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Drug-Induced Liver Injury in HIV-Infected Patients with Opportunistic Infections: Causes, Clinical Features and Predictors in Chinese Patients

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Abstract

Objective: To evaluate the prevalence, causes, patterns, severity and risk factors of drug-induced liver injury (DILI) in Chinese HIV-infected patients with opportunistic infections.

Methods: HIV-infected patients with opportunistic infections with DILI were studied in Beijing Ditan Hospital between Jan.1, 2009 and Nov.30, 2012, and risk factors of DILI were evaluated using multivariate Cox Proportional Hazards Model.

Results: In 797 patients, 144 (18.1%) were diagnosed as DILI after receiving treatment of opportunistic infections or antiretroviral therapy. The leading causes were Trimethoprim/sulfamethoxazole (TMP-SMX) (43.9%), anti-tuberculosis medications (13.7%), nevirapine (6.9%), anti-fungal drugs (4.7%) and efavirenz (1.2%). The median duration between agents' exposure and DILI recognition for hepatocellular, cholestatic and mixed pattern was statistically significant difference among 3 patterns of DILI (p=0.009), and the duration was positively correlated with CD4 count (r=0.223, p=0.007) and R value (r=0.238, p=0.004). Male sex and baseline CD4 counts were significant protective predictors for DILI.

Conclusion: TMP-SMX, anti-tuberculosis medications, non-nucleoside reverse transcriptase inhibitors (NNRTIs) and anti-fungal drugs were the leading causes of DILI. The DILI in HIV-infected patients with opportunistic infections was negatively associated with male sex and CD4 counts.

Keywords: HIV; AIDS; HAART; Opportunistic infection; Drug-induced liver injury; Risk factor

Abbreviations: OI: Opportunistic Infection; CDC: Center for Disease Control and Prevention; DILI: Drug-Induced Liver Injury; PCP: *Pneumocystis pneumonia*; TMP/SMX: Trimethoprim/Sulfamethoxazole; TB: Tuberculosis; CMV: Cytomegalovirus; ART: Antiretroviral Therapy; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; T-BIL: Total Bilirubin; D-BIL: Direct Bilirubin; ALB: Albumin; ALP: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; FPG: Fasting Plasma Glucose; WBC: White Cell Counts; Hbsag: Hepatitis B Antigen; Anti-HCV: Anti-Hepatitis C Antibody; ULN: Upper Limit of Normal; Cis: Confidence Intervals; CT: Computerized Tomography; OR: Odds Ratio; NFATP: National Free Antiretroviral Treatment Programs; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; TDF: Tenofovir; 3TC: Lamivudine; EFV: Efavirenz; AUC: Area Under the Curve; Cr: Serum Creatinine; NE: Neutrophil; HGB: Haemoglobin; PLT: Platelet; Hbsag: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus; AHR: Adjusted Hazard Ratios; NVP: Nevirapine

Background

Since the advent of effective antiretroviral therapy for HIV, there was a substantial decrease in AIDS-related morbidities and mortality and a marked increase in lifespan in HIV-infected patients in China [1,2]. Nevertheless, AIDS-related opportunistic infections (OIs) continued to cause morbidity and mortality due to being unware of HIV infection until OIs became the first indicator of their disease in HIV-infected patients in China. All HIV-infected patients with opportunistic infections should started anti-infective treatment, and then initiated antiretroviral therapy. Latest guidelines from American Center for Disease Control and Prevention (CDC) recommended that antiretroviral therapy should be provided to all AIDS-defining illnesses including opportunistic infections [3]. However, concomitant use of anti-infective agents and antiretroviral therapy was complicated and one of the serious adverse effects was drug-induced liver injury (DILI).

Antiretroviral drugs and some anti-infective agents such as anti-tuberculosis agents, anti-fungal drugs and antibiotics such as trimethoprim/sulfamethoxazole (TMP/SMX) were potential cause of DILI. The prevalence, causes and outcome of DILI varied according to geographic locations and population, in which hepatotoxicity caused by acetaminophen and complementary medicines were more common in West and Far East [4], while anti-tuberculosis drugs were the leading cause of DILI in Indian [5]. The severity of DILI was also different in terms of different population, and Lamar et al. reported [6] the higher risk of severe DILI among Hispanic HIV-infected patients after initiation of antiretroviral therapy than that among other population. Some studies [7,8] demonstrated that the pharmacogenetics was associated with DILI in different population, which indicated that the prevalence, causes, severity and risk factors of DILI in Chinese HIV-infected patients were different compared to other HIV-infected population due to genetic heterogeneity in Chinese people.

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The prevalence, causes, severity and risk factors of DILI in Chinese HIV-infected patients were rarely reported. The Beijing Ditan Hospital was a tertiary care hospital in China, which provided high-quality care and treatment to HIV/AIDS patients, including patients with opportunistic infections. The aims of the study was to evaluate the prevalence, causes, patterns, severity and risk factors of DILI in Chinese HIV-infected patients with opportunistic infections, which helped monitor closely patients, proper management of DILI and decrease DILI-related social-economic burdens in China.

Methods

Study design and setting

This observational study was conducted in the Beijing Ditan Hospital, the largest designated tertiary care hospital for HIV/AIDS patients in North China. The Research Ethics Committee of the hospital approved the study protocol and waived the need for informed consent because this analysis used the currently existing data collected during the course of routine treatment and care. The data were reported in aggregate without the use of individual identifying information.

Patients selection

834 HIV-infected patients who were definitely diagnosed as AIDS-defining illnesses were admitted to Beijing Ditan Hospital between Jan 1, 2009 and Nov 30, 2012, in which we excluded those diagnosed with AIDS-defining malignancies in our cohort. Electronic medical records were reviewed and clinical information was abstracted for these patients.

Treatment of opportunistic infections in HIV-infected patients

The diagnosis and treatment of opportunistic infections was conducted based on Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents recommended by the United States Center for Disease Control and Prevention (CDC) [3].

Pneumocystis pneumonia (PCP) was one of the most common opportunistic infection, TMP/SMX was the treatment of the preferred choice and recommended duration of therapy was 21 days. TMP/SMX (TMP15-20 mg/Kg/day and SMX 75-100 mg/Kg/day) was given in 3 divided doses per day, and prednisone was given within 72 h of PCP therapy in moderate-to-severe PCP. Secondary PCP prophylaxis (TMP/SMZ, 2 tablets per day) should be continued until CD4 cell counts in these patients increased from <200 cells/ul to >200 cells/ul for more than 3 months based on immune reconstitution.

The anti-tuberculosis regimen, including isoniazid (300 mg, one time per day), Rifampin (600 mg one time per day), pyrazinamide (500 mg three times per day) and ethambutol (1000 mg one time per day), was recommended to HIV/tuberculosis (HIV/TB) co-infected patients by Chinese CDC. The duration of intensive phase was 2 months and that of continuation phase of pulmonary or extra-pulmonary tuberculosis was 4-7 months or 7-10 months, respectively.

