

Research Article

HBV, HCV, and HBV/HCV co-infection among HIV-positive patients in Hunan province, China: regimen selection, hepatotoxicity, and antiretroviral therapy outcome¹

Running title: Hepatitis/HIV co-infected patients in China

Shu Su¹, Christopher Kincaid Fairley^{2,3}, Joe Sasadeusz², Jianmei He⁴, Xiuqing Wei⁴, Huan Zeng⁵, Jun Jing⁶, Limin Mao⁷, Xi Chen⁴, Lei Zhang^{1,2,3,6}

1 School of Public Health and Preventive Medicine, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia

¹ This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi:[10.1002/jmv.24988](https://doi.org/10.1002/jmv.24988)

This article is protected by copyright. All rights reserved.

2 Melbourne Sexual Health Centre, Alfred Health, Melbourne, Australia

3 Central Clinical School, Faculty of Medicine, Nursing and Health Sciences, Monash University, Melbourne, VIC, Australia

4 Hunan Provincial Center for Disease Control and Prevention, Hunan, China

5 School of Public Health and Management, Chongqing Medical University, Chong Qing, China

6 Research Center for Public Health, Tsinghua University, Beijing, China

7 Center for Social Research in Health, Faculty of Arts and Social Science at the University of New South Wales, Sydney, NSW, Australia.

Shu Su: shu.su@monash.edu;

Christopher Kincaid Fairley: cfairley@mshc.org.au;

Joe Sasadeusz: j.sasadeusz@mh.org.au;

Jianmei He: jmhe69@126.com;

Xiuqing Wei: wendy4257@qq.com;

Huan Zeng: zenghuan586@aliyun.com;

Jun Jing: jingjun@tsinghua.edu.cn;

Limin Mao: limin.mao@unsw.edu.au;

Corresponding authors:

Prof. Xi Chen, Email: chenxi161@sohu.com, Hunan Provincial Center for Disease Control and Prevention, Hunan, China

A/Prof. Lei Zhang Email: lei.zhang1@monash.edu, Melbourne Sexual Health Centre, Melbourne, Australia

Tel: +613 9341 6230

Postal address: Melbourne Sexual Health Centre, 580 Swanston St, Carlton VIC 3053

Abstract

Background Co-infection with hepatitis B (HBV) and C (HCV) is common among people living with HIV (PLHIV). This study investigates the impacts of hepatitis co-infection on antiretroviral therapy (ART) outcomes and hepatotoxicity in PLHIV.

Methods The cohort study included 1,984 PLHIV. Hepatotoxicity was defined by elevated alanine aminotransferase (ALT) levels. ART outcomes were measured by CD4 cell counts, viral load and mortality rate in patients.

Results Among 1,984 PLHIV, 184 (9.3%) were co-infected with HBV and 198 (10.0%) with HCV and 54 (2.7%) were co-infected with HBV and HCV. Of these patients, 156 (7.9%) had ALT elevation \geq grade 1 at baseline. During the course of ART the mortality rate and its adjusted hazard ratio (AHR) in PLHIV who were co-infected with HCV (2.6/100 py, AHR=2.3, 95%CI 1.1–4.7) was higher than for patients with mono-infected HIV, as it was for those with an elevated ALT (4.4/100 py, AHR=3.8, [1.7–8.2]) at baseline compared to those with normal ALT. After 6-12 months of ART, the incidence of hepatotoxicity among all the patients was 3.7/100 py. The risk of hepatotoxicity was higher in HCV co-infected (18.6/100 py, adjusted odds ratio (AOR)=12.4, [8.1-18.2]) than HIV mono-infected patients, and for all regimens (nevirapine: 30.0/100py, 34.2, 7.3-47.9; zidovudine/stavudine: 24.7/100py, 22.1, 7.1-25.5; efavirenz: 14.5/100py, 9.4, 3.5-19.2; lopinavir/ritonavir:40.1/100py, 52.2, 9.5-88.2) except tenofovir (4.3/100py, 4.9, 0.8-9.5). Patients with HBV/HCV co-infected had high hepatotoxicity (10.0/100py, 6.3, 1.2-23.3) over the same period.

Conclusion Patients with HCV co-infection and HBV/HCV co-infection demonstrated higher hepatotoxicity rate compared with HIV

mono-infected patients in China.

Key words: Hepatitis B virus; Hepatitis C virus; Human immunodeficiency virus; Anti-retroviral drug

Introduction

Hepatitis B virus (HBV) and hepatitis C virus (HCV) are the two most common co-infections among people living with Human Immunodeficiency Virus (HIV) (PLHIV) ¹. The prevalence of HCV co-infection differs markedly among populations with HIV; for instance, people who inject drugs (PWID) usually have high rates of HCV co-infections because they share syringes whereas those who acquire HIV through heterosexual sex do not ². Differences also exist for HBV whose primary transmission route of HBV is through sexual contact, parental contact or mother-to-child transmission ³. PLHIV co-infected with viral hepatitis demonstrate a two- to five-fold higher mortality risk than non-co-infected patients; moreover, co-infected patients liver diseases progress more rapidly when compared to those with hepatitis infection alone ⁴. China started to encourage voluntary HBV and HCV screening among antiretroviral therapy (ART) patients from 2007 ⁵. In 2012, a nationwide Chinese retrospective observational cohort study indicated that among 33,861 HIV-positive patients, 8.7% were co-infected with HBV, 18.2% with HCV and 3.3% with both ⁶. Compared with neighbouring developing countries, the HBV co-infection rate was lower than in Thailand, Malaysia, or Vietnam, but the HCV co-infection in China was higher than in countries from the TREAT Asia HIV Observational

Database (TAHOD) ⁷⁻⁹. And the hepatitis co-infected rate varied between different regions of China. One study in south-eastern China showed that the prevalence of HBV, HCV and HBV/HCV co-infection among PLHIV were 16.22%, 3.7% and 0.79%, respectively ¹⁰. These rates were generally higher than other developed countries ¹¹.

