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ORIGINAL ARTICLE

# Prophylactic effect of tenofovir on viral reactivation in immunocompromised pregnant women living with hepatitis B virus

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## Abstract

The appropriate prophylaxis for hepatitis B virus reactivation (HBVr) during gestation for immunocompromised pregnant women has yet to be determined. The prophylactic efficacy and safety of tenofovir disoproxil fumarate (TDF) in hepatitis B surface antigen (HBsAg)–positive patients and the HBVr risk in hepatitis B core antibody (HBcAb)–positive patients during gestation were investigated. Eligible pregnant women were diagnosed with rheumatic diseases and were administered prednisone (≤10 mg daily) with permitted immunosuppressants at screening. HBsAg-positive participants were instructed to take TDF; those unwilling to take TDF were followed up as the control group. Propensity score matching was applied to control for differences in confounding factors between the HBcAb-positive and uninfected groups. Hepatopathy, maternal, pregnancy, and safety outcomes were documented as endpoints. A cohort of 1292 women was recruited from 2017 to 2020, including 58 HBsAg-positive patients (29 in each group). A total of 120 pairs in the HBcAb-positive and noninfection groups were analyzed. Among HBsAg-positive patients, 6 (20.7%) cases of hepatitis flare (hazard ratio [HR]: 7.44; 95% confidence interval [CI]: 1.50–36.89; $p = 0.014$) and 12 (41.4%) cases of HBVr (HR: 8.71; 95% CI: 2.80–27.17; $p < 0.001$) occurred in the control group, while 0 occurred in the TDF prophylaxis group. The HBV level at delivery was

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the lowest (1.6 $\log_{10}$ IU/ml) for those who received TDF during the pregestation period with a good safety profile. More adverse maternal outcomes were observed in the control group (odds ratio: 0.19, 95% CI: 0.05–0.77, $p = 0.021$), including one death from fulminant hepatitis and two cases of vertical transmission. No HBVr was recorded in HBcAb-positive participants. Among immunocompromised pregnant women, prophylactic TDF during pregestation was necessary for HBsAg-positive women, whereas regular monitoring was recommended for HBcAb-positive women.

## INTRODUCTION

Infection with or the reactivation of the hepatitis B virus (HBV) is recognized as an alarming complication in immunocompromised patients.[1] However, the appropriate prophylaxis for hepatitis flare during gestation for this population has yet to be determined.[2,3]

Antiviral agents that inhibit HBV replication, such as lamivudine, tenofovir disoproxil fumarate (TDF), and telbivudine, which have been administered to pregnant women with a high HBV viral load, may reduce the risk of vertical transmission.[4] The 2020 World Health Organization recommended that pregnant women testing positive for HBsAg with an HBV DNA ≥ 200,000 IU/ml receive TDF from the 28th week of pregnancy until at least birth, to prevent mother-to-child transmission of HBV.[5] In 2018, the American Association for the Study of Liver Diseases recommended anti-HBV prophylaxis in HBsAg-positive patients receiving immunosuppressive drugs (ISDs) to prevent HBV reactivation (HBVr).[6] According to previous data, a delay in biochemical remission and a significant increase in the frequency of complications, including death, were observed in the immunocompromised patients.[7] However, the necessity of earlier prophylaxis during gestation has yet been widely recognized in the immunocompromised population.

Due to the risk of HBVr among this special population,[8,9] a randomized double-blind controlled trial is almost impossible to carry out during gestation. Therefore, we conducted this national cohort study to explore the prophylactic efficacy and safety of the administration of TDF among pregnant patients with rheumatic diseases (RDs) given ISDs to prevent HBVr in HBsAg-positive patients and to observe the risk of the HBVr in hepatitis B core antibody (HBcAb)–positive patients.

## PATIENTS AND METHODS

### Study design and participants

This observational cohort study was conducted from January 1, 2017, to December 31, 2020, at Renji Hospital, Shanghai, China. The research protocol was approved by Shanghai Jiao Tong University, School of Medicine, Renji Hospital Ethics Committee (No. [2017]201). All participating patients provided written informed consent.

Eligible patients were recruited when the following inclusion criteria were met: (1) They fulfilled the American College of Rheumatology or European League Against Rheumatism criteria for RDs; (2) they had a plan to conceive (prospective pregnant women) or were pregnant at less than 28 weeks of gestation at the time of enrollment; and (3) they were administered prednisone at a dose of 10 mg daily or less (or equivalent glucocorticoids [GCs]) and/or permitted ISDs at screening. Patients were excluded if (1) they were taking or had taken antiviral or other prohibited medications if discontinued less than the suggested period before enrollment; (2) they had any clinically significant pregnancy-related clinical or test-abnormal result as judged by the investigators; or (3) conception was not observed during the study. Patients with current and resolved infections with HBV were respectively defined as positive for HBsAg and negative for HBsAg but positive for HBcAb at enrollment. As of December 2020, the data of patients with pregnancy outcomes were extracted for analysis.

### Study procedures and outcomes

HBsAg-positive patients were instructed to take prophylactic TDF at an oral dose of 300 mg daily as prophylaxis. If patients were not willing to take antiviral treatment, they continued to be observed as a control group after being fully informed of the risks. Once antiviral indication was met, rescue therapy was given according to routine clinical practice.

All infants received 10 μg of the HBV vaccine, and infants whose mothers were positive for HBsAg received an additional 200 IU of hepatitis B immunoglobulin intramuscularly, followed by the same dose of the HBV vaccine administered at weeks 4 and 24. All mothers were followed through the assessment of adverse events and laboratory test results (chemical and hematological tests, liver function tests, and HBV-DNA levels).

Hepatopathy outcomes were recorded as primary endpoints, including HBVr and hepatitis flare. In addition, maternal, pregnancy, and safety outcomes were documented as secondary endpoints. HBVr in HBsAg-positive patients was defined as a ≥2 log (100-fold) increase in HBV DNA compared with the baseline level using reverse-transcriptase polymerase chain reaction or HBV DNA ≥3 log (1000) IU/ml in a patient with previously undetectable level (because HBV-DNA levels fluctuate).[10] A hepatitis flare was defined as alanine aminotransferase (ALT) increase to ≥3 times the baseline level and >100 U/L.[10] The rate of vertical transmission was defined as the proportion of infants who had a serum HBV-DNA level above the lower limit of detection (20 IU/ml) or were positive for HBsAg at 28 weeks. Adverse reactions to TDF were documented until postpartum week 28.