The spectrum of fungal infections included oropharyngeal candidiasis, cryptococcal meningitis, penicilliosis and invasive fungal infection in Chinese HIV/AIDS patients [9]. Oral fluconazole 100 mg once daily for 7-14 days was preferred therapy for oropharyngeal candidiasis; Amphotericin B deoxycholate (0.7 mg/kg per day intravenously) plus flucytosine (100 mg/kg per day orally in 4 divided doses) was used in patients with cryptococcal meningitis. itraconazole (200 mg 3 times daily, increased dose adjustment due to interaction between itraconazole and efavirenz) was recommended to patients with penicilliosis or invasive fungal infection.

Cytomegalovirus (CMV) infection was the most common viral infection in the spectrum of opportunistic infections in Chinese HIV-infected patients and foscarnet 60 mg/kg per 8 h intravenously for 21 days was preferred therapy in these patients.

Chinese guideline for national free antiretroviral therapy (ART) [10] provided for triple therapy with a first-line regimens of Zidovudine (AZT), Stavudine (d4T) or Tenofovir (TDF)/Lamivudine (3TC)/Nevirapine (NVP) or Efavirenz (EFV) to ART-naïve patients and first-line ART regimen was initiated in our cohort after treatment of opportunistic infections.

Data collection

The social-demographic data included gender and age, while clinical data included history of anti-infective agents and antiretroviral regimens prescribed for patients with opportunistic infections. Time evaluation for DILI was also recorded, which included duration from agent's exposure to DILI recognition, from recognition to peak levels of liver dysfunction, and from peak levels to normal of liver function.

Baseline laboratory tests were performed for liver and renal functions (including levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (T-BIL), direct bilirubin (D-BIL), albumin (ALB) and alkaline phosphatase (ALP); blood urea nitrogen (BUN), serum creatinine and fasting plasma glucose (FPG)), and blood routine test (including white cell counts (WBC), neutrophil levels, percentage of eosinophils, hemoglobin and platelet levels) within 24 h after admission. The immunologic tests were performed for CD4 cell counts, hepatitis B antigen (HBsAg) and anti-hepatitis C antibody (anti-HCV). The monitoring of liver functions was performed every week after initiation of anti-infective and/or antiretroviral treatment.

Diagnosis, pattern and severity grade of drug-induced liver injury

When patients with AIDS-defining illnesses were admitted and received anti-infective therapy, abnormal liver functions were evaluated and DILI was diagnosed when meeting established diagnostic criteria [11-15] and culprit drugs were recorded and reported to Adverse Drug Reaction Office in Ditan Hospital.

The evaluation of pattern of DILI was based on R-value defined by international DILI expert working group [12]:

Hepatocellular pattern: $R \geq 5$

Cholestatic pattern: $R \leq 2$

Mixed Hepato-Cholestatic pattern: $2<R<5$.

Abnormal levels of liver enzymes were common among patients infected with HIV who had opportunistic infections, and the severity grade of DILI was determined if the following criteria were met [13].

Grade 1 (mild): ALT levels 1.25-2.5 times upper limits of normal (ULN), or ALP meeting criteria for DILI but T-BIL<2 ULN in patients with baseline ALT or ALP below ULN, while 1.25-2.5 times baseline ALT or ALP in patients with baseline ALT or ALP above ULN.

Grade 2 (moderate): ALT levels 2.6-5.0 times ULN, or ALP meeting criteria for DILI or T-BIL ≥ 2ULN in patients with baseline

ALT or ALP below ULN, while 2.6-3.5 times baseline ALT or ALP in patients with baseline ALT or ALP above ULN.

Grade 3 (severe): ALT levels 5.1-10.0 times ULN, or ALP meeting criteria for DILI and T-BIL ≥ 2ULN or with ascites or encephalopathy in patients with baseline ALT or ALP below ULN, while 3.6-5.0 times baseline ALT or ALP in patients with baseline ALT or ALP above ULN.

Grade 4 (very severe): ALT levels >10.0 times ULN, or death in patients with baseline ALT or ALP below ULN, while >5.0 times baseline ALT or ALP in patients with baseline ALT or ALP above ULN.

Data and Statistical Analysis

All data statistical analysis was conducted using SPSS 19.0(SPSS Institute, Chicago IL, USA). Continuous variables were evaluated as median with 25th and 75th percentile due to skewed statistical distribution while Categorical variables were presented by percentages. The column charts were also used to illustrate prevalence, severity and pattern of DILI caused by different causative agents in HIV-infected patients with opportunistic infections.

Cox proportional hazard models were used to evaluate risk factors associated with DILI in the cohort, and results were expressed as the multivariate-adjusted hazard ratios (AHRs) with 95% confidence intervals (CIs) for the association between predictor variables and DILI. A significance level of 0.05 was set for all statistical testing.

Kaplan-Meier curves were computed in the cohort. Log-rank testing was performed to determine differences in cumulative hazard for time from exposure to DILI recognition stratified by different causative agents.

Spearman's rank correlation coefficient was used to evaluate the correlation between the median durations of DILI, including duration from exposure to DILI recognition, from recognition to peak levels of liver injury, and from peak levels to recovery of liver functions, and gender, age, CD4 levels, R value, or severity grade score.

Results

Demographic and clinical features

37 patients with opportunistic malignancies were excluded from the cohort of 834 in-patients with AIDS-defining illnesses in Beijing Ditan Hospital, and 797 cases were diagnosed as opportunistic infections and included in our cohort, in which 144 cases (18.1%) were found to be drug-induced liver injury after receiving treatment of opportunistic infections or antiretroviral therapy (Table 1). Of 144 DILI cases analyzed, the median age was 35 years, and 134 cases (79.8%) were male. 7 cases (4.9%) and 12 cases (8.3%) were diagnosed as chronic hepatitis B and C, respectively.

Laboratory results revealed that, in 144 DILI cases analyzed, the median baseline ALT and T-BIL levels were 53.4 U/L and 7.2 umol/L, respectively. The median baseline albumin level was 31.6 g/L while the median ALP level was 88.6 U/L. Blood routine test indicated that the median baseline eosinophil levels was 0.9% while the median haemoglobin levels was 111.3 g/L. Immunologic tests revealed that median baseline CD4 cells count was 20.5 cells/ul in these DILI cases analyzed (Table 1).