Although the widespread use of ART for HIV has significantly reduced the mortality and improved the life quality among PLHIV ¹², treatment of HIV in PLHIV with hepatitis co-infection is complicated as ART may increase the risk of hepatotoxicity and associated mortality. At least two prospective cohort studies have demonstrated that prolonged exposure to ART substantially increases the risk of hepatotoxicity ^{13,14}, which raises the concern for those taking long-term ART. Also, HIV infection has been associated with liver fibrosis in the absence of chronic hepatitis co-infection ^{15,16}. Thus, some developed countries have assessed treatment outcomes of different ART regimens in hepatitis co-infected patients and standardised therapeutic guidelines for clinicians ¹⁷⁻¹⁹. Unfortunately, first- and second-line ARV regimens are different in China from most developed countries and only six commonly regimens are provided by the national ART program, and the effects of these regimens on hepatitis infected ART patients are under-studied.

The Chinese national ART program provides four nucleoside reverse transcriptase inhibitor (NRTI) regimens, Tenofovir (TDF), Zidovudine (AZT), Stavudine (D4T) and Lamivudine (3TC) and two non-nucleoside reverse transcriptase inhibitor (NNRTI) regimens, Efavirenz (EFV) and Nevirapine (NVP) as first-line treatment and one protease inhibitor-based regimen Lopinavir/Ritonavir (LPV/r) as a second-line treatment since 2012²⁰, combination of antiretroviral regimens remained unchanged as AZT+3TC+NVP/EFV or TDF+3TC+EFV/NVP in the latest 2016 guidelines²¹. The guidelines have no specific recommendations for PLHIV who have abnormal liver functions at treatment initiation. Currently, no studies have been conducted in China to assess the hepatotoxicity of various ART regimens on hepatitis co-infections among PLHIV. This study aimed to (1) compare the hepatotoxicity and mortality rates of HBV and HCV co-infected patients with HIV mono-infected patients, and (2) evaluate the treatment effects of currently available ART regimen in co-infected patients.

Materials and methods

Study setting and data source

This retrospective cohort study was conducted in Hunan Province between January 2008 and December 2013. A clinical database was established by the Hunan Centre for Disease Control (CDC) in line with the national guidelines to compile patient and treatment information in

each jurisdictional district²². This information is synchronised real-time to the national ART database as a part of the requirements stipulated by the national CDC. Information collected from patients includes initial patient assessment, treatment follow-up, treatment regimen change, treatment/follow-up termination and transfer of care. In this analysis, data was extracted at initial patient assessment, treatment follow-up and termination section from the Hunan ART database. The treatment information of patients from different databases was linked by the treatment ID number, which is unique for each patient. Personal information was de-identified in this study.

Inclusion criteria

This study included (1) people aged 18 or above who were treatment-naïve and newly enrolled in the ART program in Hunan during the study period, and (2) patients who were tested for HBV and HCV before they initiated ART treatment. To evaluate the impact of hepatitis HIV co-infection on mortality and HIV disease progression, the study excluded deaths caused by accident or suicide and patients who received the hepatitis treatment during the first six months of ART. The latter may bias the estimate of hepatotoxicity incidence. (3) To evaluate the treatment effects of various ART regimens among hepatitis co-infections, the study excluded the patients who switched ART regimen within the first six months.

Indicators definitions

All clinical diagnoses and hepatotoxicity categorisations were conducted according to internationally recognised standards. HIV infection was tested via enzyme immunoassay (EIA) screening and confirmed by Western blot (WB) ²³. HBV-positivity was diagnosed by HBsAg via enzyme-linked immunosorbent assay (ELISA) screening and then confirmed by hep B core antibody-positive tests. HCV-positivity was detected by the presence of anti-HCV antibodies via ELISA first, then confirmed by PCR. The study measured alanine aminotransferase (ALT) levels in ART patients at baseline and 6-12 months after treatment initiation. At baseline, we defined 'ALT elevation' as ALT counts \geq Grade 1, namely, greater than 1.25 times the upper limit of the normal (ULN) ALT range ²⁴. After 6-12 months on ART, hepatotoxicity was defined based on the levels of ALT, according to acquired immune deficiency syndrome (AIDS) clinical trial group guidelines (ACTG) ²⁴. Hepatotoxicity was defined as having ALT elevation to grade 3–4 in patients who have normal ALT counts at baseline. In patients already with elevated ALT levels at baseline, hepatotoxicity was defined as a greater than 3.5 folds increase in ALT levels compared with the baseline level

^{25,26}

Characteristics at ART initiation

Data regarding HIV transmission routes and ART initiation (i.e., CD4+ T-cell count, WHO HIV stage, liver function tests results, hepatitis co-infection status and regimen) from each patient's initial clinical assessment were collected from the baseline database. The ART regimen selected was based on the criteria from the treatment guidelines and the doctors' individual clinical experience. PLHIV were categorised into four groups: (1) HIV mono-infected, (2) HIV/HCV co-infection, (3) HIV/HBV co-infection, and (4) HIV/HBV/HCV co-infection. The study used 40 IU/L of ALT as the threshold for ULN based on the Chinese standards²⁷⁻²⁹. The ART regimen patients used was recorded at ART initiation and during the treatment for each patient. The study compared the ALT level in different regimen groups, including EFV versus NVP from NNRTIs, TDF versus AZT/D4T from NRTIs, and first-line regimen versus second-line regimen (LPV/r).

Study indicators after ART initiation

At 6-12 months since treatment initiation, viral load, CD4+ T-cell counts, and liver function test results were extracted from the ART follow-up database. These indicators were measured every six months as recommended by the Chinese treatment guidelines. The mortality rate was calculated using the number of deaths that occurred during follow-up (2008-2013) and the total number of person-years of treatment. The definition of suboptimal ART outcome included virological failure, immunological failure or mortality events. Immunological failure was

defined as a CD4 Cell count fall to below 100 cells/mm³ or CD4 count fall below the baseline level after three-month ART without a concomitant diseases; virological failure was defined as plasma viral load above 1000 copies/mL based on two consecutive viral load measurements after 3 months of treatment³⁰. The incidence of hepatotoxicity incidence is defined above and uses the ACTG guidelines²⁴ after six to twelve months treatment.