## Statistical analysis

Propensity score matching (PSM) was applied to control for confounding factors in the comparison of outcomes between the HBcAb-positive and noninfection groups by accounting for differences in baseline characteristics. Logistic regression was performed on the prespecified baseline characteristic variables, including RDs, disease duration and age, to calculate the propensity score for each patient. The nearest-neighbor method was used for 1:1 matching, and the caliper value for matching was set to 0.001.

The comparisons between the study groups were performed by Student's *t* test or the Mann-Whitney *U* test for continuous measures, and Pearson's chi-square test or Fisher's exact test for categorical measures as appropriate. The cumulative incidence of viral reactivation, hepatitis flare, and the low viral load (HBV-DNA < 200 IU/ml) were calculated by the Kaplan-Meier method. Comparisons between groups were conducted by log rank testing. The changes in the average HBV DNA over time were obtained by calculating the mean at every gestational stage of each patient, and their average difference between groups was compared by specifying a linear mixed model with treatment and time as fixed factors. Odds ratios (ORs) to estimate differences between groups, their corresponding 95% confidence intervals (95% CIs), and two-sided *p* values were estimated from logistic regression models without adjustment for multiple comparisons. The results were presented as all observed data, and a complete-case analysis was used. All statistical calculations were performed using the statistical software package IBM SPSS version 25.0 for Mac. A difference for which the *p* value was below 0.05 was considered to be statistically significant, and all tests were two-sided.

# RESULTS

## Baseline characteristics

A total of 1292 (prospective) pregnant patients with RDs were recruited in the study (Figure 1). By the end of 2020, 1025 pregnant women with records of clinical outcomes were included, and their data were extracted for analysis. A total of 182 participants were infected with HBV, of whom 58 were positive for HBsAg and 124 were positive for HBcAb. Among the HBsAg-positive patients, 29 received prophylactic TDF, with 20 participants exposed during the pregestation period (median time of initiation was 15 [7.4–25] weeks before gestation), 3 during the first trimester of gestation (median time of initiation was 10.7 [9.4–11.4] weeks of gestation), and 6 during the second trimester (median time of initiation was 16.9 [14.6–28.5] weeks of gestation). The remaining 29 unwilling patients without prophylaxis were followed up as the control group. After PSM, 120 pairs in the HBcAb-positive and noninfection groups were analyzed.

The maternal characteristics at enrollment baseline were balanced among groups (Table 1). A total of 108 patients had been diagnosed with systemic lupus erythematosus, 93 with undifferentiated connective tissue disease (UCTD), 56 with anti-phospholipid syndrome, 21 with primary Sjogren's syndrome, and 20 with rheumatoid arthritis. Their regimens for RDs were similar: prednisone at a daily dose of 10 mg or less; 89.9% of participants were receiving hydroxychloroquine (HCQ) at an average daily dose of 238.4 ± 82.7 mg. The HBV-DNA level at baseline was 3.3 ± 2.0 $\log_{10}$ IU/ml in the control group and 4.2 ± 2.4 $\log_{10}$ IU/ml in the TDF prophylaxis group among HBsAg-positive women, whereas the level was below the lower limit of detection (<1.3 $\log_{10}$ IU/ml) in the HBcAb-positive group.

## HBV reactivation and hepatitis flare

In the HBsAg-positive participants, 12 (41.4%) events of HBVr were observed in the control group, whereas 0 were observed in the TDF prophylaxis group (hazard ratio [HR]: 8.71; 95% CI: 2.80–27.17; $p < 0.001$) with a median time of 14.6 (12.7–26.3) weeks of gestation (Figure 2A). Following HBVr, a hepatitis flare demonstrated by ALT elevation occurred in 6 patients. Six (20.7%) events of hepatitis flare occurred in the control group versus 0 in the TDF prophylaxis group (HR: 7.44; 95% CI: 1.50–36.89; $p = 0.014$) with a median time of 19.6 (13.3–26.1) weeks of gestation (Figure 2B). Among the 6 patients, 1 (Patient 3) died of fulminant hepatitis despite emergency rescue efforts, whose HBV-DNA level ascended to 7.6 $\log_{10}$ IU/L at