Causative agents and prevalence of DILI

In our cohort, 187 cases were diagnosed as PCP based on compatible clinical symptom, computerized tomography (CT) scan or etiologic diagnosis, and TMP-SMX was the preferred treatment of choice of PCP, in which 82 cases (43.9%) were diagnosed as DILI after taking TMP-SMX, which was the most prevalent causative agent of DILI in HIV/AIDS patients with opportunistic infections. 271 cases, diagnosed as pulmonary or extra-pulmonary tuberculosis based on etiologic or empirical diagnosis, received anti-tuberculosis medications, in which 37 cases (13.7%) were found to be DILI, which was the second most common causative agent of DILI in HIV/AIDS patients. This was followed by Nevirapine (6.9%), anti-fungal drugs (4.7%) and Efavirenz (1.2%). 181 cases were diagnosed as cytomegalovirus infection in our cohort and received antiviral therapy including foscarnet or genciclovir, but no one was diagnosed as DILI in these patients (Table 1 and Figure 1).

Charateristics	*All patients*	*DILI group*
Features		
Total (%)	797 (100)	144 (18.1)
Age (yr)*	38 (31-47)	35 (30-43.8)
Male sex (%)	530 (66.5)	134 (79.8)
Biochemistry Tests (25th, 75th percentile)		
Baseline ALT (U/L)	26.3 (15.4-47.4)	53.4 (30.1-91.6)
Baseline AST (U/L)	29.1 (19.8-47.5)	47.2 (30.3-81.5)
Baseline T-BIL (umol/L)	7.4 (5.4-10.8)	7.2 (5.3-10.6)
Baseline D-BIL (umol/L)	2.7 (1.8-4.5)	2.7 (1.9-4.4)
Baseline Albumin (g/L)	33.2 (29.0-37.6)	31.6 (27.8-36.4)
Baseline ALP (U/L)	78.2 (62.1-106.0)	88.6 (68.6-162.6)
Baseline BUN (mmol/L)	3.8 (3.0-5.2)	3.9 (3.0-5.5)
Baseline Cr (umol/L)	58.0 (48.9-71.0)	58.0 (50.1-68.0)
Baseline FPG (mmol/L)	5.1 (4.6-6.1)	5.5 (4.7-6.7)
Blood routine Tests (25th, 75th percentile)		
Baseline WBC (×10^9/L)	4.7 (3.0-6.8)	5.0 (3.0-7.3)
Baseline NE (×10^9/L)	3.0 (1.8-5.1)	3.7 (2.0-5.9)
Baseline Eosinophils (%)	1.1 (0.2-3.5)	0.9 (0.1-2.8)
Baseline HGB (g/L)	109.7 (94.6-126.0)	111.3 (92.8-128.1)
Baseline PLT (×10^9/L)	198.1 (140.9-267.7)	206.1 (144.9-283.1)
Baseline Immunologic tests		
CD4 (cells/ul)*	32.5 (12.0-90.8)	20.5 (10.0-45.8)
HBsAg (%)	72 (90.3)	7 (4.9)
Anti-HCV (%)	117 (14.7)	12 (8.3)
Causative agents and prevalence of DILI (%)		
TMP-SMX	187 (23.5)	82 (43.9)
Anti-tuberculosis drugs	271 (34.0)	37 (13.7)
Nevirapine	159 (19.9)	11 (6.9)
Anti-fungal drugs	214 (26.9)	10 (4.7)
Efavirenz	330 (41.4)	4 (1.2)

Note: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; T-BIL: Total Bilirubin; D-BIL: Direct Bilirubin; ALP: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; Cr: Serum Creatinine; FPG: Fasting Plasma Glucose; WBC: White Blood Cells; NE: Neutrophil; HGB: Haemoglobin; PLT: Platelet; HbsAg: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus; TMP-SMX: Trimethoprim/Sulfamethoxazole

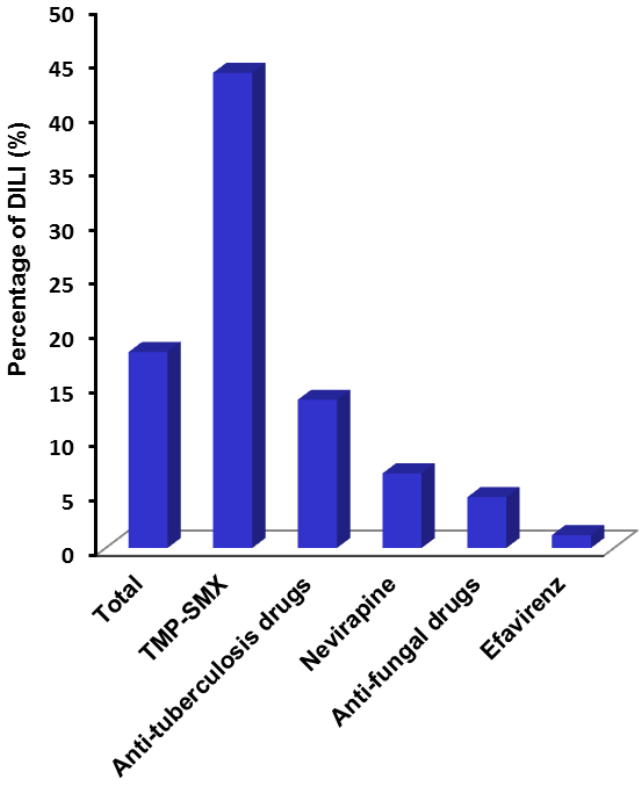
*means evaluation based on 25th, 75th percentile

Table 1: Baseline characteristics of DILI in HIV-infected patients with opportunistic infection.

Values of R: Evaluation of patterns of DILI

The R value was evaluated in 144 cases that developed DILI based on criteria of drug-induced liver disorders on the day of DILI recognition. The overall prevalence of hepatocellular, cholestatic and mixed pattern was 49% (n=62), 28.4% (n=41) and 28.4% (n=41), respectively (Table 2 and Figure 2A). The clinical and laboratory features of cases with 3 patterns of DILI caused by different causative agents were shown

in Tables 2 and 3 and Figure 2A, which indicated that hepatocellular pattern was the most common one in DILI caused by some causative agents including TMP-SMX, nevirapine and anti-fungal drugs, while cholestatic pattern was the most prevalent in efavirenz and anti-tuberculosis drug-induced liver injury.



Note: TMP-SMX: Trimethoprim/Sulfamethoxazole

Figure 1: Causative agents and prevalence of DILI in HIV-infected patients with opportunistic infections.

In 144 DILI cases analyzed, the median duration between agents exposure and DILI recognition for hepatocellular pattern was 7 days, for cholestatic pattern was 10 days, and for mixed pattern was 8 days, respectively, and there was statistically significant difference among 3 patterns of DILI (p=0.009). The median duration between DILI recognition and peak levels of liver dysfunction or between peak levels and normal of liver function were shown in Table 4, which indicated that there was no significant difference among these duration in 3 patterns of DILI.

