



OPEN The sex differences in diseases progression and prognosis among persons with HIV and HBV coinfection

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To investigate sex differences in liver disease development and prognosis in individuals with HIV and HBV co-infection. This study comprised 752 HIV/HBV co-infected people who were diagnosed with HIV and started on combination antiretroviral therapy (cART) between January 31st, 2015 and January 31st, 2023. Their clinical data, including CD4⁺ T lymphocyte counts, HBV-DNA, and FIB-4 scores, were tracked once a year. The prognosis was determined during the long-term surveillance period. Risk factors related with the progression of liver diseases were included in both univariable and multivariable logistic regression. Then, sex differences in CD4⁺ T lymphocyte counts, HBV-DNA, FIB-4 scores, changes in liver fibrosis levels, and prognosis were investigated. Multivariable logistic regression analysis identified male as an independent risk factor for liver disease progression. Compared to the male group, the female group had a significantly greater decline of HBV DNA levels at years 1, 2, 3, 3–5, and > 5 post-cART. At each assessment point, the female group showed a significantly greater rise in CD4⁺ T lymphocyte counts than the male group based on their respective baseline values. Furthermore, females had greater CD4⁺ T lymphocyte counts and a lower prevalence of liver cirrhosis than males throughout the study period. Compared to female, higher incidence of end-stage-liver disease (1.190/100 person-years vs 0.714/100 person-years), higher all-cause mortality (0.440/100 person-years vs 0.148/100 person-years) and higher mortality associated with end-stage-liver diseases (0.273/100 person-years vs 0.074/100 person-years) were found in male. Among individuals with HIV and HBV coinfection, males had a worse therapeutic effect of HBV-active therapy and poorer prognosis than females.

Keywords Human immunodeficiency virus, Hepatitis B virus, End-stage-liver disease, Sex

Hepatitis B virus (HBV) and human immunodeficiency virus (HIV) infection are both major public health issues worldwide. Co-infections of HBV and HIV are common due to similar routes of transmission¹, which varied markedly from 5 to 30% in different regions of the world^{2–4}. Studies found that co-infection with HIV and HBV was associated with an increased risk of mortality and liver-related consequences⁵.

Chronic hepatitis B is a condition that affects men more than women⁶. Males are at least two to three times more likely to develop HCC than females⁷. Males had HCC at a younger age than females, and they had a higher proportion of early-stage tumors when diagnosis⁸. Furthermore, the clinical course and prognosis of HCC caused by HBV infection appear to be significantly worse in men than in women. Male HCC progresses more aggressively than female HCC, resulting in a worse prognosis and a mortality rate that is 2–3 times higher^{7,8}. The causes of sex disparities in HBV infection-related liver illness have already been reported. The inhomogeneous distribution between male and female had been explained by the varied prevalence of risk factors (e.g., alcoholism). Furthermore, because the liver is now recognized as a sexually dimorphic that is very vulnerable to interactions with estrogens and androgens⁹, sex hormones may play a substantial role. However, data on the role of sex in disease progression and outcome among individuals with HIV and HBV coinfection in resource-limited locations areas remains limited.

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The goal of this study was to determine whether sex differences were an independent predictor of liver disease progression in HIV/HBV co-infected individuals. Then, using long-term follow-up, we attempted to investigate sex differences in HBV replication, immunological reconstruction, liver fibrosis, and prognostic alterations.

Methods

Study design and population

This was a retrospective study conducted at Zhongnan Hospital of Wuhan University. All data were collected from patients at Zhongnan Hospital of Wuhan University. For at least 6 months, all of the participants had tested positive for anti-HIV and hepatitis B surface antigen (HBsAg). Patients with HAV, HCV or HEV infections were excluded. Other exclusion criteria were any complications from severe heart, lung, kidney, brain, or blood diseases, as well as other serious systemic diseases; severe neurological or psychological illness; and pregnancy or lactation. A consort chart was used to display the objects and data collected for this investigation (Fig. 1).

This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Zhongnan Hospital of Wuhan University. Informed consent was obtained from all participants.

Data collection

Demographic data (such as age, sex, marital and financial status, height and weight), medical history (such as history of chronic disease, family history of liver disease), alcohol consumption history, HIV related indexes (such as baseline CD4⁺ T lymphocyte counts, changes in CD4⁺ T lymphocyte counts, antiretroviral drugs), HBV related indexes (such as HBeAg status, levels of HBV DNA, ALT and platelet, imaging findings of the liver), and compliance were collected.

Laboratory testing

In a stable situation, HBV DNA and CD4⁺ T lymphocyte counts were measured every 6–12 months, whereas alanine aminotransferase (ALT), aspartate aminotransferase (AST), and platelets were measured every 3–6 months. If there is a medical requirement, the detection frequency of specific indications will be increased

