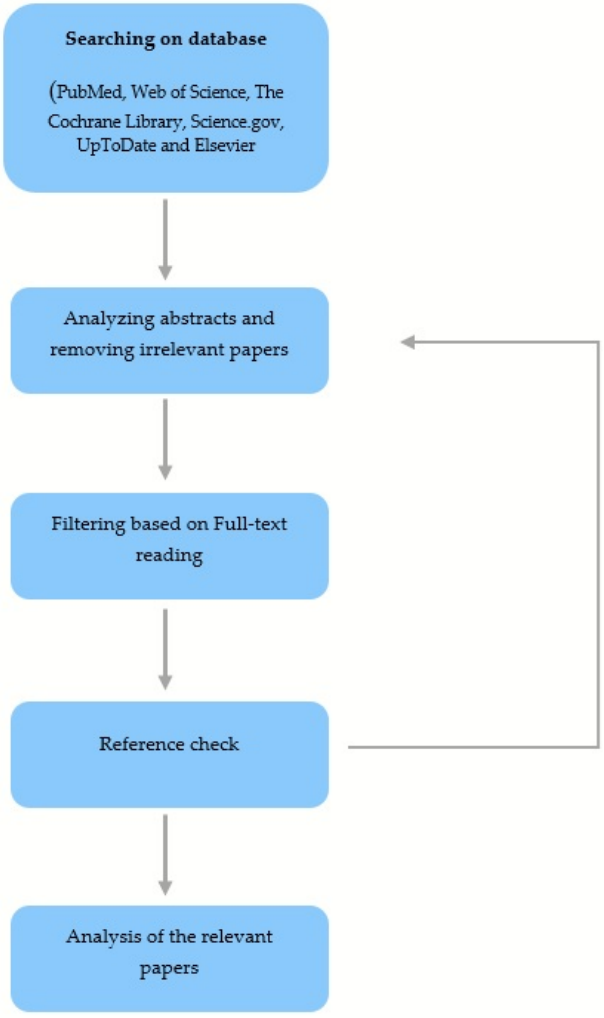

Fig. 1. The flow chart of papers selection.

Intrauterine transmission is considered to account for only a small proportion of the cases of HBV transmission that are not targeted by at birth prophylaxis. In a Chinese case-control study among 402 newborns, 15 (3.7%) had detectable serum HBsAg in the first 24 hours after birth, but there was no follow-up of infants to confirm acquired infection. HBeAg positivity, threatened preterm labor, maternal serum HBsAg titers and HBV DNA concentration were associated with a higher risk for intrauterine infection, as was the presence of HBV in placental tissue and in the endothelial cells of the villous capillaries [17]. Invasive intrauterine procedures such as amniocentesis are likely to increase the risk for MTCT, with maternal HVB DNA $>$ 7.0 log10 IU/mL and HbeAg positivity being reported as the main risk factors [18].

Treatment of HBV infection in pregnant women has been generally advised when: 1) there is active liver disease and targeted treatment could no longer be delayed; 2) in women who conceive while on therapy and 3) for prevention of HBV MTCT when high HBV DNA are measured [9]. Another potential indication is to prevent MTCT at the time of invasive procedures (placental biopsy, amniocentesis, fetal blood sampling) undertaken during pregnancy for fetal diagnosis in cases of prenatal screening anomalies, however more studies are required to clarify this issue [18]. The risks and benefits when choosing a therapeutic approach for HBV infection treatment in pregnancy must be weighted keeping in mind that the effect is on both the mother and the fetus (potential exposure to teratogenic drugs) [19]. The two options of treatment in adult population are interferon-alfa and nucleos(t)ide analogues (NAs). While interferon-alfa is contraindicated in pregnancy, the concept of NA agents in pregnant women with a high HBV DNA in order to reduce the rate of mother to child transmission has been proposed and extensively investigated over the last years.

The current paper has taken into consideration the following NAs: Tenofovir disoproxil fumarate (TDF), Lamivudine (LAM), Tenofovir alafenamide, Telbivudine (TBV), Entecavir and Adefovir. Table 1 is a brief description of the main characteristics of these drugs.

Among the oral anti-HBV agents, TDF is a potent antiviral drug preferred during pregnancy [20, 21]. While an issue with other NAs, with TDF, resistance is developing rarely, and this is important because many women that are treated during pregnancy might require treatment for the liver condition in their future life [20, 21]. Tenofovir disoproxil fumarate, a nucleotide reverse transcriptase inhibitor, is an analogue of adenosine 5'-monophosphate; it interferes with the HBV viral RNA dependent DNA polymerase resulting in inhibition of viral replication. The drug is first converted intracellularly by hydrolysis to Tenofovir and thereafter phosphorylated to the active tenofovir diphosphate. Tenofovir inhibits replication of HBV by inhibition of HBV polymerase (Fig. 2) [28].

