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# Combination Antiretroviral Therapy Is Associated With Reduction in Liver Fibrosis Scores in HIV-1-Infected Subjects

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**Abstract:** HIV increases the risk of liver disease as do two common coinfections, hepatitis B and C viruses (HBV and HCV). However, whether combination antiretroviral therapy (cART) reverses or exacerbates hepatic fibrosis remains unclear.

This was an observational retrospective study. cART-naïve HIV-infected subjects without a history of substance abuse (including alcohol) had liver disease stage determined by aspartate aminotransferase-to-platelet ratio indices (APRIs) and fibrosis-4 (FIB-4) before and 24 and 48 weeks after cART. All the data were retrieved from previously established cohorts. Values before and after cART were compared using Wilcoxon test for paired samples. Regression analyses were used to determine factors associated with moderate-to-severe liver disease.

Of the 1105 HIV-infected subjects, 120 were HBV coinfected and 64 were HCV coinfected. About 20% of HIV monoinfected participants had APRI and FIB-4 scores consistent with moderate-to-significant fibrosis compared to ~36% of HIV–HBV coinfected and 67% to 77% of HIV–HCV coinfected participants. In adjusted analyses compared with HIV monoinfection, HBV coinfection was associated with 1.18-fold higher APRI ($P < 0.001$) and a 1.12-fold higher FIB-4 ($P = 0.007$) prior to cART; while HCV coinfection was associated with 1.94-fold higher APRI ($P < 0.001$) and a 1.43-fold higher FIB-4 ($P < 0.001$). After 48 weeks of cART, both fibrosis scores decreased in all subjects; however, HCV coinfection was still associated with higher fibrosis scores at week 48 compared to HIV monoinfection.

cART was associated with improvement in hepatic fibrosis scores in the majority of HIV-hepatitis coinfected and HIV-monoinfected Chinese participants.

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**Abbreviations**: ALT = alanine aminotransferase, APRI = aspartate aminotransferase-to-platelet ratio index, AST = aspartate aminotransferase, cART = combination antiretroviral therapy, CCR5 = C-C chemokine receptor type 5, FIB-4 = fibrosis-4, HBsAg = hepatitis B surface antigen, HBV = hepatitis B virus, HCV = hepaitits C virus, HIV = human immunodeficiency virus, IQR = interquartile range, PLT = platelet, ULN = upper limit of normal.

## INTRODUCTION

After the introduction of combination antiretroviral therapy (cART), morbidity and mortality rates have decreased dramatically in people living with HIV; however, non-AIDS defining diseases are now the leading causes of death with liver-related deaths one of the most common.[1–4] Given that hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) have overlapping routes of transmission, viral hepatitis and HIV coinfection is common and accounts for the majority of liver disease in subjects with HIV.[3] It is well established that in HIV/viral hepatitis coinfection, HIV accelerates the progression of viral hepatitis and its related liver disease, including liver fibrosis, cirrhosis, and hepatocellular carcinoma.[5–7] However, there are limited data on the prevalence of fibrosis in HIV-infected subjects both with and without viral hepatitis.

A recent study by Price et al suggests that HIV infection per se is associated with increased aspartate aminotransferase (AST)-to-platelet (PLT) ratio index (APRI), a surrogate marker for hepatic fibrosis. However, this article does not further distinguish the fibrogenic effects of HBV and HCV coinfection and does not demonstrate whether cART reverses the fibrogenic effect of HIV infection.[8] Other studies focus on the effect of cART on the regression of hepatic fibrosis in HIV/HCV coinfection, but the results are discordant.[9,10] In HIV/HBV coinfected population, one French study found that long-term tenofovir use was associated with a decrease in fibrosis scores[11]; however, that study did not have HIV monoinfected subjects as a comparison group. There are no data regarding fibrosis prevalence and cART response in HIV-infected subjects from Asia.

