The evaluation of antiretroviral treatment in HIV and hepatitis B virus (HBV) co-infected persons in Beijing, China, 2010-2018: a retrospective cohort study

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Abstract

There is limited long-term data on the effect of ART on clinical outcomes in HIV/HBV patients in China. The objective of this study was to understand the ART treatment effect and the factors associated with the loss to follow-up or death of HIV/HBV co-infected patients in the city of Beijing, China. Methods: This study examined clinical indicators for HIV mono-infected or HIV/HBV co-infected patients from Jan. 2010 to Sep. 2018. Included patients were followed for a mean duration of 34.5 months after ART. Covariance analysis for repeated measures was used to analyze the changes of clinical indicators; multivariate logistic regression and Cox model were used to analyze the influencing factors of the abnormal incidence of clinical indicators and the lost to follow-up or death in HIV patients. Results: A total of 841 HIV/HBV co-infected patients and 2000 HIV patients were analyzed. Adherence was estimated to be 93% in all patients. At baseline, ALT, AST, OIs and APRI≥0.5 in HIV/HBV patients were higher, while the CD4 and CD4/CD8 ratio were lower. After ART treatment, the rate of APRI≥0.5 (4.4%) were still higher in HIV/HBV patients and HBV co-infection affect the prevalence of APRI≥0.5 (OR=2.745, 95% CI 1.041-7.243). The variables related to LTFU or death in HIV patients were initial CD4 (HR=0.784, 95% CI 0.652-0.943), APRI≥0.5 (HR=4.647, 95% CI 1.331-16.227), OIs (HR=4.910, 95% CI 2.352-10.247) and age (HR=1.336, 95% CI 1.004-1.778). HBV coinfection was not associated with increased LTFU or overall mortality in HIV patients (p>0.05). Conclusion: With good ART treatment and adherence rate, the clinical indicators were improved significantly in HIV/HBV co-infected patients. However, the incidence of hepatic fibrosis was higher in these patients.

Introduction

Liver diseases that are caused by the hepatitis B virus (HBV), including cirrhosis and hepatocellular carcinoma (HCC) [1,2], have become increasingly important in patients infected with HIV as their life expectancy is getting longer with successful ART [3-5]. Worldwide, approximately 37 million people are infected with HIV and about 5-20% are co-infected with HBV [6,7]. By the end of Sep. 2018, a total of 849,602 HIV patients were alive in China [8], 67.3% of whom had received antiretroviral therapy (ART) treatment [9], and the prevalence of HIV and HBV co-infection was 8.7-14% [4,10]. HIV and HBV shared transmission routes, including intravenous drug abuse, blood transfusion or blood products, sexual and mother-to-child transmission, whereas the immunodeficiency also caused by HIV enhances the likelihood of HBV persistence [1,2,7]. All these reasons lead to a gradual increase in the incidence of HIV/HBV co-infected patients.

Another reason may be related to hepatitis B vaccine which is an excellent intervention for preventing HBV infection [1,2,11]. At present, the hepatitis B vaccine vaccination rates in children under 5 years old remains above 90% in China, however, this rates in adults was fewer than 10% [11-14]. The rate of effective vaccination against HBV was only 7.7% in HIV-infected patients in west China [15]. In addition, HBV vaccine response rates is only 20 to 70% in HIV infected adults [16]. So vaccination of HBV vaccine in HIV high-risk population may help to reduce the incidence of HIV/HBV co-infection.

Among HIV patients receiving ART treatment, HBV status shows no effect on virological failure (OR=0.93, 95% CI 0.80-1.10) and CD4 counts (OR=0.93, 95% CI 0.82-1.05) [4,17-20]. At present, more and more attention is being paid to mortality and hepatotoxicity in ART treatment for HIV/HBV co-infected patients. It is estimated that approximately 10-15% of mortalities in HIV patients globally are due to liver diseases, and about 25% of the liver deaths could be attributed to an HBV infection [1,21,22]. While the majority of those infected with HBV will naturally clear the infection, the risk of chronic HBV infection is estimated three- to six-fold higher in HIV patients than in those who are not infected with HIV [23-25]. ART induced liver toxicity is an additional concern in such patients. The incidence of hepatotoxicity in HIV patients taking ART is approximately 4.5-11% [18,26,27]. Incidence of hepatic fibrosis (14.2%)

and cirrhosis (9.2%) is more likely to occur in HIV/HBV co-infection patients [28-31] and the liver-related mortality in these patients was 8 times higher than that in HIV mono-infection patients [2,32]. Besides, HIV/HBV coinfection is a risk factor for in-hospital mortality [33], which also heightened overall mortality rates (Incidence Rate Ratio: 1.24) [34-37].

