Author’s response to reviews

Title: Telbivudine can safely reduce mother-to-child transmission in chronic hepatitis B women after 12 weeks of gestation

Authors:

Li-Fen Han (13655083639@163.com)
Jian-Ming Zheng (zhengjianming@fudan.edu.cn)
Li-qing Zheng (wom70@163.com)
Hai-bing Gao (gaohb605@163.com)
Li-xia Chen (532918102@qq.com)
Qing-ling Xu (491098648@qq.com)
Yi-hong Chai (caiyihong1966@126.com)
Xin Zhang (67431566@qq.com)
Chen Pan (panchencry@163.com)
Lv-Feng Yao (yaolf05@163.com)

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Telbivudine reduces mother-to-child transmission in chronic hepatitis B patients

Li-Fen Han; Jian-Ming Zheng; Li-qing Zheng; Hai-bing Gao; Li-xia Chen; Qing-ling Xu; Yi-hong Chai; Xin Zhang; Chen Pan; Lv-Feng Yao

BMC Infectious Diseases

Dear BMC Infectious Diseases Editors and Reviewers:
Thank you for your letter and for the reviewers’ comments concerning our manuscript entitled “Telbivudine reduces mother-to-child transmission in chronic hepatitis B patients” (ID: INFD-D-18-00581R3). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have made correction which we hope meet with approval. Revised portion are marked in red in the paper. The main corrections in the paper and the responds to the reviewer’s comments are as flowing.

Responds to the reviewer’s comments:

Syed Iqbal (Reviewer 1): Please include all comments for the authors in this box rather than uploading your report as an attachment. Please only upload as attachments annotated versions of manuscripts, graphs, supporting materials or other aspects of your report which cannot be included in a text format. Please overwrite this text when adding your comments to the authors.

Response: Thanks for the reviewer’s comments.

Monique Andersson (Reviewer 3): Telbivudine reduces mother-to-child transmission in chronic hepatitis B patients

The aim of this study was to evaluate the efficacy and safety of telbivudine administered during the 2nd and 3rd trimester of pregnancy.

241 women were recruited - 139 in the telbivudine group and 102 controls. The telbivudine group were started on therapy during the 2nd and 3rd trimester of pregnancy. Infants were screened between 7 and 12 months post-delivery. One baby in the telbivudine group and eight babies in the control group tested HBsAg positive. There was no evidence of any increase in adverse events in the antiviral group vs controls. 57.6% of women commenced therapy between 12 and 27 weeks of pregnancy. 47.5% were undetectable at delivery, 14.3% seroconverted from eAg positive to eAg negative in the telbivudine group.

MAJOR COMMENTS
1. The women in the control group appear to have been receiving a number of drugs for liver function. Why were they given these agents? Were these agents given to the antiviral group? What is known about how they might affect the risk of HBV MTCT?

Response: All of the patients in two groups with abnormal liver function were received glycyrrhizin (Minophagen Pharmaceutical Co., Ltd., Japan), Polyene Phosphatidylcholine (Essentiale, Sanofi Beijing Pharma Ltd.), ademetionine (Simeitai, Abbott Laboratories Ltd.) or other agents for improving liver function. These agents were also given to the antiviral group. These agents did not affect viral load. There was no statistically significant difference between HBV DNA levels at baseline and that at delivery in control group (Fig.2 D and Fig.3). Because both of the two groups used drugs, they may not affect the results of the study. We have emphasized this in the text now (line#121). Thank you very much for your comments and suggestions.

2. What information was given to women at the time of consent? Can you clarify how almost 50% of cases agreed to take the drug and 50% did not (and the two groups were not different) at a time when antiviral therapy was not available to women? It is surprising that more women did not opt for therapy.

Response: Our study was developed from January 2012 to March 2015. Before the national guidelines update at the end of 2015, it does not mention whether antiretroviral therapy can reduce mother to child transmission in HBV infected pregnant women with high viral load in national guidelines 2010 version. All the patients were informed that whether antiretroviral therapy can reduce mother to child transmission is still unknown, telbivudine is class B drug for pregnancy, can be used in pregnant women, and all of the adverse reactions of drug in the instructions. The patients were assigned to the telbivudine group or without antiviral treatment groups according to their own preferences. A total of 288 at 12-34 weeks of gestation women with chronic hepatitis B were screened, 23 patients did not meet the eligibility criteria and were excluded. In the remaining 265 individuals, there were 143 patients in telbivudine group and 122 patients in control group. The telbivudine group was 21 patients (21/122, 17%) more than the control group. There are some concerns about the use of antiviral therapy during pregnancy, so many people do not use telbivudine.

3. Please can you clarify how adherence was monitored?

Response: Because it is an observational study, adherence was monitored by frequency of dispensing and asking for residual drugs.
4. Please provide more details of the timing of therapy for each of the mothers. Currently the only data is 57.6% started at 12-27 weeks and that the average duration was 13+/-6 weeks duration.

Response: In telbivudine group, three patients started antiviral treatment at 12 weeks, 1 patient started at 13 weeks, 5 patients started at 14 weeks, 5 patients started at 15 weeks, 4 patients started at 16 weeks, 2 patients started at 17 weeks, 8 patients started at 18 weeks, 5 patients started at 19 weeks, 4 patients started at 20 weeks, 9 patients started at 21 weeks, 5 patients started at 22 weeks, 7 patients started at 23 weeks, 2 patients started at 24 weeks, 6 patients started at 25 weeks, 9 patients started at 26 weeks, 4 patients started at 27 weeks, 18 patients started at 28 weeks, 8 patients started at 29 weeks, 8 patients started at 30 weeks, 6 patients started at 31 weeks, 8 patients started at 32 weeks, 5 patients started at 33 weeks, 7 patients started at 34 weeks, respectively. We have re-written this part according to the reviewer’s suggestion (Line#159-166). Thank you very much for your comments and suggestions.