Severity grade of DILI

The severity grade was evaluated in 144 cases who developed DILI and the overall prevalence was 17.4% (grade I, n=25), 45.8% (grade II, n=66), 26.4% (grade III, n=38) and 10.8% (grade IV, n=15), respectively (Table 2 and Figure 2B). The clinical and laboratory features of cases with different severity grade caused by causative agents were shown in Tables 2 and 3 and Figure 2B, which indicated that grade II was the most common severity in DILI caused by some causative agents including TMP-SMX, nevirapine, anti-fungal drugs and efavirenz, while grade I was the most prevalent severity in anti-tuberculosis drug-induced liver injury.

There was significant interaction between severity and DILI pattern (p=0.002). severity grade 3 and 4 were more prevalent in patients presenting hepatocellular (45.2% and 20.9%) patterns while 51.2% and 41.9% of cases presenting cholestatic pattern had grade 1 and 2 (Table 2).

In 144 DILI cases analyzed, the median duration from peak levels to recovery of liver dysfunction for mild/moderate DILI (grade 1 and 2) was 20 days, and for severe one (grade 3 and 4) was 25 days, respectively, and there was statistically significant difference between 2 groups (p=0.004) (Table 4).

Course of liver injury

In 144 DILI cases analyzed, the median time for DILI from agent exposure to DILI recognition in different drugs was significantly different (Figure 3 and Table 3). The median time for anti-fungal drugs-induced liver injury was shortest and was 4.5 (4-7.3) days,

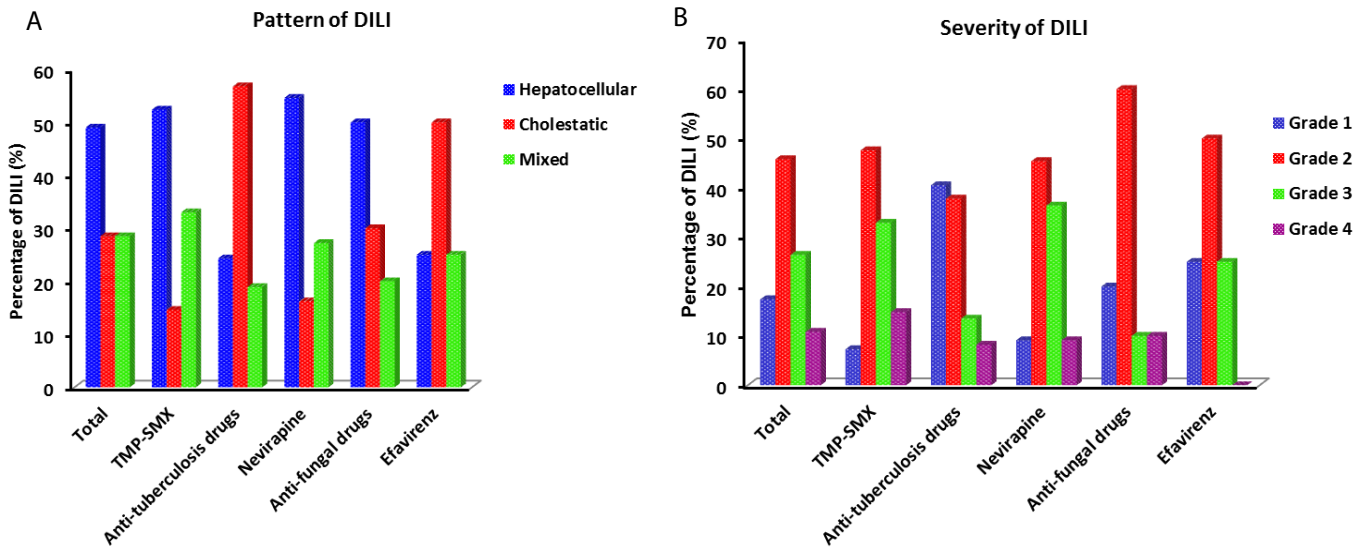


Figure 2A & 2B: The severity and pattern of DILI of different causative agents in HIV-infected patients with opportunistic infections.

Characteristics	*Total (n=144)*	*Hepatocellular (n=62)*	*Cholestatic (n=41)*	*Mixed (n=41)*	*P value*
Age (yrs)*	35.0 (30.0-43.7)	35.0 (30.0-44.3)	35.0 (28.0-43.0)	39.0 (33.0-45.0)	0.108
Male sex (%)	134 (93.1)	59 (95.2)	38 (92.7)	37 (90.2)	0.626
Immunologic tests					
CD4 (cells/ul)*	20.5 (10.0-45.8)	19.5 (11.0-43.8)	26.0 (10.0-57.0)	20.0 (8.0-40.5)	0.396
HBsAg (%)	7 (4.9)	4 (6.5)	1 (2.4)	2 (4.8)	0.651
Anti-HCV (%)	12 (8.3)	3 (4.8)	7 (17.1)	2 (4.8)	0.057
Liver biochemistries, DILI recognition (25th, 75th percentile)					
ALT (U/L)	112.1 (71.6-173.4)	149.6 (89.2-279.9)	71.6 (53.6-118.1)	110.4 (78.2-147.6)	**0.005**
AST (U/L)	78.7 (56.7-148.2)	87.8 (56.7-182.7)	88.7 (63.3-126.1)	73.1 (52.9-139.4)	0.159
T-BIL (umol/L)	6.8 (4.9-10.5)	6.2 (4.6-9.2)	9.4 (6.4-29.5)	6.0 (4.2-7.7)	0.654
D-BIL (umol/L)	2.6 (1.6-5.4)	2.2 (1.4-4.0)	5.2 (2.9-18.4)	2.0 (1.5-3.3)	0.303
ALP (U/L)	110.6 (75.6-194.1)	77.9 (63.0-97.4)	236.3 (151.4-469.6)	123.0 (92.4-157.2)	**0.006**
Eosinophil (%)	1.2 (0.2-4.2)	1.6 (0.1-4.0)	0.8 (0.6-1.6)	2.7 (0.3-5.7)	0.917
Liver biochemistries, DILI peak values (25th, 75th percentile)					
ALT (U/L)	145.5 (118.6-251.5)	251.1 (155.6-360.4)	95.3 (57.9-121.5)	133.3 (120.0-195.0)	**<0.001**
AST (U/L)	113.6 (75.7-190.6)	134.2 (85.3-290.3)	113.4 (70.6-126.1)	82.0 (65.9-141.6)	**0.030**
T-BIL (umol/L)	7.3 (5.1-12.4)	6.2 (4.9-10.5)	10.9 (7.9-31.8)	6.0 (4.5-8.1)	0.220
D-BIL (umol/L)	3.0 (1.7-6.9)	2.3 (1.5-5.4)	6.4 (3.7-22.7)	2.3 (1.6-3.5)	0.098
ALP (U/L)	123.1 (78.8-250.0)	78.8 (67.3-102.8)	315.0 (228.9-487.7)	130.3 (103.6-191.4)	**<0.001**
Eosinophil (%)	1.5 (0.2-5.8)	1.9 (0.4-6.7)	0.9 (0.1-2.0)	2.8 (0.3-7.0)	0.667
Severity of liver injury (%)					
Grade I	25 (17.4)	0 (0.0)	21 (51.2)	4 (9.8)	**0.002**
Grade II	66 (45.8)	21 (33.9)	17 (41.5)	28 (68.3)	
Grade III	38 (26.4)	28 (45.2)	2 (4.9)	8 (19.5)	
Grade IV	15 (10.8)	13 (20.9)	1 (2.4)	1 (2.4)	