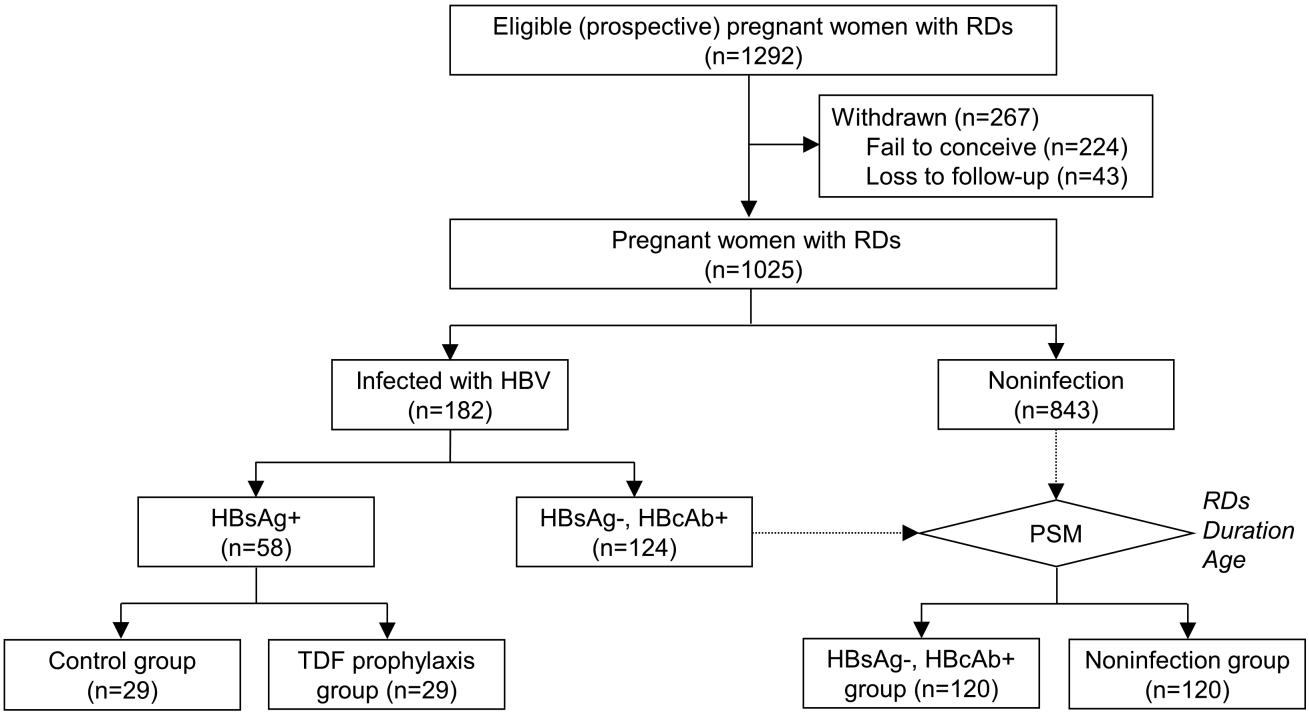


**FIGURE 1** Study profile. HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; PSM, propensity score matching; RD, rheumatic disease; TDF, tenofovir disoproxil fumarate.

26.7 weeks of gestation, followed by a rise of ALT to 584 U/L and over 2000 U/L at 27 weeks of gestation. There was no change in the treatment regimen of the primary disease (UCTD) during this period (Figure 2C). The changes of HBV-DNA level and ALT over time of the 6 patients were expatiated in Figure S1. Five (17.2%) patients in the control group had an HBV-DNA level of more than 200,000 IU/ml at delivery and thus a high risk of vertical transmission, whereas the proportion of patients with a low viral load (HBV-DNA < 200 IU/ml) was higher in the TDF prophylaxis group than in the control group (51.7% vs. 89.7%, $p = 0.003$) (Table 2 and Table S1). The median time to achieve a low viral load after the administration of TDF was 21 ± 0.8 weeks in this immunocompromised population (95% CI: 19.4–22.6) (Figure S2). The dynamic changes in HBV-DNA levels over time in 25 patients exposed to TDF with complete follow-up records among HBsAg-positive participants were shown in the Figure 2D. There was a significant difference in the average change in HBV-DNA levels over time between groups according to when patients were given TDF at different stages of gestation ($p = 0.006$). Referring to the HBV-DNA level of patients receiving TDF during the pregestation period, the level was 2.5 $\log_{10}$ IU/ml higher (95% CI: 1.0–3.9, $p = 0.002$) in the first trimester group, 1.0 $\log_{10}$ IU/ml higher in the second trimester group (95% CI: 0.2–2.3; $p = 0.100$), and 1.6 $\log_{10}$ IU/ml higher in the third trimester group (95% CI: 0.2–3.0; $p = 0.031$). Additionally, viral reactivation was not observed in the HBcAb-positive group throughout the follow-up.

## Maternal and pregnancy endpoints

More adverse maternal outcomes were recorded in the control group than in the TDF prophylaxis group (37.9% vs. 10.3%; OR: 0.19; 95% CI: 0.05–0.77; $p = 0.021$) among HBsAg-positive patients (Figure 3), including One (3.4%) (Patient 3) death due to fulminant hepatitis despite emergency rescue efforts, and 3 (10.3%) patients transferred to the intensive care unit for hepatitis in the control group.

More adverse pregnancy outcomes were observed in the HBsAg-positive patients than in the control group (55.2% vs. 37.9%; OR: 0.50; 95% CI: 0.17–1.42), although the difference was not statistically significant ($p = 0.190$). Two (6.9%) cases of vertical transmission were observed in the control group despite the hepatitis B immunoglobulin injection and the vaccine. More cases of fetal distress occurred in the control group than in the TDF prophylaxis group (20.7% vs. 3.4%; OR: 0.14; 95% CI: 0.02–1.22; $p = 0.075$).

Significant differences in adverse maternal outcomes (OR: 1.23; 95% CI: 0.70–2.15, $p = 0.476$) and pregnancy outcomes (OR: 0.62; 95% CI: 0.37–1.04, $p = 0.070$) were not found between the HBcAb-positive and the uninfected group (Figure S2).

## Safety endpoints

In the HBsAg-positive group, a total of 9 women reported side effects during follow-up, 7 (24.1%) in the control group and 2 (6.9%) in the TDF prophylaxis

