

# 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*

Gonzague Jourdain<sup>1–3</sup>  
Nicole Ngo-Giang-Huong<sup>1–3</sup>  
Woottichai Khamduang<sup>2</sup>

<sup>1</sup>Unit 174-PHPT, Institut de recherche pour le développement (IRD), Marseille, France; <sup>2</sup>Faculty of Associated Medical Sciences, Chiang Mai University, Chiang Mai, Thailand; <sup>3</sup>Department of Immunology and Infectious Diseases, Harvard TH Chan School of Public Health, Boston, MA, USA

**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>

Correspondence: Gonzague Jourdain  
PHPT – IRD Unit 174, Institut de  
Recherche pour le Développement (IRD),  
195 Kaew Nawarat Road (3-4 Fl.), Wat  
Ked, Muang Chiang Mai 50000, Thailand  
Tel +6 681 883 0065  
Email [Gonzague.Jourdain@ird.fr](mailto:Gonzague.Jourdain@ird.fr)

## 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 1** 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 HBV 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 (HBV Ig) 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 s145R 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 HBV Ig 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>

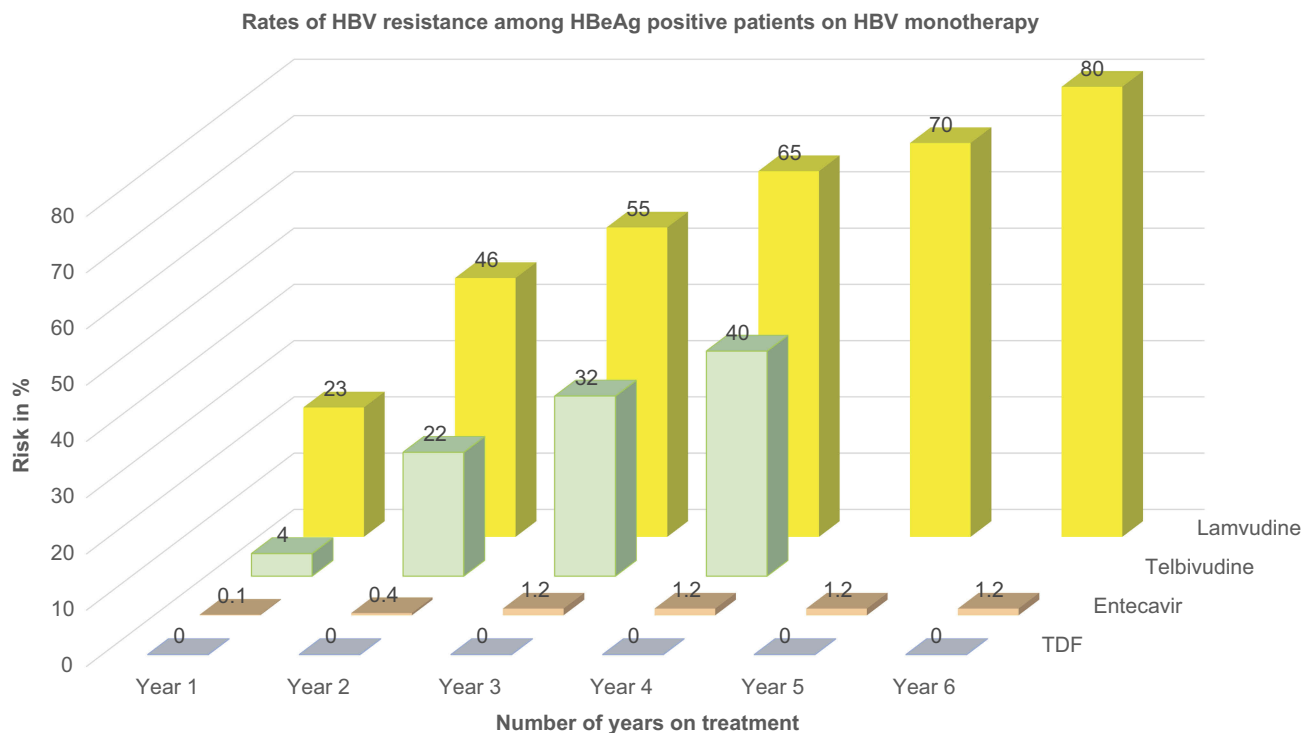
In the context of HIV-HBV co-infection, the use of TDF has been associated with high rates of virological suppression.<sup>82,83</sup> However, a small percentage of co-infected patients on TDF-containing antiretroviral treatment have experienced suboptimal responses after long-term therapy and, in rare 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 rtA181T/V	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.