5. 47.5% of women were undetectable, what was the viral load spread of those women who were detectable?

Response: The median (range) of viral load of those women who were detectable, was 5.51(3.04-8.06) log10 IU/mL, 4.12(2.70-7.43) log10 IU/mL, 3.20(2.70-6.76) log10 IU/mL, after 2 weeks, 4 weeks, 8 weeks of telbivudine treatment, respectively. (Table 2)

6. Please provide the data on how long after delivery telbivudine was taken (it is clear that 5 women stopped post delivery) and what % of women had a post natal flare.

Response: The patients in telbivudine group continued to use telbivudine therapy, but five patients stopped telbivudine treatment after delivery. None of them had virological breakthrough for 6 months after delivery, who continued to use telbivudine therapy(Line#124, 181-182). Thank you very much for your comments and suggestions.

7. The results do not confirm that HBIG was administered to all women and that birth dose vaccine was given within 12 hours and week 4 and 24 HBV vaccines were administered. Could you provide details on vaccine and HBIG administration please?

Response: All newborns were vaccinated with genetically engineered hepatitis B vaccine 10μg in the deltoid muscle within 12 h of birth, at week 4 and 24 and HBIG 100-200 IU in the gluteus maximums within 12 hours of birth. This part of content has been added in the results to confirm
that HBIG was administered to all infants (line#193-195). Thank you very much for your
comments and suggestions.

8. Please confirm that no other interventions took place during pregnancy that might have
increased the risk of MTCT of HBV.

Response: According to the AASLD guidelines, there is no alternative to reduce the risk of
MTCT of HBV (references: Terrault NA, Bzowej NH, Chang KM, Hwang JP, Jonas MM,
Murad MH; American Association for the Study of Liver Diseases. AASLD guidelines for

9. Please list any other adverse drug reactions to telbivudine other than CK which were
identified during the study.

Response: The rate of adverse events was 4.3% (6/139) in telbivudine group, and was 5.9%
(6/102) in control group (χ2 = 0.305, P = 0.581), respectively (Table 3). Serious adverse
events as those were reported in a Phase III clinical trial, published at The New England Journal of
Medicine, were collected in our study (references: Lai CL, Gane E, Liaw YF, et al. Telbivudine
This study did not pay particular attention to the adverse events, which was mild and the
incidence of them was less than 10% in the previous studies (references: Zhang H, Pan CQ, Pang
Q, Tian R, Yan M, Liu X. Telbivudine or lamivudine use in late pregnancy safely reduces
perinatal transmission of hepatitis B virus in real-life practice. Hepatology. 2014; 60(2):468-
476). Thank you very much for your comments and suggestions.

10. The HBeAg seroconversion rate seems high. Please provide some hypotheses as to why this
might be so.

Response: Among the 126 HBeAg positive mothers in telbivudine group, 14.3% (18/126)
patients had HBeAg seroconversion at delivery. A Phase III clinical trial involving 921 patients
showed that there was no difference in the rate of HBeAg seroconversion in the patients who
received telbivudine compared to those who received lamivudine after 1 year of treatment: 23%
versus 22%. In that trial, the mean (rang) years of age was 32 (16–63) years old, but that was
26(20-43) years old in our study. In that trial, the median (range) of serum HBV DNA was 9.6
(3.8–16.0) log10 copies/ml, but that was 7.73(6.04–9.30) log10 IU/mL in our study. The patients
in our study is younger and with lower HBV DNA levels, that might be why HBeAg
seroconversion rate seems high in our study. (references: Lai CL, Gane E, Liaw YF, et al.
MINOR COMMENTS

1. The study design is an interventional study as a drug has been given to one group, and the impact of this drug is being studied. By definition this is an interventional study. Please correct from 'observational study'

Response: In our study, the patients were received telbivudine or not for antiviral therapy, according to their own preferences. Thus, this is an observational study. We have re-written this part according to the reviewer’s suggestion and corrected from this study is an interventional study (Line#107).

2. Please provide more details of the Abbott assay used for HBV serological testing and the PCR test. Is there some published data on the performance of the PCR test?

Response: HBV serum markers were detected by the Abbott chemiluminescence assay (commercial kit) based on ARCHITECT i2000SR. Serum HBV DNA levels were detected by fluorescence quantitative PCR (Shanghai Fosun Pharmaceutical Co., Ltd.) based on ABI7500. The performance of the PCR test is published at 2006. (references: Dou YL, Ni AP, Han JH, Sun JY, Yu RR. [Correlation of hepatitis B e antigen with hepatitis B virus DNA in the serum of chronic hepatitis B patients after treatment]. Zhonghua Yi Xue Za Zhi. 2006 Sep 5;86(33):2348-51)

3. The absolute numbers of infants infected with HBV together with the percentage should be given in the abstract.

Response: We have re-written this part according to the reviewer’s suggestion. Thank you very much for your comments and suggestions (Line#55-56).

4. The rates of c-section are very high. Could you provide some background explain why this is?

Response: The caesarean delivery on maternal request appears to be a considerable driver behind the increasing c-section rate in mainland China. The relaxation of China's "one-child policy" may

We tried our best to improve the manuscript and made some changes in the manuscript. These changes will not influence the content and framework of the paper. We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions.

We would like to express our great appreciation to you and reviewers for comments on our paper. Looking forward to hearing from you.

Thank you and best regards.

Yours sincerely,

Corresponding author:

Lv-feng Yao

Email: yaolf05@163.com