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Liver damage in patients living with HIV on antiretroviral treatment with normal baseline liver function and without HBV/HCV infection: an 11-year retrospective cohort study in Guangxi, China

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ABSTRACT

Objective To characterise the association between duration of exposure to antiretroviral treatment (ART) and liver damage in HIV patients with an initially normal baseline liver function and without hepatitis B virus (HBV)/hepatitis C virus (HCV) infection.

Methods A retrospective cohort study was conducted in HIV-infected individuals with normal liver function parameters at ART initiation and without HBV/HCV infection, from 14 April 2004 to 13 April 2015 in Guigang city, Guangxi, China. The association between duration of ART and liver damage (grade II–IV liver enzyme elevation [LEE] and/or total bilirubin elevation [TBE]), was analysed. Cox regression was used to examine the factors related to liver damage.

Results Of 2119 eligible patients, 12.41% (263/2119) developed liver damage (grade II–IV LEE/TBE) and contributed 4.11/100 person-years crude incidence rate. The highest liver damage incidence was observed in patients with 6–12 months' ART (15.16/100 person-years). The incidence decreased to 5.56/100 person-years in patients with 12–18 months' ART and 3.13/100 person years in patients with 18–24 months' ART, and then maintained at a relatively low and stable level in patients with 2 years' ART or longer (average of 3.65/100 person-years). Cox regression analysis revealed that current WHO disease stage II, III or IV (compared with stage I) were the risk factors for liver damage, while baseline disease stage II, III (compared with stage I) and current regimen 3TC+AZT+NVP were the protective factors for liver damage.

Conclusions Liver damage always exists among HIV-infected patients on ART with normal baseline liver function and without HBV/HCV infection. Nevertheless, cumulative ART duration does not increase the risk of liver damage. ART could tend to be long-term, however, monitoring and management of liver damage among patients on ART are also important in clinical therapy.

Strengths and limitations of this study

- ► The study retrospectively collected 11-year records of HIV/AIDS patients on antiretroviral treatment (ART) and involved in larger samples than several other similar studies.
- ► Cumulative ART duration does not increase the risk of liver damage.
- ► Monitoring and management of liver damage among patients on ART are still important in clinical therapy.
- ► Confounding factors such as smoking, alcohol consumption, and other opportunistic infections besides hepatitis B virus/hepatitis C virus could not be estimated and ruled out.
- ► Lack of information about further progression of liver diseases such as hepatocarcinoma and liver dysfunction-related mortality limits our findings to be associated with clinical outcomes.

INTRODUCTION

Antiretroviral treatment (ART) has significantly reduced morbidity and mortality in persons living with HIV worldwide.[1] An estimated 19.5 million people globally had received ART by 2016.[2] With the implementation of ART, the life expectancy of HIV-infected individuals is now approaching that of the general population.[3] However, ART has some adverse effects, especially hepatic damage, which comes along with the treatment.[4] An earlier study showed that the prevalence of liver transaminase elevation among HIV-positive individuals on ART ranged from 14% to 20%.[5] Consistently, some researchers have found the incidence of hepatic injury in ART-treated patients was increased.[4] However, quite a few other studies indicated that the

approved antiretroviral agents have low liver toxicity and generally are considered to be well tolerated.[6 7]

Mechanisms of liver damage among HIV-1 infected patients are multiple, probably attributing to HIV infection itself,[8] hepatitis viral co-infections, ART-related hepatotoxicity,[9] AIDS related neoplasm,[10] or experiencing age-related co-morbid conditions.[11] Hepatitis viral infections, either hepatitis B virus (HBV) or hepatitis C virus (HCV), have been reported to lead to hepatotoxicity.[12 13] Elevated hepatotoxicity was observed to be associated with ART in HIV/AIDS patients co-infected with HBV or HCV.[4 12] ART-related hepatotoxicity was also reported in quite a few previous studies.[6 11 13] Furthermore, didanosine is no longer recommended as the first-line antiretroviral drugs for HIV patients because of its hepatotoxicity.[14] Although there are many studies focusing on relationship of ART and liver function among HIV-1 infected patients, after extended exposure to antiretroviral therapy, whether the association between ART and hepatic dysfunction remains true is unclear. Moreover, even though most of the previous studies were controlled for baseline liver enzymes level,[5 7–9] there were still some studies had no initial liver function[15] or co-infection with viral hepatitis[4 6 12] reported. Since ART generally lasts for many years and even lifelong, the effect of long-term ART on liver function needs to be elucidated, which is crucial to ascertain whether the risks of hepatic impairment are self-limiting, and to help to make better clinical decision and monitoring.