## References

1. World Health Organization. *Global Hepatitis Report 2017*. Geneva: World Health Organization & Global Hepatitis Programme; 2017. Available from: <http://apps.who.int/iris/bitstream/10665/255016/1/9789241565455-eng.pdf?ua=1>.
2. Hutin Y, Desai S, Bulterys M. Preventing hepatitis B virus infection: milestones and targets. *Bull World Health Organ*. 2018;96(7):443–443A. doi:10.2471/BLT.18.215210
3. Beasley RP. Hepatitis B virus. The major etiology of hepatocellular carcinoma. *Cancer*. 1988;61(10):1942–1956.
4. World Health Organization. *Prevention and Control of Viral Hepatitis Infection: Framework for Global Action*. World Health Organization; 2012. Available from: <https://www.who.int/hiv/pub/hepatitis/Framework/en/>.
5. World Health Organization. WHO guidelines approved by the guidelines review committee. In: *Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection*. Geneva: World Health Organization; 2015.
6. Stevens CE, Beasley RP, Tsui J, Lee WC. Vertical transmission of hepatitis B antigen in Taiwan. *N Engl J Med*. 1975;292(15):771–774. doi:10.1056/NEJM197504102921503
7. Hyams KC. Risks of chronicity following acute hepatitis B virus infection: a review. *Clin Infect Dis*. 1995;20(4):992–1000.
8. Komatsu H, Inui A, Sogo T, Tateno A, Shimokawa R, Fujisawa T. Tears from children with chronic hepatitis B virus (HBV) infection are infectious vehicles of HBV transmission: experimental transmission of HBV by tears, using mice with chimeric human livers. *J Infect Dis*. 2012;206(4):478–485. doi:10.1093/infdis/jis293
9. World Health Organization. *Hepatitis B and Breastfeeding*. World Health Organization; 1996. Available from: [http://www.who.int/maternal\\_child\\_adolescent/documents/pdfs/hepatitis\\_b\\_and\\_breastfeeding.pdf](http://www.who.int/maternal_child_adolescent/documents/pdfs/hepatitis_b_and_breastfeeding.pdf).
10. Hepatitis B Questions and Answers for the Public | CDC. (2018, June 13). Available from: <https://www.cdc.gov/hepatitis/hbv/bfaq.htm>. Accessed December 2, 2018.
11. Middleman AB, Baker CJ, Kozinetz CA, et al. Duration of protection after infant hepatitis B vaccination series. *Pediatrics*. 2014;133(6):e1500–e1507. doi:10.1542/peds.2013-2112
12. Van Damme P. Long-term protection after hepatitis B vaccine. *J Infect Dis*. 2016;214(1):1–3. doi:10.1093/infdis/jiv750
13. World Health Organisation. Worldwide implementation of hepatitis B vaccination of newborns, 2006. *Wkly Epidemiol Rec*. 2008;83(48):429–434.
14. Wong VC, Ip HM, Reesink HW, et al. Prevention of the HBsAg carrier state in newborn infants of mothers who are chronic carriers of HBsAg and HBeAg by administration of hepatitis- B vaccine and hepatitis- B immunoglobulin. Double-blind randomised placebo-controlled study. *Lancet*. 1984;1(8383):921–926.
15. World Health Organisation. Hepatitis B vaccines. *Wkly Epidemiol Rec*. 2004;79(28):255–263.



