Combination Antiretroviral Therapy is Associated with Reduction in Liver Fibrosis Scores in Patients with HIV and HBV Co-Infection

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Research

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Abstract

Objective To evaluate the risk factors for liver fibrosis in HIV/HBV co-infection population, and further to clarify whether ART reverses fibrogenic effect of HIV infection.

Methods This was an observational retrospective study. Multivariate Cox regression was used to assess predictors of liver fibrosis in HIV/HBV co-infection patients. FIB-4 scores before and after cART were compared using Wilcoxon test for paired samples.

Results In this study enrolled 458 cases of HIV/HBV co-infection patients, we found ART (HR 0.016, 95% CI: 0.009-0.136; $P < 0.001$) were one of protection factors to against liver fibrosis. Forty cases of those who had normal levels of ALT, AST and PLT during the whole course of diseases were stratified into $\text{FIB-4} < 1.45$ ($n=14$), $1.45 \leq \text{FIB-4} \leq 3.25$ ($n=19$) and $\text{FIB-4} > 3.25$ ($n=7$) groups by their FIB-4 scores before ART. After ART, in $1.45 \leq \text{FIB-4} \leq 3.25$ group, FIB-4 grade in 57.9%(11/19) of the patients dropped to a lower FIB-4 grade ($\text{FIB-4} < 1.45$); in $\text{FIB-4} > 3.25$ group, 85.7%(6/7) of the patients dropped to $1.45 \leq \text{FIB-4} \leq 3.25$ grade, while 14.3%(1/7) dropped to $\text{FIB-4} < 1.45$ grade. In ART-naive group, 1 year, 2-5 years and 5-10 years after ART groups, FIB-4 scores were 4.29 ± 0.43 , 3.63 ± 0.38 , 2.90 ± 0.36 and 2.52 ± 0.38 , respectively ($P=0.034$); and the incidence of liver fibrosis were 7.38%(104/141), 63.6%(98/154), 60.8%(62/102) and 47.5%(29/61), respectively ($P=0.004$).

Conclusion ART was associated with improvement of FIB-4 scores and the benefit of ART in reversing liver fibrosis can sustain for a decade in patients with HIV/HBV co-infection.

Introduction

In human immunodeficiency virus (HIV)-infected patients, chronic hepatitis B virus (HBV) infection is common due to shared modes of transmission, and accounts for the majority of liver disease in subjects with HIV [1]. Published studies have also shown that HIV accelerates the progression of viral hepatitis and its related liver disease, including liver fibrosis, cirrhosis, and hepatocellular carcinoma [2–4]. Liver fibrosis is an accumulation of extracellular matrix in the liver in response to various chronic liver injuries. A study suggests that HIV infection perse is associated with increased aspartate aminotransferase (AST)-to-platelet (PLT) ratio index (APRI), a surrogate marker for hepatic fibrosis [5]. A recent study by Kong et al suggests that entecavir can lead to histological reversal of fibrosis in chronic hepatitis B patients [6]. However, there are limited data regarding fibrosis prevalence and cART response in HIV-infected subjects from China.

In this study, we evaluate the prevalence and risk factors for hepatic fibrosis, as measured by FIB-4, in HIV/HBV co-infection population. We also demonstrate whether cART reverses the fibrogenic effect of HIV infection.

Methods

Study design and population

HIV/HBV co-infected patients were screened for eligibility. The inclusion criteria were (1) laboratory assessment allowing FIB-4 calculation (AST, ALT, platelet count) performed on the same day; (2) absence of HAV and HEV infection; (3) absence of heavy alcohol consumption (40 g pure alcohol per day); (4) absence of other liver comorbidity including hemochromatosis, Wilson's disease, 1-antitrypsin deficiency, autoimmune hepatitis, alcoholic or nonalcoholic steatohepatitis. The exclusion criteria were decompensated cirrhosis, liver disease of other etiologies, HCC and other malignancies, and major systematic diseases, as reported previously [7].

