Original Article

Efficacy and Safety of Tenofovir and Lamivudine in Combination with Efavirenz in Patients Co-infected with Human Immunodeficiency Virus and Hepatitis B Virus in China

Ya-Song Wu[1], Wei-Wei Zhang[1], Xue-Mei Ling[2], Lian Yang[2], Shao-Biao Huang[3], Xi-Cheng Wang[4], Hao Wu[5], Wei-Ping Cai[6], Min Wang[7], Hui Wang[8], Yan-Fen Liu[3], Hao-Lan He[6], Fei-Li Wei[5], Zun-You Wu[1], Fu-Jie Zhang[1,9]

[1]National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 100050, China
[2]Department of Infectious Diseases, The Third People's Hospital of Hengyang City, Hengyang, Hunan 421005, China
[3]Department of Infectious Diseases, The Fourth People's Hospital of Nanning City, Nanning, Guangxi 530023, China
[4]Department of Infectious Diseases, Yunnan Provincial Infectious Disease Hospital, Kunming, Yunnan 650301, China
[5]Center for Infectious Diseases, Beijing You'an Hospital, Capital Medical University, Beijing 100069, China
[6]Department of Infectious Diseases, Guangzhou No. 8 People's Hospital, Guangzhou, Guangdong 510060, China
[7]The Institute of HIV/AIDS, The First Hospital of Changsha, Changsha, Hunan 410005, China
[8]Department of Infectious Diseases, Shenzhen Third People's Hospital, Shenzhen, Guangdong 518112, China
[9]Department of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China

Abstract

Background: The prevalence of hepatitis B virus (HBV) infection is high among individuals infected with human immunodeficiency virus (HIV) in China. Both HIV and HBV can be treated with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC), so we evaluated the safety and efficacy of combination antiretroviral therapy (ART) that included TDF, 3TC, and efavirenz (EFV) among ART-naive individuals who were co-infected with HIV and HBV.

Methods: One hundred HIV/HBV co-infected ARV-naive individuals were started on the regimen of TDF, 3TC, and EFV, and the levels of plasma HBV DNA, HIV RNA, and biochemical evaluation related to the function of liver and kidney were analyzed.

Results: Concerning efficacy, this study found that by week 48, the vast majority co-infected participants receiving this ART regimen had undetectable HBV DNA levels (71%) and/or HIV RNA levels (90%). Concerning safety, this study found that the median estimated glomerular filtration rate of participants decreased from baseline (109 ml·min^{-1}·1.73 m^{-2}) to week 12 (104 ml·min^{-1}·1.73 m^{-2}) but was almost back to baseline at week 48 (111 ml·min^{-1}·1.73 m^{-2}).

Conclusion: This combination ART regimen is safe and effective for patients with HIV/HBV co-infection.

Trial Registration: ClinicalTrials.gov, NCT01751555; https://clinicaltrials.gov/ct2/show/NCT01751555.

Key words: Antiretroviral Therapy; Co-infection; Hepatitis B Virus; Human Immunodeficiency Virus; Tenofovir Disoproxil Fumarate

Introduction

Hepatitis B virus (HBV) infection is prevalent worldwide, but its distribution varies across geography and risk populations.[1-4] Since human immunodeficiency virus (HIV) and HBV share common risk pathways, HIV/HBV co-infection is frequent in China.[5-8] Such co-infection is associated with increased morbidity and mortality than either infection alone or infection including increased risks of liver cirrhosis, hepatocellular carcinoma, decompensated liver disease, and progression

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Address for correspondence: Dr. Fu-Jie Zhang, National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing 100050, China
E-Mail: treatment@chinaaids.cn

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to AIDS.[9-11] Both viral infections can be treated with the nucleoside reverse transcriptase inhibitors (NRTIs) such as tenofovir disoproxil fumarate (TDF) and lamivudine (3TC), and it is recommended that antiretroviral therapy (ART) for HIV/HBV co-infection should be initiated with the combination of TDF + 3TC or TDF + emtricitabine (FTC) as the NRTI backbone of a regimen.[12] This is important since a common ART regimen in China contains TDF, 3TC, and efavirenz (EFV); however, there are few data on the safety and efficacy of this regimen for HIV/HBV co-infected patients in China.