16. World Health Organisation. Hepatitis B vaccines. *Wkly Epidemiol Rec.* 2009;84(40):405–419.
17. World Health Organization. Hepatitis B: fact sheet. (Reviewed July 2017). Available from: <http://www.who.int/mediacentre/factsheets/fs204/en/>. Accessed April 11, 2018.
18. Wu JN, Li DJ, Zhou Y. Association between timely initiation of hepatitis B vaccine and completion of the hepatitis B vaccine and national immunization program vaccine series. *Int J Infect Dis.* 2016;51:62–65. doi:10.1016/j.ijid.2016.08.018
19. Yusuf HR, Daniels D, Smith P, Coronado V, Rodewald L. Association between administration of hepatitis B vaccine at birth and completion of the hepatitis B and 4:3:1:3 vaccine series. *JAMA.* 2000;284(8):978–983.
20. Creati M, Saleh A, Ruff TA, et al. Implementing the birth dose of hepatitis B vaccine in rural Indonesia. *Vaccine.* 2007;25(32):5985–5993. doi:10.1016/j.vaccine.2007.05.055
21. Cui F, Liang X, Gong X, et al. Preventing hepatitis B through universal vaccination: reduction of inequalities through the GAVI China project. *Vaccine.* 2013;31(Suppl 9):J29–J35. doi:10.1016/j.vaccine.2012.07.048
22. Murakami H, Van Cuong N, Huynh L, Hipgrave DB. Implementation of and costs associated with providing a birth-dose of hepatitis B vaccine in Viet Nam. *Vaccine.* 2008;26(11):1411–1419. doi:10.1016/j.vaccine.2008.01.002
23. Beasley RP, Hwang LY, Lee GC, et al. Prevention of perinatally transmitted hepatitis B virus infections with hepatitis B immune globulin and hepatitis B vaccine. *Lancet.* 1983;2(8359):1099–1102.
24. Chen SC, Toy M, Yeh JM, Wang JD, Resch S. Cost-effectiveness of augmenting universal hepatitis B vaccination with immunoglobulin treatment. *Pediatrics.* 2013;131(4):e1135–e1143. doi:10.1542/peds.2012-1262
25. World Health Organization. *Guidelines for the Prevention, Care and Treatment of Persons with Chronic Hepatitis B Infection.* Geneva: World Health Organization; 2015. Retrieved from: <http://www.ncbi.nlm.nih.gov/books/NBK305553/>
26. Eke AC, Eleje GU, Eke UA, Xia Y, Liu J. Hepatitis B immune globulin during pregnancy for prevention of mother-to-child transmission of hepatitis B virus. *Cochrane Database Syst Rev.* 2017;2:CD008545.
27. Brown RS Jr, McMahon BJ, Lok AS, et al. Antiviral therapy in chronic hepatitis B viral infection during pregnancy: A systematic review and meta-analysis. *Hepatology (Baltimore, Md).* 2016;63(1):319–333. doi:10.1002/hep.28302
28. Pan CQ, Duan Z, Dai E, et al. Tenofovir to prevent hepatitis B transmission in mothers with high viral load. *N Engl J Med.* 2016;374(24):2324–2334. doi:10.1056/NEJMoa1508660
29. Jourdain G, Ngo-Giang-Huong N, Harrison L, et al. Tenofovir versus placebo to prevent perinatal transmission of hepatitis B. *N Engl J Med.* 2018;378(10):911–923. doi:10.1056/NEJMoa1708131
30. European Association for the Study of the Liver. Electronic address eee, European Association for the Study of the L. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. *J Hepatol.* 2017;67(2):370–398. doi:10.1016/j.jhep.2017.03.021
31. Sarin SK, Kumar M, Lau GK, et al. Asian-Pacific clinical practice guidelines on the management of hepatitis B: a 2015 update. *Hepatol Int.* 2016;10(1):1–98.
32. Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. *Hepatology (Baltimore, Md).* 2018;67(4):1560–1599. doi:10.1002/hep.29800
33. Zeng H, Cai H, Wang Y, Shen Y. Growth and development of children prenatally exposed to telbivudine administered for the treatment of chronic hepatitis B in their mothers. *Int J Infect Dis.* 2015;33:97–103. doi:10.1016/j.ijid.2014.09.002
