virus; the clinical benefit of this difference was observed with superior efficacy in one trial.[4] In our trial, tNIV induced significantly greater HAI responses than IIV3-HD against the A/Singapore strain — a variant that was recently selected to be the A(H3N2) vaccine component in the next influenza season (2018–2019).[5] Although confirmation is needed, tNIV may represent a step toward a more effective influenza vaccine, offering avoidance of mismatch resulting from egg-adaptive mutations and potentially broader protection against evolving drift variants.

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Tenofovir to Prevent Perinatal Transmission of Hepatitis B

TO THE EDITOR: Prevention of vertical transmission of hepatitis B virus (HBV) is central to reducing the burden of infection globally.[1] Jourdain and colleagues (March 8 issue)[2] provided immune prophylaxis to infants with high success and timeliness, but administration of hepatitis B immune globulin a median of 1.3 hours after birth and administration of vaccine a median of 1.2 hours after birth is not likely to be generalizable. Furthermore, since the observed mother-to-child transmission rate with the administration of hepatitis B immune globulin and vaccine in the placebo group was low (2% instead of the expected 12%), the trial was underpowered to detect a benefit of tenofovir disoproxil fumarate (TDF). This issue was acknowledged by the authors, but it was probably missed by the casual reader of the conclusions and the headlines that followed the publication of the results of the trial.

The American Association for the Study of Liver Diseases (AASLD) continues to advocate for antiviral treatment in the third trimester in pregnant women with HBV DNA levels higher than 200,000 IU per milliliter,[3] given the substantial evidence of benefit in reducing mother-to-child transmission of HBV.[4,5] The trial by Jourdain et al. highlights the importance of prompt delivery of vaccine and hepatitis B immune globulin to infants, but it should not dissuade clinicians from administering antiviral therapy to pregnant women in the third trimester when appropriate. Indeed, a multifaceted approach is needed to protect as many infants as possible from a lifetime of chronic HBV.

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TO THE EDITOR: Jourdain et al. report on the results of their trial on prevention of mother-to-child transmission of HBV in Thailand. Surprisingly, they did not find a need to reduce high viremia before delivery because passive and active vaccination of the newborns alone provided almost complete protection. However, a similar trial performed in China showed transmission of the virus to 18% of the infants in the control group in spite of passive and active immunization and a significantly lower rate of mother-to-child transmission among infants born to mothers who received TDF beginning at week 30 to 32 of pregnancy than among those born to mothers in the control group.[1] The reasons for this contradiction are unexplained.[2]

The trial by Jourdain et al. may have been biased by excluding mothers with signs of HBV-related liver disease (alanine aminotransferase level of >30 IU per liter), whereas the previous trial[1] included patients with an aminotransferase level of up to 200 IU per liter. This may have favored the proportion of patients infected with HBV genotype B over HBV genotype C, because genotype C is more pathogenic than genotype B.[3] Both genotypes coexist in China and Thailand. The current passive and active vaccination protects more reliably against genotype B than against genotype C.[4] We suggest maintaining the current international recommendations[2] to reduce very high HBV viral loads (>200,000 IU per milliliter) before delivery in hepatitis B e antigen (HBeAg)–positive pregnant women. However, treatment should start before delivery, several weeks earlier than in the trial performed in China.[1]

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TO THE EDITOR: Jourdain et al. report that the use of TDF from 28 weeks of gestation in HBeAg-positive mothers did not result in a reduction of immunoprophylaxis failure in infants at 6 months of age, when the last dose of HBV vaccine was administered to infants. The Centers for Disease Control and Prevention (CDC) recommended that serologic testing of infants after vaccination should not be performed before they are 9 months of age[1] in order to avoid detection of transient antigenemia[2] and increase the likelihood of detection of immunoprophylaxis failure.[1] Early horizontal infection is possible, as evidenced by the third infected child in the trial, in whom the hepatitis B surface antigen (HBsAg) first appeared at 6 months with decreasing levels of antibodies from birth; this risk increases according to the age of the child at testing.[3] Data on the levels of HBsAg in the infants at 9 to 12 months of age would be valuable.

Both the TDF and placebo groups consisted of mothers with low viral loads at baseline. In our study, we found that the risk of immunoprophylaxis failure was low when the HBV DNA level was less than 200,000 IU per milliliter, and the risk increased when the HBV DNA level was at least 7.9 $\log_{10}$ IU per milliliter.[4] In the trial by Jourdain et al., the median HBV DNA level in both groups was approximately 8.0 $\log_{10}$ IU per milliliter, so approximately half the infants were at low risk for HBV transmission even if they had not received TDF. The low HBV DNA levels could have contributed to the negative findings in this trial.

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THE AUTHORS REPLY: Decreasing the viral load of HBV with the use of maternal antiviral prophylaxis to limit exposure to the fetus appears to be a logical step to prevent mother-to-child transmission of the virus. Although it had a larger sample size than previous studies, our double-blind, randomized clinical trial did not show a significant difference between the TDF and placebo groups, with no transmissions among the 147 infants in the TDF group (0%; 95% confidence interval [CI], 0 to 2), as compared with an unexpectedly low rate of transmission among 3 of 147 infants in the placebo group (2%; 95% CI, 0 to 6). This does not imply that antiviral agents do not have efficacy. Indeed, in two other trials[1,2] with higher background transmission, significant differences were observed. We agree with Terrault and colleagues that careful consideration is needed with regard to the implications of these findings in clinical practice. We also agree that our results do not warrant changes in current AASLD guidelines.

There is no rationale for delaying the administration of vaccine and immune globulin to infants after birth. Early administration was feasible in the 17 small-to-medium-size Thai hospitals in our trial. However, our trial does not show that early administration explains the low transmission rate.

Our trial was designed to assess the safety of planned discontinuation of TDF; thus, we excluded women with an alanine aminotransferase level higher than 30 IU per liter who potentially had an increased risk of disease exacerbation and may have benefited from continuous treatment. Gerlich and Glebe suggest that this selection may have increased the proportion of patients who had HBV genotype B over HBV genotype C, and thus the transmission risk may have been decreased. However, the prevalence of genotype C is 85% in Thailand, and only 94 of 2512 women (4%) were excluded on the basis of the alanine aminotransferase level. Therefore, it is unlikely that the exclusion of these patients was the main reason for our findings. Approximately half the women in our trial had an HBV DNA load of less than 8 $\log_{10}$ IU per milliliter at trial entry, but the transmission rate in the upper half of the sample would still be low (especially since the mother of one infected infant had an HBV DNA level of 7.7 $\log_{10}$ IU per milliliter at trial entry). More data are needed to determine at which threshold antiviral prophylaxis would be most useful (e.g., ≥200,000 IU per milliliter as recommended by the AASLD or ≥7.9 $\log_{10}$ IU per milliliter — 400 times more — as advocated by Cheung and colleagues).

In clinical practice, to prevent a false positive diagnosis of chronic HBV infection due to transient antigenemia, the CDC recommends testing infants after 9 months of age. In our trial and other trials,[1,2] the primary efficacy analysis was based on data from infants through 6 or 7 months of age. However, we did retest both the HBV DNA level and the level of antibody to HBsAg in infants at 9 months as well as the level of antibody to HBsAg at 12 months, and we found that the serostatus in infants remained unchanged.

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Since publication of their article, the authors report no further potential conflict of interest.

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