Statistical analysis

Statistical Analysis System 9.4 (SAS 9.4) was used for all calculations. Descriptive and inferential statistical analysis was performed. The median and interquartile ranges (IQR) were used to summarise the numerical variables at the baseline, and frequencies and percentages were used to summarise the categorical variables. A chi-square test was used to compare all the categorical variables, for the expected frequency of variable smaller than five we adopted the results from Fisher's exact test. Three multivariable logistic regression models were constructed, two were applied to identify the impact of hepatitis co-infection on ART treatment outcomes (each for immunological and virological failure events), whereas the third investigated the impact of ART regimens on hepatotoxicity. A marginal structural logistic regression model was used to estimate the causal effects of regimen switch on the hepatotoxicity of the patients. A multivariable Cox proportional hazards model was used to

explore the association between hepatitis co-infection and mortality rate observed from the overall follow-up. Variables with p-value <0.2 in the univariate analysis were included in the multivariate regression. A p-value of less than 0.05 was considered significant in the final model.

Results

Demographic characteristics and hepatitis infection at baseline

A total of 1,984 PLHIV initiating ART and were tested for HBV and HCV at baseline (Table 1). The median age of patients was 39 years (IQR 30-49), and the median CD4⁺ T-cell count was 152 cells/mm³ (IQR 43-254). The majority were males (1353, 68.2%) and the main route of HIV acquisition was heterosexual contacts (1360, 68.5%) followed by injecting drug use (227, 11.4%) and homosexual sex (205, 10.3%). The proportion of the patients with WHO clinical stage I/II (946, 47.7%) and III/IV (1038, 52.3%) was similar among the patients.

Among all the 1984 PLHIV, 10.0% (198/1984), 9.3% (184/1984), and 2.7% (54/1984) were co-infected with active HCV, HBV and HBV/HCV, respectively. Of them, 7.9% (156/1,984) had elevated ALT levels at baseline (Table 1). The elevated ALT percentage was 5.4% (84/1548) in HIV mono-infected patients, 15.2% (30/198) in HIV/HCV co-infected patients, 19.6% (36/184) in HIV/HBV co-infected patients, and 11.1%

(6/54) in HIV/HBV/HCV co-infected patients ($p<0.01$, $X^2=62.77$).

ALT level and ART regimens at baseline

EFV was used in more than half of the patients (1,024/1984, 51.6%) while 42.7% (848/1984) used NVP. For the NRTI regimen, only 18.8% (372/1984) patients used TDF-based regimen, by contrast, AZT/D4T users accounted for the majority (1529, 77.1%). There were 5.6% (112) patients initiating ART with the second-line regimen. Notably, 19.7% (391/1,984) of the total patients was still using D4T, a regimen outdated by the Chinese treatment guidelines.

The proportion of using NVP-based regimens among patients with normal ALT levels (44.0%, 805/1828) is significantly higher than that in patients with elevated ALT levels (27.6%, 43/156, $\chi^2=15.94$, $p<0.01$). Correspondingly, a lower proportion of EFV-based regimens use was found among patients with normal ALT levels (50.4%, 922/1828) than that in patients with elevated ALT levels (65.4%, 102/156, $\chi^2=12.86$, $p<0.01$). No significant differences in the use of other ART regimens were found between the two groups (Table 2).

Inferior ART outcomes in hepatitis co-infected patients

Hepatitis co-infected patients had inferior treatment outcomes compared with the HIV mono-infected patients. At the first follow-up after 6-12 months of ART, 6.0% HIV mono-infected patients developed virological failure and 24.1% demonstrated immunological failure. In comparison, HCV co-infected patients had a threefold higher risk (10.8%, AOR=2.92, 95% CI [1.55–5.51]) of virological failure and were 1.5 times (29.2%, AOR=1.69, [1.20–2.34]) more likely to experience immunological failure. HBV-co-infected patients only demonstrated a higher immunological failure rate (27.5%, AOR=1.40, [1.08–1.92]). HCV/HBV co-infected patients were more likely (8.3%, AOR=1.42, [1.04–4.15]) to suffer virological failure than HIV mono-infected patients.

At the end of the study observation period, the cohort accumulated 4,664 person-years of follow-up. Fifty-seven patients died during this time, corresponding to an overall mortality rate of 1.2/100 person years. In comparison, the risk of mortality in HCV co-infected patients was more than two times higher (2.6/100 person years, AHR=2.28, [1.11–4.68]) than HIV mono-infected patients. The mortality rate in HBV co-infected patients showed no differences in comparison to HIV mono-infected patients (Table 3). Patients with elevated ALT levels at baseline were three times more likely to die (4.4/100 person years, AHR=3.78 [1.76-8.24]) during treatment than otherwise.

Association between hepatotoxicity and hepatitis co-infection and ART regimens

Among the 1,417 (71.4%) patients who had liver function tests performed after 6-12 months of treatment, the incidence of hepatotoxicity was 3.7/100 py (47/1,417). HCV (18.6/100 person years, AOR=12.4, [8.1-18.2]) and HBV/HCV (10.0/100 person years, AOR=6.3, [1.2-23.3]) co-infected patients were associated with significantly higher hepatotoxicity risk compared with HIV mono-infected group (1.8/100 person years). Notably, HCV co-infection contributed to significantly higher risk of hepatotoxicity in patients on second-line treatment at baseline (40.1/100 person years, AOR=52.21, [9.5–88.2]) and patients (8/198) who switched from a first-line regimen to a second-line regimen (63.3/100 person years, AOR=64.3, [6.9–88.7]). The risk of hepatotoxicity was also significantly higher in patients using NVP- (30.0/100 py, AOR=34.2, [7.3-47.9]), AZT/D4T- (24.7/100 py, AOR=22.1, [7.1-25.5]), EFV- (14.5/100 py, AOR=9.4, [3.5-19.2]) and LPV/r-based (40.1/100 py, AOR=52.2, [9.5-88.2]) regimen than HIV mono-infected patients. Co-infection with both HBV and HCV contributed to a high risk of hepatotoxicity among patients using NVP (18.7/100 person years, AOR=21.0, [1.8–79.8]) and TDF-based regimens (10.9/100 person years, AOR=8.5, [1.3–37.6]). On the contrary, for HBV co-infected patients, no regimen was significantly associated with increasing hepatotoxicity risk, and those who used TDF-based regimen have the lower incidence of hepatotoxicity (1.4/100 py) than people with other regimens ($p < 0.05$) (Figure 1).

