

# Current progress in the prevention of mother-to-child transmission of hepatitis B and resulting clinical and programmatic implications

This article was published in the following Dove Press journal:  
*Infection and Drug Resistance*

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**Abstract:** There is currently no cure for hepatitis B chronic infections. Because new hepatitis B infections result mainly from perinatal transmission, preventing mother-to-child transmission is essential to reach by 2030 the goal of hepatitis B elimination set by the World Health Organization. The universal administration of hepatitis B vaccine to all infants, regardless of maternal status, starting with the birth dose, is the cornerstone of the strategy for elimination. Additional interventions, such as hepatitis B immune globulin administered to newborns and antiviral prophylaxis administered to hepatitis B infected pregnant women, may contribute to reaching the goal earlier. Hepatitis B immune globulin may remain out of reach of many pregnant women in low- and middle-income countries due to cost and logistic issues, but antivirals are cheap and do not require a cold chain for distribution. However, it has been observed that some viruses harbor mutations associated with escape from vaccine-elicited antibodies following immunization or administration of hepatitis B immune globulin. Also, resistance associated mutations have been described for several drugs used for treatment of hepatitis B infected patients as well as for the prevention of mother-to-child transmission. Whether these mutations have the potential to compromise the prevention of mother-to-child transmission or future treatment of the mother is a question of importance. We propose a review of important recent studies assessing tenofovir disoproxil fumarate for the prevention of mother-to-child transmission, and provides detailed information on the mutations possibly relevant in this setting.

**Keywords:** hepatitis B, mother-to-child transmission, prevention, antiviral, resistance

## Introduction

The World Health Organization (WHO)<sup>1</sup> estimated that, in 2015, 257 million individuals, ie, more than 3% of the global population, were affected by chronic hepatitis B virus (HBV) infection, resulting in almost 900,000 deaths.<sup>2</sup> Typically, HBV is acquired early in infancy after exposure to an infected individual, and the infection remains asymptomatic for decades before the apparition of life threatening complications: liver cirrhosis (about 20–30%) and hepatocellular carcinoma (HCC) (about 1%).<sup>3</sup> In 2010, the World Health Assembly adopted the WHA63.18 resolution recognizing the burden of viral hepatitis and expressing the need for more prevention and control of viral hepatitis,<sup>4</sup> and WHO released its first ever guidelines for the prevention, care, and treatment of persons with chronic hepatitis B infection in 2015.<sup>5</sup>

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## Risk of mother-to-child transmission

In the absence of any prophylactic measure, mother-to-child transmission (MTCT) of HBV is frequent. Without immunization, about 20%–40% of infants born to HB surface antigen (HBsAg) carrier mothers are found to be infected by 1 year of age, with large variations, depending on maternal risk factors;<sup>6</sup> in particular, infants born to HB e antigen (HBeAg) positive mothers have a 70–90% risk of being infected. While 90% of infants infected during delivery or in infancy become HBsAg chronic carriers, 25–30% of children infected later, between 1 and 5 years of age, develop chronic infection.<sup>7</sup>

## Route and timing of transmission

HBV may be transmitted from an infected mother to her infant in utero, during delivery, or thereafter through close contact. It remains unclear what specific close contacts are most involved in HBV transmissions. HBV is highly contagious. For example, it can be transmitted to humanized mice using tears from HBV infected children.<sup>8</sup> In contrast, it seems unlikely that breast feeding is associated with MTCT of HBV. The World Health Organization (WHO) recommends that HBsAg positive mothers breastfeed their infants, based on studies finding similar rates of HBV infection in breastfed compared to bottle fed children.<sup>9</sup> Most often, the exact timing and route of transmission – vertical versus horizontal – cannot be determined. First, the time needed to establish HBV infection in the liver after virus entry into the fetus or infant body is unknown, and may be variable. While, in adults, symptoms appear on average 90 days after exposure with large variations (8 weeks to 5 months),<sup>10</sup> infant HBV infection is usually asymptomatic. Second, unless a phylogenetic analysis is performed, it remains impossible to know whether the virus originates from the mother or someone else.