CD4 T-cell counts prior to ART initiation, compliance to HIV therapy, economic level, regional differences and other related factors, can affect the therapeutic effect of HIV or HIV/HBV patients [7,28,38-40]. Especially in China, the economic level, health resource allocation, urban and rural factors among regions were greatly differentiated [15,41]. For example, the co-infection rate of HIV/HBV in west China was 14.4%, and it is 47% among men who have sex with men (MSM) population in some areas of China [7,15,42,43]. While the impact of ART on clinical outcomes in HIV/HBV infected patients has been studied, little is known about its comparative performance or efficacy in conventional clinical settings in China [7]. By the end of Sep. 2018, the total mortality rate of the 19,567 HIV patients who had received ART treatment in Beijing was 0.92% (180 cases), the total lost to follow-up (LTFU) rate was 1.6% (304 cases), and about 4.3% of all HIV patients are co-infected with HBV. The present study assessed the effect of HBV co-infection on HIV clinical progression, virological and immunological responses in HIV patients receiving combination ART in Beijing, China. The results will reflect the therapeutic results of HIV/HBV patients in good ART environment, thus improving the willingness of this population to receive treatment.

Methods

Study population

Data was retrospectively collected from the Beijing Center for Diseases Prevention and Control (Beijing CDC). Since 2010, Beijing CDC database has recorded the comprehensive and reliable information of HIV patients, and all HIV/HBV patients started ART therapy from 2010. This study examined clinical characteristics and examination indicators for HIV mono-infected individuals or HIV/HBV co-infected patients after ART from Jan. 2010 to Sep. 2018. Patients with inconsistent or critical missing data were excluded.

In our study, 19,567 HIV patients received ART treatment in Beijing, of whom 81% (15877 cases) were MSM. The numbers of HIV patients that were excluded: 1) HIV patients begin ART treatment before 2010 (757 cases); 2) age<18 year (221 cases); 3) ART treatment time is less than 6 months or the treatment time is uncertain (2751 cases); 4) HIV patients without HBV or HCV testing (433 cases); 5) HIV/HCV or HIV/HBV/HCV co-infected patients (315 cases). Chronic hepatitis B was defined as hepatitis B surface antigen seropositive on at least one occasion within the past 6 months [see Additional file 1].

HIV case report databases routinely record patients baseline and follow-up data including age, gender, marital status, route of HIV infection, opportunistic infections (OIs), ART regimen, CD4 count (Free testing twice a year), viral load (Free testing once a year), aspartate transaminase (AST), alanine aminotransferase (ALT), glucose (Glu), creatinine (Cr), triglyceride (TG), total cholesterol (TC), platelet (Plt), and among other related variables.

Aspartate aminotransferase-to-Platelet Ratio Index (APRI) was categorized using validated cutoffs [28] : significant fibrosis (APRI≥0.5) and no significant fibrosis (APRI<0.5).ART adherence was reflected by the question of "Number of missed dose in recent 7 days", missed dose≥1 time (during follow-up, the HIV patient had at least one missed dose).

Follow-up

This study evaluated data from HIV patients and HIV/HBV co-infected patients between Jan. 1st 2010 and Sep. 30th 2018. As per national guidelines at the time (Change of HARRT eligibility criteria in China: 2004-2007, CD4 count< 200cells/μL; 2008-2011, CD4 count≤350 cells/μL; 2012-2015, CD4 count< 500cells/μL; 2016-Now, immediate treatment), ART eligible individuals have three adherence counselling visits and a medical examination (include weight, height, vital signs, medication history, routine urine, blood tests, tests of the liver and kidney, CD4, VL, *etc.*) prior to treatment initiation. Following ART initiation, patients were received in the clinic at 2, 4, 8, and 12-week as well as 3-month intervals, or more frequently in the case of pressing medical needs. In this study, we collected baseline data and follow-up variables for patients (the end of follow-up was Sep. 30th 2018).