34. Zhou C, Yu Y, Yang Q, et al. Motor development delay in offspring is associated with prenatal telbivudine exposure. *Medicine (Baltimore).* 2018;97(9):e0053. doi:10.1097/MD.00000000000010053
35. Ip HM, Lelie PN, Wong VC, Kuhns MC, Reesink HW. Prevention of hepatitis B virus carrier state in infants according to maternal serum levels of HBV DNA. *Lancet.* 1989;1(8635):406–410.
36. Soderstrom A, Norkrans G, Lindh M. Hepatitis B virus DNA during pregnancy and post partum: aspects on vertical transmission. *Scand J Infect Dis.* 2003;35(11–12):814–819.
37. Ter Borg MJ, Leemans WF, de Man RA, Janssen HL. Exacerbation of chronic hepatitis B infection after delivery. *J Viral Hepat.* 2008;15(1):37–41. doi:10.1111/j.1365-2893.2007.00894.x
38. Coursaget P, Kane MA. Overview of clinical studies in developing countries. In: Ellis RW, editor. *Hepatitis B Vaccines in Clinical Practice.* New York: Marcel Dekker, Inc; 1993: 209–228.
39. Han GR, Cao MK, Zhao W, et al. A prospective and open-label study for the efficacy and safety of telbivudine in pregnancy for the prevention of perinatal transmission of hepatitis B virus infection. *J Hepatol.* 2011;55(6):1215–1221. doi:10.1016/j.jhep.2011.02.032
40. Mahtab MA, Rahman S, Khan M, Karim F. Hepatitis B virus genotypes: an overview. *Hepatobiliary Pancreat Dis Int.* 2008;7(5):457–464.
41. Hollinger FB. Hepatitis B virus genetic diversity and its impact on diagnostic assays. *J Viral Hepat.* 2007;14(Suppl 1):11–15. doi:10.1111/j.1365-2893.2007.00910.x
42. Carman WF. Molecular variants of hepatitis B virus. *Clin Lab Med.* 1996;16(2):407–428.
43. Carman WF, Trautwein C, van Deursen FJ, et al. Hepatitis B virus envelope variation after transplantation with and without hepatitis B immune globulin prophylaxis. *Hepatology (Baltimore, Md).* 1996;24(3):489–493. doi:10.1002/hep.510240304
44. Cooreman MP, Leroux-Roels G, Paulij WP. Vaccine- and hepatitis B immune globulin-induced escape mutations of hepatitis B virus surface antigen. *J Biomed Sci.* 2001;8(3):237–247. doi:10.1159/000054039
45. Francois G, Kew M, Van Damme P, Mphahlele MJ, Meheus A. Mutant hepatitis B viruses: a matter of academic interest only or a problem with far-reaching implications? *Vaccine.* 2001;19(28–29):3799–3815.
46. Kay A, Zoulim F. Hepatitis B virus genetic variability and evolution. *Virus Res.* 2007;127(2):164–176. doi:10.1016/j.virusres.2007.02.021
47. Chiou HL, Lee TS, Kuo J, Mau YC, Ho MS. Altered antigenicity of ‘a’ determinant variants of hepatitis B virus. *J Gen Virol.* 1997;78(Pt 10):2639–2645. doi:10.1099/0022-1317-78-10-2639
48. Waters JA, Kennedy M, Voet P, et al. Loss of the common ‘A’ determinant of hepatitis B surface antigen by a vaccine-induced escape mutant. *J Clin Invest.* 1992;90(6):2543–2547. doi:10.1172/JCI116148
49. Cariani E, Ravaggi A, Tanzi E, et al. Emergence of hepatitis B virus S gene mutant in a liver transplant recipient. *J Med Virol.* 1995;47(4):410–415.
50. Carman WF, Zanetti AR, Karayiannis P, et al. Vaccine-induced escape mutant of hepatitis B virus. *Lancet.* 1990;336(8711):325–329.
51. Kajiwara E, Tanaka Y, Ohashi T, et al. Hepatitis B caused by a hepatitis B surface antigen escape mutant. *J Gastroenterol.* 2008;43(3):243–247. doi:10.1007/s00535-007-2150-9
52. Ghaziasadi A, Alavian SM, Norouzi M, Fazeli Z, Jazayeri SM. Mutational analysis of HBs Ag-positive mothers and their infected children despite immunoprophylaxis. *Iran J Allergy Asthma Immunol.* 2013;12(4):352–360.