Guangxi Zhuang Autonomous Region, a province in western China, has the second highest HIV-infected reported cases in China, with more than 100 000 reported HIV/AIDS cases by the end of 2016,[16] which accounting for ~13% of total national HIV/AIDS cases. Guigang city is a prefecture-level city in Guangxi, and there were more than 5000 reported HIV/AIDS cases during 2008–2013, which listed in the top five among all cities in Guangxi.[17] Previous studies have shown that most of HIV/AIDS patients in Guigang city had receive ART. However, the mortality reached 6.13%, which is higher than those in other places such as South Africa during 2004–2013.[18] Of the HIV/AIDS death cases in Guigang city, 74.21% died of HIV-related diseases.[19] In this study, we retrospectively collected the data from the ART cohort in Guigang city, aiming to investigate the association between duration of exposure to ART and elevation of liver function parameters (grade II–IV liver enzyme elevation [LEE] and/or total bilirubin elevation [TBE]) in HIV patients with an initially normal baseline liver function and without HBV/HCV infection.

METHODS

Study site and population

This retrospective cohort study was conducted in Guigang city, Guangxi, China. All HIV-positive individuals from Guigang People's Hospital or Guigang Centers for Disease Control (CDC) and Prevention were reported to the National Notifiable Disease Monitoring System. Of them, HIV patients whose CD4 cell count was lower than 350 cells/μL (the standard in 2008 was changed to 200 cells/μL) or at WHO disease stage III or IV, met the Chinese national treatment criteria and were referred for treatment with standard ART.

The individuals receiving ART were followed up at 0.5, 1, 2 and 3 months after ART initiation and then every 3 months by staff of local CDC, with clinical indexes detected. If the ART regimen changed, the follow-up schedule was restarted. The ART information and clinical data were reported to the China's National Free Antiretroviral Treatment Program (NFATP) of Information System for the Prevention and Control of AIDS.

We retrospectively collected the data during 14 April 2004 to 13 April 2015 from NFATP. Patients were included in this study if they met the following inclusion criteria: treatment-naive HIV/AIDS patients on ART, aged 16 years old or older, had normal baseline liver function parameters (alanine aminotransferase [ALT], aspartate aminotransferase [AST], total bilirubin in serum [TBIL]) at ART initiation, had at least once liver function measurements during the follow-up. Patients were excluded if the following conditions occurred: had liver dysfunction (abnormal level of AST, ALT, or TBIL) at ART initiation, HBV and/or HCV positive (HBV infection was diagnosed by a positive HBsAg, HBeAg, HBcAb, or detectable HBV DNA. HCV infection was diagnosed by HCV seropositivity or detectable HCV RNA). All of the HIV/AIDS patients receiving ART in Guigang city were routinely tested for HBV/HCV infection at baseline or during follow-up, had no baseline CD4 cell count, had none of the three liver function parameters (AST, ALT, TBIL), had no CD4 cell count records during follow-up. Censoring occurrence included lost to follow-up, referral to other hospital, death, discontinuation of ART, or end of the observation period.

Definitions

For this study, ART was defined as combined use of three or more antiretroviral drugs from any drug class. Baseline was defined as various clinical indexes from the most recent record before or after ART initiation. The upper level of normality (ULN) was defined as AST=40 U/L, ALT=40 U/L and TBIL=20 μmol/L according to the division of *AIDS Toxicity Guidelines*.[20] Any one index exceeding the ULN was considered as abnormal levels (grade I–IV LEE/TBE). Grade I–IV LEE were defined when elevation reaches 1–2.5, 2.5–5.0, 5.0–10.0, >10.0 times as high as the ULN, respectively; and grade I–IV TBE were defined when elevation reaches 1–1.5, 1.5–2.5, 2.5–5.0, >5.0 times as high as the ULN, respectively (according to the division of *AIDS Toxicity Guidelines*[20]). The stages of AIDS progression were defined by CD4 lymphocyte counts: stage I (≥500 cells/μL), stage II (200–499 cells/μL), stage III (50–199 cells/μL) and stage IV (<50 cells/μL) as recommendation of WHO. Follow-up time for each individual was calculated until the last visit plus 3 months, or last

liver function detection date plus 3 months, to allow for report delay.

The eligible patients were divided into two groups according to the occurrence of grade II–IV LEE/TBE during follow-up. The normal hepatic function group included patients who did not have LEE/TBE or had only grade I LEE/TBE, and the liver damage group included the patients who had grade II or III or IV LEE/TBE.

