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Ending Vertical Transmission of Hepatitis B: The Third Trimester Intervention

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Mother-to-child transmission (MTCT) is the most common mode of acquiring chronic hepatitis B virus (HBV) infection in endemic countries.[1] Immunoprophylaxis using hepatitis B immune globulin (HBIG) and HBV vaccination within 12 hours of birth plays a major role in preventing perinatal transmission, but 10-15% of children born to hepatitis B surface antigen (HBsAg)-positive mothers still develop chronic HBV infection, despite immunoprophylactic measures.[2,3] Efforts to effectively reduce the risk of MTCT to zero are highly desired in the global goal to eradicate chronic HBV. High maternal HBV viral load at delivery is an established risk factor for MTCT, and antiviral therapy in the third trimester has been shown to decrease the risk of perinatal transmission.[4–8]

In using antiviral agents in pregnancy, one must consider whether the mother has active and/or advanced disease that requires treatment initiation or continuation during pregnancy, or if treatment is not indicated, whether antiviral therapy in the third trimester is indicated to decrease the risk of MTCT (Fig. 1). While all major liver society guidelines recommend third trimester antiviral therapy for women at higher risk of MTCT (Table 1),[9–11] several areas of controversy remain, including the preferred antiviral drug, the HBV viral load threshold that warrants treatment, the gestational week at which to initiate therapy, and when to stop treatment after delivery.

Lamivudine (LAM), telbivudine (TBV), and tenofovir (TDF) have all shown efficacy in preventing MTCT when initiated in the third trimester (Table 2). The study by Zhang et al., [12] published in this issue of HEPATOLOGY, adds to the treatment experience and is the first to provide a direct comparison between antiviral agents. In their on-treatment analysis of LAM (n = 52), TBV (n = 252), and no therapy (n = 345), they identified HBV transmission in 2.8% of controls, while none of the infants born to LAM- or TBV-treated women had detectable HBsAg at week 52 of follow-up. HBV DNA levels were successfully reduced to $<10^6$ copies/mL in all treated mothers. Similar findings were reported in two controlled TBV studies that reported no MTCT in the TBV groups compared to ~8% MTCT in untreated controls.[4,7] A meta-analysis of 15 randomized controlled trials including 1,693 mothers with chronic hepatitis B found a 70% reduction in MTCT using LAM (relative risk [RR] 0.3, 95% confidence interval [CI] 0.2-0.5) defined by detectable HBsAg at birth or 6-12 months after birth.[5] When the analysis was restricted to MTCT defined by positive HBsAg at birth only, LAM use was not associated with decreased MTCT, unless maternal

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HBV viral load at delivery decreased to $<10^6$ copies/mL. Most studies started LAM from gestational week 28 onwards, with one study using LAM from week 32. This latter study failed to show a risk reduction in MTCT, leading the authors to conclude that LAM treatment starting at week 28, with a reduction of HBV viral load to $<10^6$ copies/mL, was most efficient at interrupting HBV transmission. Two studies to date have investigated MTCT using TDF. In terms of TDF efficacy, among 45 women with HBV DNA levels $>10^7$ copies/mL started on TDF at weeks 18-27, none of the TDF-treated mothers had MTCT compared to 2 (8.3%) controls ($P = 0.02$).[6] These findings were similar to those of an uncontrolled case series of 11 mothers with HBV DNA $\geq 10^6$ copies/mL who were treated with TDF at a median gestational age of 29 weeks. Interestingly, 5/11 women failed to suppress HBV DNA to $<10^6$ copies/mL at delivery, but all had successful prevention of MTCT.[8]

Data are converging on the appropriate HBV threshold at which to initiate antivirals to prevent MTCT. A study from Australia identified 3/138 babies with MTCT despite immunoprophylaxis and all were born to HBeAg-positive mothers with HBV DNA levels $>10^8$ copies/mL.[13] A larger study from China characterized 869 infant-mother pairs and the rate of immunoprophylaxis failure by predelivery HBV DNA was 0% for HBV DNA levels $<10^6$, 3.2% for levels of $10^{6\text{-}6.99}$, 6.7% for levels between $10^{7\text{-}7.99}$, and 7.6% for HBV DNA levels $\geq 10^8$ copies/mL.[14] These data suggest the risk threshold for MTCT is an HBV viral load over 10^6 copies/mL (>200,000 IU/mL). These findings are supported by the meta-analysis of LAM to prevent MTCT, which found that suppression of HBV DNA $<10^6$ copies/mL prevented HBV transmission.[5]

The exact week within the third trimester at which to initiate therapy has not been established; however, a delay in antiviral therapy past gestational week 32 poses the risk of insufficient duration of therapy to achieve an HBV viral load reduction to $<10^6$ copies/mL, particularly in women with high pretreatment HBV DNA levels. In one study of third-trimester TBV therapy, the average decline in HBV DNA (copies/mL) was from 10^8 at baseline to $10^{4.9}$ at week 2, and 10^4 by week 4.[4] A study of LAM started at gestational weeks 32-34 found less rapid viral suppression with an average decline from 10^9 copies/mL at baseline to 10^7 by week 4, and with 18% of infants born to mothers receiving LAM late in pregnancy failing immunoprophylaxis and becoming HBsAg-positive.[3] No viral kinetic data are currently available for third-trimester TDF treatment. While third-trimester antiviral therapy has traditionally started between weeks 28-32, earlier initiation of treatment, starting at week 28, may be necessary for women with very high HBV DNA levels or for women taking a less potent antiviral agent, such as lamivudine.

