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CLINICAL

Is tenofovir the answer to further preventing mother-to-child transmission of hepatitis B?

[1]MI Abdul Hafidz, [2]S-S Tan, [3]YY Lee
[1]Gastroenterology Fellow, Faculty of Medicine, Universiti Teknologi MARA, Sg Buloh, Selangor, Malaysia; [2]Consultant Hepatologist, Department of Hepatology, Selayang Hospital, Selangor, Malaysia; [3]Professor of Medicine, Consultant Gastroenterologist and Hepatologist, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia

TITLE Tenofovir to prevent hepatitis b transmission in mothers with high viral load

AUTHORS Pan CQ, Duan Z, Dai E et al.

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Correspondence to MI Abdul Hafidz
Fakulti Perubatan Universiti Teknologi MARA
Tingkat 7, Cluster Medikal
Kampus Sungai Buloh
47000 Sungai Buloh
Selangor
Malaysia

e-mail m.i.abdulhafidz@gmail.com

SUMMARY

This trial was designed to determine the efficacy and safety of tenofovir disoproxil fumarate (TDF) therapy for prevention of mother-to-child hepatitis B virus (HBV) transmissions in mothers who have an HBV DNA level of more than 200,000 IU/ml. It was a multicentre, open-label, randomised controlled trial, with a parallel group design. Two hundred mothers were recruited from academic tertiary centres in five geographic regions of China. They were randomly assigned in a 1:1 ratio, to receive usual care without antiviral therapy or to receive 300 mg of TDF daily, starting at 30 to 32 weeks of gestation and continuing until 4 weeks postpartum; the mothers and their babies were followed until 28 weeks postpartum. All infants received immunoprophylaxis.

Study participants were pregnant women aged 20–35 who had chronic HBV infection, were HBeAg-positive, and had an HBV DNA level of more than 200,000 IU/ml. The main exclusion criteria were co-infection with HIV type 1, hepatitis C virus, or hepatitis delta virus; a history of abortion, pregnancy loss, or congenital malformation in a previous pregnancy, previous treatment for HBV infection (except when antiviral agents were used for the prevention of mother-child transmission during a previous pregnancy and discontinued > 6 months before the current pregnancy); a history of renal dysfunction and evidence of hepatocellular carcinoma or liver decompensation.

The primary outcomes were the rates of mother-to-child transmission and birth defects. The secondary outcomes were the safety of TDF, the percentage of mothers with an HBV DNA level of less than 200,000 IU/ml at delivery, and loss or seroconversion of HBeAg or HBsAg at 28 weeks postpartum.

At delivery, 68% of the mothers in the TDF group (66/97), as compared with 2% in the control group (2/100), had an HBV DNA level of less than 200,000 IU/ml ($p < 0.001$). At 28 weeks postpartum, the rate of mother-to-child transmission was significantly lower in the TDF group than in the control group, both in the intention-to-treat analysis (with transmission of virus to 5% of the infants [5/97] vs 18% [18/100], $p = 0.007$) and the per-protocol analysis (with transmission of virus to 0 vs 7% [6/88], $p = 0.01$). The infant safety profiles were similar in the TDF group and the control group, including birth-defect rates (2% [2/95 infants] and 1% [1/88], respectively; $p = 1.00$), although more mothers in the TDF group had an increase in creatine kinase levels. After discontinuation of TDF, alanine aminotransferase (ALT) elevations above the normal range occurred more frequently in the TDF group than in the control group (45% [44/97 women] vs 30% [30/100], $p = 0.03$). The maternal serologic HBV outcomes did not differ significantly between the groups.

OPINION

Hepatitis B infection continues to be a major threat to public health and is associated with cirrhosis and liver cancer.[1,2] Reducing transmission of the virus remains the most effective way of eradicating the global burden of the disease.[3,4] The World Health Organization Global Health Sector Strategy on viral hepatitis for 2016–2021 aims to eliminate hepatitis B and C as public health problems. Among the interventions to be expanded is the prevention of mother-to-child transmission of HBV.[5] Tenofovir, a nucleotide analogue and a potent inhibitor of HBV polymerase,[6] may be useful in the prevention of mother-to-child transmission, which is a critical step in the eradication of HBV.