## HB vaccine for the prevention of perinatal infection

Most new cases of chronic infections are acquired early in life, and the infant's mother is the most frequent source of infection. An efficient vaccine has been available since the early 1980s, and is now produced with recombinant DNA techniques. It contains the highly immunogenic HBsAg “a” determinant, which elicits neutralizing anti-HBsAg antibodies and long-term cellular immunity with cross genotype protection in healthy individuals.<sup>11,12</sup> Produced in high quantities, the cost of the vaccine is low, less than USD 0.5 a dose.

Children who have not been immunized are susceptible to HBV infection through contacts with infected individuals (parents, siblings, other family members, etc.). Worldwide, about half of the infants are born in countries where chronic HBV infection is highly endemic, therefore they are at high risk of early infection.<sup>13</sup> In 1992, the incorporation of hepatitis B vaccine in the Expanded Programs for Immunization (EPI) was recommended by the World Health Assembly (WHA 45.17). Hepatitis B vaccine is often administered as one of five or six individual vaccines conjugated into one vial (pentavalent or hexavalent vaccine) to immunize infants against life-threatening infections, ie, diphtheria, tetanus, poliomyelitis, pertussis, *Haemophilus influenzae* type B, and hepatitis B, with the first administration of the multivalent vaccine scheduled at 6 weeks or 2 months of age. Less developed member states receive support from the Global Alliance for Vaccines and Immunizations (GAVI). This resulted in a dramatic increase in vaccine coverage in infants from 1% in 1990 to 84% in 2015. All countries where hepatitis B vaccine has been integrated in the EPI have seen dramatic decreases in HBV prevalence in children.

However, globally, the prevalence of chronic hepatitis B infection in children under 5 years remains relatively high, 1.3% in 2015, with large variations between WHO regions and up to 3.0% in the African Region.<sup>1</sup> Indeed, newborns are susceptible to infection before the first administration of the multivalent vaccine at 2 months of age and those born to HBV infected mothers are the most at risk. As the determination of whether an infant may be exposed to persons with HBV infection is practically impossible, the need for immunization of all infants regardless of HBV maternal status starting at birth (birth dose, using a monovalent vaccine) has been recognized since the 1980s.<sup>14</sup> WHO recommendations have been more and more insistent on the need for a timely birth dose, ie, administered within 24 hours of birth.<sup>15,16</sup> A timely birth dose seems more effective in preventing perinatal infection than if administered in the following days,<sup>17</sup> though a late birth dose may still prevent infection before the administration of the first pentavalent vaccine at 2 months of age, as long as the infant has not already been infected. In addition, studies in the USA and in China have shown that the administration of the birth dose was associated with an increased likelihood of completing the HB vaccine series.<sup>18,19</sup> Pregnancy tracking, coordination with traditional birth attendants to ensure timely administration of the vaccine by village-based healthcare workers, and

the use of compact, prefilled autodisable devices are among innovative approaches to ensure the timely administration of the HBV birth-dose vaccine that have been evaluated in rural settings in countries such as Vietnam, Indonesia, and China. These strategies have enabled districts to achieve between 84% and 97% vaccination coverage in home-based birth settings.<sup>20–22</sup>

## HBIG in association to HB vaccine to prevent perinatal HBV infection

Immunization using the vaccine starting at birth has been shown to decrease the risk of perinatal transmission, but the addition of immune globulin administration after birth is more efficacious to prevent transmission, though this strategy cannot prevent all transmissions.<sup>14,23</sup> However, the administration of HBIG to infants born to HBV chronically infected mothers is more challenging than the administration of HB vaccine at birth, a basic preventive measure that has still not been implemented in many health facilities in the world.<sup>24</sup> As noted in the 2015 WHO Guidelines,<sup>25</sup> HBIG “may not be feasible in most settings.” This is related to multiple factors, including the need for maintenance of refrigerated HBIG stocks, short shelf life, cost considerations, and access to a reliable source of HBIG production from immunized donors. Although the situation has improved for infants born in health facilities, the implementation of the vaccine+HBIG strategy is challenging in settings where pregnant women deliver at home, usually at significant distance from health facilities. The concomitant administration of HBIG and vaccine will remain probably out of reach for a large proportion of infants born to HBV infected women for a long time.