**TABLE 1** Baseline characteristics of participants ($n$ = 298)

| Characteristics | Control group ($n$ = 29) | TDF prophylaxis group ($n$ = 29) | $p$ value | HBcAb+ group ($n$ = 120) | Noninfection group ($n$ = 120) | $p$ value[a] |
|---|---|---|---|---|---|---|
| Age (years), mean (SD) | 31.7 (5.0) | 32.2 (4.9) | 0.711 | 32.7 (3.3) | 32.8 (3.7) | 0.797 |
| Systolic blood pressure (mm Hg), mean (SD) | 120.8 (8.5) | 119.1 (2.0) | 0.529 | 122.3 (12.2) | 122.3 (12.6) | 0.992 |
| Diastolic blood pressure (mm Hg), mean (SD) | 73.7 (6.8) | 69.9 (9.8) | 0.096 | 78.4 (11.2) | 76.3 (10.0) | 0.136 |
| Primipara, $n$ (%) | 23 (79.3) | 27 (93.1) | 0.253 | 101 (84.2) | 95 (79.2) | 0.317 |
| Pregnant, $n$ (%) | 9 (31.0) | 7 (24.1) | 0.557 | 54 (45.0) | 44 (36.7) | 0.189 |
| Gestation (weeks), mean (SD) | 11.6 (8.4) | 15.0 (5.2) | 0.362 | 13.2 (6.5) | 12.4 (6.5) | 0.543 |
| Disease duration (months), median (IQR) | 12.0 (7.0, 24.0) | 24.0 (12.0, 24.0) | 0.320 | 24.0 (12.0, 72.0) | 25.5 (12.0, 71.5) | 0.621 |
| RDs, $n$ (%) | | | | | | |
| UCTD | 14 (48.3) | 20 (69.0) | 0.182 | 31 (25.8) | 28 (23.3) | 0.653 |
| APS | 6 (20.7) | 3 (10.3) | 0.470 | 28 (23.3) | 19 (15.8) | 0.143 |
| SLE | 3 (10.3) | 5 (17.2) | 0.706 | 45 (37.5) | 55 (45.8) | 0.190 |
| pSS | 4 (13.8) | 1 (3.4) | 0.352 | 8 (6.7) | 8 (6.7) | 1.000 |
| RA | 2 (6.9) | 0 | 0.491 | 8 (6.7) | 10 (8.3) | 0.624 |
| Comorbidities, $n$ (%) | 9 (31.0) | 8 (27.6) | 0.773 | 34 (28.3) | 38 (31.7) | 0.573 |
| Medications, $n$ (%) | | | | | | |
| Drug varieties | 3.4 (1.1) | 3.3 (0.9) | 0.320 | 3.6 (1.0) | 3.4 (0.9) | 0.074 |
| GC use | 20 (69.0) | 23 (79.3) | 0.550 | 113 (94.2) | 109 (90.8) | 0.327 |
| GCs (mg/day), mean (SD) | 9.1 (2.0) | 9.0 (1.8) | 0.929 | 8.8 (2.1) | 9.0 (2.0) | 0.450 |
| HCQ use | 28 (96.6) | 28 (96.6) | 1.000 | 104 (86.7) | 108 (90.0) | 0.421 |
| HCQ (mg/day), mean (SD) | 217.9 (67.0) | 246.2 (79.3) | 0.151 | 246.2 (81.0) | 234 (88.8) | 0.310 |
| ASA use | 25 (86.2) | 28 (96.6) | 0.352 | 107 (89.2) | 99 (82.5) | 0.139 |
| ASA (mg/day), mean (SD) | 54.0 (15.6) | 53.6 (8.9) | 0.901 | 52.1 (15.9) | 53 (13.2) | 0.564 |
| Heparin use | 20 (69.0) | 17 (58.6) | 0.585 | 74 (61.7) | 70 (58.3) | 0.598 |
| Heparin (ml/day), mean (SD) | 1.0 (0.0) | 1.1 (0.3) | 0.668 | 0.4 (0.1) | 0.4 (0.1) | 0.857 |
| Laboratory evaluation, $n$ (%) | | | | | | |
| Positive ANA | 16 (55.2) | 12 (41.4) | 0.431 | 84 (70.0) | 91 (75.8) | 0.309 |
| ds-DNA (IU/ml) median (IQR) | 11.9 (8.0, 65.1) | 13.9 (10.2, 13.2) | 0.744 | 12.2 (8.7, 20.2) | 12.8 (8.0, 28.7) | 0.842 |
| Positive HBsAg | 29 (100) | 29 (100) | 1.000 | 0 | 0 | 1.000 |
| Positive HBeAg | 9 (31.0) | 13 (44.8) | 0.417 | 0 | 0 | 1.000 |
| Positive HBcAb | 29 (100) | 28 (96.6) | 1.000 | 120 (100) | 0 | <0.001 |
| Positive HBsAb | 1 (3.4) | 0 | 1.000 | 111 (92.5) | 109 (90.8) | 0.640 |
| HBV-DNA (log10 IU/ml), mean (SD) | 3.3 (2.0) | 4.2 (2.4) | 0.092 | <1.3 | — | — |
| HBV DNA<20 IU/ml | 5 (17.2) | 1 (3.4) | 0.194 | 120 (100) | — | — |
| ALT (U/L), mean (SD) | 23.6 (11.9) | 31.0 (17.1) | 0.064 | 20.6 (14.1) | 20.1 (10.7) | 0.754 |
| Platelet count ($10^9$/L), mean (SD) | 210.3 (57.7) | 211.7 (66.9) | 0.935 | 221.5 (69.4) | 227.9 (71.3) | 0.480 |

Abbreviations: ANA, antinuclear antibody; APS, anti-phospholipid syndrome; ds-DNA, double stranded DNA; IQR, interquartile range; pSS, primary Sjogren's syndrome; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

[a]Significant differences were compared between the control and TDF groups in HBsAg-positive patients and between the HBcAb-positive and noninfection groups after PSM.

group ($p$ = 0.144), including headache, nausea, diarrhea, pruritus, and cough (Table 2).

A total of 275 live infants were born during follow-up, with a live birth rate of 89.9%. Among the HBsAg-positive patients, the infant characteristics at birth were similar between groups (Table 2). On the other hand, the fetal weight (2.8 vs. 3.0 kg; $p$ = 0.008), length (48.1 vs. 49.1 cm; $p$ = 0.006), and Apgar score at 1 min (9.7 vs. 9.9; $p$ = 0.047) were lower in the HBcAb-positive group than in the noninfection group (Table S2). Six cases of