Note: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; T-BIL: Total Bilirubin; D-BIL: Direct Bilirubin; ALP: Alkaline Phosphatase; HbsAg: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus

*means evaluation based on 25th, 75th percentile

Table 2: Characteristics of hiv-infected patients with different patterns of DILI.

which was followed 7 (5-12) days for TMP-SMX, 10 (5-20) days for anti-tuberculosis medications, and 18 (7.5-51) days for non-nucleotide reverse transcriptase inhibitors, respectively.

In 144 DILI cases analyzed, the median duration between agent exposure and DILI recognition was 8 days. The duration was significantly positively correlated with CD4 count (r=0.223, p=0.007) and R value (r=0.238, p=0.004). There was no statistically relationship between the duration and gender, age, or severity grade score.

The median duration between DILI recognition and peak value for liver dysfunctions was 0 (0-7) days, and the median duration between peak value and normal of liver dysfunction was 20 (14-30) days. There was no significant correlation between these durations and gender, age, CD4 levels, R value, or severity grade score.

Predictors of DILI in HIV-infected patients with opportunistic infections

As seen in Table 5, univariate models indicated that age was a risk factor for DILI in HIV-infected patients with opportunistic infections (Hazard ratio (HR)=0.982, 95% confidence interval (CI)=0.968-0.997, p=0.016) while Male sex was a protective factor (HR=0.346, CI=0.182-0.658, p=0.001). Laboratory tests indicated that baseline ALT (HR=1.005, CI=1.004-1.006, p<0.001) and AST levels (HR=1.002, CI=1.001-1.004, p<0.001) were associated with increased odds of DILI, baseline alkaline phosphatase level (HR=1.002, CI=1.001-1.003, p<0.001) also indicated a worse prognosis, and baseline neutrophil levels (HR=1.044, CI=1.003-1.086, p=0.033) had a poor outcome in HIV-infected patients, while CD4 count was a protective factor (HR=0.994, CI=0.991-0.997, p<0.001).

In multivariate analysis, the strongest protective predictors for DILI in HIV-infected patients with opportunistic infections were male sex (AHR=0.050, CI=0.020-0.126, p<0.001) and CD4 counts (AHR=0.994, CI=0.991-0.997, p<0.001), which indicated that female patients and lower CD4 counts were more prone to develop DILI in HIV-infected patients with opportunistic infections. The risk factors for DILI were baseline ALT levels (AHR=1.010, CI=1.008-1.013, p<0.001) and ALP levels (AHR=1.002, CI=1.001-1.003, p<0.001), which indicated that higher baseline ALT and ALP levels may be more prone to develop DILI in patients.

Discussion

This observational study was the first one in China to analyze prevalence and causes of DILI, and evaluate the predictors of DILI in a cohort of HIV-infected patients with opportunistic infections. To make a diagnosis of DILI was a difficult task, particularly in a retrospective study. In spite of retrospective nature of the study, when patients were admitted in hospital, abnormal liver functions were evaluated and DILI was diagnosed based on diagnostic criteria. In this study, we used the Benichou criteria [12] for DILI diagnosis initially, while the criteria applied for DILI definition was replaced with new criteria in order to exclude false positive cases. We re-evaluated DILI with Aithal et al. [11] criteria and did not find false positive cases in this population. Abnormal levels of liver enzymes were common among patients