Statistical analysis

Categorical variables were expressed as frequency or proportion. Quantitative variables were described by median±IQR range. χ^2 test or Fisher's test (for categorical variables) and non-parametric test (for quantitative variables) were used to compare the characteristics between normal hepatic function and liver damage groups. The crude incidence rates (incidence densities) of liver damage (per 100 person-years) of different ART duration were calculated in patients sorted by 6-month interval according to their ART duration time. We assumed that there is a linear association between cumulative ART duration and LEE/TBE based on the crude incidence rate. χ^2 linear trend test was conducted for analysis of the change of incidence rates along with the ART duration time. The Cox regression analysis was used to evaluate the related factors for liver damage. The data were analysed using SPSSV.23.0 (SPSS Inc., Chicago, USA) and GraphPad Prism V.6.0 (GraphPad Software, San Diego, California, USA).

Patient and public involvement

The patients and public did not involve in study design or conduct of the study. We just simply extracted data from records of NFATP of Information System for the Prevention and Control of AIDS.

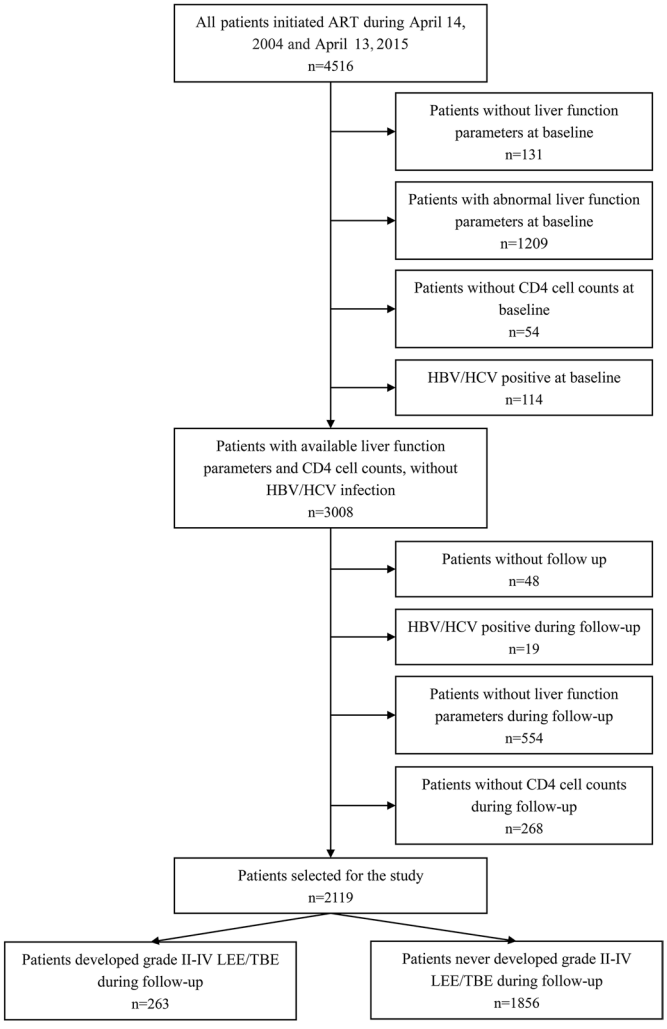

Figure 1 Patients flowchart. ART, antiretroviral treatment; HBV, hepatitis B virus; HCV, hepatitis C virus; LEE, liver enzyme elevation; TBE, total bilirubin elevation.

RESULTS

Demographic characteristics of eligible HIV/AIDS patients at baseline

A total of 4516 patients who initiated ART during April 14, 2004 and April 13, 2015 were enrolled in this study from the Information System for the Prevention and Control of AIDS in Guigang city. Of them, 2397 patients were excluded, including 185 patients who had none of the three baseline liver function parameters (131) or CD4 cell count record (54), 1209 had abnormal baseline liver function parameters, 114 HBV/HCV positive at baseline, 48 without follow-up, 19 HBV/HCV positive during follow-up, 554 had none of the three liver function parameters record during follow-up and 268 had no CD4 cell count record during follow-up. Finally, 2119 patients fulfilled inclusion criteria and were included in this study (figure 1).

The 2119 eligible individuals contributed 6397.13 person-years of follow-up, table 1 shows demographic characteristics of eligible HIV/AIDS patients at baseline. The median age at diagnosis was 47.81 years old (IQR: 34.85–59.54), the median age at initiation of ART was 48.31 years old (IQR: 35.44–59.81). Of the 2119 patients, 61.5% were male, 75.8% were married or cohabitation, 96.6% were residents in Guigang city, and 90.7% acquired HIV heterosexually or homosexually [4.1% acquired HIV by blood/plasma transfusion (82 patients were infected by intravenous drug injection, and five patients were infected by blood/plasma transfusion)]. The eligible patients were divided into two groups according to the occurrence of grade II–IV LEE/TBE: 87.59% (1856/2119) belonged to normal hepatic function group (did not have LEE/TBE or had only grade I LEE/TBE), and 12.41% (263/2119) belonged to liver damage group (grade II–IV LEE/TBE). The differences in residence, diagnosis age, ART initiation age and transmission route between normal hepatic function group and liver damage group were statistically significant ($p<0.05$) (table 1).