## Antivirals

Therefore, several studies have been conducted to clarify whether alternative or additional approaches could help reduce mother-to-child transmission, in particular using antenatal maternal administration of HBIG or antivirals. Several studies that have investigated the effect of immune globulin administered to the mother during pregnancy on HBV transmission to the fetus/newborn have not demonstrated the efficacy of this approach.<sup>26</sup> In contrast, maternal antiviral agents administered during the end of pregnancy may decrease the risk of transmission of HBV from a mother to her infant. An extensive review and meta-analysis of the efficacy and safety of the approach

by Brown et al<sup>27</sup> was published in 2016. Three oral antiviral drugs, lamivudine (Pregnancy Category C), telbivudine (Category B), and tenofovir disoproxil fumarate (TDF) (Category B) were found to reduce the rates of MTCT in HBeAg-positive women with high viral loads ( $>10^6$  copies IU/mL). However, this conclusion was considered of “moderate to low quality of evidence, rated down due to risk of bias”. As for the safety for the mothers, there were no significant differences in occurrence of severe adverse events, but the quality of the evidence was “very low due to the observational nature of the studies, imprecision, and indirectness”. In infants, there were no differences in congenital malformation rate, prematurity rate, and Apgar scores, with the quality of the evidence considered as “moderate to low, down-rated due to risk of bias and imprecision”. The authors concluded that the results of larger-scale randomized clinical trials were eagerly awaited. Later in 2016, the results of a randomized, open label, clinical trial conducted in academic tertiary care centers in east, south, west, north, and southwest China from March 2012 to June 2013 were reported by Pan et al.<sup>28</sup> All infants received vaccine and immune globulin starting at birth, then following national recommendations. None of the 92 infants born to mothers who received TDF from 30–32 weeks of gestation until week 4 postpartum were infected, compared to six of 88 infants (7%) born to mothers who received usual care without antiviral therapy. In 2018, Jourdain et al<sup>29</sup> reported the results of a larger, randomized, double blind, placebo-controlled, clinical trial (iTAP-1) conducted in 17 provincial and community hospitals in Thailand from January 2013 to August 2015. The trial was designed both to assess the efficacy of maternal course of TDF from 28 weeks gestational age to 2 months postpartum for the prevention of MTCT and its safety for the mothers and infants with a 1-year mothers’ and infants’ follow-up after delivery/birth. In this trial also, there were no infections among 147 infants born to mothers in the TDF arm, and only three infections (2%) among those 147 infants born to mothers in the placebo arm. The reasons for the differences in rates of infection between the two studies remain unclear (see Table 1 for a comparison of selected characteristics of the two trials). Infants in China received immune globulin twice compared to the once in Thailand. In Thailand, HB vaccine was administered very early after birth (a median 1.2 hours), with four boosters after the birth dose (at 1, 2, 4, and 6 months of age), compared to two in China (2 and 6 months). In both studies, there were

**Table I** Comparison of selected characteristics of two recent clinical trials to assess the efficacy and safety of tenofovir disoproxil fumarate (TDF) for the prevention of mother-to-child transmission of hepatitis B virus