A potential problem in relation to the use of TDF is its renal action. Extensive clinical data revealed that TDF might have an impact on renal function, particularly on tubular function, with no clinical expression unless exacerbated by certain risk factors such as age, hypertension/preeclampsia, diabetes, HIV associated kidney disease, or combination therapy with ritonavir-boosted protease inhibitors. Clinically, renal dysfunction induced by TDF manifests as partial or complete Fanconi syndrome: glycosuria with average serum glucose, uricosuria with hypouricemia, phospha-

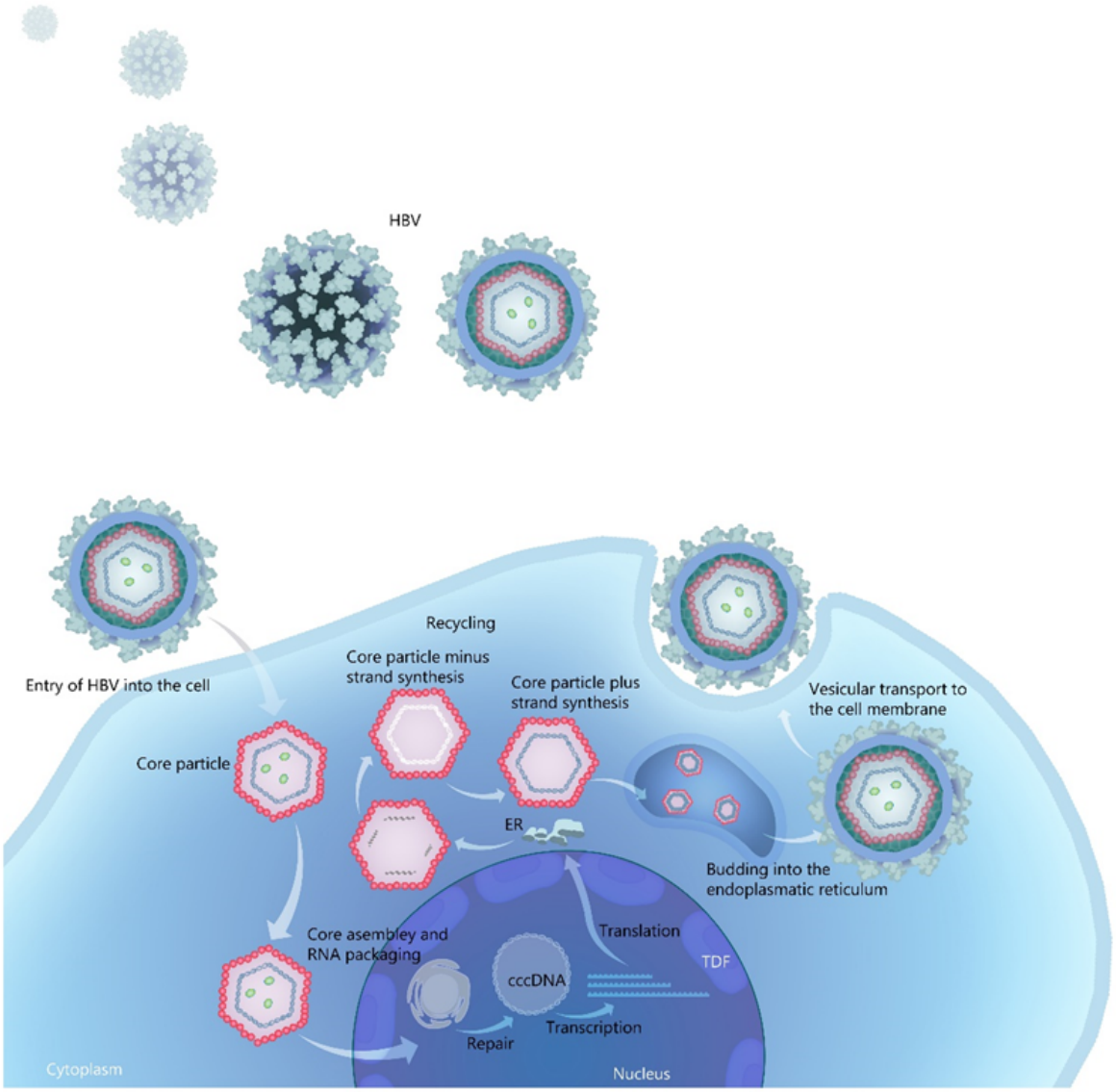

Fig. 2. Tenofovir disoproxil fumarate (TDF) - mechanism of action .