The duration of antiviral therapy after delivery is not clearly defined, although most experts recommend discontinuation within 1 month postpartum. For women who wish to breastfeed, stopping antiviral therapy at the time of delivery is prudent, to minimize any exposure of the infant to the antiviral drugs. However, infant plasma drug concentrations are very low: 96% and 98% lower than maternal plasma or breast milk, respectively, so the clinical significance of this exposure is not clear.[15] For mothers receiving antivirals for prevention of MTCT, stopping the medication at the time of delivery appears safe. In the study by Zhang et al., 5% of treated women experienced alanine aminotransferase (ALT) elevations after discontinuing

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antiviral therapy after delivery, compared to 2% of women in the control group. All ALT elevations resolved by postpartum week 16, with no severe hepatic flares or decompensation. Similar results have been reported in LAM-treated mothers.[5]

In terms of the specific antiviral to use for prevention of MTCT (Table 2), TDF, TBV, and LAM are all considered safe in pregnancy. Other approved antivirals should not be used. TBV and TDF are pregnancy class B agents, indicating lack of data of teratogenic effects, while LAM is a class C agent, based on some first-trimester teratogenic effects in rabbits. The largest source of human safety data derives from the Antiretro-viral Pregnancy Registry (APR), an international, prospective, voluntary, drug exposure-registration cohort. The risk of infant birth defects after first or second/third trimester LAM exposure were 3.1% and 2.9%, respectively, and with first or second/third trimester TDF exposure were 2.3% and 2.1%, respectively, which are similar to a control population of unexposed mothers of 2.7%. Too little data on TBV in the APR are available to draw meaningful conclusions (n = 24).[16] The study by Zhang et al. makes an important contribution regarding TBV safety. In their prospective study of 700 HBV-infected women using LAM (n = 52), TBV (n = 252), or no therapy (n = 345), they found no significant differences in infant height, weight, or Apgar score between the three groups, or differences in adverse infant events. Despite reassuring data on the lack of birth defects, with all three drugs recommended for prevention of MTCT, longitudinal follow-up of infants exposed to antivirals late in pregnancy is limited. There is some concern of decreased bone mineral density among TDF-exposed infants, with reports of slightly lower adjusted mean z-scores for length and/or head circumference in infants with in utero TDF exposure (compared to TDF unexposed)[17] but with no differences evident beyond 2 years of age.[18] Most data derive from studies of human immunodeficiency virus (HIV)-infected women on TDF, and whether these results are applicable to HBV-infected women with third-trimester exposures is not clear.

Finally, the issue of whether the choice of antiviral drug affects the mother's safety deserves comment. The study by Zhang et al. contributes comprehensive safety data on maternal events from LAM and TBV exposure. Creatinine kinase elevation developed in 1.5% of TBV-exposed women, which was mild in nature (<2× upper limit of normal [ULN]), and resolved upon treatment cessation. No severe adverse events were reported in women exposed to LAM or TBV. On-treatment liver enzyme elevations were more common in treated groups (15% for TBV and 11% for LAM) compared to controls (5%), although no mother developed severe hepatitis flares (ALT >10× ULN). Another aspect of risk relates to the possibility of drug resistance that may limit future antiviral treatment options. In a recent study of 21 women exposed to LAM during pregnancy for a mean of 53 days, LAM-resistant viral variants were identified in almost 20%.[19] Similar studies in TBV and TDF-exposed women are not available but risk of resistant variants would be predicted to be lower.

In summary, there are compelling data that provision of third-trimester antiviral therapy is a safe and effective means of reducing MTCT and that efficacy is highest if a viral load reduction to $<10^6$ copies/mL is achieved. Three antiviral drugs options, LAM, TBV, and TDF are available, all with acceptable safety profiles but with TBV and TDF preferred over LAM, given greater potency and/or more rapid viral decline with short-duration therapy, and

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higher barrier to resistance. In composite, available data support starting antiviral therapy at 28-32 weeks of gestation, with mothers with baseline HBV DNA levels $>10^8$ copies/mL, or mothers treated with LAM, started on antiviral therapy no later than week 28 to ensure sufficient time to achieve an HBV viral load reduction to $<10^6$ copies/mL by delivery. Treatment can be discontinued at the time of delivery and is prudent in women who are breastfeeding, or in the first month postpartum if no breastfeeding is planned. Most important, this strategy requires that all pregnant women who are HBsAg-positive have HBV DNA testing in the third trimester and evaluation for consideration of antiviral therapy. If widely adopted, this practice could further reduce the global burden of chronic HBV infection, particularly in highly endemic countries.