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For the evaluation of hepatic fibrosis in large populations, liver biopsy, the gold standard, is not feasible due to its cost, invasiveness, and complications. APRI and fibrosis-4 (FIB-4), two noninvasive markers for hepatic fibrosis, have been validated in HBV- and HCV- infected populations.[12–15] They have also been used to evaluate hepatic fibrosis in HIV/HBV or HIV/HCV coinfected populations[8,16–18] and are reported to have moderate concordance.[19] In addition, they are closely associated with morbidity and mortality in HIV and viral hepatitis coinfected population.[20–22]

In this study, we used four large multicenter cohorts of HIV-infected Chinese subjects including HIV monoinfected, HIV–HBV coinfected, and HIV–HCV coinfected to evaluate the prevalence and risk factors for hepatic fibrosis, as measured by APRI and FIB-4, prior to cART. We also evaluated the impact of cART on these hepatic fibrosis measurements.

## SUBJECTS AND METHODS

### Study Population

Subjects in this study came from one the following four HIV cohorts in China: 10th 5-year (10-5) cohort (recruited between 2005 and 2007, previously reported in,[23] n = 148), 11th 5-year (11-5) cohort (recruited between 2008 and 2010, previously reported in,[24] n = 484), 12th 5-year (12-5) cohort (recruited between 2012 and 2014, n = 402), and outpatient clinics (OP, recruited between 2012 and 2014, only from Peking Union Medical College Hospital, n = 71). The clinical centers in Northeastern, Northwestern, and Southeastern China are located in urban areas and are tertiary/specialized hospitals; while District CDC in Nanning, Longtan Hospital in Nanning, Nanning Forth People's Hospital, Yunnan AIDS Care Center, Kunming Third People's Hospital, and Honghe First People's Hospital are all tertiary/specialized hospitals located in less-developed areas in Southwestern China. This research was approved by Institutional Review Board of Peking Union Medical College Hospital and was in compliance with relevant local laws and the ethical requirements of the Declaration of Helsinki. Informed consent was obtained from every patient. Inclusion criteria for these parent cohorts were determined by the individual studies,[23,24] including CD4 cells lower than 350 cells/μL in 10th 5-year cohort and 11th 5-year cohort, CD4 cells lower than 500 cells/μL in 12th 5-year cohort and outpatient clinics; cART-naïve; no intravenous drug use; no heavy alcohol use (defined as more than 40 g/d for male and 20 g/d for female or drinking that prevents the patient from taking the medications regularly, based on self-report); alanine transaminase (ALT) and AST lower than 140 IU/L and platelet count (PLT) higher than 40,000 per μL. In this study, we only included subjects with baseline HBV serology and HCV RNA profiles available. For those with positive anti-HCV antibody but negative HCV RNA, we considered them as HIV monoinfected. Subjects visited local medical centers for blood sample collection and clinical evaluation at baseline (pre-cART) and at the following weeks after cART initiation: 4, 8, 12, and then every 12 weeks. In this study, we retrieved data at baseline and at weeks 24 and 48 after cART initiation. Subjects received zidovudine or stavudine or didanosine in combination with lamivudine + nevirapine in 10th 5-year cohort, zidovudine or stavudine in combination with lamivudine + nevirapine/efavirenz in 11th 5-year cohort, tenofovir + lamivudine + efavirenz or nevirapine in 12th 5-year cohort, and zidovudine or stavudine or tenofovir in combination with lamivudine + nevirapine or efavirenz or protease inhibitors at the outpatient clinic. The subjects were divided into HIV monoinfection, HIV–HBV coinfection (hepatitis B surface antigen [HBsAg] positive), and HIV–HCV coinfected (anti-HCV antibody and HCV RNA positive) based on testing at the baseline visit. Subjects who were both HBsAg and anti-HCV positive were excluded (n = 7).