This randomised controlled trial demonstrates that, in addition to conventional active and passive immunoprophylaxis, maternal TDF administered from 30–32 weeks of gestation until postpartum week 4 can further enhance the effectiveness in preventing HBV transmission in infants born to HBeAg positive mothers with a baseline HBV DNA level higher than 200,000 IU/ml. In the TDF group, five cases were considered treatment failures only because of unavailable results (one stillbirth, one withdrawal from the study, one newborn death at day 2 and two cases which were lost to follow-up). In fact, infant HBV infection rates in the TDF group were 0% in the modified intention-to-treat and per-protocol analyses.

It has been shown that immunoprophylaxis fails to prevent mother-to-child transmission in 10–30% of infants born to mothers with an HBV DNA level of more than 6 $\log_{10}$ copies/ml,[7–13] and all of the six confirmed HBV infected infants in this study were born to mothers with HBV DNA levels of more than 200,000 IU/ml at the time of delivery, confirming the risk of high viral load in mothers. In this study, starting TDF at 30–32 weeks gestation managed to reduce maternal HBV DNA levels to less than 200,000 IU/ml in only 68% of mothers by the time of delivery. The rate was lower at 61% in mothers with baseline HBV DNA level of more than 8 $\log_{10}$ IU/ml, compared to 75% in those with baseline HBV DNA levels of less than 8 $\log_{10}$ IU/ml. This highlights the remaining uncertainty about the optimum timing of TDF initiation especially in those with high baseline HBV DNA levels; should anti-viral prophylaxis be started earlier at 28 weeks of gestation in these patients? Failure to attain HBV DNA levels of less than 200,000 IU/ml at delivery was also encountered in mothers who missed 2–7 doses of TDF before delivery, stressing the importance of strict treatment adherence in this short duration of prophylaxis treatment (mean duration of TDF=8.6 ± 0.5 weeks).

There was a significantly higher frequency of ALT flare in the TDF group compared to the control group after mothers in the TDF group stopped taking TDF (45% in the TDF group vs 30% in the control group, $p = 0.03$). One patient in the TDF group who developed an ALT flare of more than 10 times the upper limit of normal range at postpartum week 28 had to be restarted on anti-viral therapy which normalised the ALT. However, maternal flares after stopping TDF could still occur beyond the post-treatment follow-up period. Careful monitoring for flares may need to be extended, and the risk of ALT flares may be higher in mothers with more severe liver fibrosis or concomitant fatty liver.

Despite only 2% of mothers in the control group achieving a HBV DNA level of less than 200,000 IU/ml, the rate of mother-to-child transmission was still only 18%. This could be explained by the combination of passive and active immunisation measures, as no obvious confounders could be identified. The investigators also reported a significant difference of higher frequency of elevated creatine kinase levels among the mothers in the TDF group compared to the control group (7% vs 0, $p = 0.006$), although these findings were not clinically significant with normal electrocardiograms; all mothers were asymptomatic. The figure of 7% is in keeping with figures quoted from the manufacturers of tenofovir.[14] The significance of this to the unborn foetus is unknown.

This study has several strengths which include a clearly defined study population, intervention and outcomes. An adequate sample size ensured this study was sufficiently powered, although 17 patients who were lost to follow up or discontinued treatment. Extensive exclusion criteria helped to reduce confounders. However, it was notable that this was not a blinded study. Bias could easily have been introduced at many points during this study. The investigators also described adherence to the TDF regimen was determined by means of pill counts at each visit. This may not have been the most stringent method to measure adherence.

As this study was performed on patients recruited exclusively from China, it would be interesting to see if similar results can be replicated in other parts of the world. If so, this would certainly provide a compelling case to change our current practice. In real life clinical practice, clinicians need to take into account the timing of HBV DNA testing, initiation of anti-viral prophylaxis, monitoring post-cessation of treatment, extent of liver disease and the mother's ability to withstand hepatitis flares, breastfeeding issues and its acceptance by the mothers.

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