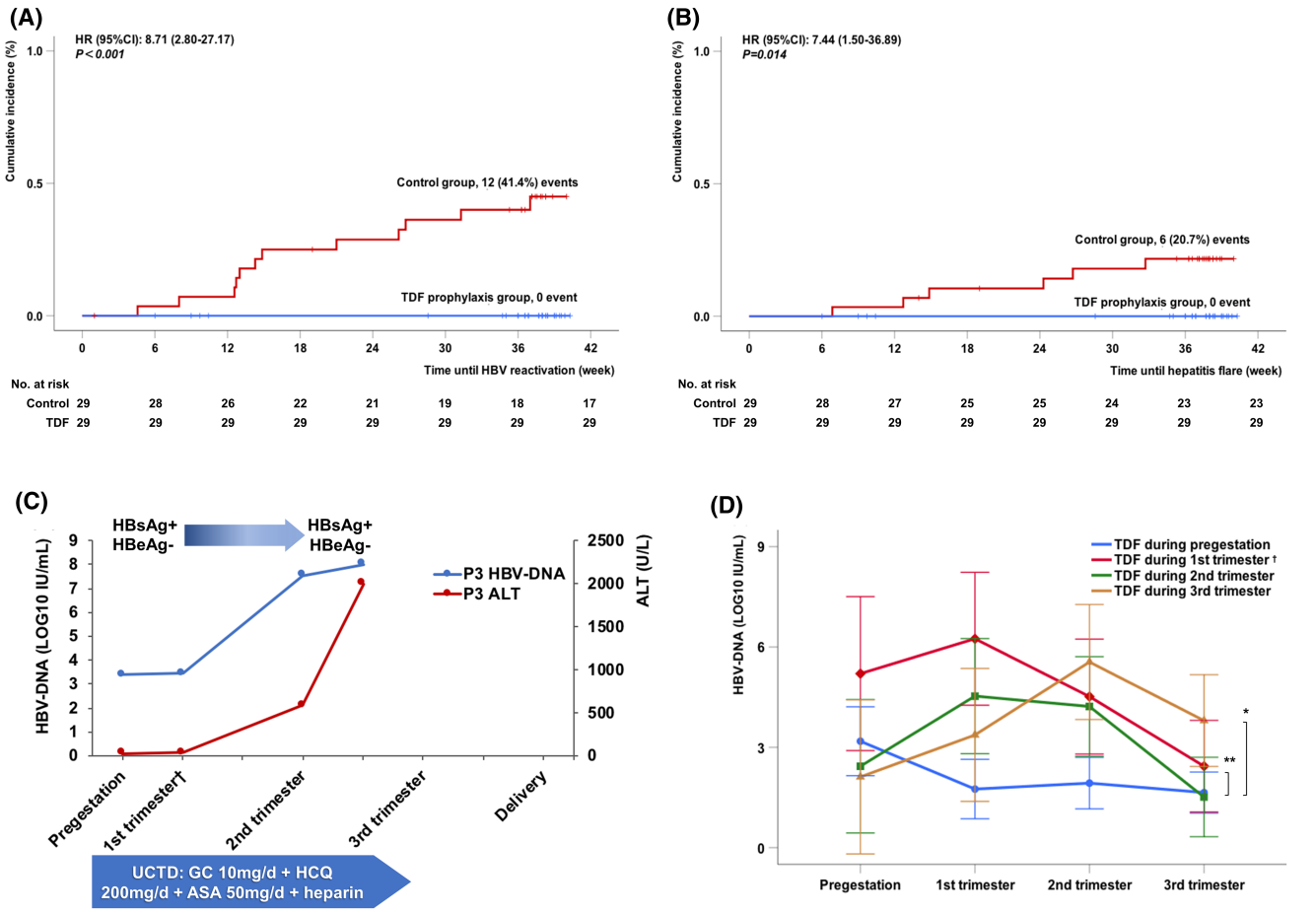


**FIGURE 2** (A,B) Kaplan-Meier curve for time to HBV reactivation (A) and hepatitis flare (B) in HBsAg-positive patients. The red line represents the control group, and the blue line represents the TDF prophylaxis group. (C) The changes of HBV-DNA and alanine aminotransferase (ALT) level over time in Patient 3 (P3) died of hepatitis flare. The blue line represents the HBV-DNA level, and the red line represents ALT level. (D) The dynamic changes in HBV-DNA levels in the patients given TDF prophylaxis. Circles connected by a blue line represent the viral load in the TDF exposure group during the pregestation period; rhombuses connected by a red line represent the first trimester of gestation; squares connected by a green line represent the second trimester of gestation; and triangles connected by a yellow line represent the third trimester of gestation (**$p$ = 0.002, *$p$ = 0.031). †Trimesters of pregnancy were defined by the time since the first day of the last menstrual period (LMP) and distinguished as the first (up to 12 weeks and 6 days of gestation), second (13–28 weeks and 6 days of gestation), and third (any time at or after 29 weeks of gestation) trimesters. ASA, aspirin; CI, confidence interval; GC, glucocorticoid; HBeAg, hepatitis B e antigen; HCQ, hydroxychloroquine; HR, hazard ratio; UCTD, undifferentiated connective tissue disease.

fetal malformation were recorded during the follow-up. One case of craniocerebral malformation at 14 weeks of gestation was reported in the control group 5 days after the participant took TDF, but the possibility of the malformation being due to TDF was ruled out according to the panel's determination (Table 2). Three cases of fetal malformations were reported in the HBcAb-positive group, including 1 tetralogy of Fallot, 1 interventricular septal defect, and 1 cheilopalatognathus. Two cases of fetal malformations were reported in the noninfection group, including 1 case of complex congenital heart disease and 1 interventricular septal defect (Table S2).

## DISCUSSION

In this real-world cohort study on immunocompromised pregnant women carrying HBV, a risk of fatal hepatitis flare was observed during gestation in HBsAg-positive patients. In the control group, 12 (41.4%) cases of HBVr occurred with a median time of 14.6 weeks of gestation, and 6 (20.7%) cases of hepatitis flare occurred with a median time of 19.6 weeks of gestation. One death due to fulminant hepatitis despite emergency rescue efforts and 2 cases of vertical transmission despite immunization occurred in the control group, whereas no cases of HBVr or hepatitis flare occurred in the TDF prophylaxis group with fewer adverse maternal outcomes. Furthermore, prophylactic TDF during the pregestation period resulted in a lower viral load during the perinatal period without additional side effects, which further reduced the risk of hepatitis-related events. In the control group, 2 patients (Patient 3 and Patient 6) refused to check the viral load according to the follow-up schedule, leading to an abruptly high viral load during the perinatal period. Therefore, it is necessary to be given prophylaxis