Clinical characteristics of study population

Among the eligible 2119 patients, the proportion of patients at four WHO disease stages at baseline was 37.3%

Table 1 Demographic characteristics of study population at baseline

Characteristics	Total (n=2119)	Liver function parameters (ALT, AST, TBIL)		χ^2	P value
		Normal hepatic function group (n=1856)	Liver damage group (n=263)		
Gender				1.13	0.29
Male	1304 (61.5%)	1150 (62.0%)	154 (58.6%)		
Female	815 (38.5%)	706 (38.0%)	109 (41.4%)		
Marital status				6.92	0.14
Unmarried	215 (10.1%)	178 (9.6%)	37 (14.1%)		
Married/cohabitation	1607 (75.8%)	1419 (76.5%)	188 (71.5%)		
Divorced/separated	51 (2.4%)	44 (2.4%)	7 (2.7%)		
Widowed	236 (11.1%)	205 (11.0%)	31 (11.8%)		
Others	10 (0.5%)	10 (0.5%)	0 (0)		
Residence				13.26 *	<0.001
Guigang city	2047 (96.6%)	1803 (97.1%)	244 (92.8%)		
Other cities in Guangxi	67 (3.2%)	48 (2.6%)	19 (7.2%)		
Other provinces	5 (0.2%)	5 (0.3%)	0 (0)		
Age (years) at diagnosis				6.85	0.03
<40	722 (34.1%)	616 (33.2%)	106 (40.3%)		
40–60	884 (41.7%)	777 (41.9%)	107 (40.7%)		
≥60	513 (24.2%)	463 (24.9%)	50 (19.0%)		
Age (years) at ART initiation				7.66	0.02
<40	704 (33.2%)	600 (32.3%)	104 (39.5%)		
40–60	890 (42.0%)	781 (42.1%)	109 (41.4%)		
≥60	525 (24.8%)	475 (25.6%)	50 (19.0%)		
Transmission route				22.33	<0.001
Blood transfusion	87 (4.1%)	62 (3.3%)	25 (9.5%)		
Sexual transmission	1921 (90.7%)	1697 (91.4%)	224 (85.2%)		
Other or unknown	111 (5.2%)	97 (5.2%)	14 (5.3%)		

*Fisher's exact test.
ALT, alanine aminotransferase; ART, antiretroviral treatment; AST, aspartate aminotransferase; TBIL, total bilirubin in serum.

(stage I), 17.7% (stage II), 32.0% (stage III) and 12.9% (stage IV), respectively. Baseline median CD4 cell count at ART initiation was 164.0 cells/μL (IQR: 56.0–264.0). Baseline AST, ALT, TBIL was 24.0 U/L, 17.3 U/L, 8.3 μmol/L, respectively, and follow-up AST, ALT, TBIL was 24.0 U/L, 20.2 U/L, 7.1 μmol/L, respectively. Median CD4 cell count during follow-up was 308.0 cells/μL (IQR: 194.0–441.0). The eligible patients had a median ART duration time of 2.7 years (IQR: 1.5–4.2) (table 2). Among them, 263 had developed grade II–IV LEE/TBE during follow-up, and made up liver damage group, contributing 4.11/100 person-years crude incidence rate of follow-up (95% CI 3.63 to 4.60). The remaining 1856 patients did not develop LEE/TBE or only had grade I LEE/TBE during follow-up, and made up normal hepatic function group (figure 1, tables 1 and 2). The differences in baseline CD4 cell count, baseline AST, current disease stage, current ART regimen, median AST, ALT, TBIL during follow-up, duration of ART between normal hepatic function group and liver damage group were statistically significant (p<0.05).

Crude incidence rates of grade II–IV LEE/TBE in patients at different ART duration times

With all patients sorted by 6-month interval according to their ART duration time, the crude incidence rates of liver damage (grade II–IV LEE/TBE) (per 100 person-years) in each interval of ART duration were calculated. The liver damage occurred in all patients at different ART duration intervals, and the overall liver damage incidence was 4.11/100 person-years (95% CI 3.63 to 4.60). The highest incidence was observed in patients with 6–12 months' ART (15.16/100 person-years, 95% CI 9.37 to 20.95), and then the incidence decreased to 3.13/100