53. Seddigh-Tonekaboni S, Lim WL, Young B, et al. Hepatitis B surface antigen variants in vaccinees, blood donors and an interferon-treated patient. *J Viral Hepat.* 2001;8(2):154–158. doi:10.1046/j.1365-2893.2001.00275.x
54. Yan B, Lv J, Feng Y, et al. Temporal trend of hepatitis B surface mutations in the post-immunization period: 9 years of surveillance (2005–2013) in eastern China. *Sci Rep.* 2017;7(1):6669. doi:10.1038/s41598-017-07085-z
55. Carman WF, Van Deursen FJ, Mimms LT, et al. The prevalence of surface antigen variants of hepatitis B virus in Papua New Guinea, South Africa, and Sardinia. *Hepatology (Baltimore, Md).* 1997;26(6):1658–1666. doi:10.1002/hep.510260640
56. Chang MH. Breakthrough HBV infection in vaccinated children in Taiwan: surveillance for HBV mutants. *Antivir Ther.* 2010;15(3Pt B):463–469. doi:10.3851/IMP1555
57. Chong-Jin O, Wei Ning C, Shiuan K, Gek Keow L. Identification of hepatitis B surface antigen variants with alterations outside the “a” determinant in immunized Singapore infants. *J Infect Dis.* 1999;179(1):259–263. doi:10.1086/314553
58. He C, Nomura F, Itoga S, Isobe K, Nakai T. Prevalence of vaccine-induced escape mutants of hepatitis B virus in the adult population in China: a prospective study in 176 restaurant employees. *J Gastroenterol Hepatol.* 2001;16(12):1373–1377.
59. Ho M, Mau Y, Lu C, et al. Patterns of circulating hepatitis B surface antigen variants among vaccinated children born to hepatitis B surface antigen carrier and non-carrier mothers. A population-based comparative study. *J Biomed Sci.* 1998;5(5):355–362. doi:10.1007/BF02253445
60. Khamduang W, Gaudy-Graffin C, Ngo-Giang-Huong N, et al. Analysis of residual perinatal transmission of hepatitis B virus (HBV) and of genetic variants in human immunodeficiency virus and HBV co-infected women and their offspring. *J Clin Virol.* 2013;58(2):415–421. doi:10.1016/j.jcv.2013.06.025
61. Lazarevic I. Clinical implications of hepatitis B virus mutations: recent advances. *World J Gastroenterol.* 2014;20(24):7653–7664. doi:10.3748/wjg.v20.i24.7653
62. Lee KM, Kim YS, Ko YY, et al. Emergence of vaccine-induced escape mutant of hepatitis B virus with multiple surface gene mutations in a Korean child. *J Korean Med Sci.* 2001;16(3):359–362. doi:10.3346/jkms.2001.16.3.359
63. Oon CJ, Lim GK, Ye Z, et al. Molecular epidemiology of hepatitis B virus vaccine variants in Singapore. *Vaccine.* 1995;13(8):699–702.
64. Santantonio T, Gunther S, Sterneck M, et al. Liver graft infection by HBV S-gene mutants in transplant patients receiving long-term HBIG prophylaxis. *Hepatogastroenterology.* 1999;46(27):1848–1854.
65. Velu V, Saravanan S, Nandakumar S, et al. Transmission of “a” determinant variants of hepatitis B virus in immunized babies born to HBsAg carrier mothers. *Jpn J Infect Dis.* 2008;61(1):73–76.
66. von Weizsacker F, Pult I, Geiss K, Wirth S, Blum HE. Selective transmission of variant genomes from mother to infant in neonatal fulminant hepatitis B. *Hepatology (Baltimore, Md).* 1995;21(1):8–13.
67. Kwak MS, Kim YJ. Occult hepatitis B virus infection. *World J Hepatol.* 2014;6(12):860–869. doi:10.4254/wjh.v6.i12.860
68. Pan CQ, Yi W, Liu M, Wan G, Hu YH, Zhou MF. Lamivudine therapy during the second vs the third trimester for preventing transmission of chronic hepatitis B. *J Viral Hepat.* 2017;24(3):246–252. doi:10.1111/jvh.12640
69. Xu WM, Cui YT, Wang L, et al. Lamivudine in late pregnancy to prevent perinatal transmission of hepatitis B virus infection: a multicentre, randomized, double-blind, placebo-controlled study. *J Viral Hepat.* 2009;16(2):94–103. doi:10.1111/j.1365-2893.2008.01056.x