### Clinical and Laboratory Data

At each visit, HIV RNA (COBAS Ampliprep/TaqMan48 real-time RT-PCR, Roche Diagnostics, Indianapolis, IN), CD4 cell count (flow cytometry, Beckman-Coulter, Brea, CA), ALT, AST, and platelets were measured. The upper limit of normal (ULN) for ALT and AST was 40 IU/L. HBsAg and anti-HCV were determined by Architecture i2000SR platform (Abbott Diagnostics, Abbott Park, IL) and HCV RNA was determined by COBAS Ampliprep/TaqMan48 real-time RT-PCR (Roche Diagnostics) at the baseline visit. All baseline tests were obtained within 2 weeks prior to cART initiation.

APRI was defined as (AST/ULN)/PLT × 100,[13] and an APRI > 0.5 was considered as moderate-to-significant hepatic fibrosis.[8,25] FIB-4 was defined as (AST × Age)/(PLT × square root of ALT), and FIB-4 > 1.45 was considered as moderate-to-significant fibrosis.[18,19] The unit for platelets in both definitions is $10^9$/L. These APRI and FIB-4 cut-offs have been shown in meta-analyses to have moderate diagnostic accuracy for significant or greater liver disease.[26,27]

### Statistical Analysis

Noncategorical variables were analyzed by using Kruskal–Wallis test and were summarized with median and interquartile ranges (IQRs). Categorical variables were analyzed by Chi-squared test or Fisher exact test. Risk factors for having moderate-to-significant hepatic fibrosis at baseline were determined by both logistic regression and linear regression. In logistic regression, APRI and FIB-4 scores were treated as categorical scores with cut-off values of 0.50 and 1.45, respectively. Since distributions of both scores were right-skewed, the scores were natural log-transformed (Ln); coefficients of all risk factors in linear regression were reported as fold changes (previously described in the study by Price et al[8]). To compare fibrosis scores at weeks 24 and 48 with baseline levels, Wilcoxon test for paired samples was used. In order to evaluate factors associated with significant fibrosis at week 48, we conducted multivariate linear regressions and included all subjects with data available at week 48. In this analysis, CD4 cell count change was calculated as CD4 cell count at week 48 minus CD4 cell count at baseline and then divided into 4 quartiles. For all tests except Wilcoxon tests for paired samples, $P < 0.05$ was considered to be statistically significant. For Wilcoxon tests for paired samples, $P < 0.025$ was considered to be statistically significant according to Bonferroni correction. In multivariate regressions, factors with $P < 0.15$ in univariate models were included, and age, sex, routes of transmission, and cohorts were adjusted for in all cases. Stata 13 (StataCorp, College Station, TX) was used for all analyses.

## RESULTS

### Baseline Characteristics

This study included 1105 HIV-infected subjects of whom 120 (10.9%) were HIV–HBV coinfected and 64 (5.8%) were HIV–HCV coinfected. Most of the subjects were 30 to 40 years old, male, and infected via sexual transmission