Features	*Total (n=144)*	*Underlying causes of DILI*				
		TMP-SMX (n=82)	*Anti-tuberculosis drugs(n=37)*	*NVP (n=11)*	*Anti-fungal drugs(n=10)*	*EFV (n=4)*
Age, (yrs)*	35.0 (30.0-43.7)	37.5 (32.0-46.0)	34.0 (28.0-41.0)	35 (29-43)	31.5 (28.5-47.0)	30.0 (27.3-34.3)
Male sex (%)	134 (93.1)	77 (93.9)	34 (91.9)	10 (90.9)	9 (90.0)	4 (100.0)
Immunologic tests						
CD4 (cells/ul)*	20.5 (10.0-45.8)	16.5 (8.8-36.3)	43.0 (16.5-84.5)	31 (10-132)	14.0 (4.0-31.8)	30.0 (22.8-37.3)
HBsAg (%)	7 (4.9)	5 (6.1)	2 (5.4)	0 (0.0)	0 (0.0)	0 (0.0)
Anti-HCV (%)	12 (8.3)	2 (2.4)	5 (13.5)	3 (27.3)	1 (10.0)	1 (25.0)
Liver biochemistries, DILI recognition (25th, 75th percentile)						
ALT (U/L)	112.1 (71.6-173.4)	119.4 (82.4-188.0)	77.1 (55.0-125.6)	128.4 (76.4-274.9)	104.6 (66.1-126.3)	140.4 (53.6-198.0)
AST (U/L)	78.7 (56.7-148.2)	73.4 (52.3-133.0)	88.9 (65.1-137.5)	149.3 (53.2-331.0)	83.1 (53.1-158.8)	91.7 (58.2-245.5)
T-BIL (umol/L)	6.8 (4.9-10.5)	6.1 (4.3-8.0)	9.3 (5.9-15.3)	8.2 (6.0-10.4)	6.4(4.9-26.4)	17.5 (5.6-33.5)
D-BIL (umol/L)	2.6 (1.6-5.4)	2.0 (1.3-3.3)	4.9 (2.6-9.9)	2.4 (1.5-4.1)	2.7 (1.9-12.2)	12.2 (2.4-24.3)
ALP (U/L)	110.6 (75.6-194.1)	97.9 (72.4-151.6)	140.1 (98.7-290.8)	120.0 (83.0-178.8)	76.9 (74.9-116.4)	462.6 (176.1-658.0)
Esoinophil (%)	1.2 (0.2-4.2)	1.0 (0.1-4.4)	1.3 (0.2-2.7)	3.3 (1.0-6.6)	0.9 (0.1-6.7)	2.1 (0.5-6.8)
Liver biochemistries, DILI peak values (25th, 75th percentile)						
ALT (U/L)	145.5 (118.6-251.5)	190.1 (122.3-281.5)	113.6 (66.2-137.4)	196.9 (121.0-340.8)	127.8 (108.3-202.6)	140.4 (78.3-263.4)
AST (U/L)	113.6 (75.7-190.6)	109.8 (71.7-196.1)	109.7 (74.2-137.5)	191.6 (80.8-333.6)	115.9 (81.5-158.8)	118.0 (69.1-400.3)
T-BIL (umol/L)	7.3 (5.1-12.4)	6.0 (4.6-8.4)	9.9 (6.3-17.4)	8.6 (6.8-10.9)	8.0 (5.1-26.4)	20.5 (5.6-50.5)
D-BIL (umol/L)	3.0 (1.7-6.9)	2.1 (1.5-4.5)	5.5 (3.4-12.5)	3.0 (2.4-3.8)	3.5 (1.9-12.2)	15.7 (2.4-36.0)
ALP (U/L)	123.1 (78.8-250.0)	114.9 (78.7-196.9)	177.0 (96.5-343.6)	133.3 (83.0-178.8)	82.7 (74.9-153.4)	504.5 (197.1-728.8)
Eosinophil (%)	1.5 (0.2-5.8)	1.9 (0.3-6.7)	1.2 (0.3-2.3)	3.2 (0.2-8.7)	1.5 (0.1-6.7)	2.6 (0.8-6.8)
Time evaluation for DILI (Days) (25th, 75th percentile)						
From exposure to Recognition	8 (5-14)	7 (5-12)	10 (5-20)	15 (10-50)	4.5 (4-7.3)	20.5 (5.8-52.5)
From recognition to peak ALT level	0 (0-7)	2 (0-7)	0 (0-6.5)	7 (0-14)	0 (0-13.3)	3.5 (0-9.3)
From recognition to peak T-BIL level	0 (0-7)	2.5 (0-7)	0 (0-4.8)	7 (0-14)	0 (0-13.3)	3.5 (0-9.3)
From recognition to peak ALP level	0 (0-7)	2.5 (0-7.3)	0 (0-4)	7 (0-14)	0 (0-14.5)	3.5 (0-9.3)
From peak levels to normal	20 (14-30)	21 (14.8-38.3)	16 (10-30)	30 (21-32)	14.5 (14.0-20.3)	45 (22.5-60.0)
Severity of liver injury (%)						
Grade I	25 (17.4)	6 (7.3)	15 (40.5)	1 (9.1)	2 (20.0)	1 (25.0)
Grade II	66 (45.8)	39 (47.6)	14 (37.8)	5 (45.4)	6 (60.0)	2 (50.0)
Grade III	38 (26.4)	27 (32.9)	5 (13.5)	4 (36.4)	1 (10.0)	1 (25.0)
Grade IV	15 (10.8)	10 (14.8)	3 (8.2)	1 (9.1)	1 (10.0)	0 (0.0)
Patterns of liver injury (%)						
Hepatocellular	62 (49.0)	43 (52.4)	9 (24.3)	5 (54.6)	5 (50.0)	1 (25.0)
Cholestatic	41 (28.5)	12 (14.6)	21 (56.8)	2 (18.2)	3 (30.0)	2 (50.0)
Mixed	41 (28.5)	27 (33.0)	7 (18.9)	4 (27.2)	2 (20.0)	1 (25.0)

Note: ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; T-BIL: Total Bilirubin; D-BIL: Direct Bilirubin; ALP: Alkaline Phosphatase; HbsAg: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus; TMP-SMX: Trimethoprim/Sulfamethoxazole; NVP: Nevirapine; EFV: Efavirenz

*means evaluation based on 25th, 75th percentile

Table 3: Characteristics of HIV-infected patients with dili and underlying causes of DILI in ditan hospital from 2009 to 2012.

Median days (25th, 75th percentile)	*Overall cohort (n=144)*	*Severity of DILI*			*Pattern of DILI*			
		Mild/Moderate DILI (n=91)	*Severe DILI (n=53)*	*P*	*Hepatocellular (n=62)*	*Cholestatic (n=41)*	*Mixed (n=41)*	*P*
From exposure to Recognition	8 (5-14)	8 (5-14)	8 (5.5-12)	0.221	7 (5-10.3)	10 (5.5-20.5)	8 (6.5-17)	**0.009**
From recognition to peak ALT level	0 (0-7)	0 (0-7)	3.5 (0-7)	0.637	2.5 (0-7)	0 (0-7)	3 (0-7)	0.886
From recognition to peak T-BIL level	0 (0-7)	0 (0-7)	4 (0-7)	0.341	3 (0-7.3)	0 (0-7)	3 (0-7)	0.538
From recognition to peak ALP level	0 (0-7)	0 (0-7)	3.5 (0-7.8)	0.324	3 (0-7.3)	0 (0-6)	3 (0-7.5)	0.607
From peak levels to normal	20 (14-30)	20 (14-30)	25 (15-33)	0.004	20 (14.8-32.3)	25 (14-38.5)	20 (14-30)	0.194

Note: DILI: Drug-Induced Liver Injury; ALT: Alanine Aminotransferase; T-BIL: Total Bilirubin; ALP: Alkaline Phosphatase

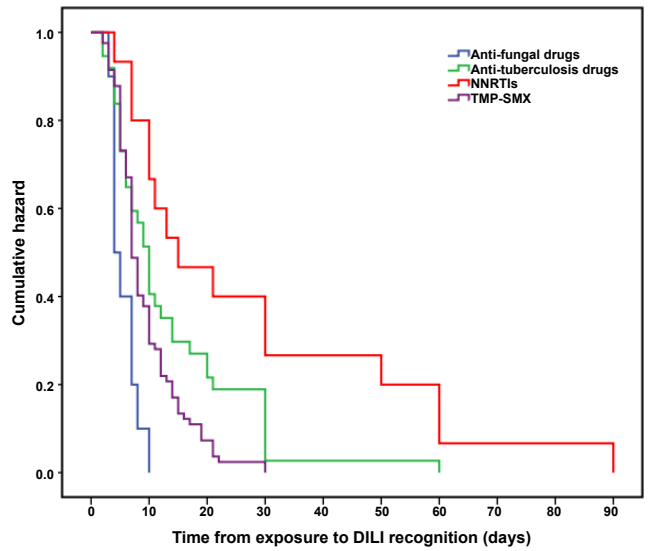
Table 4: Course of DILI based on severity grade and patterns in HIV-infected patients with opportunistic infections.

infected with HIV who had opportunistic infection, the severity of DILI was evaluated based on below or above ULN of liver functions (see methods), which avoided the selection bias in the population.