turia with hypophosphatemia and proteinuria (mainly beta-2 microglobulin). Screening for tubular dysfunction in patients undergoing treatment with TDF may be undertaken by the use of beta-2 microglobulin [29, 30]. There is a small decrease in glomerular filtration rate (GFR) associated with long-term use of the drug [31], meaning that pregnant women receiving TDF for MTCT prevention should not be at risk in this regard. Baseline estimated GFR (eGFR) calculations using CKD-EPI creatinine measurements, followed by repeated measurements every 1 to 3 months seems an appropriate management strategy to screen for renal disease, although this data derives from the recommendations of the Southern African HIV Clinicians Society, British and European HIV Societies regarding treatment with TDF in HIV patients. Also, some entities advocate urine dipstick testing and measuring albumin-to-creatinine ratio if risk factors are present [32, 33]. Overall, most studies show that TDF is safe in pregnant women in regards to clinical renal function for short to medium term use.

1.1 Objective and scope

This review aims to bring together current data on the efficacy and safety of TDF during pregnancy in women with HBV infection. We discuss timing of treatment initiation for reducing MTCT, other indications for treatment including the appropriate selection of pregnant patients, dosage consideration and the aspects of management. The paper was designed to offer a multidisciplinary view of the topic. There are many meta-analysis and literature reviews on efficacy and safety of TDF during pregnancy, but we aimed to bring together the perspective of maternal-fetal medicine, infectious disease, gastroenterology, and nephrology specialists.

Table 1. Nucleos(t)ide analogues - Essential Characteristics [20–27].

	Tenofovir disoproxil fumarate (TDF)	*Lamivudine (LAM)*	*Tenofovir alafenamide*	*Telbivudine (TBV)*	*Entecavir*	*Adefovir*
Safety	Appear safe	Appear safe	Not enough data	Appears safe	Not enough data	Not enough data
Prevention of MTCT	Yes	Yes	Not enough data	Yes	Not enough data	Not enough data
Resistance	Very rare	High risk	Not enough data	High risk	Not enough data	Not enough data
Teratogenicity	No	No (in human trials)	Not enough data	No	Not enough data	Not enough data
Bone abnormalities	No, according to recent data	Not associated	Less than TDF	Not associated	Not associated	Not associated

MTCT = mother-to-child-transmission

2. Methods

An online literature search was performed between February 2020 and July 2020 to identify relevant English articles regarding the efficacy and safety of tenofovir disoproxil fumarate (TDF) in the prevention of MTCT of Hepatitis B. We searched for comparing purposes articles regarding the other most used antivirals, Lamivudine (LAM), Tenofovir alafenamide, Telbivudine (TBV), Entecavir and Adefovir. Publications and abstracts up to 2020 were searched and obtained from the following databases: PubMed, Web of Science, The Cochrane Library, Science.gov, UpToDate and Elsevier. Different variations of the following phrase were searched mainly in the abstracts: "Tenofovir disoproxil fumarate and Lamivudine and Telbivudine and Entecavir and pregnancy (pregnant) and transmission and safety and HBV (hepatitis B)". Moreover, cited articles in the selected studies were manually examined to prevent any omission of related studies. Relevant articles that had one or more of the following criteria were excluded: animal studies, case reports and letters to the editor (Fig. 1).

2.1 Efficacy of TDF in preventing MTCT of HBV infection

Despite active-passive immunoprophylaxis, HBV transmission occurs in 1 up to 4% of children born to mothers with HBV (HBeAg positive or detectable HBV DNA) [34]. Primary factors contributing to mother to child transmission include HBeAg-positivity, high HBV-DNA (HBV-DNA $>$ 200,000 IU/mL), intrauterine infection and viral mutation [34]. Mechanisms reported to be probably involved in the intrauterine infection are passage of the serum through the damaged placenta, transmission of infected germ cells and the transfer of infected placenta or peripheral blood mononuclear cells [8]. Viral mutation might also be a matter of concern. First identified in 1988, a point mutation in the surface antigen region lead to the emergence of a vaccine-induced escape mutant of HBV that produced infection in infants born to HBsAg carrier mothers despite active-passive immunoprophylaxis [35, 36]. Also, drug resistant HBV mutants may appear as a consequence of treatment with NAs (especially Lamivudine) and apart from the alterations in the "Pol" gene, they may cause alterations in the S gene encoding the surface protein, thus infecting both naïve and immunized people [37]. Currently, vaccine escapes mutants are still rarely accounted for and they do not pose a serious public threat [38].

