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Authors
Price, Jennifer C
Seaberg, Eric C
Phair, John P
et al.

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Highly Active Antiretroviral Therapy Mitigates Liver Disease in HIV Infection

Jennifer C. Price, MD, PhD[1], **Eric C. Seaberg, PhD**[2], **John P Phair, MD**[3], **Mallory D. Witt, MD**[4], **Susan L Koletar, MD**[5], and **Chloe L. Thio, MD**[6]

[1]Department of Medicine, Division of Gastroenterology and Hepatology, University of California, San Francisco [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland [3]Department of Medicine, Division of Infectious Diseases, The Feinberg School of Medicine, Northwestern University, Chicago, Illinois [4]Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles Biomedical Research Institute at Harbor–UCLA, Torrance, California [5]Department of Medicine, Division of Infectious Diseases, Ohio State University, Columbus, Ohio [6]Department of Medicine, Division of Infectious Diseases, Johns Hopkins School of Medicine, Baltimore, Maryland

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

Corresponding author: Jennifer C. Price, 513 Parnassus Avenue, S-357, San Francisco, CA 94143, Tel: 415-502-1429, Fax: 415-476-0659.

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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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References

1. Weber R, Sabin CA, Friis-Moller N, et al. Liver-related deaths in persons infected with the human immunodeficiency virus: the D:A:D study. Arch Intern Med. Aug 14-28; 2006 166(15):1632–1641. [PubMed: 16908797]
2. Towner WJ, Xu L, Leyden WA, et al. The effect of HIV infection, immunodeficiency, and antiretroviral therapy on the risk of hepatic dysfunction. J Acquir Immune Defic Syndr. Jul 1; 2012 60(3):321–327. [PubMed: 22343179]
3. Price JC, Seaberg EC, Badri S, Witt MD, D'Acunto K, Thio CL. HIV monoinfection is associated with increased aspartate aminotransferase-to-platelet ratio index, a surrogate marker for hepatic fibrosis. J Infect Dis. Mar 15; 2012 205(6):1005–1013. [PubMed: 22291196]
4. DallaPiazza M, Amorosa VK, Localio R, Kostman JR, Lo Re V 3rd. Prevalence and risk factors for significant liver fibrosis among HIV-monoinfected patients. BMC Infect Dis. 2010; 10:116. [PubMed: 20465840]
5. Blackard JT, Welge JA, Taylor LE, et al. HIV Mono-infection Is Associated With FIB-4 - A Noninvasive Index of Liver Fibrosis - in Women. Clin Infect Dis. Mar; 2011 52(5):674–680. [PubMed: 21248367]
6. Benhamou Y, Bochet M, Di Martino V, et al. Liver fibrosis progression in human immunodeficiency virus and hepatitis C virus coinfected patients. The Multivirc Group. Hepatology. Oct; 1999 30(4): 1054–1058. [PubMed: 10498659]
7. Mocroft A, Soriano V, Rockstroh J, et al. Is there evidence for an increase in the death rate from liver-related disease in patients with HIV? AIDS. Dec 2; 2005 19(18):2117–2125. [PubMed: 16284461]
8. Towner WJ, Xu L, Leyden WA, et al. The Effect of HIV Infection, Immunodeficiency and Antiretroviral Therapy on the Risk of Hepatic Dysfunction. J Acquir Immune Defic Syndr. Feb 16.2012
9. Brau N, Salvatore M, Rios-Bedoya CF, et al. Slower fibrosis progression in HIV/HCV-coinfected patients with successful HIV suppression using antiretroviral therapy. J Hepatol. Jan; 2006 44(1): 47–55. [PubMed: 16182404]
10. Pineda JA, Garcia-Garcia JA, Aguilar-Guisado M, et al. Clinical progression of hepatitis C virus-related chronic liver disease in human immunodeficiency virus-infected patients undergoing highly active antiretroviral therapy. Hepatology. Sep; 2007 46(3):622–630. [PubMed: 17659577]
11. Qurishi N, Kreuzberg C, Luchters G, et al. Effect of antiretroviral therapy on liver-related mortality in patients with HIV and hepatitis C virus coinfection. Lancet. Nov 22; 2003 362(9397):1708–1713. [PubMed: 14643119]
12. Mendeni M, Foca E, Gotti D, et al. Evaluation of liver fibrosis: concordance analysis between noninvasive scores (APRI and FIB-4) evolution and predictors in a cohort of HIV-infected patients

without hepatitis C and B infection. Clin Infect Dis. May; 2011 52(9):1164–1173. [PubMed: 21467023]