Statistical analysis

Mean ± SD or median and interquartile ranges (Q) were used to describe numerical values, and percentage (%) was employed to describe count data. Differences in baseline indicators among the two groups were examined using the Mann-Whitney *U* test for non-parametrically distributed variables, and *t* test for normally distributed variables. Categorial variables compared via the χ^2 test. Analysis of covariance (ANCOVA) for repeated measures was used to analyze the changes of biochemical indicators in HIV/HBV co-infected patients. Multiple logistic regressions (variable selection implemented via stepwise approach) was used to analyze the influencing factors of the abnormal incidence of clinical indicators and Cox model was used to analyze the influencing factors of LTFU and death in HIV patients. Statistical analyses were conducted with SAS 9.4 software.

Results

A total of 2,841 HIV patients were included in our study: 2,000 patients were HIV mono-infected individuals and 841 patients were co-infected with HIV and HBV [see Additional file 1] . Demographic and baseline clinical characteristics of the sample are presented in Table 1. Median time interval (from diagnosis to anti-retro viral treatment), ALT and AST for HIV/HBV co-infected patients were statistically higher than those of HIV mono-infected patients. Baseline CD4 count, CD4/CD8 ratio, platelet and hemoglobin for HIV/HBV co-infected patients were statistically lower than those of of HIV mono-infected patients.

As shown in Table 1, the incidence of OIs (9.3% *vs* 4.5%) and APRI≥0.5 (7.9% *vs* 1.8%) in HIV/HBV co-infected patients was higher than that in HIV mono-infected patients (*P<0.05,*Table 1).

Table 1 Baseline characteristics of individuals included in the analysis

Variables	HIV mono-infected (n=2000)	HIV/HBV co-infected (n=841)	*P* value
Age(years)	33.0 ± 10.7	33.6 ± 9.6	0.143
BMI(kg/m^2)	22.1 ± 3.1	22.0 ± 3.2	0.728
HIV diagnosis to ART initiation interval (months)	1.1 (0.5-4.8)	1.4 (0.6-4.7)	0.011
CD4 count (cells/μL)	302.0 (188.0-427.5)	261.0 (143.6-378.0)	<0.001
CD4/CD8 ratio	0.29 (0.18-0.43)	0.26 (0.15-0.40)	0.001
Log_{10}VL	4.4 ± 0.9	4.4 ± 0.8	0.665
ALT (U/L)	21.7 (15.6-34.3)	29.3 (20.9-45.4)	<0.001
AST (U/L)	22.4 (18.8-28.0)	27.3 (22.0-37.1)	<0.001
GLU (mmol/L)	5.4 ± 1.1	5.3 ± 1.2	0.395
TG (mmol/L)	1.2 (0.8-1.7)	1.1 (0.8-1.6)	0.336
TC (mmol/L)	4.0 ± 0.9	4.0 ± 0.9	0.305
Cr (μmol/L)	71.7 ± 13.0	71.8 ± 17.7	0.831
Platelet (×10^9/L)	208.3 ± 58.8	185.4 ± 59.3	<0.001
Hemoglobin (g/L)	147.2 ± 18.1	145.0 ± 20.7	0.009
APRI≥0.5 (%)	34 (1.8)	62 (7.9)	<0.001
Gender			
Male	1924 (96.2)	804 (95.6)	0.455
Female	76 (3.8)	37 (4.4)	
Marital status			
Single	1408 (70.4)	555 (66.0)	0.948
Married or lives with partner	465 (23.3)	244 (29.0)	
Others	167 (6.3)	42 (5.0)	
Route of HIV infection			
MSM	1688 (84.4)	657 (78.1)	<0.001
Hetero-sexual	180 (9.0)	108 (12.8)	
Others or unknown	132 (6.6)	76 (9.0)	
WHO stage when eligible for treatment			
Stage 1	1539 (77.0)	563 (66.9)	<0.001
Stage 2	239 (12.0)	122 (14.5)	
Stage 3/4	222 (11.0)	156 (18.6)	
Opportunistic infections	90 (4.5)	78 (9.3)	<0.001
Missed dose ≥1 time	58 (6.9)	135 (6.8)	0.871
ART regimen			
TDF	1528 (76.4)	744 (88.5)	<0.001
Second-line ART(LPV/r)	77 (3.9)	45 (5.4)	
Others	395 (19.8)	52 (6.2)	
Year to enter ART treatment			
2010	19 (2.2)	24 (1.2)	<0.001
2011	62 (7.4)	77 (3.9)	
2012	73 (8.7)	129 (6.5)	
2013	115 (13.7)	174 (8.7)	