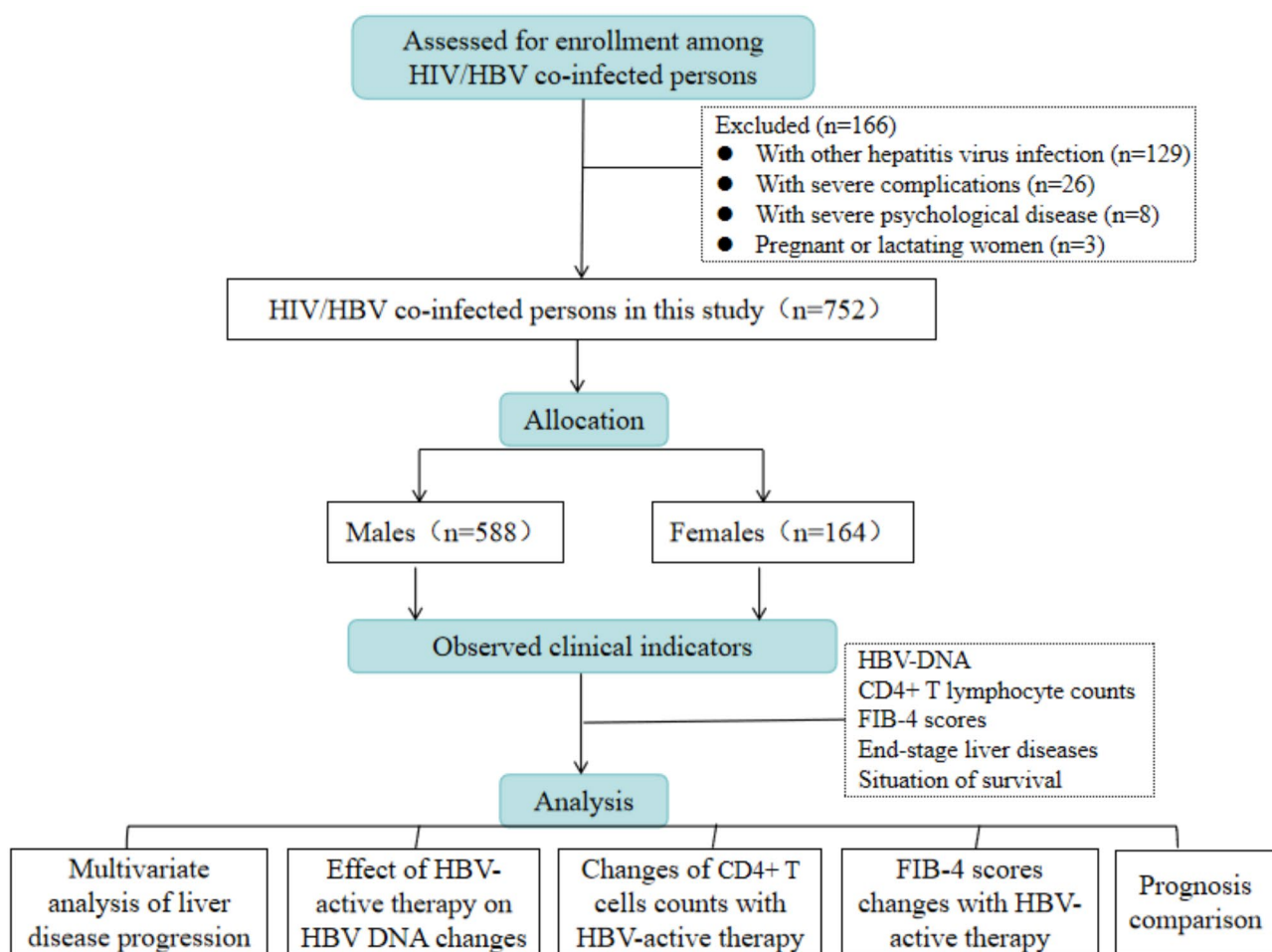


Fig. 1. A consort chart of this study.

accordingly. The average values of HBV DNA, CD4⁺ T lymphocyte counts and transaminase levels in the current year were taken for analysis.

HBV DNA quantification was performed by using PCR-Fluorescence detection kits for hepatitis B viral nucleotides (QIAGEN, Hilden, Germany), and the minimum detection limit was 20 IU/ml. Detectable HBV DNA was defined as ≥ 20 IU/mL.

CD4⁺ T lymphocyte counts (cells/ μ L) was measured by multiple-color flow cytometry with human monoclonal anti-CD3-fluorescein isothiocyanate (FITC), anti-CD4-phycoerythrin (PE) and anti-CD8-allophycocyanin (APC) antibodies (BD Multitest) according to the manufacturer's instructions. The cells were autoanalyzed on a BD FACS Canto II flow cytometry system (BD Biosciences).

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) were measured using Architect c8000 (Abbott Laboratories, USA), and platelet count were measured using the ABX Pentra XL80 (Horiba, Japan). Age was calculated based on date of birth.

Definitions

End-stage-liver diseases (ESLD) were liver cirrhosis, hepatocellular carcinoma and severe reactivation of apreeexisting chronic hepatitis B in this study. Reference standards for ESLD diagnosis were similar to those in Matthews' study¹⁰. Liver disease progression was defined as the emergence of an ESLD event in this study.

The following published serum models were used to assess liver fibrosis¹¹. FIB-4: Age (years) \times AST (U/L) / ALT (U/L)^{1/2} \times PLT $\times 10^9$. Refer to prior study¹², FIB-4 score > 3.25 was representative of advanced fibrosis or cirrhosis.

Causes of death were ascertained according to medical documents and death certificates. An ESLD-related death was defined as one that happened after ESLD hospitalization or was listed on a death certificate. Mortality associated with ESLD = Number of deaths due to ESLD in a given period \div Total observation person-years in the same period $\times 100\%$.

Statistical analysis

Categorical variables were described as frequency rates and percentages, and quantitative data were expressed as mean \pm SD. Comparisons between groups were analyzed by chi-square test or Fisher's exact test for categorical variables and by Student's *t*-test for quantitative variables.