**TABLE 1.** Baseline Characteristics

| | Total (n = 1105) | HIV Monoinfection (n = 921) | HIV–HBV Coinfection (n = 120) | HIV–HCV Coinfection (n = 64) | *P* |
|---|---|---|---|---|---|
| Age, y (IQR) | 34 (28–43) | 34 (28–43) | 35 (30–43) | 37 (31–44) | 0.10 |
| Age group, n (%) | | | | | 0.012 |
| 18–30 | 357 (32.3) | 316 (34.3) | 30 (25.0) | 11 (17.2) | |
| 30–40 | 388 (35.1) | 310 (33.7) | 51 (42.5) | 27 (42.2) | |
| 40–50 | 236 (21.4) | 188 (20.4) | 27 (22.5) | 21 (32.8) | |
| >50 | 124 (11.2) | 107 (11.6) | 12 (10.0) | 5 (7.8) | |
| Male, n (%) | 792 (71.7) | 652 (70.8) | 101 (84.2) | 39 (60.9) | 0.001 |
| Route of transmission, n (%) | | | | | <0.001 |
| MSM | 411 (37.2) | 360 (39.1) | 49 (40.8) | 2 (3.1) | |
| Heterosexual | 508 (46.0) | 430 (46.7) | 63 (52.5) | 15 (23.5) | |
| Blood | 89 (8.0) | 47 (5.1) | 0 (0.0) | 42 (65.6) | |
| Others/unknown | 97 (8.8) | 84 (9.1) | 8 (6.7) | 5 (7.8) | |
| ALT, IU/L (IQR) | 23 (16–36) | 21 (16–33) | 29 (20–43) | 47 (29–72) | <0.001 |
| >40, n (%) | 218 (19.7) | 148 (16.1) | 31 (25.8) | 39 (60.9) | <0.001 |
| AST, IU/L (IQR) | 25 (21–32) | 24 (20–30) | 27 (23–39) | 43 (34–58) | <0.001 |
| PLT, $\times 10^9$/L (IQR) | 182 (147–221) | 186 (151–224) | 175 (148–208) | 140 (108–184) | <0.001 |
| PLT < 150, n (%) | 298 (27.0) | 228 (24.8) | 33 (27.5) | 37 (57.8) | <0.001 |
| APRI (IQR) | 0.34 (0.26–0.50) | 0.32 (0.25–0.45) | 0.39 (0.29–0.59) | 0.89 (0.50–1.26) | <0.001 |
| APRI > 0.5, n (%) | 274 (24.8) | 181 (19.7) | 44 (36.7) | 49 (76.6) | <0.001 |
| FIB-4 (IQR) | 1.02 (0.73–1.48) | 0.97 (0.71–1.36) | 1.06 (0.76–1.65) | 1.76 (1.25–2.33) | <0.001 |
| FIB-4 > 1.45, n (%) | 288 (26.1) | 202 (21.9) | 43 (35.8) | 43 (67.2) | <0.001 |
| CD4 cell count, cells/μL (IQR) | 222 (135–303) | 226 (141–306) | 188 (99–277) | 202 (132–299) | 0.009 |
| HIV RNA, log copies/mL (IQR) | 4.65 (4.22–5.11) | 4.65 (4.21–5.10) | 4.70 (4.23–5.16) | 4.55 (3.97–4.93) | 0.46 |
| HBV-active NRTI, n (%) | | | | | <0.001 |
| TDF + 3TC based | 413 (37.4) | 370 (40.2) | 38 (31.7) | 5 (7.8) | |
| 3TC based (+ AZT or d4T) | 645 (58.4) | 518 (56.2) | 76 (63.3) | 51 (79.7) | |
| No | 47 (4.2) | 33 (3.6) | 6 (5.0) | 8 (12.5) | |
| Third medication | | | | | <0.001 |
| NVP | 674 (61.0) | 535 (58.1) | 80 (66.7) | 59 (92.2) | |
| EFV | 426 (38.5) | 382 (41.5) | 39 (32.5) | 5 (7.8) | |
| PI | 5 (0.5) | 4 (0.4) | 1 (0.8) | 0 (0.0) | |
| Cohort | | | | | <0.001 |
| Outpatient | 71 (6.4) | 65 (7.1) | 6 (5.0) | 0 (0.0) | |
| 11-5 | 484 (43.8) | 389 (42.2) | 63 (52.5) | 32 (50.0) | |
| 10-5 | 148 (13.4) | 107 (11.6) | 14 (11.7) | 27 (42.2) | |
| 12-5 | 402 (36.4) | 360 (39.1) | 37 (30.8) | 5 (7.8) | |

Continuous variables are reported as medians and interquartile ranges. *P* values represent the overall differences among the 3 groups.

3TC = lamivudine, ALT = alanine aminotransferase, APRI = AST to platelet ratio index, AST = aspartate transaminase, AZT = zidovudine, d4T = stavudine, EFV = efavirenz, FIB-4 = fibrosis-4, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IQRs = interquartile ranges, IU = international unit, MSM = men who have sex with men, NRTI = nucleoside reverse transcriptase inhibitors, NVP = nevirapine, PI = protease inhibitor, PLT = platelet, TDF = tenofovir disoproxil fumarate.