Available guidelines advise initiation of antivirals in the third trimester of pregnancy as an additional method to HBIG and vaccination for the reduction of MTCT [39]. Their protective effect was evident in a meta-analysis of 26 studies involving 3622 pregnant women [21]. Among antivirals, TDF is the preferred choice because it is rarely associated with resistance and also, because TDF is well investigated in terms of efficacy and safety. Several trials on its use were published during the last years, out of which two were randomized-controlled trials (RCTs) (Table 2). The results showed that TDF, administered in the last trimester of pregnancy up to one month postpartum, decreased the rate of MTCT of HBV significantly versus placebo for HBeAg-positive women with high HBV DNA. Surprisingly, the most recent RCT failed to detect a significant difference between the TDF group and the placebo arm (no infections vs three infections, respectively). TDF was administered from 28 weeks of gestation up to 2 months post-delivery in HBeAg-positive women, most of them having a HBV DNA $>$ 200,000 IU/mL [40]. The results of this trial interpreted as a negative trial, rose questions over the usefulness of NAs, and specifically TDF, as an additional preventive measure during the last part of pregnancy. Although the sample size was larger than that in the previous randomized trial, the HBV transmission rate in the placebo group was only 2%, lower than in previous data showing a transmission rate of about 7 to 12% in the group of infants who received HBV vaccine and HBIG as standard care. This lower transmission rate could be the result of an earlier administration after birth of the first dose of HBV vaccine.

Despite different results of the two randomized trials, several non-randomized studies showed the beneficial effect of TDF in reducing the rate of MTCT when administered in selected cases during the third trimester of pregnancy [20–22].

A recent prospective uncontrolled study of 147 patients looked at the efficacy and safety of TDF. HBsAg was detected in 13.9% of newborns at birth, but it did not persist in any of the cases at 28 weeks postpartum, with mother to child transmission rates among infants of 0% per protocol. The study concluded that TDF was tolerated well with no significant side effects for mothers nor infants and reduced mother to child transmission of HBV in mothers with a high HBV DNA [41].

Another retrospective study, enrolling 145 pregnant women with HBV DNA $>1.0 \times 10^7$ copies/mL and increased

ALT, confirmed the efficacy of TDF. The findings showed no MTCT in patients on TDF treatment while a rate of 11.1% ($P < 0.001$) was reported in patients without anti-HBV treatment [42].

2.2 When and how to use TDF in pregnancy

In order to prevent MTCT pregnant women should be screend, in those with high HBV DNA levels antiviral therapy should be given, regardless whether they are acutely or chronically infected and passive-active immunisation to newborns of mothers who are HBsAg positive should be offered. Screening in pregnant women is universally recommended in the first trimester by assessing serum HBsAg [29]. For women who screen positive for HBV (HBsAg positive) in the first trimester, further testing is required to measure the baseline HBeAg, HBV DNA and aminotransferase levels. If the HBV DNA load is low in the first trimester, the recommendation is to repeat the test around 26-28 week's gestation [39]. In the cases with HBV DNA greater than 200,000 IU/mL in the first trimester, the women should also be referred to a hepatologist. The most recent international guidelines recommend the use of antiviral prophylaxis starting from week 24-28 of pregnancy if the HBV DNA is higher than 200.000 IU/mL [39]. This threshold for treatment was established based on the observations of a retrospective study involving 869 pregnant women in which the failure in preventing MTCT occurred only in infants born to HBeAg-positive mothers with viral loads > 200.000 IU/mL [43]. World Health Organization 2020 Guideline on antiviral prophylaxis in pregnancy recommend that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA $\geq$ 5.3 log10 IU/mL ($\geq$ 200,000 IU/mL) receive tenofovir prophylaxis from 28 weeks until at least at birth [14]. In resource-limited countries where quantitative determination of HBV DNA is not feasible, patients are eligible for TDF prophylaxis taking into account the presence of AgHBe, given a systematic review commissioned by WHO that showed the overall sensitivity and specificity of HBeAg for diagnosis of high HBV viral load (defined as $\geq$ 200,000 IU/mL) was 88.2% and 92.6% respectively [14].

The management for women with autoimmune hepatitis or with advanced fibrosis is as per that of non-pregnant women. In case of severe hepatitis in a pregnant woman, differential diagnosis is essential to exclude conditions specific to pregnancy, such as acute fatty liver of pregnancy or HELLP (hemolysis, elevated liver enzymes and low platelets) syndrome. Once the viral the etiology is certain, the recommendations applying to the general adult population should be followed, and in selected cases, the treatment should rely on NA agents (Fig. 3).