All variables as potential predictors for the development of liver diseases were analyzed using univariable and stepwise multivariable logistic regression models. The conventional ART regimen includes three medications with anti-HIV activity, some of which also have anti-HBV activity, such as TDF, 3TC, and FTC. In the analysis of risk factors related with the progression of liver diseases, HBV-active therapy and antiretroviral medicines were chosen as two distinct variables to minimize the unpredictable effects of patients' pharmaceutical choices on liver disease outcomes. Variables with a *P*-value < 0.10 in univariable logistic regression models were considered for inclusion in the multivariable model. Each covariate was assigned an odds ratio (OR) and a 95% confidence interval (95% CI). A factor with an OR > 1 is a risk factor for liver disease development, while an OR < 1 indicates a protective factor. The 95% CI is an estimate of the population mean based on the mean of the specimen data.

Changes in HBV DNA levels, CD4 counts, and FIB-4 scores at various ART time points by sex were expressed as mean \pm SD. To control for other confounding factors, the generalized estimating equations (GEE) model was employed to evaluate longitudinal changes in the aforementioned outcomes. Based on the assumption that the *P*-value was statistically significant, OR > 1 showed that the observation measure increased at a treatment time point relative to the prior treatment time point. OR < 1 implies a decrease in the observed indication. The 95% CI is an estimate of the population mean based on the mean of the specimen data.

Kaplan–Meier analysis was used to estimate the incidence of end-stage liver diseases (ESLD), mortality of all-cause and ESLD-related death by sex. The log-rank test was used to assess the difference between the survival curves. All tests were two-sided and a *P*-value < 0.05 was taken as significant.

All the analysis were performed using SPSS Statistics version 27.0 software. GraphPad Prism Version 8 was used to analyze and generate figures from the clinical follow-up data.

Results

Characteristics of HBV/HIV co-infected individuals grouped by sex

A total of 752 HIV/HBV co-infected persons were enrolled in the study, with 588 (78.2%) males and 164 (21.8%) females. The median age was 42 (IQR: 35–58) years, the baseline CD4⁺ T lymphocyte counts was 140 (IQR, 35–367) cells/ mm^3 , 18.8% (141/752) were HBeAg positive, the proportion of detectable HBV DNA was 61.2% (460/752). The median follow-up time was 4(2–6) years in this study. Of all participants, 86.8% (653/752) were on combination antiretroviral therapy (cART) during the follow-up time, 86.2% (648/752) had complete suppression of HIV RNA, 84.4% (635/752) had suppressed HBV DNA (< 20 IU/mL), 40.4% (304/752) had Lamivudine (3TC)-based ART regimen, 46.4% (349/752) had Tenofovir disoproxil fumarate (TDF)/3TC-based ART regimen.

As shown in Table 1, there was no significant difference in age, baseline CD4⁺ T lymphocyte counts, ART coverage, HBeAg positive rate, proportion of complete suppression of HIV RNA and HBV DNA, proportion of 3TC and TDF/3TC-based ART regimen, or median duration of ART between male and female groups, whereas males had a higher proportion of detectable HBV DNA at baseline (63.6% vs 52.4%).

Risk factors associated with the progression of liver diseases

Univariable logistic regression identified risk factors for liver disease progression, including age > 50 years at baseline, male gender, BMI > 24 kg/ m^2 , alcohol consumption, baseline CD4⁺ T lymphocyte counts < 200 cells/ μ L, detectable HBV DNA, baseline ALT more than twice the upper limit of normal values, hypoplatelet count

	Male (n = 588)	Female (n = 164)	Statistics	P
At baseline				
Median age (years, IQR)	43 (36–60)	41 (34–54)	0.658	0.410
Body mass index (Mean ± Standard Deviation, kg/m ² , IQR)	23.4 ± 5.2	20.3 ± 4.7	2.087	0.037
Alcohol consumption (n,%)	138 (23.5)	8 (4.9)	28.329	<0.001
Smoking (n,%)	247 (42.0)	2 (1.2)	96.321	<0.001
CD4 ⁺ T lymphocyte counts (/ul)	135 ± 38	142 ± 29	0.261	0.560
Detectable HBV-DNA (n,%)	374 (63.6)	86 (52.4)	6.732	0.009
HBeAg(+) (n,%)	117 (19.9)	24 (14.6)	2.332	0.127
A family history of HBV infection	477 (81.1)	140 (85.4)	1.568	0.211
At the end of follow-up				
ART coverage (n,%)	508 (86.4)	145 (88.4)	0.458	0.499
Complete suppression of HIV RNA(<20 Copies/mL) (n,%)	507 (86.2)	141 (86.0)	0.007	0.935
Complete suppression of HBV DNA(<20 IU/mL) (n,%)	495 (84.2)	140 (85.4)	0.136	0.712
3TC-containing therapy (n,%)	231 (39.3)	73 (44.5)	1.454	0.228
TDF/3TC-containing therapy (n,%)	277 (47.1)	72 (43.9)	0.530	0.467
EFV-containing therapy (n,%)	307 (52.2)	90 (54.9)	0.366	0.545
Kaletra-containing therapy (n,%)	225 (38.3)	59 (36.0)	0.286	0.593
NVP-containing therapy (n,%)	56 (9.5)	15 (9.2)	0.021	0.884
Mean duration of follow-up [Mean ± SD, years, IQR]	4.3 ± 1.1	4.3 ± 1.4	0.558	0.425
HIV acquisition mode				
Heterosexual people	257 (43.7)	107 (65.2)	23.815	<0.001
Men who have sex with men (MSM)	253 (43.0)	/	/	/
Contaminated blood recipients	22 (3.7)	30 (18.3)	42.183	<0.001
Former paid blood donors	25 (4.3)	24 (14.6)	22.693	<0.001
Injection drug users	31 (5.3)	3 (1.8)	3.521	0.061