(Table 1). ALT elevation was seen in 218 (19.7%) subjects at baseline, but most of them had ALT <80 IU/L; however, in subjects with HBV and HCV coinfection, 25.8% and 60.9% of subjects had ALT elevation, respectively. In addition, median CD4 count in subjects with normal ALT was 232 cells/μL while that in subjects with elevated ALT was 189 cells/μL ($P = 0.002$).

Some baseline characteristics differed between cohorts. Cohort 10-5 had the highest proportion of HCV coinfected (18.2%) subjects and of blood transmission (29.7%) (both $P < 0.001$). Cohort 12-5 had higher baseline CD4 cell count (299 cells/μL) and 100% tenofovir disoproxil fumarate use, which is expected given the inclusion criteria for that cohort.

## Factors Associated With Hepatic Fibrosis at Baseline

Overall, APRI, and FIB-4 scores had an 82.1% agreement, with kappa value 0.53 ($P < 0.001$). At baseline, approximately 20% of HIV-monoinfected participants had scores considered as moderate-to-significant hepatic fibrosis (19.7% by APRI and 21.9% by FIB-4 scoring systems, Table 1) with higher proportions in both HBV and HCV coinfected participants. Specifically, 36.7% of HIV–HBV coinfected participants had an APRI > 0.5 and 35.8% had an FIB-4 > 1.45. This distribution was the same in HBeAg positive and HBeAg negative participants (data not shown). In HIV–HCV coinfected participants, the prevalence of fibrosis scores above these cut-offs was highest at 76.6% and 67.2% by APRI and FIB-4, respectively.

In univariate logistic regression models for both APRI and FIB-4, HBV and HCV coinfections were significantly associated with scores considered as moderate-to-significant hepatic fibrosis at baseline while CD4 count >200 cells/μL was protective (Table 2). In multivariate models, the association of HBV and HCV coinfections remained in both scoring systems while the association with CD4 count >200 cells/μL only remained in the APRI scoring system (Table 2). HIV RNA was not significantly associated with higher fibrosis scores in either scoring system (Table 2).

Similar to logistic models, the multivariate linear regression models demonstrated HBV and HCV coinfections to be associated with higher fibrosis scores in both scoring systems but CD4 T-cell count was not associated (Supplementary Table S1, http://links.lww.com/MD/A666).

In addition, we did a sensitivity analysis by using AST as a surrogate marker for hepatic fibrosis to avoid PLT, as reported in Price et al[8] and also found that HBV and HCV coinfections were associated with elevated AST (fold increase in AST 1.15 and 1.61, respectively, both $P < 0.001$).

## cART Was Associated With Regression of Hepatic Fibrosis Scores

After 24 weeks of cART, both median APRI and FIB-4 fibrosis scores were lower compared to pre-cART values in all groups, and continued to decline through 48 weeks of cART (Table 3). The median values were only significantly lower in the HIV monoinfected and HIV–HBV coinfected groups.

We also evaluated factors associated with fibrosis scores after 48 weeks of cART (Table 4). In multivariate linear regression models, HIV–HBV and HIV–HCV coinfections were associated with higher APRI, but only HIV–HCV coinfection was associated with higher FIB-4. Greater CD4 cell count recovery was associated with lower FIB-4 scores.

## DISCUSSION

In this study of over 1000 HIV-infected Chinese participants who had liver fibrosis assessed by APRI and FIB-4 before and after cART initiation, 20% of the HIV-monoinfected subjects had scores considered as moderate-to-significant liver fibrosis prior to starting cART. Lower CD4 cell count tended to be associated with an increased risk for higher liver fibrosis scores. Furthermore, this study suggests that both HBV and HCV coinfections are associated with increased risk of hepatic fibrosis in HIV-infected subjects prior to cART. Interestingly, cART use was associated with a significant reduction in fibrosis scores, especially in HIV-monoinfected and HIV–HBV coinfected subjects.