Pregnancy does not seem to interfear with the evolution of a chronic HBV infection in women without advanced liver disease [11]. However, flares may occur in pregnancy because of altered immunity. The prevalence of flares has been reported in 6%-14% of cases during pregnancy and in 10% to 50% of women postpartum [44]. However, most flares appear to be mild and self-limiting, with little progression to hepatic decompensation or jaundice in the absence of advanced fibrosis or hepatitis delta co-infection. In a prospective study of 126 pregnant women with chronic HBV infection, 27 patients (25%) developed a post-partum flare (defined as twice the upper limit of normal (ULN) ALT or twice the upper limit of baseline ALT if this was elevated above normal) and only 2 patients presented a flare while pregnant [45]. Younger age and HBeAg positivity were associated with post-partum flares, the risk of a post-partum flare being double in case of HBeAg positive women [45].

Acute hepatitis B can be diagnosed in the presence of HBsAg and IgM hepatitis B core antibody (IgM-antiHBc). In the early phase, AgHBe, high HBV DNA levels and elevated aminotransferase levels are also present. During the window phase of the acute infection, HBsAg and HBeAg are negative, but in the setting of IgM-antiHBc positivity and detectable HBV DNA. AgHBs persistence for more than 6 months represents a chronic HBV infection [46].

Women with acute hepatitis B and low HBV DNA levels will require only supportive treatment, serial monitoring and, very importantly, the infant to receive HBIG in addition to the first dose of vaccine at birth. Studies have shown that acute HBV infection early in pregnancy has been associated with 10% perinatal transmission rate [47]. This transmission rate increases if an acute infection occurs near the time of delivery, and for these cases, antiviral treatment may be considered to reduce MTCT [47]. In the situation of acute hepatitis B, the main goal of treatment should be to prevent acute liver failure [48].

When antivirals are indicated only to reduce MTCT, treatment may be discontinued at delivery or kept up to 4-12 weeks after delivery to reduce the risk of flares [30]. In a prospective study where 91 women received antiviral therapy to prevent transmission, extending antiviral therapy beyond delivery did not appear to reduce the frequency of HBV flares over a median of a 48 week-follow-up [49].

In women becoming pregnant while receiving antiviral therapy, the risk and benefit of continuing treatment should be discussed on an individual basis. Continuing treatment may pose a risk to the fetus, while discontinuing treatment may pose a risk of hepatitis flare for the mother. Tenofovir disoproxile fumarate or lamivudine should replace entecavir, adefovir or other antiviral treatment in these cases.

For HbsAg positive women requiring invasive procedures for prenatal diagnosis during pregnancy, HVB DNA and HbeAg should be checked. In those of higher risk of MTCT (DNA > 7.0 log10 IU/mL and HbeAg positivity) alternative non-invasive prenatal testing could be used if feasible. A course of 4 weeks of antiviral treatment could also be considered if the procedure can be postponed [18].

2.3 Dosage considerations

The recommended dose, according to the European Medicines Agency is 245 mg (one tablet) once daily, taken with food, from 28-32 weeks gestation through 1 to 2 months

Table 2. Efficacy and safety of TDF during pregnancy.

Author, year	*Study*	*Participants*	*Inclusion criteria*	*Results*
Chen HL, 2015 **[20]**	Prospective Non-RCT	118	Pregnant women positive for HBsAg and HBeAg with an HBV DNA level ≥ 7.5 log10 IU/mL	TDF at 30 weeks of gestation reduces maternal viral HBV-DNA at the time of delivery, a mean viral load of 4.29 ± 0.93 log10 IU/mL in the TDF group was achieved.
Brown RS, 2016 **[21]**	Systematic review and meta-analysis	26 studies -3622 pregnant women		Antiviral therapy reduced MTCT. No significant differences were found in the congenital malformation rate, prematurity rate, and Apgar scores. Lamivudine or telbivudine improved maternal HBV DNA suppression at delivery and during the 4 to 8 weeks' postpartum follow-up. Tenofovir showed improvement in HBV DNA suppression at delivery.
Pan CQ, 2016 **[22, 41]**	Double-blind RCT	200	Pregnant women positive for HBeAg and HBV DNA level higher than 200,000 IU/mL	At delivery, 68% of the mothers in the TDF group (66 of 97 women), as compared with 2% in the control group (2 of 100), had an HBV DNA level less than 200,000 IU per milliliter. MTCT at 28 weeks postpartum was significantly lower in the TDF group than in the control group. The maternal and infant safety profiles were similar in the TDF group and the control group, including birth-defect rates, although more mothers in the TDF group had an increase in the creatine kinase level.
Jourdain G, 2015 **[40]**	Double-blind RCT	331	Pregnant women positive for HBeAg with an alanine aminotransferase level < 60 IU/L	In a setting in which the rate of HBV MTCT was low with the administration of hepatitis B immune globulin and hepatitis B vaccine, the additional maternal use of TDF did not result in a significantly lower rate of transmission.
Ming Wang, 2019 **[41]**	Open-label Single-arm study	147	Pregnant women positive for HBeAg with HBV-DNA > 6 log10 IU/mL	At delivery, 93.7% (134/143) of the mothers achieved HBV-DNA < 200 000 IU/L. On-treatment, alanine aminotransferase (ALT) flares were observed in 8.4% (12/143) of the mothers. After TDF cessation, ALT increased by 7.7% (11/143) of the mothers and 2.8% (4/143) achieved HBeAg negativity, but none had HBsAg loss. At birth, HBsAg was detected in 13.9% (20/144) of newborns and none at postpartum week 28. Mother to child transmission rates among infants were 0.7% (intention-to-treat) and 0% (per-protocol). No infants had congenital disabilities. No serious adverse effects were reported in either mothers or infants.
Zeng, 2019 **[42]**	Observational study	145	HBV DNA ≥ 1.0×10^7 copies/mL and increased alanine aminotransferase levels	For the infants, there were no significant differences among body weight, height, head circumference, or Apgar score. Administration of Lamivudine or TDF to HBV-infected mothers are effective and safe to reduce HBV MTCT.