Table 1. Characteristics of persons with HIV and HBV coinfection at baseline. Note: The symbol “/” means HIV acquisition mode as MSM, which was meaningless in the female group.

at baseline, virological rebound of HBV DNA, and poor compliance. In contrast, CD4⁺ T lymphocyte counts change ≥ 150 cells/ul within 3 months, undetectable HBV DNA levels at year 1 following HBV-active therapy, HBV-active therapy, 3TC-containing therapy, and TDF/3TC-containing therapy were protective factors for progression of liver disease (Table 2).

Multivariable logistic regression further identified male, BMI > 24 kg/m², baseline CD4⁺ T lymphocyte counts < 200 cells/ul, detectable HBV DNA at baseline as independent risk factors related to the progression of liver disease. Conversely, CD4⁺ T lymphocyte counts change ≥ 150 cells/ul within 3 months, TDF/3TC-containing therapy, and undetectable HBV DNA levels at year 1 post HBV-active therapy had a favorable effect against the progression of liver disease (Table 2).

Sex difference of the changes of HBV replication during cART

Table 3 shows how the GEE was used to compare the differences in detectable HBV DNA levels between the female and male groups at different study time periods. In comparison to the male group, the female group exhibited a considerably higher reduction throughout all evaluation time points, with a between-group difference in changes from baseline to T1 (at year 1) of 0.15 times (95% CI, 0.11 to 0.21; $P < 0.001$); to T2 (at year 2), 0.17 times (95% CI, 0.11 to 0.27; $P < 0.001$), to T3 (at year 3), 0.27 times (95% CI, 0.13 to 0.58; $P = 0.001$); to T4 (at year 3–5), 0.31 times (95% CI, 0.18 to 0.56; $P < 0.001$); and to T5 (at year > 5), 0.42 times (95% CI, 0.18 to 0.95; $P = 0.038$).

Sex difference of the changes of CD4⁺ T lymphocyte counts during cART

As indicated in Table 3, CD4⁺ T lymphocyte counts grew in both groups over time and showed significant differences. The female group demonstrated a considerably larger augmentation than the male group during the cART period, with a between-group difference in changes from baseline to T1 (OR 1.44; 95% CI 1.36 to 1.53, $P < 0.001$); to T2 (OR 1.56; 95% CI 1.45 to 1.68, $P < 0.001$); T3 (OR 1.63; 95% CI 1.50 to 1.78, $P < 0.001$); T4 (OR 1.75; 95% CI 1.61 to 1.89, $P < 0.001$); T5 (OR 2.00; 95% CI 1.84 to 2.18, $P < 0.001$).

Figure 2A and B show variations in CD4⁺ T lymphocyte counts over time in males and females, respectively. Then, in Fig. 2C, a male–female comparison was shown, revealing that the trend line of CD4⁺ T lymphocyte counts in female was higher than in male at all time points without crossover.

Sex difference of the changes of FIB-4 scores and liver fibrosis levels during cART

As demonstrated in Table 3, although FIB-4 scores decreased at all time points when compared to the baseline, there was no significant difference in the rate of decline between males and females. However, liver fibrosis was

Parameter variable	Univariable analysis		Multivariable analysis	
	Odds ratio (95% CI)	P	Odds ratio (95% CI)	P
Age > 50 years at baseline	2.158 (1.533–3.038)	0.032	2.693 (0.563–12.884)	0.215
Male	2.443 (1.077–2.680)	0.025	2.540 (1.102–3.001)	0.018
Singlehood	1.005 (0.701–1.552)	0.245	–	–
Economic income below the national average	0.824 (0.479–2.233)	0.588	–	–
BMI > 24 kg/m ²	3.131 (1.200–5.703)	0.012	2.405 (1.856–3.573)	0.020
Alcohol consumption	2.220 (1.204–4.093)	0.011	0.056 (0.007–2.860)	0.129
Smoking	1.872 (1.256–3.002)	0.040	2.110 (0.526–5.632)	0.420
Sexual transmission of HIV	3.002 (1.250–5.263)	0.017	1.024 (0.289–2.563)	0.508
Baseline CD4 ⁺ T lymphocyte counts < 200 cells/ul	2.247 (1.137–4.439)	0.020	6.503 (6.410–7.201)	0.013
HBeAg positive at baseline	0.914 (0.394–2.123)	0.835	–	–
Detectable HBV DNA at baseline	1.670 (1.352–2.020)	0.047	2.927 (1.644–5.198)	0.039
Baseline ALT more than twice the upper limit of normal values	8.431 (5.26–13.511)	0.001	2.020 (0.407–4.110)	0.355
Baseline bilirubin more than twice the upper limit of normal values	107.0 (0.230–25.631)	0.997	–	–
Hypoplatelet count at baseline	3.431 (1.260–13.517)	0.001	1.028 (0.466–3.763)	0.655
CD4 ⁺ T lymphocyte counts change ≥ 150 cells/ul within 3 months	0.152 (0.030–0.189)	0.001	0.042 (0.009–0.750)	0.036
Undetectable HBV DNA levels at year 1 post HBV-active therapy	0.533 (0.147–0.887)	0.002	0.647 (0.257–0.860)	0.044
Virological rebound of HBV DNA	5.480 (1.647–10.002)	0.011	61.85 (0.97–95.238)	0.402
HBV-active therapy	0.257 (0.012–0.552)	0.001	0.082 (0.019–7.744)	0.739
Antiretroviral drugs				
3TC-containing therapy	0.426 (0.228–0.795)	0.007	2.034 (0.018–9.427)	0.437
TDF/3TC-containing therapy	0.211 (0.008–0.622)	0.005	0.247 (0.102–0.844)	0.032
AZT-containing therapy	2.030 (0.635–4.800)	0.497	–	–
EFV-containing therapy	1.001 (0.435–3.412)	0.662	–	–
Kaletra-containing therapy	3.030 (0.451–8.112)	0.560	–	–
NVP-containing therapy	0.881 (0.471–7.220)	0.852	–	–
Poor compliance	5.082 (2.340–10.887)	0.034	21.85 (0.570–35.117)	0.863

