Furthermore, the date of last patients enrollment in reference 35 was September 2010 and the infants were followed up at 1 year old; it required at least 14 months completing infant follow-up; however, the article was submitted for publication in August 2011. The time conflict is hard to interpret.

Third, the infection rates in infants of control mothers were as high as 15.9%-45% in references 27, 30, 32, 35, and 46. Interpretation of high infection rate is difficult, because it is usually <10% in children of hepatitis B e antigen (HBeAg)-positive mothers after combined immunoprophylaxis.[2-4] Even in daily practice with suboptimal immunoprophylaxis between 2002 and 2004, only 12.2% of the children of HBeAg-positive mothers were infected.[5]

Last, almost no adverse event was reported in the references by mainland Chinese authors, which is unusual. Actually, others (references 37 and 50) documented congenital abnormalities in infants of treated mothers.

Therefore, more high-quality studies are required before anti-HBV therapy is routinely recommended in women with high viral loads to prevent mother-to-child transmission of HBV.

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## REPLY:

We appreciate the letter to the editor regarding our systematic review analyzing the impact of oral antivirals in preventing mother-to-child transmission of hepatitis B. The author points out some of the limitations of systematic reviews of studies, such as difficulty in accounting for and identifying overlapping populations from the same center, and shortcomings due to limitations of the original studies, such as incomplete reporting, selection bias, and loss to follow-up.

To overcome some of these limitations, we formed a multidisciplinary systematic review team of hepatologists, methodologists, a statistician, and a native Chinese-speaking researcher. Nevertheless, we remained limited by the quality of data and adequacy of reporting of the primary studies. To explicitly address the challenges in the literature and the uncertainty around the estimate of effect, we used the GRADE approach and downgraded the quality of evidence when appropriate based on risk of bias, inconsistency, indirectness, imprecision, or publication bias. The guideline writing group similarly downgraded the strength of the recommendations based on the quality of the evidence.

Our review shows that the majority of studies report that oral antiviral therapy in the third trimester for women with high hepatitis B viral loads reduces the rate of mother-to-child transmission. Although, the magnitude of this difference and the risk of transmission without antiviral therapy in the mother may be debated, the transmission risk is certainly at least as high as 9%. Whether this transmission rate is acceptable is a societal and patient-physician decision. Our systematic review demonstrates that antiviral therapy reduces the rate of transmission. Given that elimination of vertical transmission of hepatitis B is a public health goal, we believe the data lead to a recommendation for this therapy, despite the limitations. A future trial would provide additional data, but potential information gained should be weighed against the already

reported reduced risk with antiviral prophylaxis in women with high hepatitis B viral loads and, thus, whether such a trial would be ethical or feasible. Finally, the goal of systematic reviews and practice guidelines is to make care recommendations with the currently best available evidence. Consequently, we continue to believe that we have provided the best inference from the data available at the present time and that the independent guideline committee appropriately phrased its recommendation.

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# Treating Hepatitis B Virus/Hepatitis C Virus Coinfected Patients With Direct-Acting Hepatitis C Virus Antivirals Only Is Not Safe

## TO THE EDITOR:

Direct-acting antivirals (DAAs) enabled cure of chronic hepatitis C (CHC) in high rates with acceptable tolerability. Hepatitis B (HBV) and C virus (HCV) coinfected patients may not benefit if only CHC is treated with DAAs. We reviewed the medical literature and noticed 4 cases (Table 1).

Takayama et al. described an HBV reactivation after use of daclatasvir and asunaprevir on day 15 with alanine aminotransferase (ALT) of 237 IU/mL.[(1)] Baseline HBV-DNA of 2.5 log copies/mL increased to 7 logs copies/mL. Entecavir initiated after day 50 controlled HBV flare.

Collins et al. described 2 coinfected patients[(2)]: Eight weeks after sofosbuvir and simeprevir, ALT increased to 1,495 IU/L and total bilirubin to 12.2 mg/dL. Tenofovir/emtricitabine combination controlled HBV flare. Another patient, a 57-year-old male, had HCV and isolated anti-HBcIgG (hepatitis B core immunoglobulin G antibody) positivity. At week 2 of sofosbuvir and simeprevir treatment, HBV DNA increased to 353 IU/mL and in week 4 to 11,255 IU/mL. Tenofovir was added for HBV reactivation.

Another report described liver failure after using HCV drugs for a coinfected patient.[(3)] A 59-year-old female had HCV and isolated anti-HBcIgG positivity. She was given simeprevir, sofosbuvir, and ribavirin. In week 11,