

Longitudinal Effect of Antiretroviral Therapy on Markers of Hepatic Toxicity: Impact of Hepatitis C Coinfection

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To characterize longitudinal hepatic toxicity of antiretroviral therapy in HIV-infected women with and without hepatitis C virus (HCV) infection, we measured alanine and aspartate aminotransferase values among women initiating highly active antiretroviral therapy (HAART). For 312 HIV/HCV coinfecting women who received HAART for a mean of 1.8 years, the prevalence of elevated aminotransferase levels >3 times and >5 times the upper limit of normal (ULN) was low (<12% and <4%, respectively), and the prevalence of elevated aminotransferase levels declined over time. When we analyzed trends in aminotransferase levels according to type of HAART received among HCV-infected and uninfected women, we found that mean aminotransferase levels declined among 539 women receiving therapy with protease inhibitors (decreases of 5.34%–4.23% of the ULN per year; *P* values for trend of .007–.06), but mean values among 128 women receiving therapy with non-nucleoside reverse-transcriptase inhibitors remained stable (from decreases of 1.65% to increases of 7.57% of the ULN per year; *P* values of .19–.71). Our findings lend support to assertions that antiretroviral therapy is safe for women with HCV infection.

As the era of highly active therapy against HIV-1 continues, the extent and significance of antiretroviral therapy (ART) toxicities are becoming more completely understood. It is clear from clinical trials and short-term clinical cohort studies that some HIV-1-infected patients, often those with hepatitis C or B coinfection, experience acute hepatocellular injury after the initiation of ART [1–9]. Several studies have identified female sex as an additional risk factor for hepatic toxicity [3, 6]. Whether and how often longer-term hepatotoxicity of ART occurs is less clear. Given the prolonged duration of ART and the high prevalence of chronic viral hepatitis among persons with HIV, fully under-

standing the effect of ART on the liver over years of use is imperative.

To characterize the chronic hepatic effects of ART among women with and without hepatitis C virus (HCV) infection, we measured alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels in women participating in the Women's Interagency HIV Study (WIHS) during a period that included the beginning of the HAART era. The WIHS is a longitudinal, observational study of women with or at risk for HIV-1 infection. The baseline seroprevalence of HCV infection in the WIHS was 43% among HIV-infected women.

Serum aminotransferase levels are imperfect measurements of hepatic injury and cannot be used alone to monitor liver disease but do correlate with hepatic inflammation and fibrosis on the population level [10–12]. Although the ALT level is most specific for hepatocytes, both ALT and AST levels are broadly used clinically to screen for and monitor hepatic injury from

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medications and to follow the clinical course of chronic hepatitis [10]. Interest in the role of AST has risen lately, because preliminary data suggest that the elevation of AST levels, which is of hepatic mitochondrial and cytosolic origin, may be an independent predictor of mortality in HIV disease [13, 14].

METHODS

From October 1994 to November 1995, the WIHS enrolled 2628 American women; 2059 HIV-infected and 569 uninfected at-risk women were enrolled at 6 sites: Chicago, Illinois; Northern California; New York (2 sites); Washington, D.C.; and Los Angeles, California. Informed consent was obtained from all participants, in accordance with the US Department of Health and Human Services guidelines and the institutional review boards of participating institutions. Women were seen semiannually for an interview, a physical examination, and collection of blood and genital specimens. Cohort recruitment methods and demographic characteristics are detailed elsewhere [15].

Laboratory methods. AST and ALT values were measured in fresh specimens by standard methodology in Clinical Laboratory Improvement Amendments–certified laboratories (Quest Diagnostics, Baltimore, MD; Labcorp, Burlington, NC; Unilab, Tarzana, CA; University Hospital of Brooklyn, Brooklyn, NY; and Los Angeles County Laboratory, Los Angeles, CA) annually from October 1994 through March 2001 and semiannually thereafter. We chose the upper limit of normal (ULN) for the individual laboratories as our benchmark because this is the value used as a reference by clinicians and in most clinical trials. Individual patients' aminotransferase levels were divided by the ULN to standardize results across multiple laboratories. The ULN for these laboratories ranged from 40 to 65 IU/L for ALT levels and from 35 to 50 IU/L for AST levels. Moderate elevation in aminotransferase levels was defined as >3 times the ULN and severe elevation as >5 times the ULN.