70. Zhang H, Pan CQ, Pang Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces perinatal transmission of hepatitis B virus in real-life practice. *Hepatology (Baltimore, Md).* 2014. doi:10.1002/hep.27034
71. Han GR, Jiang HX, Yue X, et al. Efficacy and safety of telbivudine treatment: an open-label, prospective study in pregnant women for the prevention of perinatal transmission of hepatitis B virus infection. *J Viral Hepat.* 2015;22(9):754–762. doi:10.1111/jvh.12379
72. Piratvisuth T, Han GR, Pol S, Dong Y, Trylesinski A. Comprehensive review of telbivudine in pregnant women with chronic hepatitis B. *World J Hepatol.* 2016;8(9):452–460. doi:10.4254/wjh.v8.i9.452
73. Tan Z, Yin Y, Zhou J, Wu L, Xu C, Hou H. Telbivudine treatment of hepatitis B virus-infected pregnant women at different gestational stages for the prevention of mother-to-child transmission: outcomes of telbivudine treatment during pregnancy. *Medicine (Baltimore).* 2016;95(40):e4847. doi:10.1097/MD.00000000000004864
74. Wu Q, Huang H, Sun X, et al. Telbivudine prevents vertical transmission of hepatitis B virus from women with high viral loads: a prospective long-term study. *Clin Gastroenterol Hepatol.* 2015;13(6):1170–1176. doi:10.1016/j.cgh.2014.08.043
75. Chen JZ, Liao ZW, Huang FL, et al. Efficacy and safety of tenofovir disoproxil fumarate in preventing vertical transmission of hepatitis B in pregnancies with high viral load. *Sci Rep.* 2017;7(1):4132. doi:10.1038/s41598-017-04479-x
76. Lai CL, Dienstag J, Schiff E, et al. Prevalence and clinical correlates of YMDD variants during lamivudine therapy for patients with chronic hepatitis B. *Clin Infect Dis.* 2003;36(6):687–696. doi:10.1086/368083
77. Lok AS, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology.* 2003;125(6):1714–1722.
78. Pallier C, Castera L, Soulier A, et al. Dynamics of hepatitis B virus resistance to lamivudine. *J Virol.* 2006;80(2):643–653. doi:10.1128/JVI.80.2.643-653.2006
79. Liaw YF, Gane E, Leung N, et al. 2-Year GLOBE trial results: telbivudine is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology.* 2009;136(2):486–495. doi:10.1053/j.gastro.2008.10.026
80. Chang TT, Lai CL, Kew Yoon S, et al. Entecavir treatment for up to 5 years in patients with hepatitis B e antigen-positive chronic hepatitis B. *Hepatology (Baltimore, Md).* 2010;51(2):422–430. doi:10.1002/hep.23327
81. Liu Y, Corsa AC, Buti M, et al. No detectable resistance to tenofovir disoproxil fumarate in HBeAg+ and HBeAg- patients with chronic hepatitis B after 8 years of treatment. *J Viral Hepat.* 2017;24(1):68–74. doi:10.1111/jvh.12613
82. Boyd A, Gozlan J, Maylin S, et al. Persistent viremia in human immunodeficiency virus/hepatitis B coinfecting patients undergoing long-term tenofovir: virological and clinical implications. *Hepatology (Baltimore, Md).* 2014;60(2):497–507. doi:10.1002/hep.27182
83. Price H, Dunn D, Pillay D, et al. Suppression of HBV by tenofovir in HBV/HIV coinfecting patients: a systematic review and meta-analysis. *PLoS One.* 2013;8(7):e68152. doi:10.1371/journal.pone.0068152
84. Bihl F, Martinetti G, Wandeler G, et al. HBV genotypes and response to tenofovir disoproxil fumarate in HIV/HBV-coinfecting persons. *BMC Gastroenterol.* 2015;15:79. doi:10.1186/s12876-015-0308-0
85. Gish R, Jia JD, Locarnini S, Zoulim F. Selection of chronic hepatitis B therapy with high barrier to resistance. *Lancet Infect Dis.* 2012;12(4):341–353. doi:10.1016/S1473-3099(11)70314-0