2014	98 (11.7)	222 (11.1)
2015	152 (18.1)	324 (16.2)
2016	132 (15.7)	392 (19.6)
2017	126 (15.0)	407 (20.4)
2018	64 (7.6)	251 (12.6)

The mean follow-up time for all patients was 34.5 months (SD: 24.2 months) per person in our study. The trajectory of key biochemical indicators plotted alongside ART treatment time is shown in Figure 1. The effect of baseline data on indicator changes during ART was adjusted by covariance analysis for repeated measures. Although, CD4 count levels were still statistically different between HIV mono-infected and HIV/HBV co-infected patients after 42 months of ART treatment (P<0.05), no statistical difference was found between the two groups in the ART treatment effect after adjusting the influence of the baseline CD4 count (P=0.3226, Figure 1A); In the course of treatment, the TG and TC means in HIV/HBV co-infected patients were lower than that in HIV mono-infected patients (P_g<0.05, Figure 1F-G). Besides, with the increase of ART treatment time, ALT in HIV/HBV patients was different from that in HIV patients at 3 months. And 3 months later, ALT gradually decreased and there was no difference with HIV mono-infected patients (P_{g*t}<0.001, Figure 1D). As for other indicators, AST, GLU, Cr, CD4/CD8 ratio, platelet and hemoglobin, the interaction between group and time effects was not significant (P>0.05).

Of the 841 HIV/HBV co-infected patients treated (present mean duration for 34.5 months), 6.1% (45 cases) did not achieved CD4≥200 cells/μL (as of 30 Sep.2018, the data of patients' last clinical examination results) and 1.8% (13 cases) did not achieved VL≤400 copies/mL，which had no significant difference with HIV mono-infected patients (P=0.7858，0.3102). The rate of AST abnormalities (20.9% *vs* 14.4%) and APRI≥0.5 (4.4% *vs* 1.0%) in HIV/HBV co-infected patients was higher than that in HIV patients (P<0.05). After ART treatment, there was no difference in the rate of ALT>40 U/L, TC>5.69 mmol/L, CD4/CD8 ratio <0.30, OIs, death and LTFU among the HIV/HBV co-infected and HIV mono-infected patients (P>0.05, Table 2).

We further analyzed the influencing factors of adverse events in HIV patients. Initial CD4 count (OR=0.443), duration of ART (OR=0.456), initial OIs status (Or=4.240) and WHO stage (OR=1.485) were shown to be significantly associated with CD4<200 cells/μL (Final follow-up results of patients up to Sep. 2018) in HIV patients (P<0.05). Initial CD4 count (OR=0.568), initial CD4/CD8 ratio (OR=0.149), duration of ART (OR=0.466), and patients undergoing second-line ART (OR=1.952) were shown to be significantly associated with CD4/CD8 ratio<0.30 in HIV patients (P<0.05). Initial CD4 count (OR=0.743) were shown to be significantly associated with VL>400 copies/mL in HIV patients (P<0.05). Besides, HBV coinfection was no associated with CD4<200 cells/μL, CD4/CD8 ratio<0.30 and VL>400 copies/mL in HIV patients (p>0.05, Table 2).

Initial APRI≥0.5 (OR=11.425) and HBV co-infection (OR=2.745) were shown to be significantly associated with APRI≥0.5 in HIV patients (P<0.05, Table 2).