**TABLE 2** Safety profiles in HBsAg-positive pregnant women ($n$ = 58)

| Characteristics | Control group (n = 29) | TDF prophylaxis group (n = 29) | $p$ value | Trimesters of maternal TDF exposure[a] | | |
|---|---|---|---|---|---|---|
| | | | | Pregestation ($n$ = 20) | First trimester ($n$ = 3) | Second trimester ($n$ = 6) |
| Maternal adverse event, $n$ (%) | 7 (24.1) | 2 (6.9) | 0.144 | 1 (5) | 0 | 1 (16.7) |
| Headache | 1 (3.4) | 0 | 1.000 | 0 | 0 | 1 (16.7) |
| Nausea | 3 (10.3) | 0 | 0.237 | 0 | 0 | 0 |
| Diarrhea | 1 (3.4) | 1 (3.4) | 1.000 | 1 (5) | 0 | 0 |
| Pruritus | 1 (3.4) | 0 | 1.000 | 0 | 0 | 0 |
| Cough | 1 (3.4) | 1 (3.4) | 1.000 | 0 | 0 | 1 (16.7) |
| Viral load at delivery, $n$ (%) | | | | | | |
| HBV DNA (log10 IU/ml), mean (SD) | 3.2 (2.4) | 1.6 (0.5) | 0.002 | 1.6 (0.5) | 1.7 (0.5) | 1.8 (0.7) |
| HBV DNA>200,000 IU/ml | 5 (17.2) | 0 | 0.052 | 0 | 0 | 0 |
| HBV DNA<200 IU/ml | 15 (51.7) | 26 (89.7) | 0.003 | 18 (90) | 3 (100) | 5 (83.3) |
| Infant characteristics at birth, $n$ (%) | | | | | | |
| Live birth | 26 (89.7) | 25 (86.2) | 1.000 | 16 (80) | 3 (100) | 6 (100) |
| Gestation (weeks), mean ± SD[b] | 37.7 (1.1) | 37.9 (3.1) | 0.763 | 37.6 (2.78) | 40.0 (6.6) | 37.5 (0.9) |
| Caesarean section[b] | 25 (86.2) | 23 (79.3) | 0.610 | 14 (70) | 3 (100) | 6 (100) |
| MSAF[b] | 5 (19.2) | 0 | 0.051 | 0 | 0 | 0 |
| Male fetus[c] | 15 (51.7) | 16 (64.0) | 0.417 | 9 (45) | 1 (33.3) | 6 (100) |
| Weight (kg), mean ± SD[c] | 3.0 (0.5) | 3.0 (0.6) | 0.848 | 3.0 (0.7) | 2.8 (0.1) | 3.2 (0.5) |
| Length (cm), mean ± SD[c] | 49.0 (1.6) | 48.9 (3.6) | 0.914 | 48.9 (4.3) | 47.7 (3.2) | 49.7 (0.5) |
| Apgar score at 1 min, mean ± SD[c] | 9.6 (0.9) | 9.9 (0.3) | 0.174 | 9.9 (0.3) | 9.7 (0.6) | 10.0 (0) |
| Low body weight[c] | 5 (17.2) | 2 (8.0) | 0.431 | 2 (10) | 0 | 0 |
| Fetal malformation | 1 (3.4) | 0 | 1.000 | 0 | 0 | 0 |

Abbreviation: MSAF, meconium staining of the amniotic fluid.

[a]Trimesters of pregnancy were defined as the time since the first day of the LMP and distinguished as the first (up to 12 weeks and 6 days of gestation), second (13–28 weeks and 6 days of gestation), and third (any time at or after 29 weeks of gestation) trimesters.

[b]Gestation, caesarean section, and MSAF were calculated in women with live births.

[c]Fetal sex, weight, length, Apgar score, and low body weight were calculated in born infants: 29 in the control group and 25 in the TDF prophylaxis group.

for this population, and better to start during the pregestation stage. Because the viral reactivation did not occur throughout follow-up among the HBcAb-positive women, regular monitoring was recommended for them.

The management of HBV infection in the special population of pregnant and immunocompromised patients remains a serious issue. In this study, 60% of participants had received systemic GCs and immunosuppressive drugs concomitantly before recruitment for at least 2 years, including tacrolimus, azathioprine, cyclosporine, mycophenolate mofetil, methotrexate (MTX), and HCQ. Although the regimen was adjusted to a low dose of prednisone (≤10 mg daily) with permitted immunosuppressants (mostly HCQ) at the baseline, they were still at high risk of HBVr in consideration of the prior therapy. After adjustment, patients should be stable for remission for more than half a year before pregnancy preparation was allowed. From the results, HBVr was observed in 12 (41.4%) patients in the control group with a median time of 14.6 weeks of gestation, and a 20.7% incidence of hepatitis flares was recorded with a median time of 19.6 weeks of gestation. Therefore, it is necessary for HBsAg-positive patients to be given prophylaxis to prevent HBVr,[10,11] and better to start during the pregestation stage considering the median time of occurrence. In previous studies, among HBcAb-positive patients, the HBVr rates of patients receiving biological agents ranged from 2% to 8%.[12,13] Regarding nonbiological agents, HBVr during MTX therapy has also been reported in some cohort studies, in which participants who suffered from HBVr had received low-dose GCs concomitantly and none had received any antiviral prophylaxis.[14,15] With regard to other nonbiological agents, such as leflunomide, sulfasalazine, HCQ and azathioprine, cases of HBVr were rare.[8,12,14] The incidence of HBVr in HBcAb-positive patients administered