The 20% of HIV-monoinfected subjects who had scores considered as moderate-to-significant hepatic fibrosis is high given that in Chinese subjects with fatty liver, only 4.5% by APRI scoring system (APRI > 0.5) and 9.8% by FIB-4 scoring system (FIB-4 > 1.30) had moderate-to-significant hepatic fibrosis.[28] This high proportion, though, is consistent with previous studies where the prevalence of moderate-to-severe fibrosis ranged from 13.5% to 35.7% in HIV-monoinfected subjects (defined as APRI > 0.5 or FIB-4 > 1.45).[8,10,29] In addition, our study found that higher CD4 protects against liver disease, an association that was stronger in the APRI rather than the FIB-4 scoring system. Taken together, these data support that HIV infection may be an important factor in the development of hepatic fibrosis, as observed by Price et al.[8] The biological explanation for this finding is unknown, but there are several possibilities. HIV has been shown to infect human hepatic stellate cells, which express C–C chemokine receptor type 5 (CCR5), and are considered as a source of fibrogenesis.[5] Interestingly, maraviroc, a CCR5 antagonist, is associated with regression of hepatic fibrosis.[30] In addition to direct infection of HSCs, HIV-related immune activation may also hasten the progression of liver fibrosis.[31] Other mechanisms, including

**TABLE 2.** Factors Associated With APRI and FIB-4 Considered as Moderate-to-Significant Hepatic Fibrosis

| | APRI Score > 0.5 | | | | FIB-4 Score > 1.45 | | | |
|---|---|---|---|---|---|---|---|---|
| | Univariate | | Multivariate | | Univariate | | Multivariate | |
| | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P | OR (95% CI) | P |
| Coinfection | | | | | | | | |
| HIV monoinfection | 1 | | 1 | | 1 | | 1 | |
| HIV–HBV coinfection | 2.37 (1.58–3.55) | <0.001 | 2.15 (1.40–3.30) | <0.001 | 1.99 (1.33–2.98) | 0.001 | 2.24 (1.40–3.59) | 0.001 |
| HIV–HCV coinfection | 13.36 (7.32–24.35) | <0.001 | 8.24 (4.13–16.45) | <0.001 | 7.29 (4.23–12.56) | <0.001 | 6.35 (3.15–12.82) | <0.001 |
| Baseline CD4 cell count, cells/μL | | | | | | | | |
| <200 | 1 | | 1 | | 1 | | 1 | |
| >200 | 0.56 (0.42–0.74) | <0.001 | 0.65 (0.47–0.89) | 0.007 | 0.64 (0.49–0.84) | 0.001 | 0.80 (0.57–1.14) | 0.22 |
| Baseline HIV RNA (per 1 log copies/mL) | 1.13 (0.93–1.37) | 0.21 | | | 1.24 (1.02–1.50) | 0.028 | 1.08 (0.85–1.36) | 0.54 |

Models also adjusted for age, sex, routes of transmission, and cohorts (10th 5-y cohort, 11th 5-y cohort, 12th 5-y cohort, and outpatient clinics). ORs for the factors with $P$ values < 0.15 were included in the multivariate models.

APRI = AST to platelet ratio index, CI = confidence interval, FIB-4 = fibrosis-4, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, OR = odds ratio.