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.

Virological and biochemical assays

Serum HBsAg, anti-HBs, HBeAg, anti-HBe and anti-HBc were measured by electrochemiluminescence immunoassay (Architect i2000, ABBOTT, Wiesbaden, Germany). Serum HBV DNA levels were determined in the central laboratory by COBAS® TaqMan® HBV Test (Roche Molecular Systems, Branchburg, NJ, USA) with a detectable level of 20 IU/mL. Haematology and serum biochemical markers, including platelet count (PLT), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured by autoanalyser according to the manufacturer's instructions.

Noninvasive measurement of liver fibrosis

Serum AST and ALT activities were routinely measured ; usual upper normal values were 35 IU/l and 45 IU/l, respectively. Platelet counts were performed in the same day; normal values were $(100-300) \times 10^9/l$. The FIB-4 values were calculated automatically using the formula: $\text{age (years)} \times \text{AST [U/l]} / (\text{platelets } [10^9/l] \times (\text{ALT [U/l]})^{1/2})$. The FIB-4 index was considered in the first Sterling study to delineate patients with no or moderate fibrosis (F0-F1-F2-F3) when the score is ≤ 1.45 from those with extensive fibrosis or cirrhosis (F4-F5-F6) when the score is ≥ 3.25 (in the ISHAK classification of fibrosis) [8].

Statistical Analysis

Descriptive statistics including mean $\pm$ SD, counts and percentages were used to describe the demographics and clinical characteristics of the patients. Independent sample *t* tests or Mann[1]Whitney *U* test was conducted to compare continuous variables. Paired *t* test was used to compare FIB-4 scores and associated indexes of the same patients before and after ART. One-Way ANOVA was used to compare FIB-4 scores of patients at different duration of ART. Chi-square or Fisher's exact test was used to compare categorical variables. All calculations were made using SPSS (version 11.0.4.0) software (SPSS Inc., Chicago, IL). A *P* value of less than 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 458 HIV/HBV-co-infected patients were included in this study (Table 1). The mean age was 46 years, and 362 (79.0%) were male. Their mean BMI was 21.37, and the proportion of alcohol use was 2.8%(13/458). The mean levels of ALT, AST and platelets were 42.8 IU/L, 44.7 IU/L and $159 \times 10^9/L$. The mean FIB-4 scores was 4.869 and 65.9%% of the study population had FIB-4 scores ≥ 1.45 . 57.2% of the study population had CD4⁺ T lymphocyte count < 200 cells/ul. 31.7% of the study population had detectable HIV RNA (> 20 copies/mL), and 41.3% had detectable HBV DNA (> 20 copies/mL), respectively. HBeAg was positive in 27.3%, and Anti-HBe was positive in 41.3%.

Table 1
Baseline characteristics of the study population

Characteristic	HIV/HBV co-infected (n = 458)
Male (%)	362(79.0)
Age Yrs, Mean $\pm$ SD	46 $\pm$ 12
BMI, Mean $\pm$ SD	21.37 $\pm$ 2.43
Alcohol use, yes (%)	13(2.8)
ALT IU/L, Mean $\pm$ SD	42.8 $\pm$ 4.3
AST IU/L, Mean $\pm$ SD	44.7 $\pm$ 4.9
Platelets $10^9/L$, Mean $\pm$ SD	159 $\pm$ 4
FIB-4, Mean $\pm$ SD	4.869 $\pm$ 0.913
<1.45(%)	156(34.1)
1.45–3.25(%)	164(35.8)
>3.25(%)	138(30.1)
CD4 cell count, Mean $\pm$ SD	161 $\pm$ 11
CD4 < 200 cells/ul(%)	262(57.2)
CD4 $\geq$ 200 cells/ul(%)	196(42.8)
HIV RNA > 20 copies/ml(%)	145(31.7)
HBV DNA > 20 copies/ml(%)	189(41.3)
HBeAg positive(%)	125(27.3)
Anti-HBe positive(%)	189(41.3)