Table 2 Rate of adverse events and the risk factors for those in HIV patients

Rate of adverse events	Group	CD4<200 (cells/μL)	VL>400 (copies/mL)	ALT>40 (U/L)	AST>50 (U/L)	APRI≥0.5	TC>5.69 (mmol/L)
	HIV	108/1679 (6.4)	21/1636 (1.3)	583/1026 (56.8)	134/932 (14.4)	7/671 (1.0)	179/1678 (10.7)
	HIV/HBV	45/733 (6.1)	13/711 (1.8)	294/488 (60.2)	98/469 (20.9)	15/341 (4.4)	59/733 (8.1)
	P value	0.7858	0.3102	0.2073	0.002	0.001	0.0893
	Group	CD4/CD8 ratio <0.30	OIs	Death	LTFU	Discontinued treatment	--
	HIV	192/1674 (11.5)	37 (1.9)	6 (0.3)	14 (0.7)	29 (1.5)	--
	HIV/HBV	88/733 (12.0)	25 (3.0)	4 (0.5)	12 (1.4)	20 (2.4)	--
	P value	0.706	0.068	0.495	0.082	0.113	--

Risk factors of adverse events	CD4<200 (cells/μL)			CD4/CD8 ratio <0.30		
	Variables	OR (95% CI)	*P*	Variables	OR (95% CI)	*P*
	Initial CD4	0.443 (0.368,0.533)	<0.001	Initial CD4	0.568 (0.514,0626)	<0.001
	Duration of ART	0.456 (0.301,0.691)	0.0002	Initial CD4/CD8 ratio	0.149 (0.060,0.370)	<0.001
	Initial OIs	4.240 (1.519,11.831)	0.0426	Duration of ART	0.466 (0.392,0.555)	<0.001
	WHO stage	1.485 (1.162,1.897)	0.0016	Second-line ART	1.952 (1.015,3.754)	0.0451
	HBV co-infection	1.051 (0.734,1.505)	0.7858	HBV co-infection	1.053 (0.805,1.378)	0.7059
	VL>400 (copies/mL)			APRI≥0.50		
	Initial CD4	0.743 (0.637,0.865)	0.0006	Initial APRI≥0.5	11.425 (4.260,30643)	<0.001
	HBV co-infection	1.432 (0.713,2.877)	0.3126	HBV co-infection	2.745 (1.041,7.243)	0.0413

Initial CD4, every 50 cells/μL increase in the CD4 count; Duration of ART, every 1-year-increase; Initial OIs, OIs have emerged in HIV patients at the beginning of ART treatment; Classification of initial CD4/CD8 ratio,<0.3,0.3-0.5,0.5-1.0 and >1.0.

Approximately 1.9% of HIV/HBV patients and 1.0% of HIV patients were under LTFU or death during the course of their ART. Cox regression analysis showed that initial CD4 (HR=0.784, 95% CI 0.652-0.943), APRI≥0.5 (HR=4.647, 95% CI 1.331-16.227), OIs (HR=4.910, 95% CI 2.352-10.247) and age (HR=1.336, 95% CI 1.004-1.778) predicted for LTFU or death in HIV patients. Besides, HBV coinfection was no associated with increased LTFU or death (p>0.05, Table 4).

Table 3 Predictors of LTFU or death among HIV patients in the cox model

LTFU or Death		
Variables	HR (95% CI)	*P value*
Initial CD4*	**0.784 (0.652,0.943)**	**0.0098**
Initial VL	1.011 (0.790,1.294)	0.9298
Initial CD4/CD8 ratio	0.254 (0.030,2.164)	0.2540
Initial APRI ≥0.5*	**4.647 (1.331,16.227)**	**0.0160**
Initial OIs*	**4.910 (2.352,10.247)**	**<0.001**
Duration of ART	0.254 (0.030,2.164)	0.2540
HIV diagnosis to ART initiation interval	1.009 (0.811,1.256)	0.3350
Age*	**1.336 (1.004,1.778)**	**0.0469**
Gender	2.226 (0.683,7.257)	0.1844
BMI	0.732 (0.449,1.194)	0.2155
WHO stage	1.279 (0.778,2.104)	0.3323
Marital status		
Single	1.000	--
Married or lives with partner	1.637 (0.829,3.232)	0.1556
Others	1.423 (0.437,4.642)	0.5582
Route of HIV infection		
MSM	1.000	--
Hetero-sexual	1.418 (0.551,3.648)	0.4693
Others or unknown	1.967 (0.764,5.065)	0.1610
ART regimen		
TDF	1.000	--
Second-line ART(LPV/r)	1.781 (0.871,3.644)	0.1139
Others	0.702 (0.096,5.118)	0.7266
HBV co-infection	1.735 (0.898,3.352)	0.1012