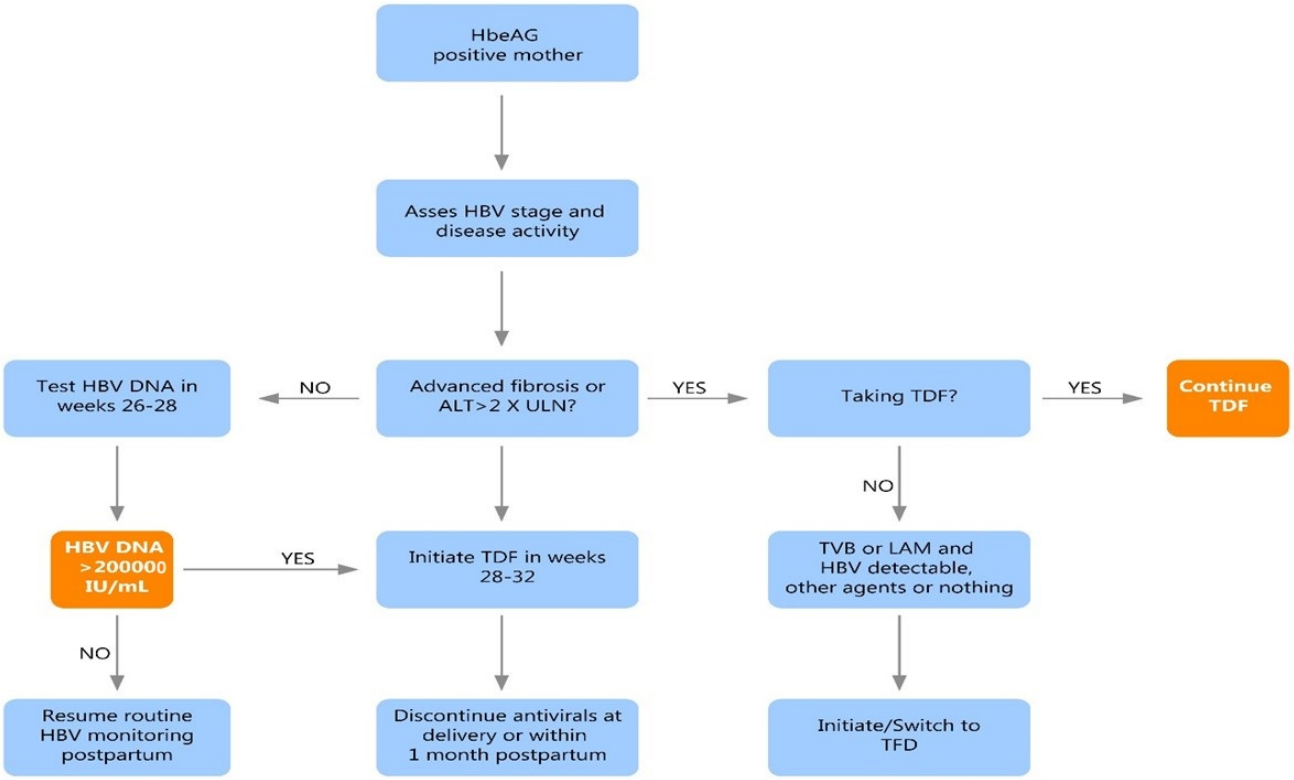

Fig. 3. Algorithm for the use of Tenofovir disoproxil fumarate in pregnancy. TDF-Tenofovir disoproxil fumarate, ALT-alanine transferase, TBV-Telbivudine, LAM-Lamivudine, ULN-the upper limit of normal.