Studies	Pan et al <sup>24</sup>	Jourdain et al (iTAP-1) <sup>25</sup>
ClinicalTrials.gov registration	NCT01488526	NCT01745822
Intervention studied	Maternal TDF 300 mg once a day versus usual care From 30–32 weeks gestational age until week 4 postpartum	Maternal TDF 300 mg once a day versus placebo From 28 weeks gestational age until 2 months postpartum
Concealment of intervention	Allocation concealment and open label after randomization and enrollment	Double blind of the randomized treatment throughout the study
Planned sample size	100 pregnant women in each group (total: 200) for ≥85% power to detect a difference of at least 18 percentage points in the transmission rate (expected rate: 20% in the control group (2-sided alpha 0.05)	164 pregnant women in each arm (total: 328) for 90% power to detect a difference of at least 9 percentage points in the transmission rate (expected rate: 12% in the placebo group) (1-sided alpha 0.049)
Main inclusion criteria	HBeAg-positive HBV DNA level >200,000 IU/mL	HBeAg-positive ALT <60 IU/L
Main exclusion criteria	History of abortion, pregnancy loss, or congenital malformation Chronic HBV infection in the biologic father	—
Breastfeeding	Not allowed	Encouraged
Planned HBIG administration to infants	At birth and 1 month of age	At birth
Planned HBV vaccine administration to infants	At birth, 1, and 6 months of age	At birth, 1, 2, 4, 6 months of age
Implementation sites	Multicenter: 4 academic tertiary care centers in China	Multicenter: 17 provincial and community hospitals in Thailand
Period of enrollment	March 2012–June 2013	January 2013–August 2015
Number of pregnant women enrolled	100 in the TDF group; 100 in the “usual Care” group	168 in the TDF arm; 163 in the placebo arm
Amniocentesis performed	Not specified	None
Cesarean sections	50%	26%
Number of infants evaluated	92 in the TDF group; 88 in the “usual Care” group	147 in the TDF arm; 147 in the placebo arm
Frequency and percentage of infants found HBV infected at 6 months of age	0/92 (0%) in the TDF arm; 6/88 (7%) in the “Usual Care” group	0/147 (0%) in the TDF arm; 3/147 (2%) in the placebo arm

no safety concerns. In the Thai study, postpartum ALT elevations above 300 IU/L were observed in both placebo and TDF groups at a similar frequency, and none was associated with clinical symptoms. Altogether, these data suggest that maternal TDF is effective in preventing perinatal transmission of HBV and that the use of TDF is not associated with safety issues. This approach is recommended by the major associations for the study of liver diseases.<sup>30–32</sup> However, this recommendation was not included in the WHO Hepatitis B Guidelines in 2015,<sup>5</sup> and the use of antivirals for the prevention of PMTCT remains “off-label” in the US due to a lack of data demonstrating the superiority of this approach compared to active-passive immunization. Of note, two studies have suggested that infant development delays may be related to telbivudine in utero exposure.<sup>33,34</sup>

## Effects of pregnancy on viral replication

HBV seems to have little effect on pregnancy, but HBV replication tends to increase during pregnancy, probably in relation to immune-suppression and increased production of adrenal corticosteroids, estrogen, and progesterone.<sup>35,36</sup> Clinical studies have shown that, within the first months after delivery, some women experience hepatitis flares, with or without HBeAg seroconversion,<sup>37</sup> presumably in relation with the rapid decrease in immunosuppression post-partum.<sup>38</sup> Comparative clinical studies have confirmed that ALT elevations do occur during the postpartum period in the absence of any antiviral treatment, and that the discontinuation of antiviral treatment in the postpartum period does trigger ALT elevations, but no clinical consequences have been reported.<sup>28,29,39</sup>

## HBV mutations

HBV is a partially double-stranded DNA virus which replicates via a reverse transcription step using its polymerase enzyme, which lacks proofreading ability. Errors occur throughout the whole HBV DNA genome at a rate of approximately  $>2 \times 10^4$  base substitutions/site/year, at least 100-fold higher than for other DNA viruses, but about 1,000-times lower than for RNA viruses.<sup>40</sup> As a result of a high replication rate,  $10^{11}$  virions per day, genetically distinct but closely related variants called quasi species are produced at each replication cycle in the host.<sup>41</sup> Because of specific selection pressure, HBV mutants with a survival advantage over wild type viruses are selected. While some mutant viruses harbor a modified S gene associated with HBV vaccine or HBIG escape, others present polymerase gene mutations conferring resistance to specific antiviral drugs.