13. Anderson JP, Tchetgen Tchetgen EJ, Lo Re V 3rd, et al. Antiretroviral therapy reduces the rate of hepatic decompensation among HIV- and hepatitis C virus-coinfected veterans. Clin Infect Dis. Mar; 2014 58(5):719–727. [PubMed: 24285848]
14. Nunez M. Clinical syndromes and consequences of antiretroviral-related hepatotoxicity. Hepatology. Sep; 2010 52(3):1143–1155. [PubMed: 20812358]
15. Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. Aug; 2003 38(2):518–526. [PubMed: 12883497]
16. Kaslow RA, Ostrow DG, Detels R, Phair JP, Polk BF, Rinaldo CR Jr. The Multicenter AIDS Cohort Study: rationale, organization, and selected characteristics of the participants. Am J Epidemiol. Aug; 1987 126(2):310–318. [PubMed: 3300281]
17. Dudley J, Jin S, Hoover D, Metz S, Thackeray R, Chmiel J. The Multicenter AIDS Cohort Study: retention after 9 1/2 years. Am J Epidemiol. Aug 1; 1995 142(3):323–330. [PubMed: 7631636]
18. Witt MD, Lewis RJ, Rieg G, Seaberg EC, Rinaldo CR, Thio CL. Predictors of the isolated hepatitis B core antibody pattern in HIV-infected and -uninfected men in the multicenter AIDS cohort study. Clin Infect Dis. Feb; 2013 56(4):606–612. [PubMed: 23090927]
19. Witt MD, Seaberg EC, Darilay A, et al. Incident Hepatitis C Virus Infection in Men Who Have Sex With Men: A Prospective Cohort Analysis, 1984-2011. Clinical Infectious Diseases. Jul 1; 2013 57(1):77–84. [PubMed: 23532480]
20. DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents.
21. Schenker EL, Hultin LE, Bauer KD, Ferbas J, Margolick JB, Giorgi JV. Evaluation of a dual-color flow cytometry immunophenotyping panel in a multicenter quality assurance program. Cytometry. 1993; 14(3):307–317. [PubMed: 8472607]
22. Kramer JR, Giordano TP, El-Serag HB. Effect of human immunodeficiency virus and antiretrovirals on outcomes of hepatitis C: a systematic review from an epidemiologic perspective. Clin Gastroenterol Hepatol. Nov; 2007 5(11):1321–1328. e1327. [PubMed: 17981246]
23. Bonnard P, Lescure FX, Amiel C, et al. Documented rapid course of hepatic fibrosis between two biopsies in patients coinfected by HIV and HCV despite high CD4 cell count. J Viral Hepat. Nov; 2007 14(11):806–811. [PubMed: 17927617]
24. Schiavini M, Angeli E, Mainini A, et al. Fibrosis progression in paired liver biopsies from HIV/HCV co-infected patients. Hepat Mon. Jul 1; 2011 11(7):525–531. [PubMed: 22706343]
25. Konerman MA, Mehta SH, Sutcliffe CG, et al. Fibrosis progression in human immunodeficiency virus/hepatitis C virus coinfected adults: prospective analysis of 435 liver biopsy pairs. Hepatology. Mar; 2014 59(3):767–775. [PubMed: 24436062]
26. Sterling RK, Wegelin JA, Smith PG, et al. Similar progression of fibrosis between HIV/HCV-infected and HCV-infected patients: Analysis of paired liver biopsy samples. Clin Gastroenterol Hepatol. Dec; 2010 8(12):1070–1076. [PubMed: 20728569]
27. Macias J, Berenguer J, Japon MA, et al. Fast fibrosis progression between repeated liver biopsies in patients coinfected with human immunodeficiency virus/hepatitis C virus. Hepatology. Oct; 2009 50(4):1056–1063. [PubMed: 19670415]
28. Lo Re V 3rd, Kallan MJ, Tate JP, et al. Hepatic decompensation in antiretroviral-treated patients co-infected with HIV and hepatitis C virus compared with hepatitis C virus-monoinfected patients: a cohort study. Ann Intern Med. Mar 18; 2014 160(6):369–379. [PubMed: 24723077]
29. Kim AY, Chung RT. Coinfection with HIV-1 and HCV--a one-two punch. Gastroenterology. Sep; 2009 137(3):795–814. [PubMed: 19549523]
30. Wada NI, Jacobson LP, Margolick JB, et al. The effect of HAART-induced HIV suppression on circulating markers of inflammation and immune activation. AIDS. Feb 20; 2015 29(4):463–471. [PubMed: 25630041]
31. Xiao P, Usami O, Suzuki Y, et al. Characterization of a CD4-independent clinical HIV-1 that can efficiently infect human hepatocytes through chemokine (C-X-C motif) receptor 4. AIDS. Sep 12; 2008 22(14):1749–1757. [PubMed: 18753859]