Risk factors for liver fibrosis in patients with HIV/HBV co-infection according to FIB-4

A total of 13 parameters were included in univariate analysis for the risk of liver fibrosis in patients with HIV/HBV co-infection, including demographic indicators (such as gender and age), HIV associated indicators (such as whether ART, whether HIV-RNA detectable, CD4 levels), HBV associated indicators (such as HBsAg titer, HBeAg and HBeAb status, whether HBV-DNA detectable), ALT, AST and PLT levels. Those variables with $P < 0.1$ were included in subsequent multivariate analysis (Table 2).

Table 2. Risk factors associated with liver fibrosis (FIB-4) in patients with HIV/HBV co-infection

	Univariate		Multivariate	
	<i>P</i>	OR(95% CI)	<i>P</i>	OR(95% CI)
Male	0.706	0.912(0.565-1.473)		
≥45 years	0.000	4.103(2.726-6.174)	0.000	7.194(3.259-15.884)
HCV co-infection	0.038	2.149(1.042-4.430)	0.147	3.155(0.668-14.899)
HBsAg<50	0.201	0.673(0.366-1.236)		
HBeAg positive	0.002	2.075(1.314-3.279)	0.009	0.158(0.040-0.634)
HBeAb positive	0.003	2.044(1.280-3.262)	0.569	1.402(0.438-4.484)
Detectable HBV-DNA	0.001	2.201(1.404-3.451)	0.309	1.759(0.592-5.225)
Detectable HIV-RNA	0.001	2.081(1.337-3.239)	0.000	27.850(1.607-81.401)
ART	0.005	0.532(0.341-0.829)	0.000	0.016(0.009-0.136)
CD4>200/uI	0.000	0.300(0.188-0.479)	0.012	0.336(0.144-0.786)
ALT>50 U/I	0.005	3.929(1.508-10.242)	0.046	20.488(1.012-60.190)
AST>40 U/I	0.000	20.941(5.054-86.773)	0.026	27.323(1.478-55.122)
PLT<100(×10 ⁹ /I)	0.000	13.901(4.351-75.232)	0.000	61.246(7.361-109.604)

At multivariate analysis, older than 45 years (HR 7.194, 95% CI: 3.259–15.884; $P < 0.001$), ALT > 50 U/I (HR 20.488, 95% CI: 1.012–60.190; $P = 0.046$), AST > 40 U/I (HR 27.323, 95% CI: 1.478–55.122; $P = 0.026$), PLT < 100(×10⁹/I) (HR 61.246, 95% CI: 7.361–109.604; $P < 0.001$) and detectable HIV-RNA (HR 27.850, 95% CI: 1.607–81.401; $P < 0.001$) were risk factors for liver fibrosis in patients with HIV/HBV co-infection. Also, HBeAg positive (HR 0.158, 95% CI: 0.040–0.634; $P = 0.009$), ART (HR 0.016, 95% CI: 0.009–0.136; $P < 0.001$) and CD4 > 200/uI (HR 0.336, 95% CI: 0.144–0.786; $P = 0.012$) were protective factors to against liver fibrosis in patients with HIV/HBV co-infection.

Effect of risk factors on the incidence of liver fibrosis in patients with HIV/HBV co-infection

The incidence of liver fibrosis and relative risk by different factors in patients with HIV/HBV co-infection were shown (Table 3). The incidence of liver fibrosis in patients ≥ 45 years were 3.688-fold higher than patients < 45 years (76.5% vs 46.9%, $P < 0.001$). Compared with patients positive for HBeAg, those patients negative for HBeAg were 2.004-fold more likely to progress to liver fibrosis ($P = 0.002$). Also, the incidence of liver fibrosis in patients who had detectable HIV-RNA were 1.975-fold higher than patients who had undetectable HIV-RNA (73.3% vs 58.2%, $P = 0.001$). The relative risk between ART and ART-naive patients was 1.914, between patients had $CD4 \leq 200/\mu l$ and $CD4 > 200/\mu l$ was 3.803. Patients had $ALT > 50U/l$, $AST > 40U/l$ and $PLT < 100(\times 10^9/l)$ were 5.079-fold, 8.428-fold and 8.415-fold more likely to progress to liver fibrosis, respectively, compared to those with normal ALT, AST and PLT levels.