## HBV mutations possibly associated with immunoprophylaxis failure

The small HBsAg (S-HBsAg), composed of 226 amino acids (aa), is the major envelope lipoprotein. Its central core (aa 99–169), the major hydrophilic region (MHR), is exposed at the virus surface and involved in binding to anti-HBs antibodies. The immunodominant and immunoprotective determinant is called “a” determinant. It spans the sequence from aa 124 to 147, which includes five cysteine residues crucial for its conformation. The “a” determinant is the main target of neutralizing antibodies either vaccine-induced or passively acquired (HBIG) from HB vaccinated subjects. It is also the target of antibodies used in diagnostic assays.<sup>42–46</sup> Any change in the “a” determinant modifying the conformation of the HBsAg is critical for antigenicity.<sup>47,48</sup> Such changes may allow the virus to escape neutralizing antibodies or cause HBV infection misdiagnosis.

Failures of hepatitis B vaccine and/or immunoglobulin prophylaxis have been associated with the emergence of mutations in infants. The most common escape mutation is a glycine to arginine substitution at amino acid 145 (sG145R), originally identified in vaccinees and patients receiving active-passive prophylaxis for liver transplantation.<sup>49–51</sup> Studies have also reported a glycine to alanine substitution at this position (sG145A).<sup>52–54</sup> Several other mutations (sT116N, sP120E/S, sT125M/A, sT/I126A/S/N/T/M, sQ129H/R, sT/N131I, sM133L, sK141E, sP142S, sT/S143W, and sD144A/E), occurring

either alone or in combination, have also been associated with vaccine failure.<sup>53,55–66</sup>

From a public health perspective, these mutations are concerning because the efficacy of HB vaccine may be compromised if vaccine escape mutants were to spread out. An evaluation of large scale HB vaccination programs in eastern China during 2005–2013 showed a 9% prevalence of vaccine escape mutants, particularly the sI126S/N, sT126A, and sG145R/A, with a significantly upward trend of the sG145R/A mutant from 9% in 2005 to 44% in 2013.<sup>54</sup> The long-term consequences of this increase are still unclear.

HBsAg diagnostic tests may turn negative in patients infected with a virus harboring HBsAg mutations in the “a” determinant region. New generations of HBsAg diagnostic kits have been developed to overcome this problem; however, there is still a concern from a public health perspective, in particular regarding MTCT, that infection in these patients may not be diagnosed although they are potentially contagious. In that case, the infection remains detectable by HBV-DNA PCR or HBeAg testing, as these tests are not affected by these mutations.<sup>67</sup> This suggests that the performance over time of the diagnostics kits to detect HBsAg should be monitored.

In conclusion, HBsAg mutations in the “a” determinant region remain of concern for the prevention of HBV infection.

## Impact of immune escape mutants on HBV replication

Due to the overlap of the envelope and polymerase genes regions, mutations in the S gene may result in mutations in the polymerase gene. The sI45R and the corresponding rtR153Q may affect polymerase activity and HBV replication. In vitro analysis showed that immune escape mutations in the “a” determinant region, sS117T, sK122R, sI126N/S/T, and sG145R, were associated with lower levels of HBsAg as compared to wild-type virus. Practically, it is unclear whether this could increase or decrease the risk of transmission: lower HBV load levels would decrease the risk, but escaping antibodies and HBIG would have the opposite effect, even at lower levels of viral load.