Table 2. Risk factors associated with the progression of liver diseases. Note: HBV-active therapy, ART regimen containing anti-HBV drugs. The symbol “–” means that variables having a *P*-value of ≥ 0.10 in univariable logistic regression models were not included in the multivariable model.

detected in 42.8% of males and 33.3% of females who had not received cART. As illustrated in Fig. 3A and B, the difference was large. Among cART patients, the overall proportion of liver fibrosis fell to 22.1% and 12.2% in males and females, respectively, with a significant difference between the two groups, as shown in Fig. 3C and D. Males exhibited a higher proportion of liver fibrosis than females at years 1, 2, 3, 3–5, and > 5 after cART (Fig. 3E).

Sex difference of the prognosis of persons with HIV/HBV co-infection

The median follow-up time was 4(2–6) years in this study. The person-years of follow-up observation were 13,191 and 4064 in male and female, respectively. The number of ESLD events in males was 157, whereas females had 29. The incidence of ESLD was greater in males than in females (1.190/100 person-years vs 0.714/100 person-years). All-cause deaths were 58 and 6 in males and females, respectively, and ESLD caused 36 and 3 deaths. Males had greater mortality of all-cause and ESLD-related death than females (0.440/100 and 0.273/100 person-years vs 0.148/100 and 0.074/100 person-years). The result of survival analysis was shown in Fig. 4.

Discussion

Studies have shown that males have a higher incidence of AIDS than females in many countries^{13,14}. According to a study conducted in Zhejiang, China, newly infected males with HIV are 4.64 times more common than females, and males have a higher overall AIDS incidence¹⁵. In this HIV/HBV coinfection cohort during 4 years of median follow-up time, males were found to have a significantly less decline of HBV DNA levels, a significantly less rise in CD4⁺ T lymphocyte counts, more liver fibrosis, and higher all-cause and liver-related mortality than females. The sex difference of the diseases progression was significant.

It was discovered that 10% of HIV/HBV co-infected individuals had persistently detectable HBV DNA after a short follow-up period¹⁶, although persistent HBV was extremely rare after 5 years of cART¹⁷. Previous studies found that 3TC-resistance mutations occurred at an annual rate of 15–20% in HIV/HBV co-infected patients using cART^{18–21}. Due to limited resources, several patients in this study were given cART with only one anti-HBV activity. In this context, we can clearly see that HBV replication levels following therapy are significantly lowered in both male and female groups, while they are still not entirely controlled below the

	Male (n = 588)	Female (n = 164)	OR (95% CI)	P value
Decline in log(HBV DNA)				
Baseline	4.63 ± 1.54	4.64 ± 1.65	–	–
T1	2.28 ± 0.76	1.45 ± 0.48	0.15(0.11–0.21)	0.000
T2	2.04 ± 0.68	1.49 ± 0.51	0.17(0.11–0.27)	0.000
T3	1.91 ± 0.53	1.58 ± 0.64	0.27(0.13–0.58)	0.001
T4	1.94 ± 0.65	1.76 ± 0.59	0.31(0.18–0.56)	0.000
T5	1.80 ± 0.54	1.61 ± 0.63	0.42(0.18–0.95)	0.038
Evolution of CD4 ⁺ T lymphocyte counts				
Baseline	138 ± 52	149 ± 56	–	–
T1	179 ± 60	266 ± 89	1.44(1.36–1.53)	0.000
T2	223 ± 74	283 ± 94	1.56(1.45–1.68)	0.000
T3	252 ± 84	304 ± 101	1.63(1.50–1.78)	0.000
T4	292 ± 97	354 ± 118	1.75(1.61–1.89)	0.000
T5	396 ± 132	493 ± 164	2.00(1.84–2.18)	0.000
Changes of FIB-4 scores				
Baseline	4.32 ± 2.41	4.41 ± 0.81	–	–
T1	3.74 ± 2.67	2.67 ± 0.89	0.62(0.12–3.22)	0.571
T2	2.99 ± 1.94	2.94 ± 0.65	0.31(0.04–2.22)	0.242
T3	2.78 ± 2.09	2.09 ± 0.72	0.26(0.03–2.13)	0.209
T4	2.43 ± 1.27	2.27 ± 0.42	0.18(0.04–2.87)	0.233
T5	2.73 ± 2.24	2.24 ± 0.75	0.54(0.05–65.71)	0.762

