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Highly Active Antiretroviral Therapy Mitigates Liver Disease in HIV Infection

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Abstract

To determine the impact of highly active antiretroviral therapy (HAART) on liver disease, we analyzed changes in the aspartate aminotransferase to platelet ratio index (APRI) pre- and post-HAART initiation among 441 HIV-monoinfected and 53 HIV-viral hepatitis-coinfected men. Pre-HAART, APRI increased 17% and 34% among the HIV-monoinfected and coinfected men, respectively. With HAART initiation, APRI decreased significantly in men who achieved HIV RNA<500 copies/ml: 16% for HIV-monoinfected and 22% for coinfected. Declines in APRI were dependent on HIV suppression. This protective effect of HAART decreased after 2 years, particularly in the HIV-monoinfected men.

Keywords

HIV; HBV; HCV; antiviral therapy; liver; hepatitis; APRI

Introduction

Coinfection with the hepatitis C virus (HCV) or hepatitis B virus (HBV) accounts for the majority of liver disease among HIV-infected individuals[1]; however, HIV monoinfection may also increase the risk for hepatic dysfunction[2-5]. Although the mechanism for this is unknown, elevated HIV RNA levels and advanced immunosuppression have been associated with more advanced liver dysfunction in HIV-infected individuals with and without viral

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hepatitis coinfection[3,6-8]. Highly active antiretroviral therapy (HAART) may reduce liver disease progression in HIV-viral hepatitis-coinfected individuals[2,9-13]. However, HAART may also increase liver disease through direct hepatotoxicity or through other mechanisms such as long-term metabolic complications from steatohepatitis [14]. Thus, prospective studies of HIV-infected individuals with and without viral hepatitis are needed to more clearly elucidate the effects of HAART on liver disease.

In a previous cross-sectional study among HAART-naïve men enrolled in the Multicenter AIDS Cohort Study (MACS), HIV and viral hepatitis were both separately and synergistically associated with an increased aspartate aminotransferase to platelet ratio index (APRI), a surrogate for hepatic fibrosis[3,15]. Furthermore, HIV RNA ≥100,000 copies/mL and CD4 count ≤200 cells/mL were associated with higher APRI values. In the current study, we determined the impact of HAART on liver disease by comparing changes in APRI in HIV-infected MACS participants before and after HAART initiation (HI).

Methods

We nested this prospective study within the MACS, an ongoing cohort study of HIV-infected and -uninfected men who have sex with men (MSM). Details of the MACS participant recruitment and characteristics have been described elsewhere[16,17]. The study population included HIV-infected HAART initiators with >5 years of follow-up after 1996 and a serum sample available from a visit 1 year before and 2 years after HI. If serum was available, we also determined APRI at 4 years pre-HI and 5 years post-HI to examine changes over a longer time period. Specifically, we evaluated APRI change for the following 3-year intervals: i) 4-years to 1-year pre-HI (interval A), ii) 1-year pre-HI to 2-years post-HI (interval B), and iii) 2-years to 5-years post-HI (interval C). All participants provided informed consent, and the IRBs at each site approved the study.

Subjects were defined as viral hepatitis-infected if they were either HBV- or HCV-infected, as previously described[18,19]. HAART was defined according to guidelines by the Department of Health and Human Services/Kaiser Panel[20]. Moderate to heavy alcohol use was defined as a self-reported average of ≥2 drinks per day over the prior 6 months. CD4 T-cell count and HIV RNA were measured at each visit using standard assays [21]. The lower limit of detection of the earliest HIV RNA assay was 500 copies/mL; this cut-off was therefore used to determine undetectable HIV RNA for analysis. AST was routinely tested at each MACS study visit starting in 2001. For study visits prior to 2001 or otherwise missing AST values, we performed AST testing at the Johns Hopkins Hospital clinical laboratory using stored serum or plasma specimens frozen at −70°C until use.

The 1-year pre-HI visit was selected to be the index visit because it is the closest visit to HI and because all participants had data at this time point. We examined changes in natural log (ln)-APRI using random effects linear regression models with maximum-likelihood estimation with ln(APRI) as the dependent variable. Linear combinations of the estimated coefficients were used to determine and compare change in APRI during the study intervals and were exponentiated to produce relative differences in APRI. The final model included the following covariates: viral hepatitis status, time interval, the interaction between viral

hepatitis and time interval, HIV RNA (categorized as <500 copies/ml, 500 to 75,000 copies/mL, or ≥75,000 copies/mL), the interaction between HIV RNA and viral hepatitis status, pre-HI CD4 count, race, and age. Analyses were performed using Stata 12.1 (StataCorp).