Table 3
Incidence of liver fibrosis by different risk factors in patients with HIV/HBV co-infection

Group	Number	No. of liver fibrosis (%)	χ^2	<i>P</i>	Relative risk (95% CI)
≥ 45 Years	264	202(76.5)	42.534	< 0.001	3.688(2.470–5.505)
< 45 Years	194	91(46.9)			
HBeAg(+)	100	51(51.0)	9.343	0.002	2.004(1.278–3.144)
HBeAg(-)	358	242(67.6)			
Detectable HIV-RNA	176	129(73.3)	10.777	0.001	1.975(1.312–2.973)
Unetectable HIV-RNA	282	164(58.2)			
ART	310	184(59.4)	8.880	0.003	1.914(1.245–2.943)
ART-naive	148	109(73.6)			
CD4 ≤ 200/ul	322	236(73.3)	40.853	< 0.001	3.803(2.497–5.792)
CD4 > 200/ul	136	57(41.9)			
ALT > 50U/l	89	78(87.6)	26.846	< 0.001	5.079(2.614–9.869)
Normal ALT	369	215(58.3)			
AST > 40U/l	149	134(89.9)	64.573	< 0.001	8.428(4.726–15.028)
Normal AST	309	159(51.5)			
PLT < 100($\times 10^9$ /l)	121	110(90.9)	51.766	< 0.001	8.415(4.368–16.214)
Normal PLT	337	183(54.3)			

Effect of ART on FIB-4 scores and associated indexes in 212 patients with HIV/HBV co-infection

In this study, 212 patients with HIV/HBV co-infection had FIB-4 scores and associated indexes before and after ART (Table 4). After ART, FIB-4 declined from 2.54 ± 0.77 to 1.57 ± 0.23 ($P < 0.001$), and the proportion of liver fibrosis declined from 81.1–56.6% ($P < 0.001$). Also, the levels of AST and PLT improved after ART. The proportion of patients who had elevated ALT and AST, and patients who had thrombocytopenia were reduced after ART.

Table 4
Comparison of FIB-4 scores and associated indexes before and after ART in 212 patients with HIV/HBV co-infection

	ART-naive	ART	Test	<i>P</i>
FIB-4	2.54 ± 0.77	1.57 ± 0.23	3.899	< 0.001
Proportion of liver fibrosis(n,%)	172(81.1)	120(56.6)	29.745	< 0.001
ALT U/l (mean ± SD)	49 ± 6	36 ± 7	1.490	0.142
ALT > 50U/l (n,%)	64(30.2)	28(13.2)	17.991	< 0.001
AST U/l (mean ± SD)	68 ± 8	37 ± 4	4.095	< 0.001
AST > 40U/l (n,%)	120(56.6)	52(24.5)	45.233	< 0.001
PLT < 100(×10 ⁹ /l) (mean ± SD)	133 ± 9	191 ± 12	-4.816	< 0.001
PLT < 100(×10 ⁹ /l) (n,%)	64(30.2)	20(9.4)	28.742	< 0.001

Effect of ART on FIB-4 scores and grades in HIV/HBV co-infected patients with normal levels of ALT, AST and PLT

Liver enzyme elevation and thrombocytopenia are common among HIV-infected individuals. In consideration of ALT, AST and platelet values are used in FIB-4 calculation, higher FIB-4 scores in patients with HIV infection may be due to HIV-related liver injuries or thrombocytopenia rather than hepatic fibrosis. To further explore this, those HIV/HBV co-infected patients who had normal levels of ALT, AST and PLT during the whole course of diseases were selected and the cases was 40.