Table 2 Clinical characteristics of study population

Characteristics	Total (n=2119)	Liver function parameters (ALT, AST, TBIL)		χ^2/Z	P value
		Normal hepatic function group (n=1856)	Liver damage group (n=263)		
Baseline diseases stage				1.38	0.71
I	791 (37.3%)	690 (37.2%)	101 (38.4%)		
II	376 (17.7%)	329 (17.7%)	47 (17.9%)		
III	679 (32.0%)	602 (32.4%)	77 (29.3%)		
IV	273 (12.9%)	235 (12.7%)	38 (14.4%)		
Baseline CD4 cell count				14.48	0.001
<200 cells/μL	1250 (59.0%)	1098 (59.2%)	152(57.8%)		
200–350 cells/μL	690 (32.6%)	587 (31.6%)	103 (39.2%)		
≥350 cells/μL	179 (8.4%)	171 (9.2%)	8 (3.0%)		
Baseline AST				10.23	0.02
<20 U/L	475 (22.4%)	428 (23.1%)	47 (17.9%)		
20–30 U/L	1063 (50.2%)	937 (50.5%)	126 (47.9%)		
30–40 U/L	480 (22.7%)	410 (22.1%)	70 (26.6%)		
Missing	101 (4.8%)	81 (4.4%)	20 (7.6%)		
Baseline ALT				3.47	0.33
<20 U/L	1294 (61.1%)	1145 (61.7%)	149 (56.7%)		
20–30 U/L	587 (27.7%)	510 (27.5%)	77 (29.3%)		
30–40 U/L	233 (11.0%)	197 (10.6%)	36 (13.7%)		
Missing	5 (0.2%)	4 (0.2%)	1 (0.4%)		
Baseline TBIL				2.38	0.30
<10 μmol/L	1409 (66.5%)	1245 (67.1%)	164 (62.4%)		
10–20 μmol/L	693 (32.7%)	596 (32.1%)	97 (36.9%)		
Missing	17 (0.8%)	15 (0.8%)	2 (0.8%)		
Current disease stage				12.34	0.01
I	1894 (89.4%)	1663 (89.6%)	231 (87.8%)		
II	109 (5.1%)	100 (5.4%)	9 (3.4%)		
III	83 (3.9%)	70 (3.8%)	13 (4.9%)		
IV	33 (1.6%)	23 (1.2%)	10 (3.8%)		
Current ART regimen				49.56	<0.001
3TC+TDF+EFV	750 (35.4%)	681 (36.7%)	69 (26.2%)		
3TC+AZT+NVP	411 (19.4%)	383 (20.6%)	28 (10.6%)		
3TC+D4T+NVP	71 (3.4%)	65 (3.5%)	6 (2.3%)		
3TC+AZT+EFV	361 (17.0%)	289 (15.6%)	72 (27.4%)		
3TC+D4T+EFV	65 (3.1%)	56 (3.0%)	9 (3.4%)		
3TC+TDF+LPV/r	294 (13.9%)	240 (12.9%)	54 (20.5%)		
Other regimens	167 (7.9%)	142 (7.7%)	25 (9.5%)		
Median CD4 cell count during follow-up				0.35	0.84
<200 cells/μL	549 (25.9%)	484 (26.1%)	65 (24.7%)		
200–350 cells/μL	703 (33.2%)	612 (33.0%)	91 (34.6%)		
≥350 cells/μL	867 (40.9%)	760 (40.9%)	107 (40.7%)		
Follow-up AST (U/L)*	24.0 (20.0–30.0)	23.7 (19.6–29.4)	26.0 (21.4–38.8)	13.2†	<0.001
Follow-up ALT (U/L)*	20.2 (15.5–27.0)	20.0 (15.3–26.0)	24.0 (16.5–39.5)	20.7‡	<0.001

Continued

Table 2 Continued

Characteristics	Total (n=2119)	Liver function parameters (ALT, AST, TBIL)		χ^2/Z	P value
		Normal hepatic function group (n=1856)	Liver damage group (n=263)		
Follow-up TBIL (μmol/L)*	7.1 (5.5–9.1)	7.0 (5.4–8.9)	8.4 (6.6–10.6)	31.1†	<0.001
During of ART (years) *	2.7 (1.5–4.2)	2.6 (1.4–4.1)	3.8 (2.2–5.2)	43.3†	<0.001

*Data are presented as median±IQR range.
†Non-parametric test.
ALT, alanine aminotransferase; ART, antiretroviral treatment; AST, aspartate aminotransferase; TBIL, total bilirubin in serum.

person-years (95% CI1.24 to 5.03) in patients with 18–24 months' ART. There is a decreasing trend of incidence rate of liver damage along with the ART duration intervals in patients with 0.5–2 years of ART (χ^2 linear trend test, χ^2=5.43, p=0.2). The incidence rate then maintained at a relatively low and stable level in patients who had longer ART duration time (≥2 years) (χ^2 linear trend test, χ^2=35.22, p<0.001), with an average of 3.65/100 person-years (95% CI 3.63 to 4.60) (figure 2).