Methods

Study design

This was a one-arm cohort study to evaluate the efficacy and safety of TDF, 3TC, and EFV in antiretroviral-naive Chinese adults with HIV/HBV co-infection (ClinicalTrials.gov, NCT01751555). TDF was dosed at 300 mg/d, 3TC at 300 mg/d, and EFV at 600 mg/d. Subjects were evaluated at 12, 24, and 48 weeks after starting this therapy. The primary outcome was the proportion of individuals with HBV DNA levels below the detection limit and HIV RNA levels below 1000 and 400 copies/ml during treatment. Alanine aminotransferase (ALT), aspartate aminotransferase (AST), and estimated glomerular filtration rate (eGFR) were used to evaluate liver and kidney function during treatment. All subjects gave informed written consent before enrollment. The study was approved by the Institutional Review Board of National Center for AIDS/STD Control and Prevention, Chinese Center for Disease Control and Prevention.

Subjects

Subjects were recruited from Guangdong, Yunnan, Hunan, Guangxi, and Beijing in China. Baseline inclusion criteria included: (1) positive serologies for HIV and HBV infection; (2) willingness to participate in the study; (3) age 18 years or older; (4) no previous or current use of ART use; (5) plasma HBV DNA >1000 copies/ml; and (6) clinical indications for initiating of ART. Baseline exclusion criteria were: (1) with severe opportunistic infections such as pneumocystis jirovecii pneumonia (PCP), recurrent severe bacterial pneumonia, central nervous system toxoplasmosis, extrapulmonary tuberculosis, cryptococcal meningitis, and disseminated mycosis; (2) blood creatinine >3 times the upper limit of normal values (i.e., >312 μmol/L); (3) total bilirubin >34 μmol/L; (4) ALT >400 U/L; or (5) presence of illnesses so severe that hospitalization is likely to be required in the near future.

Laboratory methods

Blood samples were collected within 7 days before starting ART (baseline) and at weeks 12, 24, and 48 during ART. HBV DNA testing was first performed at local hospitals and reevaluated at a central laboratory. Levels of HBV DNA were measured in 0.5 ml of blood plasma using the Cobas Taqman HBV test version 2.0 (Roche Molecular Systems, Branchburg, NJ, USA) with a limit of detection of 20 U/ml (1 U is equivalent to 5.82 copies/ml). Levels of HIV-1 RNA levels were quantified in 0.5 ml of blood plasma using the NucliSENS easyQ® HIV-1 version 2.0 (bioMérieux SA, Marcy l'Etoile, France) with limit of detection of 50 copies/ml. HBV serum markers were detected using an immunoassay (Kehua Biotechnology, Shanghai, China). CD4 T-cell counts were measured using BD Biosciences FACSCalibur flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). Liver function tests including ALT and AST were done by standard chemistry and kidney function assessed by eGFR based on the equation described by Levey *et al*.[13]

Statistical analysis

Statistical analysis was carried out using SPSS version 17.0 (SPSS Inc., Chicago, IL, USA). Descriptive data of the whole population were reported as absolute numbers, percentages, and as mean ± standard deviation (SD) and/or median and interquartile ranges (IQRs). Patient characteristics were compared using Chi-square and/or Fisher exact test for categorical variables and the Wilcoxon test for continuous variables. Logistic regression analyses were used to determine whether baseline HIV RNA level, hepatitis B e-antigen (HBeAg) positivity and HCV antibody status influenced HIV or HBV suppression. HIV RNA level >10^5 copies/ml was defined as high. A $P < 0.05$ was considered statistically significant.

Results

Demographics and patient characteristics

A total of 100 HIV/HBV co-infected individuals were recruited in the study. The baseline characteristics of enrolled subjects are described in Table 1. Over three-fourths of the participants were male (77%, 77/100) with a median age of 36 years (IQR: 29–41). At baseline, the median CD4 cell count was 186.5 cells/μl (IQR: 43.0–262.0), the median HIV RNA level was 4.2 $\log_{10}$ copies/ml (IQR: 3.5–4.8), and median HBV DNA level was 6.9 $\log_{10}$ copies/ml (IQR: 4.7–8.6). Also at baseline, median ALT was 34.0 U/L (IQR: 22.0–58.3), median eGFR was 109.0 ml·min^{-1}·1.73 m^{-2} (IQR: 92.3–130.4), and half of the patients were HBeAg-positive. Ten patients were anti-HCV antibody-positive. The most common WHO disease stage was stage 3 at 41%, followed by stage 1 at 23%, stage 4 at 19%, and stage 2 at 17%.