Discussion

This study analysed ART outcomes for PLHIV who were co-infected with viral hepatitis in China. Compared to mono-infected PLHIV, those co-infected with HCV, had a significantly higher mortality, virological failure rate, immunological failure rate, and hepatotoxicity risk, while PLHIV co-infected with HBV only had a higher immunological failure rate during treatment. These findings are consistent with the studies from other countries³¹⁻³⁴. ART regimens have different effects on hepatitis co-infected patients. With the exception of TDF, NVP-, EFV-, AZT/D4T- or LPV/r-based regimens all had a higher risk of hepatotoxicity in HCV co-infected patients. HBV co-infected patients who were treated with the TDF-based regimen did not have a higher risk of hepatotoxicity, suggesting a beneficial effect on suppressing HBV.

There are a number of possible reasons for the higher mortality and hepatotoxicity rates in HCV co-infected patients. First, there are known interactions between HIV and HCV infections, as HIV accelerates hepatic fibrosis progression of HCV, and HCV accelerates the progression of HIV to AIDS leading to the elevated mortality rate^{35,36}. The higher mortality rate in HCV infection could be explained by HCV, but not HBV being a significant risk factor for cardiovascular disease³⁷. Our finding concurs with the previous studies that mortality rate in HCV/HIV co-infected patients was significantly higher than HIV/HBV co-infected patients^{38,39}. Second, a common side effect of NNRTI drugs is liver toxicity which is associated with the hepatotoxicity rate especially in patients with prior liver disease^{40,41}. A previous study showed that NVP

leads to the serious liver damage and drug-induced liver fibrosis especially in patients with hepatitis C ⁴²⁻⁴⁴. Third, the characteristics of the susceptible population who are likely to be co-infected HCV also contribute to increasing mortality risk and hepatotoxicity risk. The majority of HCV co-infected patients in this study were PWID (69.2%), and this population usually has an unstable lifestyle, and a significant proportion (estimated 90%) of them continue to use drugs after initiating ART. ⁴⁵. Low ART adherence among drug users was reported in previous studies ^{46,47}, which may further reduce the treatment benefits of ART and increase the treatment failure risk.

The results show that ART regimens have different effects in PLHIV who are co-infected with HBV and HCV. TDF-based regimens offer substantial benefits to HBV co-infected patients compared with patients using other regimens. In addition none of HBV co-infected patients who use a TDF-regimen was found with hepatotoxicity. ^{48,49}. The expected treatment outcomes from TDF in this study concur with the previous studies in other countries ^{50,51}. This regimen is included in the Chinese free ART programme and is the only recommended regimen in the Chinese treatment guidelines for patients co-infected with HIV and HBV. In contrast, the challenge lies in treating HIV patients co-infected with both HBV and HCV, since the two current first-line regimen combinations both contribute to an elevated risk of hepatotoxicity, and virological failure in this population is high. Previous studies also reported that HIV/HBV/HCV co-infected patients have a higher mortality

rate than each of the HIV/HCV and HIV/HBV co-infected patients^{52,53}. We were not able to show this but we only had a small sample size of triple co-infection patients in our study. Currently, there are no recommendations for treating triple co-infection patients in the latest Chinese treatment guidelines²¹. The US treatment guidelines recommend the use of direct-acting antivirals (DAAs) therapy for HCV prior to ART⁵⁴, but the high out-of-pocket cost for this effective treatment is a significant barrier for the Chinese patients^{55,56} although the first DAAs medicine has only been approved recently by the Chinese Food and Drug Administration in April 2017. The majority of HCV-positive patients are still on IFN treatment, such as Pegylated IFN- α 2a or 2b in combination with ribavirin (RBV)⁵⁷. The overall higher rates of immunological failure, virological failure and mortality in HCV co-infected patients require further investigation to determine if this can be improved via more careful selection of ART regimens, early initiation of HCV treatment and enhancement of treatment adherence.

The follow-up results reflect the importance of the regimen selection at baseline. The comparison of regimen selection at baseline indicates that clinical doctors have considered ALT levels when determining ART regimens, especially their NNRTI choice at ART initiation. However, the doctor's decision does not always follow the treatment guidelines. For instance, although the treatment guidelines recommend TDF+3TC+EFV as the first-line regimen for HBV co-infected patients, less than half of HBV co-infected patients initiated ART with TDF, which may be due to

the fact that TDF-based regimen was not included in national free ART program until 2012⁵⁸ although it was recommended by China treatment guidelines as early as 2007⁵. The situation highlights the necessity to switch a better treatment plan for HBV co-infected in clinical practices in China. Similarly, treatment guidelines have recommended against the use of D4T and NVP-based regimens for HCV co-infected patients, but ~30% HCV co-infected patients have been given a regimen that includes D4T, and another one-fourth NVP. Higher hepatotoxicity incidence rate has been reported in patients who used the NVP- and AZT/D4T-based regimens during the follow-up⁵⁹.

Several limitations should be noted in this study. First, this study could not identify deaths unrelated to both HIV or viral hepatitis, so we cannot provide a disease-specific mortality rate. Second, the primary HIV infection route was sexual transmission in this setting, so it may not be representative to other settings where sharing injection equipment is more common and leads to a higher co-infected rate with HCV. Third, the limited proportion of patients who participated in the follow-up liver function test may lead to a potential bias in the results. Fourth, the duration of HBV or HCV infections cannot be identified in the study as they were all newly diagnosed at ART initiation, it may have an impact on ART outcome and hepatotoxicity risk. Fifth, the study was conducted during January 2008 and December 2013, although the treatment guidelines in China for HIV and HCV has not changed substantially during and after the study period, the more recently diagnosed patients may have better

treatment options for HCV. Our findings are limited to patients who are largely dependent only on the national free treatment program. Sixth, the small sample size of triple co-infection patients in this study may affect the precision of our estimated risk of hepatotoxicity rate in this group. Despite this, this study is the first to evaluate and compare the treatment effects of different regimens in PLHIV co-infected with HBV and HCV in China. It serves as an important reference for regimen selection in clinical practices and informs policy makers in formulating future treatment guidelines and also can be used in other developing countries.