Age, every 10-year-increase; * refers to p value significant ($p < 0.05$).

Discussion

In our study, 841 HIV/HBV co-infected patients (the prevalence rate was 4.3% among HIV-infected patients receiving ART) received ART for an average of 34.5 months, about 93.2% of them took drugs on time and the LTFU rate was 1.2%. The mortality rate of HIV/HBV co-infected patients was 0.5%, which was significantly lower than that of other studies (19.0%) [4,21,28]. We observed that HIV diagnosis to ART initiation interval, the initial incidence of OIs (9.3%) and baseline clinical characteristics ALT, AST for HIV/HBV co-infected patients were higher than those of HIV mono-infected patients. Moreover, baseline CD4 count, CD4/CD8 ratio, platelet and hemoglobin were lower in these patients. And, HBV coinfection affects the incidence of APRI≥0.5, but does not affect the incidence of CD4<200 cells/μL, CD4/CD8 ratio<0.30 and VL>400 copies/mL in HIV patients after the ART (Table 2).

After adjusting the effect of baseline CD4 count on indicator changes during ART, we found that CD4 count was still lower in HIV/HBV co-infected patients after ART treatment, but this difference was mainly affected by baseline CD4 count (Figure 1A) and the prevalence of CD4<200 cells/μL was also not higher than that in HIV mono-infected patients (Table 2), which further illustrated HBV co-infection does not affect the therapeutic effect of CD4 in HIV patients [1,4]. Further investigation demonstrated initial low CD4 count, duration of ART, initial OIs and WHO stage increased the prevalence of CD4<200 cells/μL in HIV patients. Besides, initial CD4 count affects the incidence of VL>400 copies/mL and LTFU or death (HR=0.784) in HIV patients (Table 2,3). Therefore, in order to better improve the ART effect of HIV/HBV patients, we should pay attention to the impact of these baseline CD4 [44,45].

The CD4/CD8 ratio could be used by clinicians to identity patients at risk of non-AIDS-related events and higher ratio may reflect a more " normal " immune phenotype conferring enhanced prognosis and predict posttreatment control

[46-49]. In this study, although the baseline CD4/CD8 ratio in HIV/HBV patients was lower than that in HIV mono-infected patients, there was not significant difference between the two groups patients after ART treatment. Also we found initial low CD4 count, initial low CD4/CD8 ratio, shorter duration of ART and second-line ART increased the prevalence of CD4/CD8 ratio <0.30 in HIV/HBV patients. Evidence have shown that initial CD4 count can affect the ratio in HIV patients [46,49-51]. Besides, 12% of HIV/HBV patients still receive CD4/CD8 ratio <0.30 after 34.5 months of ART.

Many studies have indicated that HIV/HBV coinfection may play a direct role in HCC, cirrhosis or liver fibrogenesis [1,32,52,53], and no clear reduction in end-stage liver disease (ESLD) risk was observed over 15 years in HIV patients, even after ART treatment [54]. We can see that baseline ALT, AST and the rate of APRI≥0.5 were higher in HIV/HBV co-infected patients (Table1). During ART treatment, the ALT of HIV/HBV patients increased significantly between 0 and 3 months. And 3 months later, ALT gradually decreased and there was no difference with HIV mono-infected patients (Figure 1B). Besides, the rate of APRI≥0.5 in HIV/HBV co-infected patients was also higher, which mainly affected by initial APRI and HBV co-infection [55].In our study we also found that initital APRI≥0.5 (HR=4.6471, 95% CI 1.331-16.227) predicted for LTFU or death in HIV patients. Some studies have shown that higher AST appear to be important mortality risk factors in HIV/HCV-coinfection [56], both AST ,ALT and APRI to predict liverrelated mortality, either alone or as components of indices of liver fibrosis [28,53,56-58]. Besides, several studies have shown a significant correlation between APRI scores and HIV viremia levels [28,59,60]. Therefore, the changes of AST,ALT and APRI in HIV/HBV patients after ART treatment need to be noticed, early detection of possible liver injury in patients and adjustment of ART regimens.