## Mutations associated with resistance to antivirals

Current anti-HBV drugs mostly target the polymerase and include oral nucleos(t)ide analogs with various levels of



genetic barrier to resistance. Drugs that have been used for the prevention of MTCT of HBV include lamivudine,<sup>68–70</sup> telbivudine,<sup>71–74</sup> and TDF.<sup>27–29,75</sup>

These three drugs have different genetic barriers to resistance, the lowest for lamivudine and the highest for tenofovir, as established in patients treated for HBV infection (Figure 1: Rates of HBV resistance among HBeAg positive patients on HBV monotherapy). The use of lamivudine selects HBV resistance mutations in up to 46% of patients treated for 2 years.<sup>76–78</sup> Resistance has been reported in up to 22% in patients on telbivudine for 2 years,<sup>79</sup> but less than 1% in patients on entecavir for 2 years.<sup>80</sup> No clinical resistance has been reported in HBV-antiviral treatment naïve patients after 8 years on TDF.<sup>81</sup>

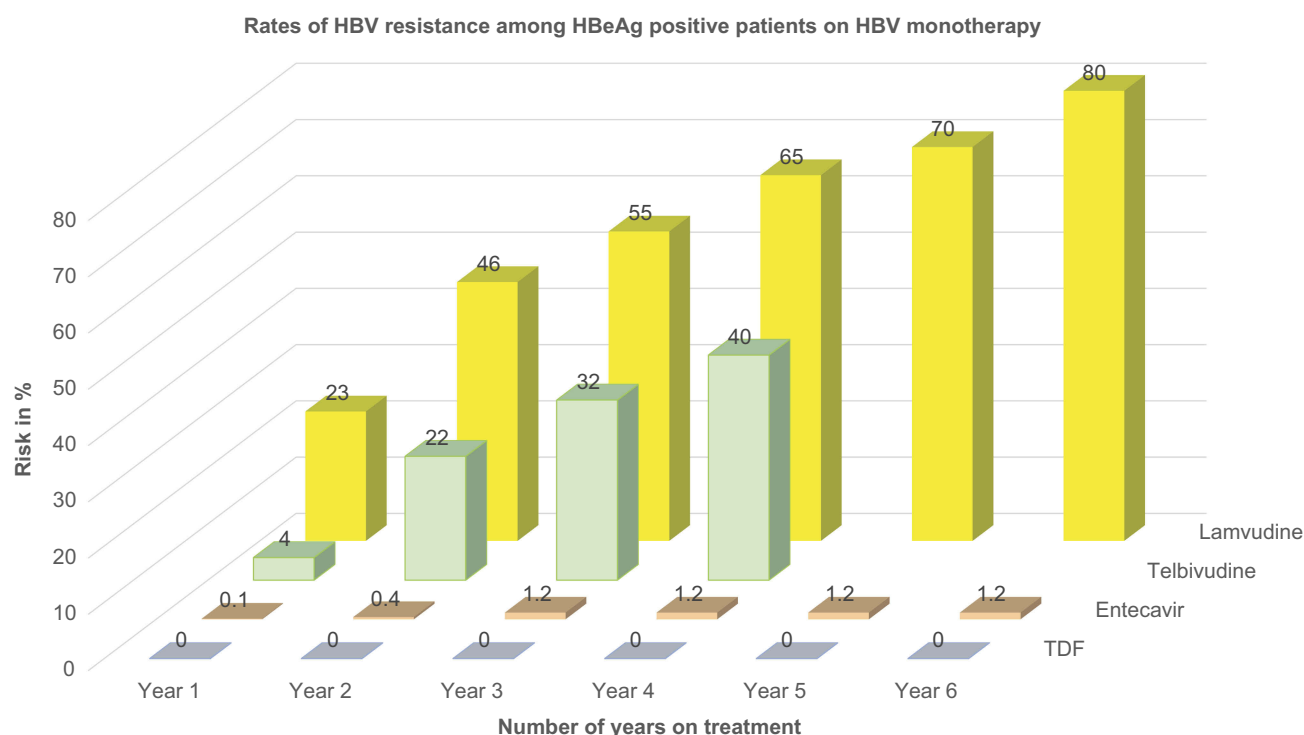
In the context of HIV-HBV co-infection, the use of TDF has been associated with high rates of virological suppression.<sup>82,83</sup> However, a small percentage of co-infected patients on TDF-containing antiretroviral treatment have experienced suboptimal responses after long-term therapy and, in rare cases, possible resistance to tenofovir has been suspected.<sup>82,84</sup>