Conclusion

This retrospective cohort study demonstrated a high mortality and hepatotoxicity rate among PLHIV co-infected with HCV in China, indicating careful and timely clinical management is necessary for HCV co-infected patients to monitor the disease progress to AIDS and liver diseases. For HBV co-infected patients, the TDF-based regimen should be strongly recommended. Further improvements in the current Chinese treatment guidelines are necessary to direct the best clinical practices for ART. This study represents the treatment situation of HIV/HBV and HIV/HCV co-infected patients in China and probably in many other similar developing country settings.

Acknowledgments

This work was supported by a grant from National Science and Technology Major Project of China (No.2012ZX1001001).

Author Contributions

Lei Zhang, Christopher Kincaid Fairley, Joe Sasadeusz and Xi Chen conceived and designed the study; Jianmei He and Xiuqing Wei collected the data; Shu Su and Lei Zhang analyzed the data; Shu Su wrote the paper; Xi Chen, Christopher Kincaid Fairley, Joe Sasadeusz, Huan Zeng, Jun Jing, Limin Mao and Lei Zhang revised the manuscript. All authors approved the final manuscript.

Ethical Considerations

This study was reviewed and approved by Monash University Human Research Ethics Committee (approval number CF15/4321 – 2015001862).

Statement of Interests

The authors declare no conflict of interest.

Reference

1. Alter MJ. Epidemiology of viral hepatitis and HIV co-infection. *Journal of hepatology*. 2006;44(1 Suppl):S6-9.
2. Degenhardt L, Charlson F, Stanaway J, et al. Estimating the burden of disease attributable to injecting drug use as a risk factor for HIV, hepatitis C, and hepatitis B: findings from the Global Burden of Disease Study 2013. *The Lancet Infectious diseases*. 2016.
3. Khosravani A, Sarkari B, Negahban H, Sharifi A, Toori MA, Eilami O. Hepatitis B Infection among high risk population: a seroepidemiological survey in Southwest of Iran. *BMC Infectious Diseases*. 2012;12:378-378.
4. Price JC, Thio CL. Liver Disease in the HIV-Infected Individual. *Clinical gastroenterology and hepatology : the official clinical practice journal of the American Gastroenterological Association*. 2010;8(12):1002-1012.
5. *Panel on National Free ART Manual*. [Treatment guidelines for China National Free Antiretroviral Treatment Program]: People's Medical Publishing House, Beijing; 2007.
6. Zhang F, Zhu H, Wu Y, et al. HIV, hepatitis B virus, and hepatitis C virus co-infection in patients in the China National Free Antiretroviral Treatment Program, 2010-12: a retrospective observational cohort study. *The Lancet Infectious diseases*. 2014;14(11):1065-1072.
7. Chen M, Wong WW, Law MG, et al. Hepatitis B and C Co-Infection in HIV Patients from the TREAT Asia HIV Observational Database: Analysis of Risk Factors and Survival. *PloS one*. 2016;11(3):e0150512.
8. Akhtar A, Khan AH, Sulaiman SA, Soo CT, Khan K. HBV and HIV co-infection: Prevalence and clinical outcomes in tertiary care hospital Malaysia. *Journal of medical virology*. 2016;88(3):455-460.

9. Huy BV, Vernavong K, Kính NV. HBV and HCV Coinfection among HIV/AIDS Patients in the National Hospital of Tropical Diseases, Vietnam. *AIDS Research and Treatment*. 2014;2014:581021.
10. Wu S, Yan P, Yang T, Wang Z, Yan Y. Epidemiological profile and risk factors of HIV and HBV/HCV co-infection in Fujian Province, southeastern China. *Journal of medical virology*. 2017;89(3):443-449.
11. Kim JH, Psevdo G, Suh J, Sharp VL. Co-infection of hepatitis B and hepatitis C virus in human immunodeficiency virus-infected patients in New York City, United States. *World journal of gastroenterology*. 2008;14(43):6689-6693.
12. Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. *Journal of acquired immune deficiency syndromes (1999)*. 2006;43(1):42-46.
13. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. *Archives of internal medicine*. 2006;166(15):1632-1641.
14. Mocroft A, Soriano V, Rockstroh J, et al. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? *AIDS (London, England)*. 2005;19(18):2117-2125.
15. Kooij KW, Wit FW, van Zoest RA, et al. Liver fibrosis in HIV-infected individuals on long-term antiretroviral therapy: associated with immune activation, immunodeficiency and prior use of didanosine. *AIDS (London, England)*. 2016;30(11):1771-1780.
16. Stabinski L, Reynolds SJ, Ocama P, et al. High prevalence of liver fibrosis associated with HIV infection: a study in rural Rakai, Uganda. *Antiviral therapy*. 2011;16(3):405-411.
17. Molina JM, Orkin C, Iser DM, et al. Sofosbuvir plus ribavirin for treatment of hepatitis C virus in patients co-infected with HIV (PHOTON-2): a multicentre, open-label, non-randomised, phase 3 study. *Lancet (London, England)*. 2015;385(9973):1098-1106.
18. Sulkowski MS, Eron JJ, Wyles D, et al. Ombitasvir, paritaprevir co-dosed with ritonavir, dasabuvir, and ribavirin for hepatitis C in patients co-infected with HIV-1: a randomized trial. *Jama*. 2015;313(12):1223-1231.
19. Kim JH, Psevdo G, Jr., Sharp V. Five-year review of HIV-hepatitis B virus (HBV) co-infected patients in a New York City AIDS center. *Journal of Korean medical science*. 2012;27(7):830-833.
20. *Panel on National Free ART Manual*. [Treatment guidelines for China National Free Antiretroviral Treatment Program]: People's Medical Publishing House, Beijing; 2014.
21. *Panel on National Free ART Manual*. [Treatment guidelines for China National Free Antiretroviral Treatment Program]: People's Medical Publishing House, Beijing; 2016.