Currently, we can observe an increasing number of studies focused on the non-AIDS complications in HIV patients [61-62], analyzing changes in biochemical indicators (e.g., cholesterol) in patients undergoing ART treatment [64,65].We found that in the course of ART treatment, the TG and TC means in HIV/HBV co-infected patients were lower than that in HIV mono-infected patients (Figure 1F-G),but the ratio of TC>5.69 mmol/L was no difference between them. HIV patients with ART are at increasing cardiovascular disease (CVD) risk and stroke, thus, the possibility to classify patients for lipid lowering treatment may be a useful tool for clinical management[66-69].But other studies showed that HIV patients with high serum total cholesterol have lower HIV RNA load and better CD4 T cell [65,70]. Therefore, there is need for prospective cohort or case control studies to determine the relationship between total cholesterol and ART outcomes in HIV patients.

Death and LTFU are the additional concerns in HIV patients [1,2,56,71,72]. With 34.5-month ART treatment, the overall mortality and loss to follow-up rate of HIV(0.3% and 0.5%) or HIV/HBV (0.7% and 1.4%) patients were lower in this study. And other studies show that LTFU at 6 and 12months compared with 9.3% and 14.4%[73-75]. The main reason may be the higher ART adherence (93%) of the HIV patients in our study. In addition to the two factors (CD4 and APRI≥0.45) mentioned above, we also found that intital OIs (HR=4.910) and age (HR=1.336) predicted for LTFU or death in HIV patients. In other studies, the overall prevalence of OIs among HIV/AIDS patients on ART was 32.5-48% [76,77], OIs that emerge very early after ART also confer an increased risk of early mortality [78].Besides, the impact of age on HIV patients has always been a topic.An exaplanation for this trend may be that older patients have poorer immunological responses than their younger counterparts [79]. Furthermore, successful ART has led to a growing number of older HIV-1-infected individuals who face both age-related and HIV-1-related inflammation, which may synergistically promote physical decline [80,81].We also found that HBV co-infection had no effect on HIV patients' loss of follow-up or death [4,32,56].

Limitations of this study were also considered. Indeed, due to individual differences, it is impossible to collect timely drug replacement information of patients, so we analyzed the ART treatment of HIV/HBV patients as a whole.

Additionally, laboratory examination of HIV patients could not guarantee that they would be checked during each follow-up. Finally, there are few data on mortality in HIV/HBV patients in this study. Further long-term study are needed about the ART effect of HIV/HBV disease progression.

In this cohort analysis of HIV/HBV co-infected patients on ART outcomes, we found that clinical indicators such as CD4 count, VL, CD4/CD8 ratio, AST, the prevalence of OIs and APRI≥0.5 were improved significantly over time on ART treatment. However, the abnormal rate of AST and APRI was higher in HIV/HBV patients, and CD4, TC and TG were lower than those in HIV patients. HBV co-infection affect the prevalence of APRI≥0.5, but it does not affect the abnormal incidence of other clinical indicators in HIV patients. Besides, initial CD4, APRI≥0.5 initial OIs status and age had related to LTFU or death among HIV patients rather than co-infection of HBV. Further long-term studies to examine the incidence of liver injury and death outcomes in HIV/HBV patients under good ART treatment are needed in prospective studies and in larger cohorts.

Declarations

Ethics approval and consent to participate

Individual confidentiality was protected as part of the management of individual information and the processing of personal data. The study protocol and consent procedure were approved by the Institutional Review Board for Human Subject Research Centre for Public Health at Tsinghua University (Project No.: 2018022607).