postpartum [50]. No dose adjustment is necessary for patients with eGFR > 50 mL/min. In those with impaired renal function, TDF should be administered at extended dosing intervals: 1 tablet (245 mg) every 48 hours in patients with eGFR between 30 and 49 mL/min, 1 tablet every 72-96 hours or twice weekly for patients with eGFR between 10 and 29 mL/min and every 7 days (following a 4-hour dialysis session) for patients in end-stage renal disease on hemodialysis (based on thrice-weekly 4-hour hemodialysis regimen) [51]. Alternatively, TDF 33 mg/g granules could be used, as follows: 132 mg (4 scoops) once daily in patients with eGFR between 30 and 49 mL/min, 66 mg (2 scoops) once daily in patients with eGFR between 20 and 29 mL/min, 33 mg (1 scoop) once daily in patients with eGFR between 10 and 19 mL/min and 16.5 mg (0.5 scoops) once daily in patients in end-stage renal disease on hemodialysis [52]. No dose adjustment is required for patients with hepatic impairment [51].

Another important issue that needs to be addressed is the pharmacokinetics (PK) of TDF in pregnant women. There are certain phyisiological changes during pregnancy, such as an increased volume of distribution (Vd), decreased peripheral vascular resistance and blood pressure and increased cardiac output (CO) that influence the absorbtion, distribution and elimination of TDF [53–55]. These changes can result in lower drug exposure of antiretroviral agents, including TDF, when compared to non-pregnant women [56]. Given these circumstances, it has been debated whether the standard dose of TDF is adequate to obtain viral supression in order to prevent MTCT of HBV. We analyzed the data derived from six cohort studies conducted between 2009 and 2018 that evaluated the PK of TDF administered peri-partum (two studies) or chronically (one study) in pregnant HIV infected women, its role in preventing MTCT of HIV - chronically administered (three studies) and HBV - chronically administered (one study).

Hirt *et al.* showed that a 600 mg dose of TDF administered to thirty-eight pregnant women just before delivery resulted in similar tenofovir AUC, Cmin and Cmax values to a 300 mg dose in other adults at steady state, due to a twice-higher elimination clearance in pregnant women than in non-pregnant women [57].

Flynn *et al.* confirmed that TDF doses of 600 mg administered during labor result in tenofovir exposure similar to that of the standard 300 mg doses used in treatent of HIV infected non-pregnant adults. Also, cord blood concentrations were similar regardless of the maternal dose (either 600 or 900 mg) [58].

Benaboud *et al.* studied the PK of TDF on a cohort on one hundred-eighty-six pregnant women using a 300 mg once-daily regimen during first, second and thrid trimester. They observed [59] that the exposure of pregnant women to tenofovir is low after the administration of 300 mg of TDF, but may be too high after the administration of 600 mg, concluding that a dose escalation should be considered in pregnant

women, but further investigations are needed [60].

In a recent study by Best *et al.* apparent Vd was 60% higher and tenofovir overall exposure was 20% lower in the third trimester compared to postpartum in the same women. Ninety-four percent of subjects had an HIV RNA $\leq$ 400 copies/mL in the 3rd trimester and none discontinued their regimen or altered their TDF dose based on their reported lower-than-target AUC. At delivery, 97% of women were virally suppressed (HIV RNA under 400 copies/mL) and no infants were infected. They conclude that standard doses appear appropiate for a majority of HIV-infected pregnant women [61].

Colbers *et al.* also suggested that aalthough pharmacokinetic exposure of the NRTIs TDF and FTC during pregnancy is approximately 25% lower, this was not associated with virological failure and did not result in mother-to-child transmission [62].

Finally, the most recent study we examined and the only one that evaluated MTCT of HBV was conducted by Cressey *et al.* This was a phase III randomized double-blind placebo-controlled trial that included 154 pregnant women. A 20% reduction in tenofovir exposure was noted during pregnancy versus to post-partum, but no mothers transmitted HBV to their infant, thus suggesting that a dose adjustment is not necessary [63].

Given the currently available evidence, suggesting that even though the physiological changes in pregnancy alter the PK of tenofovir and ultimately decrease drug exposure, this does not have a negative impact on MTCT and it appears that no dose adjustment is warranted in pregnant women receiving TDF. Still, further studies are required to confirm this statement, especially regarding MTCT of HBV.