In this study, we found that the prevalence of DILI was 18.1%, and TMP-SMX was the most common cause of DILI, followed by anti-tuberculosis medications, nevirapine, anti-fungal drugs and efavirenz.

The prevalence and causes of DILI varied due to different geographic locations and population. Chalasani et al. reported that

[16], in American population, more than one agent was implicated in causing liver injury in about 20% of cases, and antibiotics were the largest class of agent that caused DILI, and other causes included herbal supplements and dietary supplements. Andrade et al. reported [17] that 9% of cases developed DILI in Spain population, and the anti-infective group of drugs was the more frequently incriminated, amoxicillin-clavulanate accounting for the 12.8% of the whole series. In HIV-infected population with opportunistic infections, some reports were found that, through an English-language MEDLINE search, HIV-infected patients developed drug-induced liver injury after receiving antiretroviral therapy or treatment of opportunistic infections. Lamar et al. reported [6] that ART-related DILI of any grade occurred in 20% of patients and was associated with non-nucleotide reverse transcriptase inhibitors. Hassen et al. reported [18] that, in an Ethiopian nested case-control study, the incidence of anti-tuberculosis drug-induced hepatotoxicity were 11.5% in HIV/TB co-infected patients. Some studies [7,8] demonstrated that the pharmacogenetics was associated with DILI in different population, which indicated different prevalence and causes of DILI due to different genetic heterogeneity in different population. In our cohort, the anti-infective agents, including TMP-SMX, anti-tuberculosis and anti-fungal drugs, and non-nucleotide reverse transcriptase inhibitors remained the most important causes of DILI in HIV-infected patients with opportunistic infections. The median CD4 cell count was 32.5 cells/ul in this cohort, which indicated severe immunosuppression and made patients susceptible to severe opportunistic infections, including PCP, tuberculosis and fungal infection and different anti-infective drugs necessitated to be initiate, which resulted in drug-induced hepatotoxicity.



Note: TMP-SMX: Trimethoprim/Sulfamethoxazole; NNRTI: Non-Nucleotide Reverse Transcriptase Inhibitor Including Nevirapine And Efavirenz

Figure 3: Kaplan-Meier curve to evaluate the cumulative hazard for time from agent's exposure to DILI recognition stratified by different causative agents.

The sulphonamides-induced liver injury was well documented and the sulphonamide component was considered to be responsible for the most adverse hepatic effects with TMP/SMX. In this study, we found that TMP/SMX was the most common cause of DILI. It was reported [19] that sulphonamides often induced hepatocellular, cholestatic or mixed hepatocellular-cholestatic injury. The underlying mechanisms, characterized by idiosyncratic feature of toxicity [20], could lower

	Unadjusted		*Adjusted*	
Charateristics	***HR (95% CI)***	***P***	***AHR (95%CI)***	***P***
Features				
Age (yr)	0.982 (0.968-0.997)	0.016		
Male sex (%)	0.346 (0.182-0.658)	0.001	0.050 (0.020-0.126)	**<0.001**
Biochemistry Tests				
Baseline ALT (U/L)	1.005 (1.004-1.006)	<0.001	1.010 (1.008-1.013)	**<0.001**
Baseline AST (U/L)	1.002 (1.001-1.004)	<0.001		
Baseline T-BIL (umol/L)	1.000 (0.995-1.005)	0.950		
Baseline D-BIL (umol/L)	1.000 (0.992-1.007)	0.910		
Baseline Albumin (g/L)	0.978 (0.955-1.002)	0.068		
Baseline ALP (U/L)	1.002 (1.001-1.003)	<0.001	1.002 (1.001-1.003)	**<0.001**
Baseline BUN (mmol/L)	1.023 (0.984-1.063)	0.248		
Baseline Cr (umol/L)	1.000 (0.995-1.006)	0.921		
Baseline FPG (mmol/L)	1.064 (0.994-1.139)	0.074		
Blood routine Tests				
Baseline WBC (×10^9/L)	1.015 (0.985-1.046)	0.319		
Baseline NE (×10^9/L)	1.044 (1.003-1.086)	0.033		
Baseline Eosinophils (%)	0.980 (0.940-1.022)	0.347		
Baseline HGB (g/L)	1.002 (0.995-1.009)	0.517		
Baseline PLT (×10^9/L)	1.001 (0.999-1.002)	0.411		
Baseline Immunologic tests				
CD4 (cells/ul)	0.994 (0.991-0.997)	<0.001	0.996 (0.993-0.999)	**0.010**
HBsAg (%)	0.482 (0.225-1.030)	0.060		
Anti-HCV (%)	0.465 (0.257-0.839)	0.011		

Note: AHR: Adjusted Hazard Ratios; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; T-BIL: Total Bilirubin; D-BIL: Direct Bilirubin; ALP: Alkaline Phosphatase; BUN: Blood Urea Nitrogen; Cr: Serum Creatinine; FPG: Fasting Plasma Glucose; WBC: White Blood Cells; NE: Neutrophil; HGB: Haemoglobin; PLT: Platelet; HbsAg: Hepatitis B Surface Antigen; HCV: Hepatitis C Virus

Table 5: Independent risk factors of DILI.

its acetylation in some patients, which prevented its metabolism and enabled it to enter into liver-toxicity related pathway. The mild grade of TMP/SMX-induced liver injury was accordance with some reports, and severe cases have also been described in some patients [21]. In this study, we found that, in Chinese HIV-infected patients, 52.4%, 14.6% and 33% of cases had hepatocellular, cholestatic or mixed hepatocellular-cholestatic injury, and 47.6% and 47.7% presented moderate (grade 2) and severe (grade 3 and 4) DILI, which indicated that close monitoring of liver function and preventing the deterioration of liver function were crucial after taking TMP/SMX in HIV-infected patients.

The first-line anti-tuberculosis drugs, including rifampicin, isoniazid, ethambutol and pyrazinamide, induced liver injury produced an array of hepatic lesions. The anti-tuberculosis medication was involved in concomitant treatment of 3 or 4 drugs; it was hard to find the single agent-induced liver injury in the combination regimen. Rifampicin was an inducer of the hepatic cytochrome P450 and induced the production of reactive metabolites of isoniazid [22], which resulted in increased risk of liver injury. In this study, we found that 56.8%, 24.3% and 18.9% of patients who received first-line anti-tuberculosis combination had cholestatic, hepatocellular or mixed hepatocellular-cholestatic injury, while 40.5%, 37.8% and 21.7% of patients had mild (grade 1), moderate (grade 2) and severe (grade 3 and 4) severity grade, which indicated that anti-tuberculosis drugs-induced liver injury mainly presented cholestatic pattern in Chinese HIV/TB co-infected patients.