Hepatitis B virus responses

Among 91 patients with HBV DNA levels available at 48 weeks, the mean decrease in HBV DNA level was more than 3 $\log_{10}$ copies/ml at week 12 and about 5 $\log_{10}$ copies/ml at week 48 compared to baseline levels ($Z = -8.28$, $P < 0.001$) [Figure 1]. At weeks 12 and 24, there were 39% (33/84) and 55% (48/88) individuals with suppressed HBV DNA levels (<116.4 copies/ml, or <20 U/ml). After 48 weeks of treatment, the overall HBV suppression rate was 71% (65/91; 95% confidence interval [*CI*]: 61–80%). Of those who still had detectable HBV DNA, 21 patients (23%, 95% *CI*: 14–33%) had levels between 117 and 1000 copies/ml and 5 (5%; 95% *CI*: 1.8–12.4%) had 1000–5000 copies/ml. For individuals who were HBeAg-positive, the HBV DNA suppression rate after

48 weeks of ART was 56% (25/45, 95% *CI*: 40–70%) and 89% (39/44; 95% *CI*: 75–96%) for those who were HBeAg-negative ($\chi^2 = 12.00$, $P = 0.001$). We did not find impact of baseline HCV antibody positivity or baseline HIV RNA on HBV viral suppression. Among 25 patients tested for HBeAg at baseline and week 48, 44% (11/25; 95% *CI*: 24–65%) of individuals who were HBeAg-positive experienced HBeAg clearance, and 36% (9/25; 95% *CI*: 18–57%) experienced HBeAg seroconversion, i.e., developed anti-HBeAg. Further, 2.6% (2/77; 95% *CI*: 0.3–9.0%) of individuals experienced HBsAg clearance but without HBsAg seroconversion.

Table 1: Baseline characteristics of the HIV/HBV co-infected patients enrolled in this study (n = 100)

Characteristics	Values
Age (years), median (IQR)	36 (29–41)
Male/female	77/23
HIV RNA (log_{10} copies/ml), median (IQR)	4.2 (3.5–4.8)
HBV DNA (log_{10} copies/ml), median (IQR)	6.9 (4.7–8.6)
$CD4^+$ T (cells/μl), median (IQR)	186.5 (43.0–262.0)
ALT (U/L), median (IQR)	34.0 (22.0–58.3)
AST (U/L), median (IQR)	34.8 (26.2–52.8)
TBIL (μmol/L), median (IQR)	11.5 (7.7–15.2)
BMI (kg/m^2), median (IQR)	20.7 (18.4–22.9)
eGFR ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$), median (IQR)	109.0 (92.3–130.4)
HBeAg, *n* (%)	
Positive	50 (50)
Negative	48 (48)
Unknown	2 (2)
Route of HIV transmission, *n* (%)	
Injection drug use	9 (9)
MSM	30 (30)
Heterosexual	53 (53)
Other or unknown	8 (8)
WHO clinical stage, *n* (%)	
1	23 (23)
2	17 (17)
3	41 (41)
4	19 (19)

IQR: Interquartile range; MSM: Men who have sex with men; IDU: Injection drug use; BMI: Body mass index; HIV: Human immunodeficiency virus; HBV: Hepatitis B virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TBIL: Total bilirubin; HBeAg: Hepatitis B e-antigen; eGFR: Estimated glomerular filtration rate.

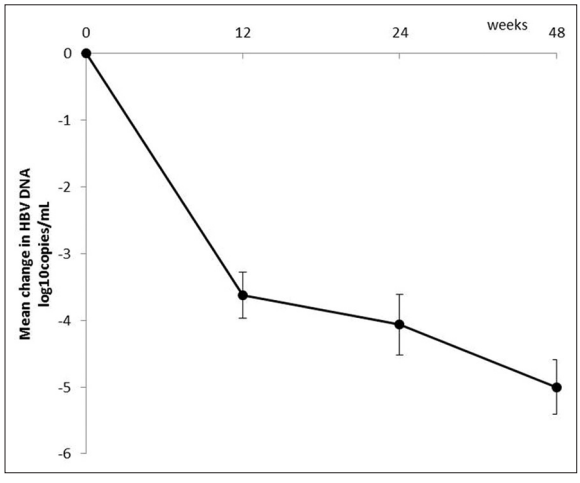

Figure 1: Changes in hepatitis B virus DNA log_{10} copies/ml levels from baseline over 48 weeks of combination antiretroviral therapy ($Z = -8.28$, $P < 0.001$ compared to baseline). Error bars indicate interquartile range.