22. Ma Y, Zhang F, Zhao Y, et al. Cohort profile: the Chinese national free antiretroviral treatment cohort. *International journal of epidemiology*. 2010;39(4):973-979.
23. Wu Z, Zhao Y, Ge X, et al. Simplified HIV Testing and Treatment in China: Analysis of Mortality Rates Before and After a Structural Intervention. *PLoS medicine*. 2015;12(9):e1001874.
24. Rockville MDoA, National Institute of Allergy and Infectious Diseases. *Table of Grading Severity of Adult Adverse Experiences*. AIDS Clinical Trials Group1996.
25. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology (Baltimore, Md)*. 2002;35(1):182-189.
26. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *Jama*. 2000;283(1):74-80.
27. Liao B, Wang Z, Lin S, et al. Significant fibrosis is not rare in Chinese chronic hepatitis B patients with persistent normal ALT. *PloS one*. 2013;8(10):e78672.
28. Wang H, Xue L, Yan R, et al. Comparison of histologic characteristics of Chinese chronic hepatitis B patients with persistently normal or mildly elevated ALT. *PloS one*. 2013;8(11):e80585.
29. Li Y, Zhang Z, Shi J, et al. Risk factors for naturally-occurring early-onset hepatocellular carcinoma in patients with HBV-associated liver cirrhosis in China. *International journal of clinical and experimental medicine*. 2015;8(1):1205-1212.
30. WHO HA. *Table 7.15 WHO definitions of clinical, immunological and virological failure for the decision to switch ART regimens*. 2013.
31. Ramirez-Mena A, Glass TR, Winter A, et al. Prevalence and Outcomes of Hepatitis B Coinfection and Associated Liver Disease Among Antiretroviral Therapy-Naive Individuals in a Rural Tanzanian Human Immunodeficiency Virus Cohort. *Open forum infectious diseases*. 2016;3(3):ofw162.
32. Hua L, Andersen JW, Daar ES, Glesby MJ, Hollabaugh K, Tierney C. Hepatitis C virus/HIV coinfection and responses to initial antiretroviral treatment. *AIDS (London, England)*. 2013;27(17):2725-2734.
33. Martin NK, Devine A, Eaton JW, et al. Modeling the impact of early antiretroviral therapy for adults coinfecting with HIV and hepatitis B or C in South Africa. *AIDS (London, England)*. 2014;28 Suppl 1:S35-46.
34. van Griensven J, Phirum L, Choun K, Thai S, De Weggheleire A, Lynen L. Hepatitis B and C co-infection among HIV-infected adults while on antiretroviral treatment: long-term survival, CD4 cell count recovery and antiretroviral toxicity in Cambodia. *PloS one*. 2014;9(2):e88552.
35. Chen JY, Feeney ER, Chung RT. HCV and HIV co-infection: mechanisms and management. *Nature reviews Gastroenterology & hepatology*. 2014;11(6):362-371.
36. Marcus JL, Leyden WA, Chao CR, et al. Differences in Response to Antiretroviral Therapy by Sex and Hepatitis C Infection Status. *AIDS patient care and STDs*. 2015;29(7):370-378.

37. Gillis J, Smieja M, Cescon A, et al. Risk of cardiovascular disease associated with HCV and HBV coinfection among antiretroviral-treated HIV-infected individuals. *Antiviral therapy*. 2014;19(3):309-317.
38. Prussing C, Chan C, Pinchoff J, et al. HIV and viral hepatitis co-infection in New York City, 2000-2010: prevalence and case characteristics. *Epidemiology and infection*. 2015;143(7):1408-1416.
39. Mena A, Meijide H, Rodriguez-Osorio I, Castro A, Poveda E. Liver-related mortality and hospitalizations attributable to chronic hepatitis C virus coinfection in persons living with HIV. *HIV medicine*. 2017.
40. Chwiki S, Campos MM, McLaughlin ME, et al. Adverse effects of antiretroviral therapy on liver hepatocytes and endothelium in HIV patients: An ultrastructural perspective. *Ultrastructural pathology*. 2017:1-10.
41. Reust CE. Common adverse effects of antiretroviral therapy for HIV disease. *American family physician*. 2011;83(12):1443-1451.
42. Wu L, Jin C, Bai S, et al. The effect of highly active antiretroviral therapy on liver function in human immunodeficiency virus-infected pediatric patients with or without hepatitis virus co-infection. *Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences*. 2015;20(2):127-132.
43. Brown HR, Castellino S, Groseclose MR, et al. Drug-induced Liver Fibrosis: Testing Nevirapine in a Viral-like Liver Setting Using Histopathology, MALDI IMS, and Gene Expression. *Toxicologic pathology*. 2016;44(1):112-131.
44. Smit C, Arends J, Peters L, et al. Effect of abacavir on sustained virologic response to HCV treatment in HIV/HCV co-infected patients, Cohere in Eurocoor. *BMC Infect Dis*. 2015;15:498.
45. Mathers BM, Degenhardt L, Bucello C, Lemon J, Wiessing L, Hickman M. Mortality among people who inject drugs: a systematic review and meta-analysis. *Bulletin of the World Health Organization*. 2013;91(2):102-123.
46. Shuper PA, Joharchi N, Irving H, et al. Differential predictors of ART adherence among HIV-monoinfected versus HIV/HCV-coinfected individuals. *AIDS care*. 2016;28(8):954-962.
47. Feelemyer J, Jarlais DD, Arasteh K, Uuskula A. Adherence to Antiretroviral Medications among Persons who Inject Drugs in Transitional, Low and Middle Income Countries: An International Systematic Review. *AIDS and behavior*. 2015;19(4):575-583.
48. Price H, Dunn D, Pillay D, et al. Suppression of HBV by tenofovir in HBV/HIV coinfecting patients: a systematic review and meta-analysis. *PloS one*. 2013;8(7):e68152.
49. Yang RR, Gui X, Chen XY, Zhu Y. Interference of replication between hepatitis B and C viruses in patients infected with HIV. *Journal of medical virology*. 2011;83(7):1159-1164.