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Abbreviations

ALT	alanine aminotransferase
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
LAM	lamivudine
MTCT	mother-to-child-transmission
RR	relative risk
TBV	telbivudine
TDF	tenofovir

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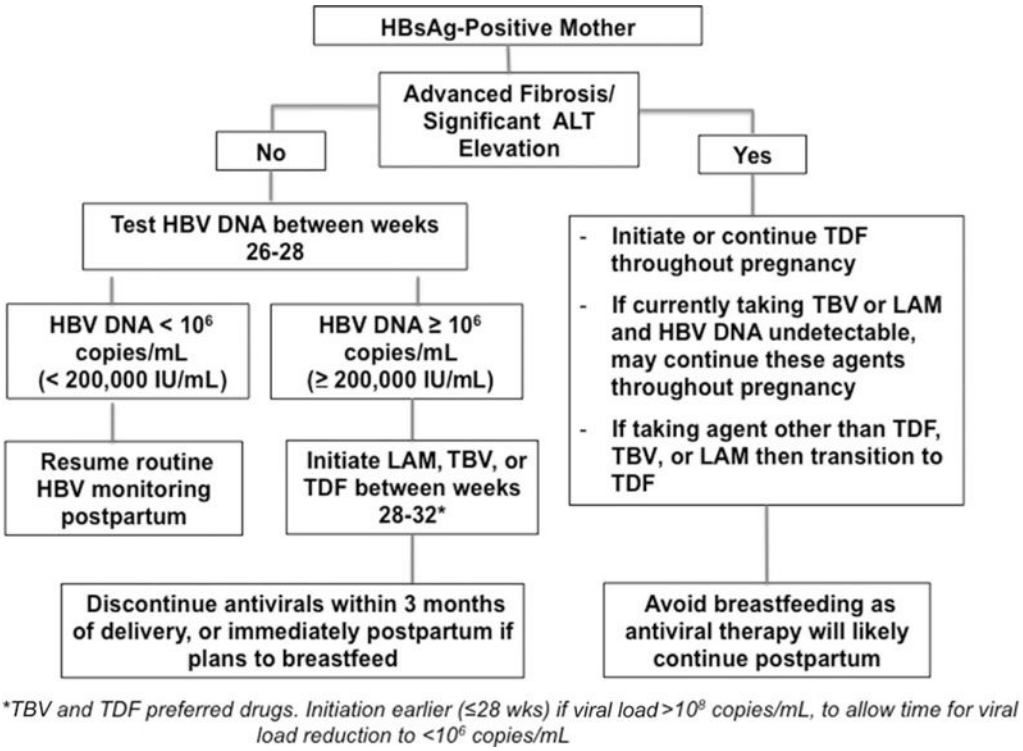

Fig. 1.
Algorithm for management of HBsAg-positive mothers.

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Table 1

Recommendations to Prevent Perinatal HBV Transmission Among Major Liver Societies

Society	Preferred Antiviral Drug	HBV DNA Threshold for 3rd Trimester Therapy	Gestational Age to Initiate Therapy	Duration of Postpartum Treatment
AASLD*	Lamivudine or Telbivudine or Tenofovir	$>2 \times 10^7$ IU/mL ($>10^8$copies/mL) Any viral load if history of prior MTCT	3rd trimester	No comment
APASL	Telbivudine or Tenofovir	$> 2 \times 10^6$ IU/mL ($>10^7$ copies/mL)	3rd trimester	No comment
EASL	Lamivudine or Telbivudine or Tenofovir	$>10^{6–7}$ IU/mL (>5 million copies/mL)	3rd trimester	Discontinue within 3 months postpartum

*No formal recommendations have been published in the AASLD guidelines. The above suggestions derive from AASLD Hepatitis B Special Interest Group Obstetrics and Gynecology Module, 2010.

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Table 2

Characteristics of HBV Antivirals Used in Third Trimester to Prevent MTCT

Antiviral	Pregnancy Class*	Resistance†	Maternal Safety	Human Fetal Safety	Efficacy
Lamivudine (LAM)	C	↑↑↑	Up to 11% mild ALT elevations (pregnancy data)	APR reports no increased birth defects compared to uninfected controls (N = 4,360)	11 RTCs, N = 1,693: Median MTCT 3% LAM versus 16% controls
Telbivudine (TBV)	B	↑↑	Up to 15% mild ALT elevations (pregnancy data)1.5% CK elevation (3rd trimester)	Minimal safety data available in APR (N = 24) Three published observational studies show no increased risk of birth defects (N = 534)	3 controlled studies, N = 534: Median MTCT 0% LdT versus 8% controls
Tenofovir (TDF)	B	None reported	Up to 10% mild ALT elevations (non-pregnancy data)	APR reports no increased birth defects compared to uninfected controls (N = 1,982) Effects on bone growth in children exposed in utero appear minimal	1 controlled study, N = 45: Median MTCT 0% TDF versus 4.4% controls

*FDA definitions. Class B: Animal reproduction studies have not demonstrated a risk to the fetus and there are no adequate and well-controlled studies in pregnant women. Class C: Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans. Potential benefits may warrant use of the drug in pregnant women despite potential risks.

†Based on nonpregnancy data.

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