Related factors for grade II–IV LEE/TBE

In order to identify related factors for liver damage (grade II–IV LEE/TBE), the data of all 2119 eligible patients were included in the Cox regression analysis. Univariable analysis were performed first, and then variables that were statistically significant (p<0.05) were included in a multivariate Cox regression analysis. As shown in table 3, patients at initial WHO disease stage II (AHR=0.49, 95% CI 0.34 to 0.70, p<0.001), or III (AHR=0.46, 95% CI 0.33 to 0.64, p<0.001) were less likely to occur liver damage compared with patients at initial WHO disease stage I. Compared with current use of 3TC+TDF+EFV, the current regimens 3TC+AZT+NVP had lower risk to develop liver damage (AHR=0.27, 95% CI 0.19 to 0.41). Except the above factors that could decrease the risk of LEE/TBE, current WHO disease stage II, III and IV (stage II, AHR=2.07, 95% CI 1.04 to 4.13; stage III, AHR=3.90, 95% CI 2.10 to 7.27; stage IV, AHR=3.36, 95% CI 1.76 to 6.43, compared with stage I, respectively) had higher risk to occur liver damage (table 3).

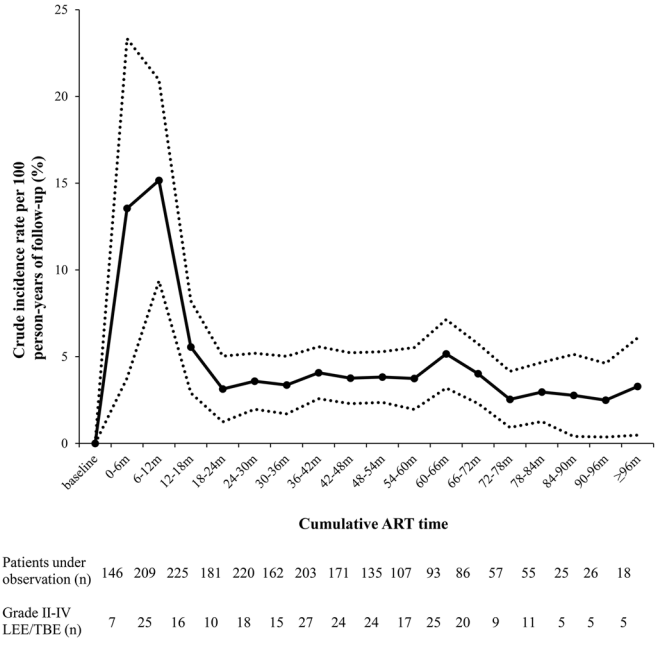

Figure 2 Crude incidence rates of liver damage [grade II–IV liver enzyme elevation (LEE)/total bilirubin elevation (TBE)] with cumulative ART time. ART, antiretroviral treatment; LEE, liver enzyme elevation; TBE, total bilirubin elevation.

DISCUSSION

This retrospective cohort study was conducted on HIV-positive individuals with an initially normal hepatic function and without HBV/HCV infection. We found that liver damage (grade II–IV LEE/TBE) occurred in all patients at different period of ART, indicating that hepatic damage always exists among HIV/AIDS patients receiving ART, which has been shown in a few previous studies,[4 5] although the incidence rate of LEE/TBE in our study was quite stable and low in the longer ART during times. Our study showed that the liver damage prevalence was 12.41% (263/2119) (figure 1), which is lower than those (14%–23%) in several previous studies conducted on HIV/AIDS patients.[21 22] In addition, the overall liver damage incidence (4.11/100 person-years, 95% CI 3.63 to 4.60) in our study is also lower than that (6.04/100 person-years of chronic LEE incidence) in a similar study on HIV-monoinfected persons by Kovari *et al*.[23] One possible reason for lower prevalence and overall incidence of liver damage in our study is that we used the grade II–IV LEE/TBE to define liver dysfunction, which is a higher threshold to define liver dysfunction compared with the similar research in several papers,[20] whereas others might use different definition of LEE.[12 23]

The highest liver damage incidence was observed in patients with 6–12 months' ART duration (11.56/100 person-years). The incidence rapidly decreased in patients with 2 years of ART and then maintained at a relatively lower level (figure 2). These findings are consistent with quite a few previous studies on liver toxicity caused by various antiretroviral drugs such as NVP, EFV, TDF,