50. Kosi L, Reiberger T, Payer BA, et al. Five-year on-treatment efficacy of lamivudine-, tenofovir- and tenofovir + emtricitabine-based HAART in HBV-HIV-coinfected patients. *Journal of viral hepatitis*. 2012;19(11):801-810.
51. Alvarez-Uria G, Ratcliffe L, Vilar J. Long-term outcome of tenofovir disoproxil fumarate use against hepatitis B in an HIV-coinfected cohort. *HIV medicine*. 2009;10(5):269-273.
52. Bauer-Staeb C, Jorgensen L, Lewis G, Dalman C, Osborn DPJ, Hayes JF. Prevalence and risk factors for HIV, hepatitis B, and hepatitis C in people with severe mental illness: a total population study of Sweden. *The lancet Psychiatry*. 2017.
53. Ishizaki A, Tran VT, Nguyen CH, et al. Discrepancies in prevalence trends for HIV, hepatitis B virus, and hepatitis C virus in Haiphong, Vietnam from 2007 to 2012. *PloS one*. 2017;12(6):e0179616.
54. Adolescents. PoAGfAa. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. 2016.
55. Welzel TM, Nelson DR, Morelli G, et al. Effectiveness and safety of sofosbuvir plus ribavirin for the treatment of HCV genotype 2 infection: results of the real-world, clinical practice HCV-TARGET study. *Gut*. 2016.
56. Welzel TM, Petersen J, Herzer K, et al. Daclatasvir plus sofosbuvir, with or without ribavirin, achieved high sustained virological response rates in patients with HCV infection and advanced liver disease in a real-world cohort. *Gut*. 2016.
57. Han Q-Y, Liu Z-W. Current treatment of chronic hepatitis C in China: Dilemma and potential problems. *World journal of gastroenterology*. 2016;22(19):4615-4618.
58. *Panel on National Free ART Manual*. [Treatment guidelines for China National Free Antiretroviral Treatment Program]: People's Medical Publishing House, Beijing; 2012.
59. Dieterich DT, Robinson PA, Love J, Stern JO. Drug-induced liver injury associated with the use of nonnucleoside reverse-transcriptase inhibitors. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2004;38 Suppl 2:S80-89.

Table 1. Patient characteristics at baseline

| Characteristics/Infection status | Total (%) | HIV-only (%) | HIV/HCV (%) | HIV/HBV (%) | HIV/HBV/HCV (%) |
|------------------------------------|--------------|--------------|-------------|-------------|-----------------|
| | 1984 (100.0) | 1548 (78.0) | 198 (10.0) | 184 (9.3) | 54 (2.7) |
| Age at ART initiation (IQR) | 39 (30-49) | 40 (30-52) | 37 (33-43) | 39 (30-49) | 38 (33-43) |

| | | | | | |
|-------------------------------------------------------|------------------|---------------------|--------------------|--------------------|------------------------|
| Gender | | | | | |
| Male | 1353 (68.2) | 1032 (66.7) | 139 (70.2) | 142 (77.2) | 40 (74.1) |
| Female | 631 (31.8) | 516 (33.3) | 59 (29.8) | 42 (22.8) | 14 (25.9) |
| CD4 at ART initiation (IQR) | 152 (43-254) | 166 (49-259) | 109 (31-214) | 129 (33-225) | 106 (25-174) |
| Transmission route | | | | | |
| Heterosexuals | 1360 (68.5) | 1165 (75.3) | 47 (23.7) | 135 (73.4) | 13 (24.1) |
| Homosexuals | 205 (10.3) | 174 (11.2) | 4 (2.0) | 25 (13.6) | 2 (3.7) |
| IDU | 227 (11.4) | 43 (2.8) | 137 (69.2) | 11 (6.0) | 36 (66.7) |
| FPD | 25 (1.3) | 19 (1.2) | 3 (1.5) | 2 (1.1) | 1 (1.9) |
| Unknown | 167 (8.4) | 147 (9.5) | 7 (3.5) | 11 (6.0) | 2 (3.7) |
| WHO Stage at ART Initiation | | | | | |
| I/II | 946 (47.7) | 818 (52.8) | 40 (20.2) | 78 (42.4) | 10 (18.5) |
| III/IV | 1038 (52.3) | 730 (47.2) | 158 (79.8) | 106 (57.6) | 44 (81.5) |
| Biochemical indices of liver at ART initiation | | | | | |
| Elevated ALT (> 50 IU/L) | 156 (7.9) | 84 (5.4) | 30 (15.2) | 36 (19.6) | 6 (11.1) |
| ART regimen at ART Initiation | | | | | |
| EFV+3TC+D4T | 201 (10.1) | 143 (9.2) | 40 (20.2) | 10 (5.4) | 8 (14.8) |
| NVP+3TC+D4T | 186 (9.4) | 148 (9.6) | 18 (9.1) | 15 (8.2) | 5 (9.3) |
| NVP+3TC+AZT | 629 (31.7) | 557 (36.0) | 28 (14.1) | 36 (19.6) | 8 (14.8) |
| EFV+3TC+AZT | 484 (24.4) | 372 (24.0) | 61 (30.8) | 38 (20.7) | 13 (24.1) |
| | Total (%) | HIV-only (%) | HIV/HCV (%) | HIV/HBV (%) | HIV/HBV/HCV (%) |
| EFV+3TC+TDF | 339 (17.1) | 215 (13.9) | 39 (19.7) | 66 (35.9) | 19 (35.2) |
| LPV/r+3TC+TDF | 83 (4.2) | 61 (3.9) | 5 (2.5) | 16 (8.7) | 1 (1.9) |
| NVP+3TC+TDF | 33 (1.7) | 27 (1.7) | 3 (1.5) | 3 (1.6) | 0 (0.0) |
| LPV/r+3TC+AZT | 25 (1.3) | 21 (1.4) | 4 (2.0) | 0 (0.0) | 0 (0.0) |
| D4T+3TC+LPV/r | 4 (0.2) | 4 (0.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) |