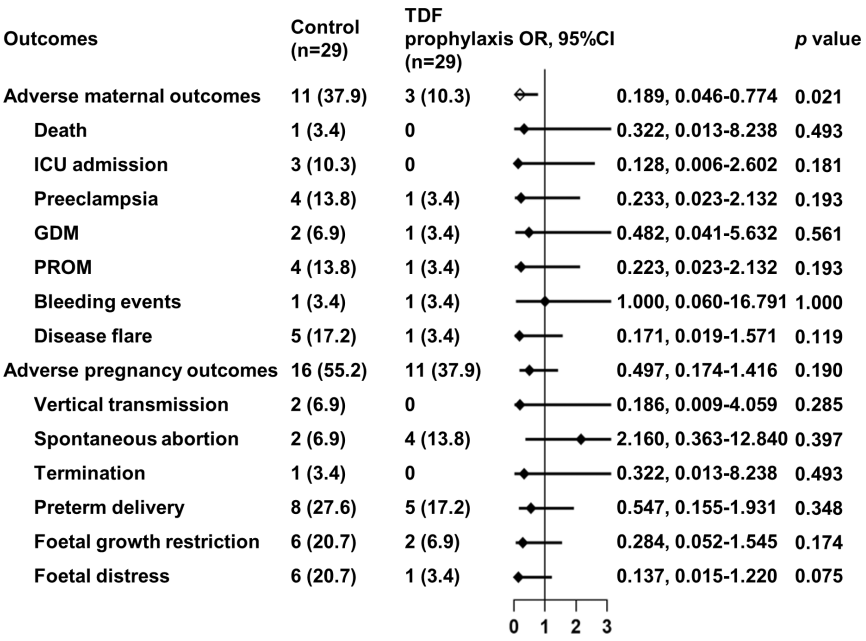


**FIGURE 3** Comparison of maternal endpoints and pregnancy endpoints between the control group and the TDF prophylaxis group among HBsAg-positive patients. CI, confidence interval; GDM, gestational diabetes mellitus; ICU, intensive care unit; OR, odds ratio; PROM, premature rupture of membranes.

GCs varied significantly in among publications.[16] The risk was higher among patients receiving systemic GCs, especially when they were administered continuously (for at least 3 months) and above a daily dose of 20 mg.[17] The proposed pathophysiological mechanism appears to involve GC suppression of T cell cytotoxic function, thus diminishing the host's immune check on the virus and directly stimulating HBV-DNA replication by activating a GC-responsive transcriptional regulatory element in the HBV genome.[18,19] From the results of our study, no reactivation was recorded at the average daily prednisone dose of 8.1 mg with HCQ at an average daily dose of 238.2 mg concomitantly throughout follow-up.

For pregnant women, the current recommendations suggested that antiviral therapy in the third trimester of gestation might be necessary for women with serum HBV-DNA levels over 200,000 IU/ml.[10] In addition, antiviral prophylaxis was a priority for high-risk patients who received prednisone at a daily dose of 10 mg or higher for a course of more than 4 weeks.[10,19–21] However, in the high-risk population, a delay in biochemical remission and a significant increase in the frequency of complications, including death, were observed.[7] From our results, the median time to HBVr was 14.6 weeks of gestation, and the median time to achieve a low viral load after antiviral therapy was approximately 21 weeks. Considering the potential risk of reduced cytotoxic T cell function and direct stimulation of an HBV genomic sequence in an immunocompromised population, prophylaxis should be considered for immunocompromised pregnant women regardless of the baseline viral load. Tenofovir, telbivudine, and lamivudine are drugs recommended in pregnancy, with TDF preferred due to the low risk for resistance and antiviral potency.[10,19,20] In our study, a favorable reduction in HBV-DNA level was achieved without additional adverse events in patients who received TDF during the pregestation period compared with the outcomes in those given TDF during the other stages of gestation, as the safety profile of TDF reported by previous studies.[22] Moreover, the risk of viral reactivation was low in HBcAb-positive patients with undetectable HBV DNA during gestation who were given prednisone at the average daily dose of 8.1 mg with concomitant HCQ at the average daily dose of 238.2 mg.

This study has several limitations. First, unlike in a randomized controlled trial, selection bias was inevitable in this real-world analysis. Although PSM was used to adjust for the baseline disease characteristics, duration, and age of the participants, the possibility of other potential confounders that exerted an impact on the outcome measurements could not be excluded. Second, patients did not strictly follow the visit schedules in the study. Consequently, the follow-up point was recorded as the trimester of gestation for the analysis of the dynamic changes in HBV-DNA and ALT levels. Moreover, as a national cohort study in China, caution should be taken when extrapolating our results to individuals in other populations or regions.

## Management suggestion

According to the aforementioned results, we developed a risk category and management recommendation for immunocompromised women carrying HBV during

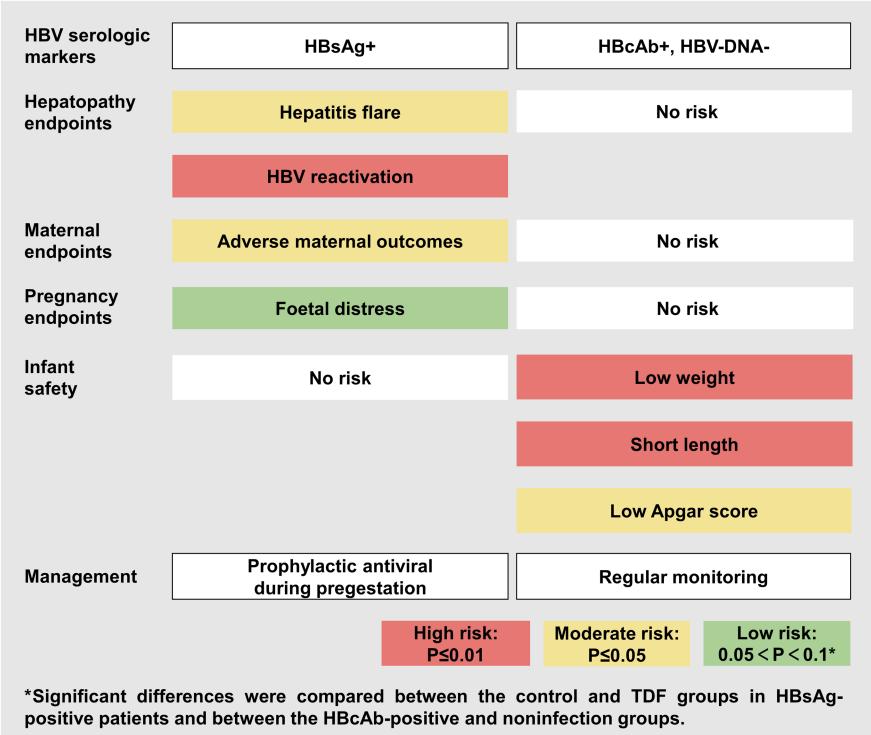


**FIGURE 4** Risk category and management recommendation for immunocompromised (prospective) pregnant women carrying HBV during gestation.

gestation (Figure 4). Prophylactic antiviral therapy was recommended for HBsAg-positive patients during pregestation, considering the median time to HBVr. For HBcAb-positive patients with negative HBV-DNA levels, regular monitoring was recommended.