Results

A total of 494 men were included consisting of 441 HIV-monoinfected and 53 HIV-viral hepatitis-coinfected men (24 HIV/HCV, 27 HIV/HBV, 2 HIV/HCV/HBV) (Supplemental Table 1). The initial HAART regimens were largely protease inhibitor (PI) based (70%). Most participants (79%) started HAART before 2001, so 87% of this study cohort was on a dideoxynucleoside analog. Of the 29 HBsAg-positive men, 28 initiated HAART that contained lamivudine and/or tenofovir.

The unadjusted mean APRI value increased prior to HI (interval A) for both the HIV-monoinfected (from 0.49 to 0.55) and coinfected (from 1.26 to 1.62) groups ($p<0.01$ and $p=0.02$, respectively, compared to the null hypothesis of no change) (Figure 1). In contrast, during the initial period after HI (interval B), the mean APRI declined for both the HIV-monoinfected (from 0.55 to 0.53) and coinfected men (from 1.62 to 1.31) ($p=0.01$ and $p=0.07$, respectively, compared to no change). Between 2-5 years after HI (interval C), mean APRI increased slightly for both groups, but the change was not significantly different from zero.

Among HIV-monoinfected men, APRI increased by 17% across interval A after adjusting for age, race, and pre-HI CD4 cell count (Table 1). The changes during interval B depended upon HIV RNA at the end of the interval. Specifically, HIV-monoinfected men with HIV RNA <500 copies/ml had a 16% decrease in APRI ($p<0.001$ compared to interval A), men with HIV RNA 500 to 75,000 copies/ml had only a 2% decrease in APRI ($p=0.02$ compared to interval A), and men with HIV RNA ≥75,000 copies/mL had a 47% increase in APRI ($p=0.07$ compared to interval A) (p-value for trend <0.001). Across interval C, APRI increased slightly while remaining below the pre-HI level, but the change was similar to interval A irrespective of HIV RNA.

Among the HIV-viral hepatitis coinfected men, the multivariable analysis demonstrated a 34% APRI increase across interval A (Table 1). Similar to the HIV-monoinfected men, the APRI changes across interval B varied by HIV RNA at the end of the interval. Men with HIV RNA <500 copies/ml had a 22% decrease in APRI ($p=0.01$ compared to interval A) while those with HIV RNA 500 to 75,000 copies/ml had a 13% decrease in APRI ($p=0.06$ compared to interval A). Since only 3 coinfected men had HIV RNA ≥75,000 copies/ml at the end of interval B, APRI change in this group was not determined. The APRI decline continued across interval C in the coinfected men with undetectable HIV RNA (mean APRI decrease of 8%), which remained significantly lower than interval A ($p=0.03$). Although the sample size precluded including type of viral hepatitis in multivariable analysis, the trends in APRI were consistent for both the HIV/HBV-coinfected and HIV/HCV-coinfected men.

To evaluate the potential impact of type of antiretroviral medication on APRI, we performed separate multivariable models including drug class (PI, NRTI, NNRTI) and specific classes or agents with known hepatic toxicity, such as dideoxynucleosides (including didanosine, zalcitabine, stavudine, and zidovudine), didanosine alone, and high-dose ritonavir. There were no significant associations when examining *current* antiretroviral agent use and APRI. However *cumulative* exposure was associated with higher APRI for NRTIs (1.3% higher/year of exposure, $p<0.001$), dideoxynucleosides (1.4%/year, $p<0.001$), and didanosine (3.4%/year, $p<0.001$). To evaluate whether this could explain the small APRI increase across interval C in HIV monoinfection, we adjusted for cumulative NRTI or dideoxynucleoside exposure. Indeed, after these adjustments, the interval C APRI change was significantly lower than interval A for the HIV-monoinfected men with undetectable HIV RNA.

Discussion

In this first longitudinal study to examine APRI, a marker of liver disease, in HIV-infected men both before and after HI, we demonstrated that HAART is associated with improvement in APRI in HIV-infected men with and without viral hepatitis. Notably, the HAART association was particularly pronounced in the early post-HI period and with HIV RNA <500 copies/ml but was not present when HIV RNA remained ≥ 75,000 copies/ml. Furthermore, in the coinfected group, this protective association only extended into the later post-HI period with maintenance of HIV RNA<500 copies/ml.