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available at Beijing Center for Diseases Prevention and Control (Beijing CDC) and may be obtained from the authors upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors take responsibility for the structure of this paper. PW, BG and JX conducted the literature review and data analysis. PW drafted the paper. All authors contributed to the study’s conception and design, interpretation of the data, and critical revisions to the paper. All authors have approved the final version for submission.

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Figures

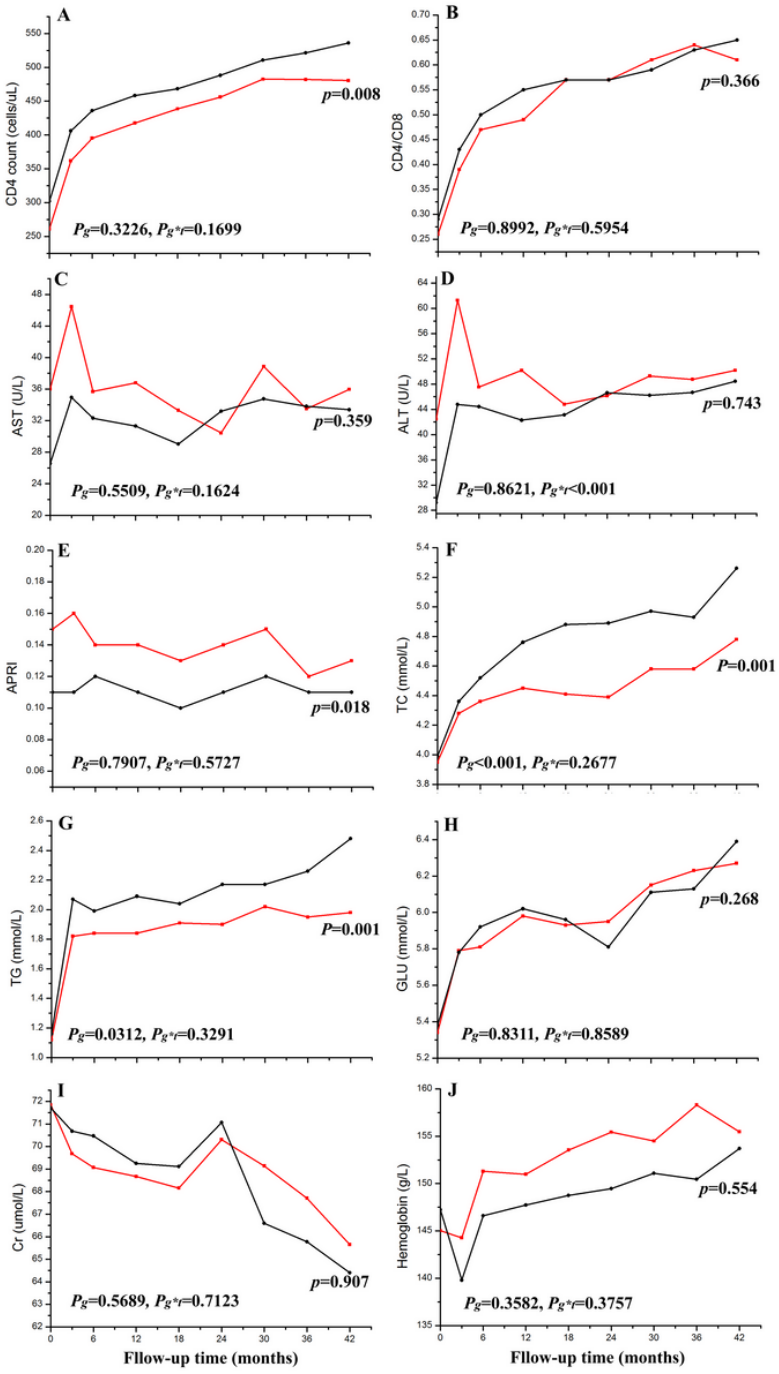

Figure 1

The tendency chart of main clinical indicators.Red line,HIV/HBV co-infected patients;black line,HIV mono-infected patients. pg, the rapeutic effect analysis of HIV and HIV/HBV patients after correction of baseline data; pg*t, the interaction between therapeutic effect and time effects; p, comparisons of two groups after 42 months of ART treatment.

Supplementary Files

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