Table 3. Study outcomes across study time points according to the generalized estimation equations. Note: T1: at year 1; T2: at year 2; T3: at year 3; T4: at year 3–5; T5: at year > 5. The “–” mark indicates that baseline amounts of variables are not compared to themselves.

detection threshold. The failure to reduce HBV replication may attribute to the disadvantage of 3TC as a single anti-HBV medication. Some studies have demonstrated that the baseline level of HBV-DNA should be taken into account when deciding on treatment options for patients with HIV/HBV co-infection^{22,23}. We anticipated that our study's reduced proportion of HBeAg-negative disease and HBV DNA levels < 20,000 IU/ml, relative to resource-rich settings^{24–27}, could explain treatment outcomes in this cohort. This study revealed that males had a slower reduction in HBV levels than females. The topic of whether males' reactions to anti-HBV medicines were delayed, or whether resistance to 3TC developed earlier due to other reasons such as compliance, merits more investigation.

Previous studies found that HIV might infect hepatocytes and activate hepatic stellate cells^{28,29}, potentially causing liver damage. Furthermore, CD4⁺ T cell concentration has been found to be negatively associated with liver fibrosis³⁰. A study indicated that immunodeficiency, defined as a CD4⁺ T cell count < 350/mm³, results in a higher overall fibrosis score and worse chances of fibrosis reversal when on cART³¹. Based on these findings, the CD4⁺ T cell count in males was lower than in females at various stages of cART in this study, resulting in a higher incidence of liver fibrosis and ESLDs, as well as liver-related mortality in males. The majority of studies found that males had a more advanced clinical stage and immunosuppression than females³², and gender can influence the proportion of patients treated late^{33,34}. In this study, the baseline CD4⁺ T cell count in males was substantially identical to that in females, contradicting the majority of previous studies. Nonetheless, males showed a smaller rise in CD4⁺ T cell count in this study, showing that they were less efficient than females in immunological reconstitution following cART. Some studies found that antiviral efficacy and safety differed between males and females^{35–38}. In a prospective research³⁷, males were four times more likely than females to attain a study endpoint, which was defined as the time from baseline to a 50% decline in CD4⁺ T lymphocyte counts, AIDS onset, or death. Furthermore, females appeared to do slightly better in terms of CD4⁺ T lymphocyte counts response than males on ZDV and ZDV/ddI treatment³⁷, which is consistent with our findings, despite the fact that the two studies used different cART regimens. As previously noted, sex inequalities in response to cART can be related to differences in absorption, blood flow, sex-specific cytochrome p450 isoenzymes, drug half-life, and pharmacokinetics differences caused by hormonal changes during the menstrual cycle^{39,40}. The effect of androgen/estrogen on cART medication absorption and metabolism is unknown at the moment and will be researched further. In the future, personalized treatment methods will incorporate sex-specific antiviral regimen recommendations.

Liver fibrosis is the normal progression of chronic liver disease into liver cirrhosis. The FIB-4 score was used as a non-invasive fibrosis marker in patients with HBV mono-infection and HIV/HBV co-infection. Males showed a higher rate of advanced liver fibrosis than females, both before and after cART. As seen in HBV-mono-infected patients, higher HBV DNA replication levels were associated with a higher overall fibrosis score^{41,42}. The finding was likewise confirmed in the HIV/HBV co-infected group. Furthermore, in HBV-mono-infected patients, a connection between body mass index (BMI) and liver fibrosis was established⁴³. The fact that males have a higher BMI than females may contribute to the higher prevalence of male liver fibrosis, which has yet to be