## CONCLUSIONS

In this cohort of immunocompromised pregnant women, we found a risk of fatal viral proliferation during gestation among the HBsAg-positive patients. The clinical outcomes were significantly improved by the administration of prophylactic TDF and were better in the pregestation group with a good safety profile. Therefore, prophylaxis is recommended for HBsAg-positive women of childbearing age. For HBcAb-positive patients with negative HBV DNA, viral reactivation did not occur throughout the follow-up, and regular monitoring is thus recommended. Our results provide suggestions for the gestational management of immunocompromised patients carrying HBV.

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## CONFLICT OF INTEREST

Nothing to report.

## AUTHOR CONTRIBUTIONS

*Research design*: Liangjing Lu. *Patient recruitment and follow-up*: Shaoying Yang, Le Zhang, Suli Wang, Yi Jin, Yuetian Yu, and Aimin Zhao. *Data analysis and manuscript draft*: Le Zhang. *Accuracy verification*: Yongfu Yu. *Manuscript review*: Yimin Mao, Aimin Zhao, and Liangjing Lu.

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## REFERENCES

1. Schmajuk G, Li J, Evans M, Anastasiou C, Izadi Z, Kay JL, et al. RISE registry reveals potential gaps in medication safety for new users of biologics and targeted synthetic DMARDs. Semin Arthritis Rheum. 2020;50:1542–8.
2. Yoo ER, Perumpail RB, Cholankeril G, Ahmed A. Indications for antiviral therapy for chronic hepatitis B in pregnant mothers. BMJ Case Rep. 2016;2016:1–3.
3. Joshi SS, Coffin CS. Hepatitis B and pregnancy: virologic and immunologic characteristics. Hepatol Commun. 2020;4:157–71.
4. Chen HL, Lee CN, Chang CH, Ni YH, Shyu MK, Chen SM, et al. Efficacy of maternal tenofovir disoproxil fumarate in interrupting mother-to-infant transmission of hepatitis B virus. Hepatology. 2015;62:375–86.
5. World Health Organization. Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy. Geneva, Switzerland: WHO; 2020.
6. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018;67:1560–99.

7. Lam KC, Lai CL, Trepo C, Wu PC. Deleterious effect of prednisolone in HBsAg-positive chronic active hepatitis. N Engl J Med. 1981;304:380–6.
8. Fukuda W, Hanyu T, Katayama M, Mizuki S, Okada A, Miyata M, et al. Incidence of hepatitis B virus reactivation in patients with resolved infection on immunosuppressive therapy for rheumatic disease: a multicentre, prospective, observational study in Japan. Ann Rheum Dis. 2017;76:1051–6.
9. Fukuda W, Hanyu T, Katayama M, Mizuki S, Okada A, Miyata M, et al. Risk stratification and clinical course of hepatitis B virus reactivation in rheumatoid arthritis patients with resolved infection: final report of a multicenter prospective observational study at Japanese Red Cross Hospital. Arthritis Res Ther. 2019;21:255.
10. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Clin Liver Dis (Hoboken). 2018;12:33–4.
11. Loomba R, Liang TJ. Hepatitis B reactivation associated with immune suppressive and biological modifier therapies: current concepts, management strategies, and future directions. Gastroenterology. 2017;152:1297–309.
12. Mochida S, Nakao M, Nakayama N, Uchida Y, Nagoshi S, Ido A, et al. Nationwide prospective and retrospective surveys for hepatitis B virus reactivation during immunosuppressive therapies. J Gastroenterol. 2016;51:999–1010.
13. Lan JL, Chen YM, Hsieh TY, Chen YH, Hsieh CW, Chen DY, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis. 2011;70:1719–25.
14. Tan J, Zhou J, Zhao P, Wei J. Prospective study of HBV reactivation risk in rheumatoid arthritis patients who received conventional disease-modifying antirheumatic drugs. Clin Rheumatol. 2012;31:1169–75.
15. Tamori A, Koike T, Goto H, Wakitani S, Tada M, Morikawa H, et al. Prospective study of reactivation of hepatitis B virus in patients with rheumatoid arthritis who received immunosuppressive therapy: evaluation of both HBsAg-positive and HBsAg-negative cohorts. J Gastroenterol. 2011;46:556–64.
16. Cheng AL, Hsiung CA, Su IJ, Chen PJ, Chang MC, Tsao CJ, et al. Steroid-free chemotherapy decreases risk of hepatitis B virus (HBV) reactivation in HBV-carriers with lymphoma. Hepatology. 2003;37:1320–8.
17. Kim TW, Kim MN, Kwon JW, Kim KM, Kim SH, Kim W, et al. Risk of hepatitis B virus reactivation in patients with asthma or chronic obstructive pulmonary disease treated with corticosteroids. Respirology. 2010;15:1092–7.
18. Tur-Kaspa R, Shaul Y, Moore DD, Burk RD, Okret S, Poellinger L, et al. The glucocorticoid receptor recognizes a specific nucleotide sequence in hepatitis B virus DNA causing increased activity of the HBV enhancer. Virology. 1988;167:630–3.
19. Perrillo RP, Gish R, Falck-Ytter YT. American Gastroenterological Association Institute technical review on prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology. 2015;148:221–244.e3.
20. Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM, Murad MH, et al. AASLD guidelines for treatment of chronic hepatitis B. Hepatology. 2016;63:261–83.
21. Koffas A, Dolman GE, Kennedy PT. Hepatitis B virus reactivation in patients treated with immunosuppressive drugs: a practical guide for clinicians. Clin Med. 2018;18:212–8.
22. Zeng QL, Zhang HX, Zhang JY, Huang S, Li WZ, Li GM, et al. Tenofovir alafenamide for pregnant chinese women with active chronic hepatitis B: a multicenter prospective study. Clin Gastroenterol Hepatol. 2021;S1542-3565(21)01306-9. https://doi.org/10.1016/j.cgh.2021.12.012


## SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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