The 40 cases of HIV/HBV co-infected patients were stratified into FIB-4 < 1.45 (n = 14), 1.45 ≤ FIB-4 ≤ 3.25 (n = 19) and FIB-4 > 3.25 (n = 7) groups by their FIB-4 scores before ART. In FIB-4 < 1.45 group, the scores declined from 0.970 ± 0.052 before ART to 0.701 ± 0.080 after ART (*P* = 0.001, Fig. 1a); all the 14 HIV/HBV co-infected patients maintained FIB-4 < 1.45 grade after ART (Fig. 1b). Interestingly, in 1.45 ≤ FIB-4 ≤ 3.25 group, the scores declined from 2.187 ± 0.109 before ART to 1.369 ± 0.115 after ART (*P* < 0.001, Fig. 1a); FIB-4 grade in 57.9%(11/19) of the HIV/HBV co-infected patients dropped to a lower FIB-4 grade (FIB-4 < 1.45) after ART (Fig. 1b). Moreover, in FIB-4 > 3.25 group, the scores declined from 3.978 ± 0.270 before ART to 1.636 ± 0.111 after ART (*P* < 0.001, Fig. 1a); FIB-4 grade in 85.7%(6/7) of the HIV/HBV co-infected patients dropped to 1.45 ≤ FIB-4 ≤ 3.25 grade, while 14.3%(1/7) dropped to FIB-4 < 1.45 grade after ART (Fig. 1b).

Taken together, these analyses suggest that differences in FIB-4 after ART may not due to the recovery of liver function by the drugs with anti HBV activity or the reconstruction of platelets after ART.

Effect of ART duration on FIB-4 scores and incidence of liver fibrosis

According to ART duration, all the patients with HIV/HBV co-infection in this study were divided into ART-naive group, 1 year, 2–5 years and 5–10 years after ART groups. In these four groups, the FIB-4 scores were 4.29 ± 0.43 , 3.63 ± 0.38 , 2.90 ± 0.36 and 2.52 ± 0.38 , respectively, which showed statistically significant differences ($P = 0.034$) (Fig. 2a).

Moreover, the incidence of liver fibrosis in ART-naive group, 1 year, 2–5 years and 5–10 years after ART groups were 7.38%(104/141), 63.6%(98/154), 60.8%(62/102) and 47.5%(29/61), respectively. There were statistically significant differences in incidence of liver fibrosis between the four groups ($P = 0.004$) (Fig. 2b).

Discussion

This study evaluated incidence and predictors of liver fibrosis progression estimated by FIB-4 index in HIV/HBV-coinfected patients. Most importantly, we found that higher levels of HIV-RNA and lower CD4 cell count tended to be associated with an increased risk for higher FIB-4 scores in our multivariate analysis. Furthermore, it was interestingly that ART use was associated with a significant reduction in fibrosis scores, which provide further support for early initiation of ART in HIV/HBV co-infection patients.

In this study, the results of multivariate analysis showed that variables related with HIV natural history (such as levels of HIV RNA and CD4⁺ T-cell count) and HIV-associated intervention (such as ART) could affect FIB-4 index and the incidence of liver fibrosis. The fact, that HIV infection plays an important role in the development of hepatic fibrosis [5], was reconfirmed in this study. The biological explanation for this finding is unknown, but there are several possibilities. In addition to direct infection of hepatic stellate cells, which can express C–C chemokine receptor type 5 (CCR5) and are considered as a source of fibrogenesis [9, 10], HIV-related immune activation [11] and increased intrahepatic apoptosis [12] may also hasten the progression of liver fibrosis. The result of CD4 > 200/ul as a protective factor to against liver fibrosis in this study supports a mechanism of immune activation, but detectable HIV-RNA as a risk factor for liver fibrosis supports a mechanism of a direct effect of HIV infection. Taken together, we believe that HIV infection accelerates the occurrence of liver fibrosis through the synergistic effect of direct infection by HIV and HIV-related immune activation.