Human immunodeficiency virus and CD4 cell responses

A key goal of ART is to achieve durable viral suppression and increase CD4 count to improve the overall health of HIV-infected individuals. By week 12 of ART, 97% of the participants (60/62; 95% *CI*: 89–100%) had a HIV RNA level below 1000 copies/ml and 90% (56/62; 95% *CI*: 80–96%) had a level below 400 copies/ml. By week 48 of ART, 95% (87/92, 95% *CI*: 88–98%) of the participants had an HIV RNA level <1000 copies/ml and 91% (84/92, 95% *CI*: 84–96%) had a level <400 copies/ml. There was no impact of baseline HIV RNA, HBV DNA, or HCV serostatus on HIV viral suppression. Median CD4 cell count sharply increased from 186.5 cells/μl at baseline to 263.0 cells/μl after 12 weeks of ART, and after 48 weeks of ART, median CD4 cell count was about 293.0 cells/μl [Figure 2].

Safety

Concerning liver toxicity, overall median ALT and AST increased slightly at week 12, but these measures decreased continuously thereafter. Hepatic flares, defined as an increase in ALT >5 times upper limit of normal level or a 100 U/L increase from baseline (if abnormal at baseline), developed in six individuals. All the flares occurred before week 12 of ART, and all patients were HBeAg-positive at baseline. One of six individuals experienced seroconversion (i.e., anti-HBe-positive) after 48 weeks. The suppression of plasma HBV DNA also coincided with improvement in serum ALT and AST levels. Concerning renal toxicity, the median eGFR decreased from 109 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ at baseline to 104 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ after 12 weeks of ART, and 105 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ at week 24. Interestingly, overall median eGFR rose to 111 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$ at the 48 week of ART [Figure 3]. Three patients had serum creatinine elevation. The most severe was a 66-year-old man who experienced eGFR decline from a baseline value of 67–42 $ml \cdot min^{-1} \cdot 1.73\ m^{-2}$. His TDF was replaced with

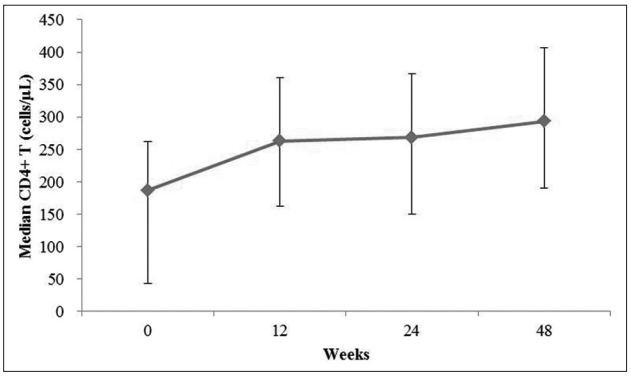

Figure 2: $CD4^+$ T-cell counts over 48 weeks of combination antiretroviral therapy. Error bars indicate interquartile range.

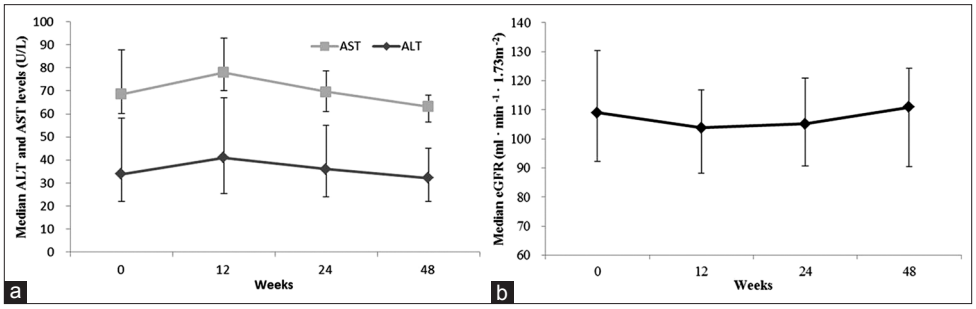

Figure 3: Liver and kidney measures over 48 weeks of combination antiretroviral therapy. (a) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels over 48 weeks of combination antiretroviral therapy. Error bars indicate interquartile range. (b) Estimated glomerular filtration rate (eGFR) over 48 weeks of combination antiretroviral therapy. Error bars indicate interquartile range.