**TABLE 3.** Median Fibrosis Scores Before and Week 24 and 48 After cART

| | | Baseline | | Week 24 | | | Week 48 | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Median | IQR (n) | Median | IQR (n) | *P* | Median | IQR (n) | *P* |
| APRI | HIV monoinfection | 0.32 | 0.25–0.45 (921) | 0.31 | 0.23–0.41 (852) | <0.001 | 0.28 | 0.22–0.37 (834) | <0.001 |
| | HIV–HBV coinfection | 0.39 | 0.29–0.59 (120) | 0.35 | 0.25–0.44 (113) | <0.001 | 0.31 | 0.25–0.44 (102) | 0.005 |
| | HIV–HCV coinfection | 0.89 | 0.50–1.26 (64) | 0.65 | 0.45–1.75 (51) | 0.13 | 0.73 | 0.48–1.27 (49) | 0.35 |
| FIB-4 | HIV monoinfection | 0.97 | 0.71–1.36 (921) | 0.84 | 0.61–1.18 (852) | <0.001 | 0.82 | 0.59–1.12 (834) | <0.001 |
| | HIV–HBV coinfection | 1.06 | 0.76–1.65 (120) | 0.91 | 0.65–1.32 (113) | <0.001 | 0.93 | 0.63–1.38 (102) | <0.001 |
| | HIV–HCV coinfection | 1.76 | 1.25–2.33 (64) | 1.57 | 1.02–3.14 (51) | 0.71 | 1.53 | 1.12–2.19 (49) | 0.068 |

*P* values were calculated by using Wilcoxon tests for paired samples to compare fibrosis scores at week 24 or 48 with those prior to cART. $P < 0.025$ was considered statistically significant according to Bonferroni correction.

APRI = AST to platelet ratio index, cART = combination antiretroviral therapy, FIB-4 = fibrosis-4, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus, IQRs = interquartile ranges.

increased intrahepatic apoptosis,[32] may also contribute to hepatic fibrosis in HIV infection. The association of higher CD4 counts with a reduction in risk of moderate-to-severe fibrosis supports a mechanism of immune activation and less likely a direct effect of HIV infection.

HBV coinfection increased the risk for fibrosis 2-fold and HCV coinfection increased the risk 6- to 8-fold after adjustment for demographic and cohort factors. This increased risk was consistent for both scoring systems and is consistent with prior studies of HIV-infected subjects,[8,10,29] which included primarily Caucasian subjects. The other studies also had more subjects with HCV[33] whereas in our cohort, prevalence of HBV coinfection was higher than that of HCV coinfection.

After 48 weeks of cART, the median APRI and FIB-4 scores decreased in the HIV monoinfected and in both HIV-hepatitis groups supporting that cART was associated with improvement in hepatic fibrosis scores early after cART initiation. Despite this, HCV coinfection was still associated with higher fibrosis scores. A cross-sectional study from Europe demonstrated that HIV–HCV coinfection was associated with more severe hepatic fibrosis compared to HCV monoinfection even when HIV infection was controlled by cART.[9] In contrast

**TABLE 4.** Factors Associated With Fibrosis Scores at Week 48

| | APRI Scoring System | | FIB-4 Scoring System | |
|---|---|---|---|---|
| | Multivariate | | Multivariate | |
| | Fold Change (95% CI) | *P* | Fold Change (95% CI) | *P* |
| Coinfection | | | | |
| HIV monoinfection | 1 | | 1 | |
| HIV–HBV coinfection | 1.11 (1.01–1.22) | 0.030 | 1.04 (0.97–1.12) | 0.27 |
| HIV–HCV coinfection | 1.97 (1.69–2.30) | <0.001 | 1.24 (1.10–1.40) | <0.001 |
| Baseline HIV RNA (per log copies/mL) | 0.92 (0.88–0.95) | <0.001 | | |
| CD4 change* | | | | |
| 1st quartile | 1 | | 1 | |
| 2nd–3rd quartile | 0.96 (0.89–1.03) | 0.23 | 0.94 (0.89–0.99) | 0.028 |
| 4th quartile | 0.95 (0.87–1.03) | 0.18 | 0.90 (0.85–0.96) | 0.002 |
| Unknown | 1.03 (0.82–1.29) | 0.78 | 1.06 (0.89–1.27) | 0.49 |
| Viral suppression (<400 copies/mL) | | | | |
| Yes | 1 | | 1 | |
| No | 0.95 (0.84–1.07) | 0.40 | 0.94 (0.86–1.04) | 0.25 |
| Unknown | 0.95 (0.80–1.11) | 0.50 | 0.89 (0.78–1.01) | 0.063 |
| Baseline fibrosis score (per 1 point) | 1.40 (1.32–1.49) | <0.001 | 1.58 (1.50–1.67) | <0.001 |