86. Zoulim F, Locarnini S. Hepatitis B virus resistance to nucleos(t)ide analogues. *Gastroenterology*. 2009;137(5):1593-1608. doi:10.1053/j.gastro.2009.08.063
87. Qi X, Xiong S, Yang H, Miller M, Delaney W. In vitro susceptibility of adefovir-associated hepatitis B virus polymerase mutations to other antiviral agents. *Antivir Ther*. 2007;12(3):355-362.
88. Sheldon J, Camino N, Rodes B, et al. Selection of hepatitis B virus polymerase mutations in HIV-coinfected patients treated with tenofovir. *Antivir Ther*. 2005;10(6):727-734.
89. Amini-Bavil-Olyaei S, Herbers U, Sheldon J, Luedde T, Trautwein C, Tacke F. The rtA194T polymerase mutation impacts viral replication and susceptibility to tenofovir in hepatitis B e antigen-positive and hepatitis B e antigen-negative hepatitis B virus strains. *Hepatology (Baltimore, Md)*. 2009;49(4):1158-1165. doi:10.1002/hep.22790
90. Lacombe K, Boyd A, Lavocat F, et al. High incidence of treatment-induced and vaccine-escape hepatitis B virus mutants among human immunodeficiency virus/hepatitis B-infected patients. *Hepatology (Baltimore, Md)*. 2013;58(3):912-922. doi:10.1002/hep.26374
91. Rodriguez-Frias F, Jardi R, Schaper M, et al. Adefovir for chronic hepatitis B treatment: identification of virological markers linked to therapy response. *Antivir Ther*. 2008;13(8):991-999.
92. Delaney W, Ray AS, Yang H, et al. Intracellular metabolism and in vitro activity of tenofovir against hepatitis B virus. *Antimicrob Agents Chemother*. 2006;50(7):2471-2477. doi:10.1128/AAC.00138-06
93. Bartholomeusz A, Locarnini S. Hepatitis B virus mutations associated with antiviral therapy. *J Med Virol*. 2006;78(Suppl 1):S52-55. doi:10.1002/jmv.20608
94. Sheldon J, Soriano V. Hepatitis B virus escape mutants induced by antiviral therapy. *J Antimicrob Chemother*. 2008;61(4):766-768. doi:10.1093/jac/dkn014
95. Torresi J, Earnest-Silveira L, Deliyannis G, et al. Reduced antigenicity of the hepatitis B virus HBsAg protein arising as a consequence of sequence changes in the overlapping polymerase gene that are selected by lamivudine therapy. *Virology*. 2002;293(2):305-313. doi:10.1006/viro.2001.1246
96. Cooley L, Ayres A, Bartholomeusz A, et al. Prevalence and characterization of lamivudine-resistant hepatitis B virus mutations in HIV-HBV co-infected individuals. *Aids*. 2003;17(11):1649-1657. doi:10.1097/01.aids.0000060414.18106.53
97. Torresi J. The virological and clinical significance of mutations in the overlapping envelope and polymerase genes of hepatitis B virus. *J Clin Virol*. 2002;25(2):97-106.
98. Clements CJ, Coghlan B, Creati M, Locarnini S, Tedder RS, Torresi J. Global control of hepatitis B virus: does treatment-induced antigenic change affect immunization? *Bull World Health Organ*. 2010;88(1):66-73. doi:10.2471/BLT.08.065722
99. Kamili S, Sozzi V, Thompson G, et al. Efficacy of hepatitis B vaccine against antiviral drug-resistant hepatitis B virus mutants in the chimpanzee model. *Hepatology (Baltimore, Md)*. 2009;49(5):1483-1491. doi:10.1002/hep.22796
100. Lee SY, Choi MS, Lee D, et al. Overlapping gene mutations of hepatitis B virus in a chronic hepatitis B patient with hepatitis B surface antigen loss during lamivudine therapy. *J Korean Med Sci*. 2005;20(3):433-437. doi:10.3346/jkms.2005.20.3.433
101. Ayres A, Yuen L, Jackson KM, et al. Short duration of lamivudine for the prevention of hepatitis B virus transmission in pregnancy: lack of potency and selection of resistance mutations. *J Viral Hepat*. 2014;21(11):809-817. doi:10.1111/jvh.12212

## Infection and Drug Resistance

### Publish your work in this journal

Infection and Drug Resistance is an international, peer-reviewed open-access journal that focuses on the optimal treatment of infection (bacterial, fungal and viral) and the development and institution of preventive strategies to minimize the development and spread of resistance. The journal is specifically concerned with the epidemiology of

antibiotic resistance and the mechanisms of resistance development and diffusion in both hospitals and the community. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/infection-and-drug-resistance-journal>

Dovepress