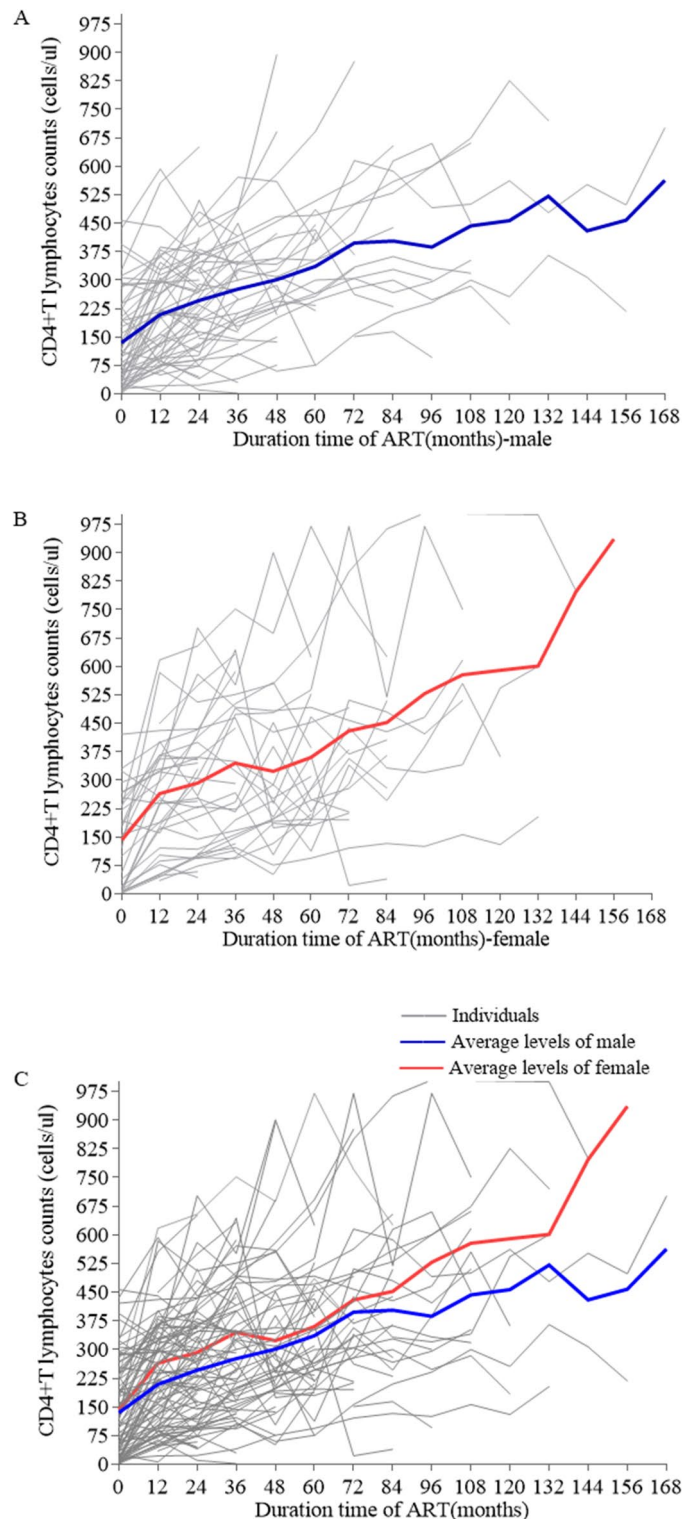


Fig. 2. Sex difference of the changes of CD4⁺ T lymphocyte counts during cART. (A) Changes in male CD4⁺ T lymphocyte counts during ART; (B) Changes in female CD4⁺ T lymphocyte counts during ART; (C) A trend test comparison of changes in male and female CD4⁺ T lymphocyte counts during ART.

shown in the context of HIV. Alcohol consumption, which is more common among males, is also a major factor to liver fibrosis. Although all HIV-infected patients are advised to avoid alcohol throughout cART, perfect compliance is rarely guaranteed. According to recent findings, HIV can stimulate hepatic stellate cells and may infect hepatocytes^{28,29}. Another study found that HIV infection was independently associated with an increased



Fig. 3. Sex difference of the changes of liver fibrosis levels during cART. **(A)** A comparison of liver fibrosis percentage in ART-naive male and female using Peason Chi-Square; **(B)** A comparison of liver fibrosis percentage in ART-treated male and female using Peason Chi-Square; **(C)** Distribution of different degrees of liver fibrosis in male and female during ART treatment using descriptive analysis.

marker of liver fibrosis³⁰. As a result, male participants in this study had reduced CD4 levels caused directly by HIV infection, which contributed to greater liver fibrosis.

Since the advent of cART, mortality rates for AIDS-related events have declined significantly, while there has been a discernible shift towards a higher proportion of fatalities due to non-AIDS-related illnesses, such as liver ailments, over time^{44–47}. People with chronic HBV and HIV infections are more likely to develop liver cirrhosis and hepatocellular carcinoma, resulting in higher mortality rates than those infected with just HIV or HBV^{48,49}. The complex relationship between HIV and hepatic viral infections is one of the major contributors to the increased cancer burden, as well as the morbidity and mortality of HIV patients, but the mechanisms underlying this interaction are still being investigated^{50,51}. People living with HIV have much higher liver-related death rates than the general population⁵². Males experienced worse outcomes than females in terms of ESLD-related morbidity and death, as well as all-cause mortality. The results were similar with those of a nationwide population-based study in Brazil⁵³. Males were more likely to have behavioral factors such as problematic drug use, heavy alcohol consumption and smoking, and obesity, which may explain the difference in disease prognosis between males and females. We considered that the more relevant and directly associated rationale was the greater incidence of liver fibrosis caused by delayed full suppression of HBV replication and slower CD4⁺ T cell count expansion after cART in males compared to females, as discussed earlier in this study.

In conclusion, given the findings of this study on the course and prognosis of liver disease in HIV/HBV coinfecting males during ART period compared to females, we hold the opinion that in medical resources limited