A published study aimed HIV/HCV co-infection patients have shown that although patients seem to be protected by cART especially in the first years after its prescription, liver fibrosis progressed faster afterwards, making HIV/HCV-coinfected patients a population that should be prioritized for access to HCV treatment [13]. However, the situation of HIV/HBV co-infected persons is different from that of HIV/HCV co-infected persons. ART with dual activity against HIV and HBV was recommended as an ideal choice for patients with HIV/HBV co-infection. In this study, we found that with lifelong ART containing anti-HBV agents, both the marker for hepatic fibrosis (estimated by FIB-4 in this study) and the incidence of liver fibrosis decreased with the prolongation of time on treatment. The result was consisted with a

French study, which concluded that long-term tenofovir use was associated with a decrease in fibrosis scores [14]. Therefore, we conclude that timely ART, in addition to reducing AIDS-related morbidity and mortality, is also an effective intervention to reduce the occurrence of liver related complications in people living with HIV and HBV co-infection.

Except for HIV-associated indicators, impaired liver function and thrombocytopenia caused by hypersplenism are characteristics for patients with advanced liver disease, and levels of AST, ALT and platelet count can directly affect FIB-4 scores, which was used as a noninvasive tests to assess hepatic fibrosis. Also, we demonstrated that older age and negative status of HBeAg were risk factors of liver fibrosis. This is in keeping with other studies that have used non-invasive measures to determine the extent of fibrosis in HIV-HBV co-infected patients [5, 15, 16]. Moreover, positive status of HBeAg was found as a protective factor to against liver fibrosis in this study. The background of HBV infection in China is difference from the European and American countries, where individuals acquired HBV infection through sexual activity or injection drug use in adulthood. In our study, chronic HBV infection mostly occurred during childhood or even earlier, during the perinatal period. Both older age and negative status of HBeAg indirectly indicates that the individuals has been infected with HBV for a relatively long time. A longer period of HBV infection is associated with a higher risk of liver fibrosis, which is the natural history of HBV infection.

We recognize that our study has limitations. An inherent limitation of this study, first of all, is that we used established serum markers (FIB-4) as a surrogate for the amount of liver fibrosis, which is less accurate than liver biopsy[17]. However, meta-analyses demonstrate that FIB-4 have moderate accuracy for assessing liver fibrosis [18]. Second, given the cross-sectional nature of the study, we were not able to obtain data before and after ART for all individuals. However, similar results were found by comparing FIB-4 scores of 52 patients whose serum markers were available before and after ART. Finally, since HIV infection is associated with reduction in PLT [19] and FIB-4 scores may be elevated due to HIV infection; therefore, we did a sensitivity analysis using only AST as a surrogate fibrosis marker, and found similar results.

In summary, this study suggests that HIV-associated indicators can predict the risk of liver fibrosis in patients with HIV/HBV co-infection. As a noninvasive tests to assess hepatic fibrosis, FIB-4 scores improve with ART. From the observation of ART for up to 10 years, we found that the benefit of ART in improving liver fibrosis was sustained for patients with HIV/HBV co-infection.

Declarations

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Competing interests

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Zhongnan Hospital of Wuhan University. Written informed consent to participate in this study can be obtained from all patients.

Consent for publication

Written informed consent for publication can be obtained from all participants.

Availability of data and material

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

RY and XG conceptualized the study design; HK and SG recruited the patients, collected clinical data; RY wrote the initial drafts of the manuscript; HK, SG, YX and XG revised the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Effect of ART on FIB-4 scores and grades in HIV/HBV co-infected patients with normal levels of ALT, AST and PLT

Figure 2

Effect of ART duration on FIB-4 scores and the incidence of liver fibrosis