In spite of the availability of National Free Antiretroviral Treatment Programs (NFATP) in China [2], many patients were not aware of HIV infection and did not administer the ART regimen until opportunistic infections became the first indicator of their disease [10]. In our cohort, after treatment of opportunistic infections in HIV/AIDS patients, only 489 patients received antiretroviral therapy during hospitalization, including 159 with nevirapine-containing regimen and 330 with efavirenz-containing regimen, while other patients initiated antiretroviral therapy in local CDC. In the different studies comparing the adverse effects of non-nucleoside reverse transcriptase inhibitor (NNRTIs) on the liver, the incidence of DILI in patients with efavirenz ranged from 1 to 8%, while in patients taking nevirapine, it ranged from 4 to 18% [23]. In this study, we found that 11 patients (6.9%) with nevirapine-containing regimen and 4 patients (1.2%) with efavirenz-containing regimen had drug-induced liver injury. It was reported that hypersensitivity was one of mechanisms of NNRTIs-induced liver injury [23]. McRac et al. [24] indicated that efavirenz inhibited bile acid transport in hepatocytes, which resulted in cholestatic liver injury, while nevirapine had no effects on bile acid transport *in vitro* and *in vivo*. In our cohort, we found that 50% and 25% of patients who received efavirenz had cholestatic and hepatocellular pattern of liver injury, while 54.6% and 18.2% of patients who received nevirapine had hepatocellular and cholestatic injury, which was consistent with that reported by McRac et al. [24]. We also found that severity grade 2 and 3 was the most common in NNRTIs-induced liver injury in this study.

The risk of liver injury was highest with itraconazole in azole derivatives, and the pattern was mostly hepatocellular, but some cases of mixed hepatocellular-cholestatic and cholestatic injury were reported. Several cases of fluconazole- and amphotericin B-induced liver injury were also reported [25]. In our cohort, 10 cases (4.7%) were diagnosed as DILI in 214 patients receiving anti-fungal therapy, including 8 cases with itraconazole, 1 with fluconazole and 1 with amphotericin B.

The median time evaluation of DILI was presented in Table 4 and Figure 3. The important finding of the study was significantly difference among the median time for DILI from agent exposure to DILI recognition in different drugs. The median time of anti-fungal drugs-induced liver injury from exposure to DILI recognition was the shortest in the management of opportunistic infections, which indicated that closely monitoring of liver enzymes was recommended soon after initiation of anti-fungal therapy in spite of low incidence of DILI. The TMP/SMX was the most common cause of DILI and the median time and longest time for the development of DILI was 7 and 30 days, respectively. The TMP/SMX was the treatment of choice of PCP and duration was 21 days, which indicated that closely monitoring of liver function was necessary during the time of PCP treatment due to higher prevalence of DILI.

The median time of anti-tuberculosis drugs-induced liver injury from exposure to DILI recognition was 10 (5-20) days in this cohort. American CDC recommended that [3], in patients with tuberculosis diseases with HIV co-infection, antiretroviral therapy should be initiated within 2 weeks of starting anti-tuberculosis treatment in patients with CD4<50 cells/ul. We found that, in our cohort, median CD4 level was 37 cells/ul, and the time points of anti-tuberculosis drugs-induced liver injury was the time of initiation of antiretroviral therapy, which indicated that it was necessary to monitor liver functions prior to initiation of antiretroviral therapy.

The first-line antiretroviral regimen recommended by Chinese CDC was TDF/3TC/EFV in HIV/TB co-infected patients [10]. McRac et al. [24] reported that efavirenz, non-neucleotide reverse transcriptase inhibitor, inhibited bile acid transport in hepatocytes. Lee et al. indicated that efavirenz elicited bile efflux transporters and UGT1A1, and reduced unconjugated and conjugated bilirubin levels, resulting in abnormal excretion of anti-tuberculosis drugs into bile [26], which indicated that efavirenz influenced excretion and transportation of anti-tuberculosis drugs in liver, and resulted in liver injury, which demonstrated that efavirenz deteriorated anti-tuberculosis regimen-induced hepatotoxicity, and in patients with tuberculosis diseases with HIV co-infection, liver enzyme tests should be monitored after ART initiation, especially in patients with CD4<50 cells/ul.

Recent studies indicated that abnormal baseline liver enzymes were independent risk factors of hepatotoxicity in HIV-infected patients [13]. A possible explanation [27] was that higher baseline liver enzymes interfered with drug metabolism *in vivo*. In multivariate Cox proportional hazard regression analysis, although we found that higher baseline liver enzymes, ALT and ALP, were associated with DILI in HIV-infected patients with opportunistic infections, the AHR for ALT and ALP level were 1.01and 1.002, respectively, which did not show strong evidence for risk factors, and the marginal effect size deserved further investigation in Chinese HIV-infected patients with opportunistic infections.

We also found that lower CD4 cell counts were another risk factor of DILI in HIV-infected patients with opportunistic infections. Yimer et al. [28] reported that anti-tuberculosis therapy-induced sub-clinical hepatotoxicity was significantly associated with the decrease in CD4 cell counts, which indicated that presence of some immunologic mechanisms for developing DILI in HIV-infected patients. Another potential explanation was that opportunistic infections were susceptible in patients with lower CD4 levels and different anti-infective drugs necessitated to be initiated, which resulted in drug-induced hepatotoxicity.

Although hepatitis B and C [29] were potential risk factors of DILI, our study failed to demonstrate the conclusion in these patients with

opportunistic infections. This may be attributed to the smaller number of patients diagnosed with hepatitis B or C in this cohort.

There were some limitations in this study. The first one was inherent biases based in observational cohort. Second, the study was conducted in one health institution, which was located in one city, and the validity of our study may be limited and our results may not represent whole country in China.

In summary, the prevalence, causes, clinical feature and risk factors of drug-induced liver injury were discussed in this study, which helped monitor closely patients and proper treatment of DILI in HIV-infected patients with opportunistic infections. TMP-SMX, anti-tuberculosis medications, NNRTIs and anti-fungal drugs were the most common causative agents and there were significantly difference in the median duration between agents' exposure and DILI recognition in different drugs and DILI patterns. The DILI was negatively associated with male sex and CD4 counts in Chinese HIV-infected patients with opportunistic infections.

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Declaration Section

Ethics (and consent to participate)

This observational study was conducted in the Beijing Ditan Hospital, the largest designated tertiary care hospital for HIV/AIDS patients in North China. The Research Ethics Committee of the hospital approved the study protocol and waived the need for informed consent because this analysis used the currently existing data collected during the course of routine treatment and care. The data were reported in aggregate without the use of individual identifying information.

Consent to publish and competing interests

All authors agreed to publish in your journal and declared no conflicts.

Authors' contributions

Conceived and designed the experiments: Hongxin Zhao; Performed experiment and wrote the manuscript: Jiang Xiao; Analyzed the data: Shuxu Du, Guiju Gao and Di Yang.

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