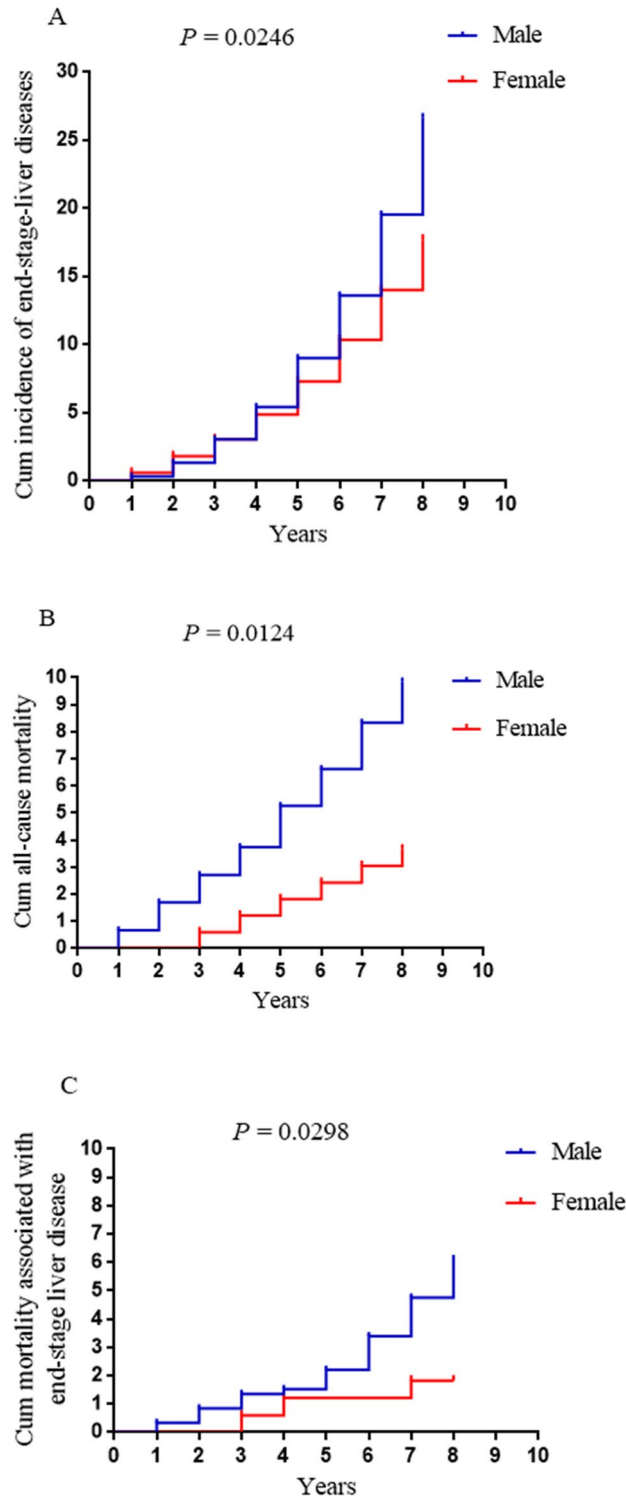


Fig. 4. Sex difference in the prognosis of persons with HIV/HBV co-infection. (A) Comparison of the incidence of end-stage liver disease in male and female using Kaplan–Meier analysis; (B) Comparison of all-cause mortality in male and female using Kaplan–Meier analysis; (C) Comparison of mortality associated with end-stage liver disease in male and female using Kaplan–Meier analysis.

areas, personalized treatment options for HIV/HBV coinfecting males should be considered. For male HIV/HBV co-infected individuals, drugs with strong anti-HBV and HIV properties should be considered as the optimal option for the initial treatment strategy, and non-invasive liver fibrosis evaluation indexes such as the FIB-4 score should be used to appropriately increase the frequency of liver disease monitoring. It can be viewed as a

technique for lowering the incidence and fatality rates of end-stage liver disease in HIV/HBV co-infected males. Especially for patients whose HBV DNA is still not controlled below the detection limit after one year of ART treatment and/or CD4⁺ T lymphocyte counts have increased by less than 150 cells/ul, the ART combination regimen with stronger anti-HBV and anti-HIV effects should be adjusted as soon as possible.

This study provides some valuable clinical insights, particularly in the rarely addressed sex differences in HIV and HBV coinfection population. More than half of the individuals in this study were born during a period when there was no active hepatitis B active immunization, and more than 80% of the subjects had a clear family history of hepatitis B infection, indicating that the majority of the subjects contracted HBV as children. One of the study's highlights is that the duration of HBV infection was long enough to see the differential influence of sex on the prognosis of liver disease. Another strength is the comparison of males and females in terms of the dynamic evolution of HBV DNA, CD4⁺ T lymphocyte levels, and FIB-4 scores throughout cART durations. However, we acknowledge that our study has certain limitations. First, because this was a retrospective cohort study, we were unable to provide complete data for all participants during the monitoring period, which reduced the continuity of a few data points to some extent. Second, due to the low acceptability of liver biopsy and the economic burden, the FIB-4 index was used to assess liver fibrosis in this study, which may not adequately reflect the liver's pathological condition. Finally, despite the small sample size, this study did not include the objective presence of occult hepatitis B infections that tested negative for HBsAg but positive for HBV DNA.

Conclusions

In conclusion, we found illness progression and prognosis in HIV/HBV co-infected persons during the course of the study, with a clear sex difference. Males experienced a smaller reduction in HBV DNA levels, a narrower growth range for CD4⁺ T lymphocyte counts, and a higher incidence of liver cirrhosis. Furthermore, males had a worse prognosis than females in terms of morbidity and mortality from ESLD, as well as overall mortality.

Data availability

Data is provided within the manuscript.

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Author contributions

R.Y. contributed to the data analysis and implementation of study. R.Y. wrote the original manuscript. Q.C. and F.J. contributed to the data collection and data interpretation. X.Y. and Y.X. contributed to the conception and study design. X.Y. and Y.X. contributed to the review and revision. AI-assisted copyediting was not used.

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Declarations

Competing interests

The authors declare no competing interests.

Ethical approval and consent to participate

This study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Zhongnan Hospital of Wuhan University. Informed consent was obtained from all participants.

Additional information

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