stavudine and the eGFR rose. Other adverse reactions included 4 patients (4%) who developed acute systemic allergic reactions and generalized urticaria, and 3 of them were thought to be related to EFV, so their regimen was changed from EFV to ritonavir-boosted lopinavir (LPV/r). Also, grade 2 rash not thought to be related to the ART regimen was seen in 2 patients, and another patient complained of vertigo and intrusive dreams, so his EFV was also replaced by LPV/r.

Discussion

The main finding of this study is that the ART regimen of TDF/3TC/EFV is efficacious and safe in Chinese patients who are co-infected with HBV and HIV. This is important since the prevalence of HBV infection is high among HIV-infected individuals in China,[7,8] and that co-infection of HBV with HIV complicates the clinical course, management and may also adversely affect therapy for HIV infection.[14] Although both TDF and 3TC can be used to treat both HBV and HIV, studies on the effect of TDF and 3TC on naive patients with HBV and HIV co-infections are rare.

Similar to the treatment of HIV, more than one active agent is needed for HBV infection to prevent the development of drug resistance, especially 3TC monotherapy. In particular, the cumulative risk of HBV resistance to 3TC was roughly linear with a 20% annual incidence rate;[15] therefore, 3TC monotherapy for HBV is no longer recommended.[16] Further, the use of TDF in HIV/HBV co-infected patients has led to a decrease in liver fibrosis in patients with advanced liver disease.[17] To evaluate the safety and efficacy of TDF and 3TC among HIV and HBV co-infected patients in China, we performed a prospective study of the TDF + 3TC + EFV combination ART.

Concerning HIV efficacy, we found that the TDF + 3TC + EFV combination ART was able to reduce quickly HIV RNA levels to undetectable levels in over 90% of the participants, and this suppression was sustained for the 48 weeks of observation. Concerning HBV efficacy, we found that this combination regimen quickly reduced the HBV DNA levels in most patients, and ultimately HBV DNA levels were suppressed in about 70% of the individuals. This rate was a higher reduction than previously reported by Wang *et al*.[18] that studied a treatment regimen of zidovudine or stavudine and 3TC and found HBV suppression rate of 65% (26/40) and a median decrease of HBV DNA 2.87 log copies/ml after 48 weeks of therapy. Further, the present study found that the HBV suppression rate in HBeAg-positive patients was lower than that in HBeAg-negative patients. This is similar to reports by Price *et al*.[19]

Concerning safety and liver toxicity, we investigated ALT and AST levels. Overall, we found that transaminases improved during therapy, likely secondary to reduced HBV activity. This study identified a number of hepatic flares occurring before 12 weeks of ART, but overall these flares were tolerated and did not develop into hepatic decompensation. Since both HBV and HIV infection can cause kidney disease,[20-23] and TDF use has been associated with renal toxicity,[24,25] we investigated eGFR. This study showed that the median eGFR decreased after 12 weeks of ART, but returned to baseline levels after 48 weeks of ART. It should be noted, however, that although patients enrolled in this study were chronically infected with HBV, they did not have any serious clinical conditions. It is likely that patients who are more ill will experience worse liver and renal toxicity. There are some limitations to this research. First, we did not exclude patients with HCV antibody-positive patients and did not test the HCV RNA level. In this study, however, we observed that HCV antibody-positive was not associated with response to ART. The results were same as our group previously reported.[6] Second, our study has limited follow-up. However, it demonstrates the effectiveness of this regimen on HIV/HBV co-infection.

Our study suggests that the use of the combination regimen of TDF + 3TC + EFV is effective and safe in the management of HIV/HBV co-infection in China. Our data also suggest that in short-term HBV, serostatus did not influence virological and immunological response to ART. Long-term efficacy of TDF/3TC/EFV on HBV in HIV infection still needs to be evaluated.

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Conflicts of interest

There are no conflicts of interest.

Disclaimer

The opinions expressed herein reflect the collective views of the co-authors and do not necessarily represent the official position of the National Center for AIDS/STD Control and Prevention, Chinese Center for Diseases Control and Prevention.

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