Table 3 Factors associated with liver damage among HIV/AIDS patients on ART

Variables	Total patients (n)	Liver damage (n)	Person-years	Liver damage per 100 person-year	HR (95% CI)	P value	AHR (95% CI) *	P value
Gender								
Male	1304	154	3800.40	4.05	1	–		
Female	815	109	2596.74	4.20	0.94 (0.74 to 1.21)	0.65		
Marital status						0.08		
Unmarried	215	37	614.04	6.03	1	–		
Married/ cohabitation	1607	188	4875.47	3.86	0.60 (0.42 to 0.85)	0.01		
Divorced/ separated	51	7	170.18	4.11	0.63 (0.28 to 1.41)	0.26		
Widowed	236	31	705.51	4.39	0.73 (0.45 to 1.18)	0.20		
Others	10	0	31.95	0.00	0.00(-)	0.93		
Residence						0.50		
Guigang city	2047	244	6084.09	4.01	1	–		
Other cities in Guangxi	67	19	298.12	6.37	0.72 (0.41 to 1.25)	0.24		
Other provinces	5	0	14.92	0.00	0.00(-)	0.93		
Age (years) at diagnosis						0.95		
<40	722	106	2442.31	4.34	1	–		
40–60	884	107	2570.05	4.16	1.02 (0.78 to 1.33)	0.90		
≥60	513	50	1384.78	3.61	1.06 (0.75 to 1.48)	0.75		
Age (years) at ART initiation						0.97		
<40	704	104	2397.52	4.34	1	–		
40–60	890	109	2585.24	4.22	1.03 (0.79 to 1.35)	0.82		
≥60	525	50	1414.38	3.54	1.03 (0.34 to 1.45)	0.86		
Transmission route						0.44		
Blood transfusion	87	25	360.66	6.93	1	–		
Sexual transmission	1921	224	5682.10	3.94	0.77 (0.50 to 1.16)	0.21		
Others	111	14	354.38	3.95	0.74 (0.38 to 1.42)	0.36		
Baseline disease stage						<0.001		<0.001
I	791	101	2065.67	4.89	1	–	1	–
II	376	47	1288.25	3.65	0.55 (0.39 to 0.78)	0.001	0.49 (0.34 to 0.70)	<0.001
III	679	77	2283.76	3.37	0.46 (0.34 to 0.62)	<0.001	0.46 (0.33 to 0.64)	<0.001
IV	273	38	759.45	5.00	0.69 (0.47 to 1.01)	0.06	0.68 (0.45 to 1.04)	0.07
Baseline CD4 cell count						0.02		0.05
<200 cells/μL	1250	152	4014.64	3.79	1	–	1	–
200–350 cells/μL	690	103	2093.44	4.92	1.45 (1.13 to 1.86)	0.004	1.42 (1.07 to 1.89)	0.02
≥350 cells/μL	179	8	289.06	2.77	1.30 (0.63 to 2.67)	0.48	1.03 (0.49 to 2.14)	0.95
Baseline AST						0.30		
<20 U/L	475	47	1360.81	3.45	1	–		

Continued

Table 3 Continued

Variables	Total patients (n)	Liver damage (n)	Person-years	Liver damage per 100 person-year	HR (95% CI)	P value	AHR (95% CI) *	P value
20–30 U/L	1063	126	3167.70	3.98	1.14 (0.82 to 1.60)	0.44		
30–40 U/L	480	70	1543.79	4.53	1.20 (0.83 to 1.74)	0.34		
Missing	101	20	324.83	6.16	1.66 (0.98 to 2.81)	0.06		
Baseline ALT						0.69		
<20 U/L	1294	149	3914.47	3.81	1	–		
20–30 U/L	587	77	1707.76	4.51	1.15 (0.88 to 1.52)	0.31		
30–40 U/L	233	36	748.83	4.81	1.14 (0.79 to 1.64)	0.49		
Missing	5	1	26.08	3.83	0.64 (0.09 to 4.57)	0.65		
Baseline TBIL						0.52		
<10 µmol/L	1409	164	4166.89	3.94	1	–		
10–20 µmol/L	693	97	2165.24	4.48	1.15 (0.89 to 1.45)	0.28		
Missing	17	2	65.01	3.08	0.82 (0.20 to 3.32)	0.78		
Current disease stage						<0.001		<0.001
I	1894	231	5994.86	3.85	1	–	1	–
II	109	9	204.03	4.41	1.81 (0.93 to 3.54)	0.08	2.07 (1.04 to 4.13)	0.04
III	83	13	133.19	9.76	4.30 (2.44 to 7.57)	<0.001	3.90 (2.10 to 7.27)	<0.001
IV	33	10	65.05	15.37	3.86 (2.05 to 7.28)	<0.001	3.36 (1.76 to 6.43)	<0.001
Current ART regimen						<0.001		<0.001
3TC+TDF+EFV	750	69	1757.18	3.93	1	–	1	–
3TC+AZT+NVP	411	28	1710.75	1.64	0.27 (0.18 to 0.43)	<0.001	0.27 (0.19 to 0.41)	<0.001
3TC+D4T+NVP	71	6	164.18	3.65	1.21 (0.52 to 2.79)	0.66	1.04 (0.44 to 2.49)	0.93
3TC+AZT+EFV	361	72	1182.47	6.09	1.35 (0.97 to 1.88)	0.08	1.23 (0.88 to 1.72)	0.23
3TC+D4T+EFV	65	9	122.93	7.32	2.87 (1.43 to 5.77)	0.003	1.88 (0.89 to 3.97)	0.10
3TC+TDF+LVP/r	294	54	964.17	5.60	1.14 (0.79 to 1.62)	0.49	1.13 (0.79 to 1.62)	0.50
Other regimens	167	25	495.47	5.05	1.23 (0.78 to 1.94)	0.38	1.15 (0.73 to 1.83)	0.55
Median CD4 cell count during follow-up						0.05		
<200 cells/µL	549	65	1396.45	4.65	1	–		
200–350 cells/µL	703	91	2234.90	4.07	0.75 (0.54 to 1.03)	0.86		
≥350 cells/µL	867	107	2765.79	3.87	0.68 (0.50 to 0.93)	0.01		