2.4 Infant outcomes after maternal TDF use during pregnancy

Besides the effectiveness of antiviral therapy during pregnancy, the safety, and long-term implications on the development of exposed infants are of primary concern. Potential adverse effects include teratogenicity, long-term effects on bone development in the infant, post-treatment transaminases flares, renal dysfunction and HBV resistant mutations.

In the two RCTs, although underpowered for differences in fetal outcomes, no statistically significant differences were seen in malformation rate, preterm birth or low Apgar score between infants exposed to TDF and the control group [16, 31]. Two stillbirths resulted in the TDF group and one neonatal death due to ventricular hemorrhage post-instrumental delivery. Jourdain *et al.* showed a significant lower Z score for weight at 6 months follow-up in infants exposed to TDF [40].

Data from Antiretroviral Pregnancy Registry (APR) analyzing 4013 women with TDF administration during pregnancy, mostly due to HIV-1 infection, showed that the malformation rate was 2.4%, with no significant difference comparing to the general population [64].

The relationship between TDF and fetal growth, particularly regarding bone development, is a matter of concern. The date on long-term follow-up for the effect of TDF on neonatal and infant growth are conflicting. Analysis from Safety Monitoring for ART toxicity (SMARTT) study of the Pediatric HIV/AIDS Cohort Study reported that for the children of women treated with TDF during pregnancy there was a higher risk of lower length-for-age and head circumference for age z-scores at one year of age, despite no difference in growth measurements at birth [65]. These findings are in contrast with those reported by the Development of Antiretroviral Therapy in Africa trial, in a subgroup analysis, that showed no effect of intrauterine exposure to TDF [66].

A recent study by Wen *et al.* showed that children with and without fetal exposure to TDF were similar in terms of bone development, long term growth and renal function up to 6-7 years after delivery [27].

As a response to SMARTT, a large study including 2025 infants compared the weight at birth and at six months for infants exposed and unexposed to TDF during pregnancy. In this large cohort of infants born to HIV-infected women receiving a combination of antiviral regimens during pregnancy, in utero exposure to TDF did not seem to be associated with infant birth weight or growth up to 6 months. Although there was a marginal association with being underweight at six months of age in women who initiated TDF in the second or third trimester, there was no association between the duration of maternal TDF use and 6-month weight outcomes. Besides, no association was found with absolute weight or overall age and sex-adjusted z-scores [67].

A systematic review that aimed to compare the potential adverse outcomes of HIV infected women receiving a TDF versus no-TDF schema antiretroviral therapy showed a decreased incidence in preterm delivery and stillbirth in the first group, but an increased risk of neonatal mortality at less then 14 days after delivery. The TDF including therapy did not increase the risk for low or very low birth weight, small for gestational age, congenital anomalies, other infant adverse outcomes, or infant mortality after 14 days and modified anthropomorphic parameters at birth [68]. The safety of HBV antiviral therapy while breastfeeding is not established. Therefore, counselling individually over the benefits versus risks of breastfeeding should be discussed with those requiring postpartum antiviral therapy. Studies have shown that limited amounts of TDF are excreted in breastmilk, and these are unlikely to cause any biologic effects on the infant [69].

Regarding maternal safety, apart from mild side effects like fatigue, nausea or pruritus, a consistent finding in two randomized studies was an acute hepatic exacerbation with higher levels of alanine aminotransferase in women taking TDF [22, 40]. Pan *et al.* also reported an increase in creatine kinase level in the group with TDF, but there were no reported clinical cardiac manifestations [22]. Nachenga *et al.* found no increased risk in maternal severe (grade 3) or potentially life-threatening (grade 4) adverse events and miscarriage in HIV positive pregnant women who received TDF based antiretroviral therapy [68].

3. Summary

As a conclusion, Tenofovir Disoproxil Fumarate is generally recommended by the current guidelines to be used during late pregnancy to reduce the hepatitis B virus transmission in HBeAg-positive mothers with a high HBV DNA. Despite decreased drug exposure physiologically occurring in pregnancy, latest evidence suggests that no dose adjustment is warranted in pregnant women receiving TDF to prevent MTCT of HBV. Regarding the safety of TDF use in the second and third trimester of pregnancy, the overall picture is reassuring for both maternal and neonatal outcomes.

Author contributions

IB, AMP and GP designed the research study. IB, AMP and AMC performed the research. IB, AMC, AMP and TV wrote the original draft. AMP, DAD and TD performed the review and editing. GP supervised the project and AMP performed the project administration. All authors contributed to editorial changes in the manuscript. All authors have read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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