Table 2. Proportion of ART regimen used in patients with normal and elevated ALT levels at treatment initiation

| Regimen/ALT status | Normal ALT (%) n=1828 | Elevated ALT (%)n=156 | Wald χ^2 , p-value |
|-------------------------------|-----------------------|-----------------------|-------------------------|
| First-line regimen | | | |
| Patients administered EFV | 922 (50.4) | 102 (65.4) | 12.86, <0.01 |
| Patients administered NVP | 805 (44.0) | 43 (27.6) | 15.94, <0.01 |
| Patients administered AZT/D4T | 1389 (76.0) | 111 (71.2) | 1.82, 0.18 |
| Patients administered TDF | 338 (18.5) | 34 (21.8) | 1.03, 0.31 |
| Second-line regimen | | | |
| Patients administered LPV/r | 101 (5.5) | 11 (7.1) | 0.63, 0.43 |

Table 3. The comparison of HIV disease progression among different co-infection patients, by multivariate logistic regression and cox proportional hazards model analysis.

| Indicators/ Infection status | HIV only | HIV/HCV | HIV/HBV | HIV/HBV/HCV |
|----------------------------------------------|---------------------|-------------------------|------------------------|------------------------|
| Virological failure (T6-12) | | | | |
| Cases/participants, (%) | 60/1004 (6.0) | 15/139 (10.8) | 10/141 (7.1) | 3/36(8.3) |
| Adjusted OR (95%CI) | Ref. | 2.92(1.55-5.51) | 1.20(0.58-2.45) | 1.42(1.04-4.15) |
| Immunological failure (T6-12) | | | | |
| Cases/participants, (%) | 301/1249 (24.1) | 47/161 (29.2) | 41/149 (27.5) | 10/41 (24.4) |
| Adjusted OR (95%CI) | Ref. | 1.69 (1.20-2.34) | 1.40(1.08-1.92) | 0.96(0.69-2.11) |
| Mortality | | | | |
| Cases/person years (% , participants) | 41/3762 (1.1, 1548) | 11/431 (2.6, 198) | 4/350 (1.1, 184) | 1/121 (0.8, 54) |
| Adjusted HR (95%CI) | Ref. | 2.28(1.11-4.68) | 0.99(0.35-2.82) | 0.74(0.1-5.47) |

The multivariate logistic regression model for virological failure and immunological failure was adjusted by age, gender, and WHO classification of AIDS stages at baseline and the multivariate cox regression model for mortality was adjusted by transmission route and WHO classification of AIDS stages at baseline

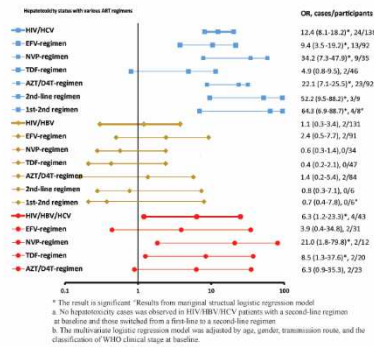
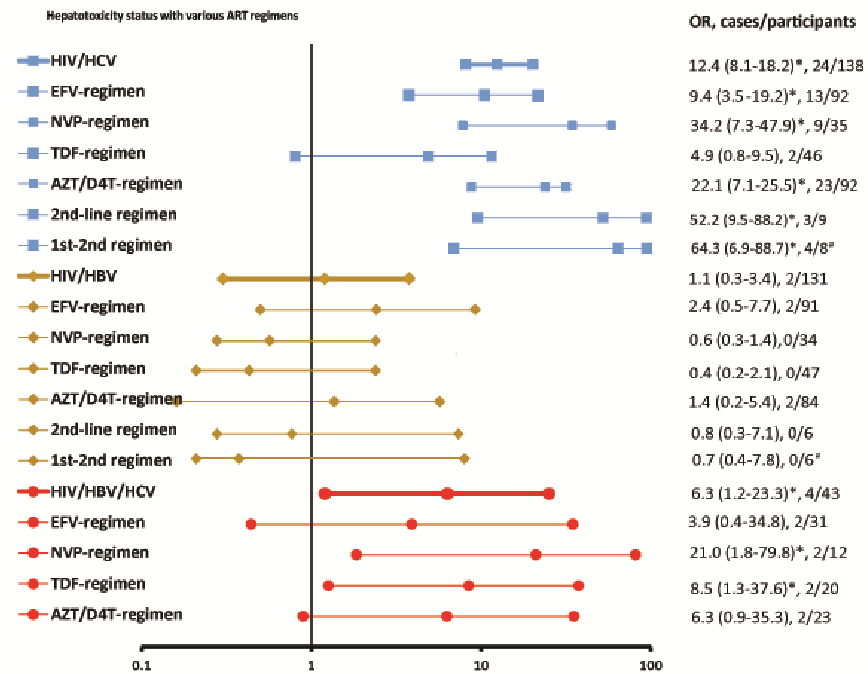


Figure 1. Risk of hepatotoxicity after 6-12 months of ART treatment with various regimens compared with HIV mono-infected patients, by multivariate logistic regression model analysis



* The result is significant ^aResults from marginal structural logistic regression model
 a. No hepatotoxicity cases was observed in HIV/HBV/HCV patients with a second-line regimen at baseline and those switched from a first-line to a second-line regimen
 b. The multivariate logistic regression model was adjusted by age, gender, transmission route, and the classification of WHO clinical stage at baseline.

Figure-1 JMV-17-6066R2 .

Author Manuscript



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Su, S; Fairley, CK; Sasadeusz, J; He, J; Wei, X; Zeng, H; Jing, J; Mao, L; Chen, X; Zhang, L

Title:

HBV, HCV, and HBV/HCV co-infection among HIV-positive patients in Hunan province, China: Regimen selection, hepatotoxicity, and antiretroviral therapy outcome

Date:

2018-03-01

Citation:

Su, S., Fairley, C. K., Sasadeusz, J., He, J., Wei, X., Zeng, H., Jing, J., Mao, L., Chen, X. & Zhang, L. (2018). HBV, HCV, and HBV/HCV co-infection among HIV-positive patients in Hunan province, China: Regimen selection, hepatotoxicity, and antiretroviral therapy outcome. *JOURNAL OF MEDICAL VIROLOGY*, 90 (3), pp.518-525.
<https://doi.org/10.1002/jmv.24988>.

Persistent Link:

<http://hdl.handle.net/11343/293929>

File Description:

Accepted version