*Covariates of the adjusted model included gender, residence, baseline disease stage, baseline CD4 cell counts, baseline AST and ALT, current disease stage, current ART regimen and CD4 cell count during follow-up.
AHR, adjusted HR; ALT, alanine aminotransferase; ART, antiretroviral treatment; AST, aspartate aminotransferase; TBIL, total bilirubin in serum.

which also observed a strong association between drugs and the development of LEE emerging within the first 2 years after drug initiation.[23] The significant decreasing trend of incidence rate of liver damage between 0.5 and 2 years of ART duration might be resulted from a number of adaptation mechanisms which are initiated

to counteract the inflicted damage.[24] Importantly, the above findings indicate that cumulative ART time does not increase the risk of liver damage, which is of great clinical importance to support the strategy of WHO to increase the number of HIV/AIDS patients on ART,[25] and the strategy has been shown to greatly reduce rate of sexual transmission of HIV in several recent HIV prevention trails.[26 27] Meanwhile, antiretroviral examined are no longer recommended by international guidelines, current evidence favours improved safety hepatic profile for IN strand transfer inhibitors, which was confirmed hepatic safety.[28]

Several related factors for liver damage were observed in the present study (table 3). Patients currently at stage II, III or IV had higher risk to develop liver damage compared with patients in stage I, indicating the level of immunodeficiency and the host immunity involve in liver damage on ART. These results are consistent with some previous studies. For example, the risk of nevirapine-induced hepatitis increases 12-fold in women with more than 250 CD4 cells/μL and fivefold in males with more than 400 CD4 cells/μL (disease stage II).[29]

In this study, we also found that patients at initial disease stage II, III were less likely to develop liver damage compared with patients at initial disease stage I (table 3). Possible reason is that the patients with more severe symptom might be more likely to take some positive measures, such as improved adherence, healthier lifestyle, than patients who had normal liver function. However, our results didn't show there is relationship between CD4 cell count (including baseline and follow-up) and liver damage. The results are consistent with some studies but inconsistent with some other studies, for example, one study showed lower risk of hepatic dysfunction come along with higher CD4 cell count in individuals on ART.[8] In fact, contradicting results were reported by different researchers in term of relationship of CD4 cell count and liver dysfunction, which may be related to the different ART regimens investigated as well as some other factors that might affect host immune status when patients were on ART.[21]

Our study also showed that patients with current regiment 3TC+AZT+NVP had lower risk to develop liver damage (grade II–IV LEE/TBE) compared with regiment 3TC+TDF+EFV. The liver toxicity of TDF and EFV has been previously described in several studies.[23 24] Since 3TC+TDF+EFV is currently considered as one of first-line regimens, the importance of combination of liver protection may need to be emphasised for this regimen. Furthermore, according to the National Guide for Free Antiviral Treatment of HIV Patients, NVP is not recommended for men with baseline CD4 cell count ≥400 cells/μL and women with baseline CD4 cell count ≥250 cells/μL because of its hepatotoxicity.[30] In our study, the median baseline CD4 cell counts were 142.0 (IQR: 40–255) in men and 194.0 (IQR: 103–279) in women, which were much lower than the above levels. Therefore, the clinical recommendation of NVP might also contribute to the lower liver damage rate in patients with the current regiment 3TC+AZT+NVP.

CONCLUSIONS

In this study, although patients with abnormal baseline liver function and with HBV/HCV infection had been excluded, the incidence of liver damage (grade II–IV LEE/TBE) still occurred among HIV/AIDS patients on ART, indicating liver damage always exists among HIV-infected patients on ART. Nevertheless, cumulative ART duration does not increase the risk of liver damage. Therefore, ART could tend to be long-term, however, monitoring and management of liver damage among patients on ART are also important in clinical therapy.

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