Although mounting evidence highlights the importance of HAART in slowing fibrosis progression in HIV-viral hepatitis coinfection, studies evaluating the impact of HAART on HIV-viral hepatitis-related liver disease have yielded inconsistent results [22-27]. While most of the studies are cross-sectional and rely on calculated fibrosis progression rates based on a single liver biopsy sample and estimated dates of infection, some investigators have analyzed progression using paired liver biopsies[23-27]. One study found that HAART was associated with a slower rate of fibrosis progression in HIV/HCV coinfection[27]. In contrast, two large prospective studies failed to find such an association, although most subjects were on HAART at the time of the first liver biopsy[25,26]. Thus, a HAART association may have been missed since our data demonstrate that the most profound changes in APRI occurred shortly after HI. Additionally, a second liver biopsy was performed in only a small minority of these cohorts, raising concern for selection bias. Supporting our findings, longitudinal studies have demonstrated reduced clinical outcomes such as hepatic decompensation and liver-related death among HAART-treated HIV/HCV-coinfected individuals, particularly when HIV RNA is suppressed and CD4 count increases on treatment[10,11,13,28].

Our finding in the HIV-monoinfected group is supported by a study reporting that effective HIV RNA suppression protected against developing significant liver fibrosis, as measured by the surrogate markers FIB-4 and APRI, among HIV-monoinfected HAART-initiators followed for 6 years[12]. We were unable to analyze change in FIB-4 because ALT values were not available from the majority of visits and ALT testing of stored serum was unreliable[3].

The mechanism by which HAART improves liver disease in HIV-infected individuals is not known. In HBV-infected men, the direct anti-viral activity of some of the nucleoside analogues against HBV can explain the improvement in APRI. Our observation that men with undetectable HIV RNA had the largest decreases in APRI and that the effect was reduced progressively with increasing HIV RNA supports the hypothesis that the beneficial hepatic effects of HAART are mediated via suppression of HIV replication. HIV activates the immune system and induces cytokine changes that promote fibrosis in the setting of HCV, and it is possible that HAART ameliorates this HIV-associated immune dysregulation [29]. This is supported by data from the MACS demonstrating a decrease in biomarkers of inflammation and immune activation in the first year after HAART-induced HIV suppression [30]. Additionally, HIV has direct and indirect hepatic effects, which could be mitigated with HAART. HIV might directly infect hepatocytes and hepatic stellate cells, thus promoting fibrogenesis[31,32]. Signaling via the HIV envelope protein gp120 can induce hepatocyte apoptosis and hepatic stellate cell activation[33,34]. HIV infection also leads to depletion of mucosal CD4 T-cells, thereby increasing intestinal microbial translocation, which has been associated with increased liver fibrosis progression in HIV/HCV coinfection[35].

A major limitation of this study is the reliance on a noninvasive marker as a surrogate for liver disease. Furthermore, although APRI is a marker of hepatic fibrosis, the changes we observed may stem from reductions in hepatic inflammation rather than fibrosis. Nevertheless, whether reflecting inflammation or fibrosis, APRI predicts all-cause mortality among HIV-infected individuals, even in the absence of viral hepatitis coinfection[36]. In addition, APRI increases over time are associated with higher risk of all-cause and liver-related mortality, including in the MACS[37-40]. This limitation is balanced by our ability to follow men before and after HI. Another limitation is that HBV- and HCV-infected subjects were analyzed together; however, APRI changes were similar when stratified by type of viral hepatitis infection. Additionally, since most of the cohort was started on a regimen that included a dideoxynucleoside analog, which has been associated with hepatic steatosis and which was associated with higher APRI values in our cohort, the beneficial effect of HAART in our study may have been underestimated[41]. Finally, our cohort was comprised entirely of men, limiting its generalizability.