32. Tuyama AC, Hong F, Saiman Y, et al. Human immunodeficiency virus (HIV)-1 infects human hepatic stellate cells and promotes collagen I and monocyte chemoattractant protein-1 expression: implications for the pathogenesis of HIV/hepatitis C virus-induced liver fibrosis. Hepatology. Aug; 2010 52(2):612–622. [PubMed: 20683959]
33. Vlahakis SR, Villasis-Keever A, Gomez TS, Bren GD, Paya CV. Human immunodeficiency virus-induced apoptosis of human hepatocytes via CXCR4. J Infect Dis. Nov 15; 2003 188(10):1455–1460. [PubMed: 14624370]
34. Bruno R, Galastri S, Sacchi P, et al. gp120 modulates the biology of human hepatic stellate cells: a link between HIV infection and liver fibrogenesis. Gut. Apr; 2010 59(4):513–520. [PubMed: 19736361]
35. Balagopal A, Philp FH, Astemborski J, et al. Human immunodeficiency virus-related microbial translocation and progression of hepatitis C. Gastroenterology. Jul; 2008 135(1):226–233. [PubMed: 18457674]
36. Post FA, Sabin CA. Aspartate aminotransferase-to-platelet ratio index is a powerful predictor of mortality among HIV-positive patients. J Infect Dis. Jan 15; 2013 207(2):367–368. [PubMed: 23107784]
37. Bambha K, Pierce C, Cox C, et al. Assessing mortality in women with hepatitis C virus and HIV using indirect markers of fibrosis. AIDS. Mar 13; 2012 26(5):599–607. [PubMed: 22156972]
38. Vergniol J, Boursier J, Coutzac C, et al. Evolution of noninvasive tests of liver fibrosis is associated with prognosis in patients with chronic hepatitis C. Hepatology. Jul; 2014 60(1):65–76. [PubMed: 24519328]
39. Jain MK, Seremba E, Bhore R, et al. Change in fibrosis score as a predictor of mortality among HIV-infected patients with viral hepatitis. AIDS Patient Care STDS. Feb; 2012 26(2):73–80. [PubMed: 22239101]
40. Price JC, Seaberg E, Hawkins C, Koletar SL, Witt M, Thio CL. Increases in APRI are asssociated with liver-related death in HIV-viral hepatitis coinfection. Hepatology. 2014; 60:978A.
41. Price JC, Seaberg EC, Latanich R, et al. Risk factors for fatty liver in the Multicenter AIDS Cohort Study. Am J Gastroenterol. May; 2014 109(5):695–704. [PubMed: 24642579]

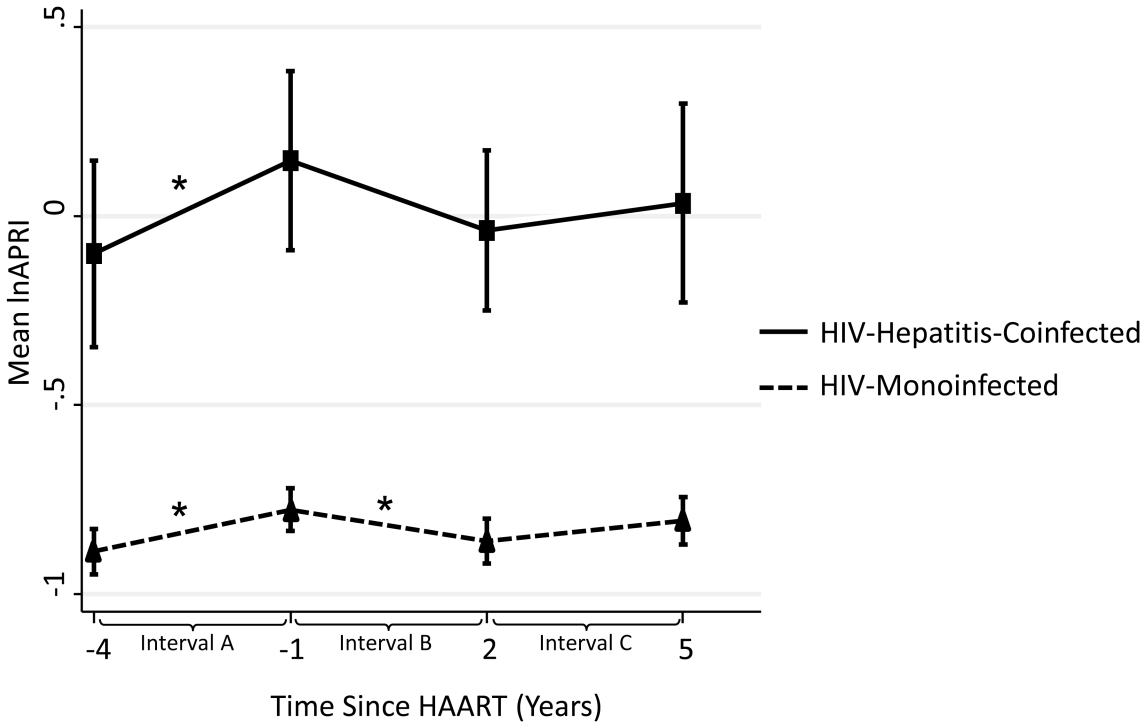

Figure 1. Mean lnAPRI (95% confidence interval) pre- and post-HAART initiation

*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