The emergence of such viral mutations, or genotypic resistance, may trigger an increase in HBV replication that can be evidenced by an increase in HBV DNA levels, ie,

a virological breakthrough. In some cases, a severe exacerbation of the underlying liver disease may occur and, in rare cases, lead to acute liver failure. However, pregnant women with indications for antiviral treatment for the prevention of MTCT of HBV usually have high viral loads and are in the immune tolerance phase of the infection. Therefore, it is unclear whether the selection of such mutation during the short course of antiviral prophylaxis can trigger clinically significant exacerbations.

## Mutations on the polymerase gene conferring resistance to nucleoside analogs

The HBV polymerase is composed of four domains. The reverse transcriptase (rt) domain is responsible for the polymerase activity and is the target of nucleoside analogs. Specific mutations associated with resistance to lamivudine include the mutations at position 204 of the reverse transcriptase domain where the wild-type position is a methionine (rtM204) in the YMDD locus of the catalytic C box of the polymerase.<sup>76,78,85,86</sup> Other mutations can occur in the A and B boxes (rtL80V/I, rtV173L, and rtL180M) and are often found along with the rtM204V/I mutations. Some



**Figure 1** Risk of HBV resistance in HBeAg positive patients on lamivudine, telbivudine, entecavir or tenofovir disoproxil fumarate (TDF) monotherapy according to duration on treatment.

of these mutations reduce susceptibility to other NAs: rtM204I/V mutations confer virus cross-resistance to telbivudine, and the rtA181T/V mutations confer cross-resistance to telbivudine and adefovir. The rtN236T mutation selected for by adefovir may confer resistance to tenofovir when present with the rtA181T/V mutations<sup>87</sup> (see Table 2).

Due to potential cross-resistance to lamivudine and entecavir, it is not recommended to use lamivudine for treatment and prophylaxis as entecavir is currently the only option for patients who cannot tolerate TDF.

As noted above, tenofovir resistance in HBV mono-infected patients has not been identified in patients on treatment and, to our knowledge, there has been no report of such resistance in women receiving TDF to prevent MTCT. However, several mutations associated with resistance to tenofovir have been described in HIV-HBV co-infected patients, though the clinical relevance of these mutations remains unclear. The rare cases described were co-infected patients previously exposed to lamivudine who achieved incomplete HBV suppression on TDF.<sup>84,88</sup> The rtA194T mutation was detected in co-infected TDF treated patients also exhibiting lamivudine-resistance mutations. In vitro phenotypic analysis showed that viruses with the rtA194T along with the lamivudine resistance rtL180M and rtM204V mutations had a 10-fold increase in the IC<sub>50</sub> for TDF as compared with wild type viruses.<sup>89</sup> However, it has been reported that a patient with the rtA194T achieved HBV replication suppression on TDF.<sup>90</sup> In another study of 111 HIV-HBV co-infected patients on long-term TDF-containing antiretroviral therapy,<sup>82</sup> 10 experienced transient viremia and 13 persistent viremia. The rtL217R mutation, previously associated with poor virology response to adefovir,<sup>91</sup> emerged in two of 10 during transient viremia, and pre-existed in two of the 13 with persistent viremia. Interestingly, mutations associated with resistance to lamivudine were detected at time of viremia. The clinical significance of these rare mutations

observed in HIV-HBV co-infected patients on TDF-containing antiretroviral treatment and previously exposed to lamivudine, remains uncertain<sup>82,84,89,92</sup> for treatment, but also for the prevention of MTCT.