In summary, APRI improves with suppression of HIV RNA replication in HIV-monoinfected and HIV-viral hepatitis-coinfected men in the first two years after HI. This improvement is greatest in those who achieve an undetectable HIV RNA in the early HAART period. After 2 years of HAART, the protective effect in both groups is decreased but more so in the HIV-monoinfected men. Further studies are needed to understand the mechanism for this improvement and to determine whether the benefits are extended long-term with newer HAART regimens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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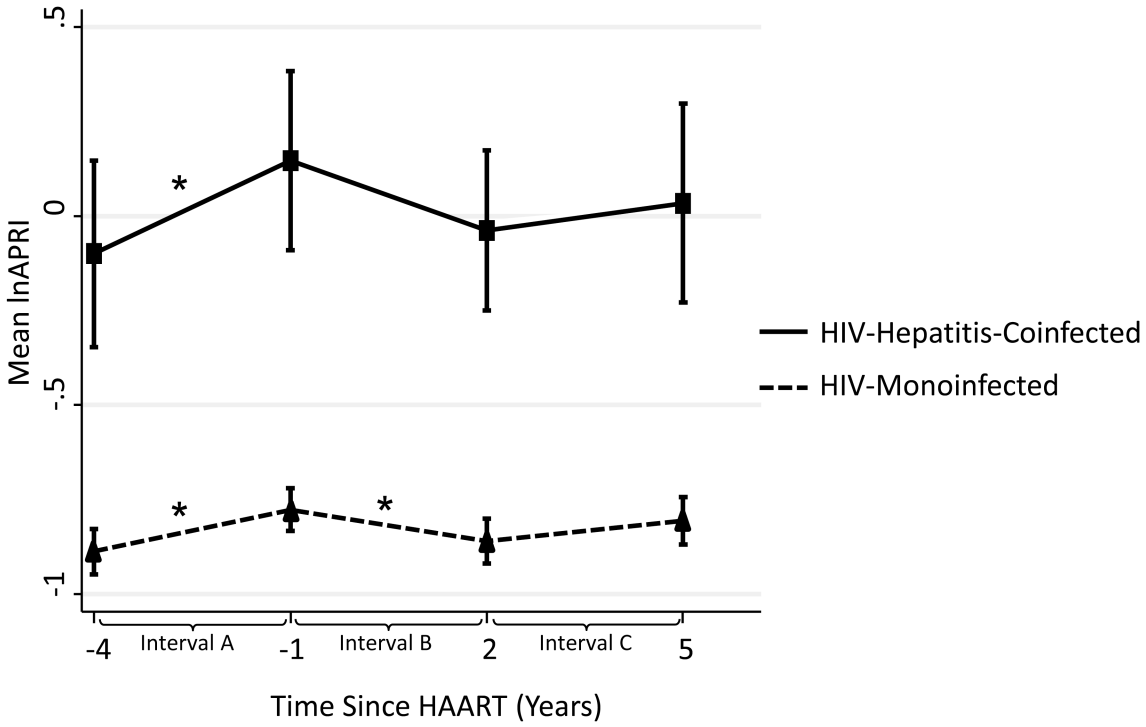

Figure 1. Mean lnAPRI (95% confidence interval) pre- and post-HAART initiation

*p<0.05 compared to no change

Table 1

Adjusted percent change in APRI across intervals A, B, and C among HIV-infected HAART initiators[1,2,3]

	Percent Change in APRI (95% CI)			
	HIV-Monoinfected			
	All	**Undetected VL[4]**	**VL Detected-75,000 copies/ml**	**VL ≥75,000 copies/ml**
Interval A	17% (8%, 25%)			
Interval B		-16% (-22%, -9%) p<0.001 (vs interval A)	-2% (-12%, 9%) p=0.02	47% (16%, 86%) p=0.07
Interval C		8% (-1.4%, 17%) p=0.15 (vs interval A)	7% (-7%, 23%) p=0.27	-1.6% (-33%, 44%) P=0.39
	HIV/Hepatitis-Coinfected			
	All	Undetected VL	VL Detected-75,000 copies/ml	VL ≥75,000 copies/ml
Interval A	34% (8%, 67%)			
Interval B		-22% (-38%, -2%) p=0.01 (vs interval A)	-13% (-36%, 20%) p=0.06	N/A[5]
Interval C		-8% (-28%, 21%) p=0.03 (vs interval A)	37% (-15%, 121%) p=0.93	N/A[5]

[1] Adjusted for age, race, and pre-HAART CD4 cell count

[2] Outcomes are ln-transformed; results are back-transformed to produce estimated relative differences in APRI.

[3] Interval A change refers to the change in APRI from the 4-years to 1-year pre-HAART interval, interval B change refers to the change in APRI from the 1-year pre-HAART to 2-year post-HAART interval, and interval C change refers to the change in APRI from 2-years to 5-years post-HAART.

[4] Refers to HIV RNA at the end of the interval (missing in 2 subjects in interval B and 1 subject in interval C):

- HIV-monoinfected interval B HIV RNA: undetectable (n=280), detectable to 75,000 copies/mL (n=120), ≥75,000 copies/ml (n=21)
- HIV-monoinfected interval C: undetectable (n=248), detectable to 75,000 copies/mL (n=89), ≥75,000 copies/ml (n=11)
- HIV-viral hepatitis-coinfected interval B HIV RNA: undetectable (n=34), detectable to 75,000 copies/mL (n=14), ≥75,000 copies/ml (n=3)
- HIV-viral hepatitis-coinfected interval C: undetectable (n=27), detectable to 75,000 copies/mL (n=7), ≥75,000 copies/ml (n=1)

[5] Not reported due to small sample size