Fold change was calculated by linear regression. Models also adjusted for age, sex, routes of transmission, and cohorts (10th 5-y cohort, 11th 5-y cohort, 12th 5-y cohort, and outpatient clinics). Baseline CD4 cell count was not included because of collinearity with CD4 increase. Fold changes for the factors with *P* values < 0.15 were included in the multivariate models.

APRI = AST to platelet ratio index, CI = confidence interval, FIB-4 = fibrosis-4, HBV = hepatitis B virus, HCV = hepatitis C virus, HIV = human immunodeficiency virus.

* CD4 cell count change was calculated as CD4 cell count at week 48 minus CD4 cell count at baseline and then divided into 4 quartiles, with 1st quartile the smallest change and 4th the largest.

to our findings, a retrospective Canadian study found that APRI scores in HIV-monoinfected subjects remained stable during 14 years of cART while APRI scores in HIV/HCV coinfected subjects increased.[10] However, this Canadian study included primarily Canadian intravenous drug users while our cohort only included Asian nondrug users, which could explain differences in the findings. Another explanation for the difference is that in the Canadian study, the APRI increase was more prominent after 1 year of cART use. Since some of the cART medications are hepatotoxic, the beneficial effect of cART on fibrosis may be outweighed by the direct toxicity of some cART medications in long term, so further follow-up of our cohort is needed to evaluate the effect of longer-term cART on hepatic fibrosis. In fact, drug toxicity could be 1 explanation for the slower decline of median APRI and FIB-4 in the HIV–HCV coinfected participants since they had a higher proportion on drugs that are more hepatotoxic (AZT and d4T, Table 1).

There are several strengths of our study. First, this is the first longitudinal study in Chinese HIV-infected subjects to compare liver fibrosis scores at baseline and during follow-up on cART. Second, we included a large number of subjects and included both HBV and HCV coinfected subjects. Third, we utilized two hepatic fibrosis scoring systems, which demonstrated concordance. Fourth, subjects with alcohol abuse or binge drinking were excluded.

An inherent limitation of this study, first of all, is that we used established serum markers as a surrogate for the amount of liver fibrosis, which is less accurate than liver biopsy[17] and has a lower positive predictive value in HIV–HCV coinfection.[34] However, meta-analyses demonstrate that these markers have moderate accuracy for assessing liver fibrosis.[26,27] This limitation is outweighed by the large number of subjects included, which would not have been feasible with liver biopsy. Furthermore, our finding that the two different markers produced concordant results also overcomes the limitation of not having liver biopsy data. Second, since HIV infection is associated with reduction in PLT[35] and both scores require PLT, these fibrosis scores may be elevated due to HIV infection rather than hepatic fibrosis; therefore, we did a sensitivity analysis using only AST as a surrogate fibrosis marker, and found similar results. Third, in this study, we cannot distinguish hepatotoxicity flares from changes in fibrosis; however, our findings warrant further study using other noninvasive tests such as transient elastography. Fourth we were not able to determine the route of transmission for HBV infection, although we presumed that most subjects acquired HBV infection via vertical transmission. Control of HBV infection may have been affected by cART, but we were not able to determine HBV DNA in follow-up in this study.

In conclusion, this study suggests that HIV infection is a risk factor for higher hepatic fibrosis scores in Chinese and these fibrosis scores improve with cART. Furthermore, both HBV and HCV coinfections are associated with higher surrogate fibrosis scores prior to cART, which are also ameliorated with cART. These data provide further support for early initiation of cART in HIV infection.

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