## Impact of resistance mutations selected by antiviral therapy on surface antigen

Due to the overlap of the envelope and polymerase genes reading frames, some polymerase resistance mutations selected during antiviral therapy can concomitantly alter the antigenicity of HBsAg. The rtM204V mutation, selected by lamivudine treatment, is associated with an amino acid residue change at position 195 of the HBsAg (sI195M), while the rtM204I mutation can result in three possible changes; sW196S, sW196L, or a stop codon.<sup>93</sup> The triple lamivudine resistance mutations (rtV173L+rtL180M+rtM204V) are linked with the changes of two amino acids in the surface gene (sE164D+sI195M).<sup>94,95</sup> As a consequence of the conformation change of the surface antigen, mutant HBsAg binding to anti-HBs is greatly reduced to levels similar to that observed with the vaccine escape mutant sG145R.<sup>96</sup> These mutations were found in up to 25% of HIV-HBV co-infected individuals and 10% of HBV mono-infected patients with HBV replication on lamivudine treatment.<sup>97</sup> The polymerase mutations, rtA181T and rtA181V, induced by adefovir, result in envelope mutations: top codon (sW172stop) and sL173F, respectively. Mutations conferring resistance to entecavir (ie, rtI169T, rtS184G, and rtS202I) also result in amino acid changes of HBsAg (sF161L, sL/V176G, and sV194F). However, their effect on the envelope structure, particularly in the “a” determinant region, and their significance for diagnostics and vaccine escape need further investigation.

**Table 2** Polymerase gene mutations associated with resistance to one or several nucleos(t)ide analogs

Polymerase boxes	A	B	C	D	E
Lamivudine Telbivudine	rtL80I	rtV173L rtL180M rtA181T/V rtA181V	rtM204V/I		
Adefovir				rtN236T rtI233T	
Entecavir		rtI169T rtL180M rtT184G rtA194T?	rtM204V/I rtS202G		rt250I/V
TDF					

Of concern for the prevention of MTCT, it has been suggested that these mutants selected by lamivudine treatment could escape recognition by anti-HBs antibodies elicited by HB vaccine<sup>98,99</sup> and, also, cause false negative HBsAg test results despite active HBV replication.<sup>100</sup> However, since 2017, TDF is no longer protected, and the price of generics has dramatically decreased, which makes the use of lamivudine less attractive. Therefore, the incidence of HBsAg mutants selected by lamivudine should decrease over time.

## HBV resistance to nucleos(t)ide analogs and prevention of MTCT

Information about the percentage of pregnant women with nucleos(t)ide analog-resistant viruses at the initiation of antiviral prophylaxis or later is scarce, and this may vary across settings depending on the extent of the use of these drugs. Transmission despite antiviral prophylaxis and associated with antiviral resistance have not been reported to our knowledge.

As for emergence of resistance during a short prophylactic course of antiviral, the issue has not been fully investigated in older MTCT clinical trials but, in 2014, Ayres et al<sup>101</sup> reported the emergence of low frequency rtM204I/V and rtA181T resistant viruses to lamivudine or minor variants using ultra-deep pyrosequencing in seven of 21 pregnant women who received lamivudine during the third trimester of pregnancy.

## Conclusion

Maternal antiviral prophylaxis during pregnancy, in addition to active-passive immunization, has been proposed to further prevent MTCT of HBV. Recent clinical trials assessing TDF in this setting have suggested the efficacy and safety of the approach. Major associations for the study of liver diseases have included this approach in their guidelines for PMTCT of HBV but, to date, not WHO, and the use of TDF for the prevention of MTCT of HBV remains “off-label” in the US. Immune escape mutants and nucleos(t)ide analog resistant viruses do not seem to represent a major threat to this approach, but need to be monitored. The question of whether the administration of HBIG is needed when a mother receives antiviral prophylaxis remains unanswered. As new infections are essentially the results of perinatal transmission, reaching by 2030 the goal of hepatitis B elimination set by WHO, ie, 90% reduction

in new chronic infections, relies first on the accurate administration of HB vaccine to all infants starting with the birth dose, which has the potential of lifelong protection. Additional interventions, such as antiviral prophylaxis in pregnant women or HBIG to infants, may help but not replace the vaccine.

## Disclosure

The authors declare that they have no conflicts of interest in this work.

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