Because data on HCV viremia were not available, we used HCV antibody status to define HCV coinfection (HCV EIA, version 2.0; Abbott Laboratories). A seroincidence study performed in 1999, which tested for HCV RNA by PCR and HCV EIA, version 3.0 (Ortho-Diagnostic Systems), revealed that 8 HIV-infected study subjects acquired HCV infection (incidence, <3 cases per 1000 person-years) [16]. These 8 women were eliminated from this study. We assumed the rate of subsequent HCV acquisition was approximately equal to that found in the previous study, and, therefore, the small number of expected seroconversions (~ 8) would not skew the data. Treatment of HCV infection was rare among the WIHS participants during the study period (1.8% of HCV-infected women had received treatment, as of late 2001) and is unlikely to have affected the data.

Definition of HAART. Data on ART were collected by self-report facilitated by photographs of medications. HAART was defined as the use of any of the following combinations:

(1) ≥ 2 nucleoside analogue reverse-transcriptase inhibitors (NRTIs) with at least 1 protease inhibitor (PI) or nonnucleoside reverse-transcriptase inhibitor (NNRTI); (2) 1 NRTI with at least 1 PI and at least 1 NNRTI; (3) a regimen containing zidovudine and zalcitabine with 1 NRTI and no NNRTIs; (4) a regimen containing abacavir with ≥ 3 NRTIs. The midpoint between the last date receipt of HAART was not reported and the first date it was reported was designated as the date of HAART initiation. This date was designated as time 0, and the first aminotransferase measurement obtained while the patient was receiving HAART was designated as time 0.5 years, the second measurement as time 1.5 years, and so on.

Study population. The population involved in this study included 456 HCV antibody–positive and 650 HCV antibody–negative WIHS participants who first reported receipt of HAART between 1 April 1995 and 31 March 2002. Longitudinal analyses included 312 HCV-positive and 446 HCV-negative patients who received continuous HAART, tested negative for hepatitis B surface antigen, and had aminotransferase values recorded from, at least, the visit before and the visit after HAART initiation, and were followed up until the last visit that HAART receipt was reported.

Subanalysis included 539 women (of whom 212 were HCV positive and 327 were HCV negative) who initiated HAART with PIs but no NNRTIs and 128 women (of whom 54 were HCV positive and 74 were HCV negative) who initiated HAART with NNRTIs but no PIs; these women were followed up until the first visit at which either a change in the category of therapy or HAART discontinuation was reported.

Statistical analysis of changes across categories and time. The primary outcome measurement was the serum aminotransferase level, which was evaluated in 2 ways: as the mean percentage of the ULN (actual value/[ULN \times 100]) and as the proportion of women with aminotransferase values >1 , >1.5 , >2 , >3 , or >5 times the ULN. For both methods of evaluation, generalized estimating equations (GEEs) were used to account for the correlation between observations regarding the same woman. For the continuous method of measuring, we used a \log_{10} transformation to normalize the distribution and then specified the model with the identical link under a Gaussian distribution. For this method, we also used random coefficient analysis as a sensitivity analysis for trends and statistical inferences. For the proportional method of measuring outcome, we used dichotomous variables for each observation and specified the model with the logit link under a binomial distribution. All models included time relative to HAART initiation as the primary exposure of interest and also included 3 secondary exposures of interest: age, concurrent body mass index (BMI), and alcohol use (average number of drinks per week in the prior 6 months). For each model, we tested for significant

Table 1. Demographic and clinical characteristics of 1106 HIV-infected participants in the Women's Interagency HIV Study who ever received HAART.

Characteristic	HCV antibody positive (N = 456)	HCV antibody negative (N = 650)	P
Qualitative characteristics			
Race or ethnicity			.04
African American	267 (59)	331 (51)	
White	82 (18)	120 (18)	
Latino/Hispanic	99 (22)	179 (28)	
Other	8 (2)	20 (3)	
Hepatitis B surface antigen positive	18 (4)	15 (1)	.12
HIV transmission risk category			<.0001
Injection drug use	316 (69)	29 (5)	
Heterosexual sex	106 (23)	377 (59)	
Transfusion recipient	13 (3)	34 (5)	
None known	21 (5)	199 (31)	
Recent alcohol use			<.0001
None	266 (59)	363 (57)	
Light (<3 drinks per week)	80 (18)	178 (28)	
Moderate (3–13 drinks per week)	59 (13)	74 (12)	
Heavy (>13 drinks per week)	41 (9)	25 (4)	
First HAART regimen			.08
PI-based	325 (71)	481 (74)	
NNRTI-based	88 (19)	122 (19)	
PI- and NNRTI-based	32 (7)	43 (7)	
NRTI-based	11 (2)	4 (1)	
Received NRTI therapy immediately prior to HAART			.04
Yes	305 (67)	471 (73)	
No	150 (33)	176 (27)	
Quantitative characteristics, mean value ± SD			
Date of HAART initiation	24 Dec 97 ± 533 days	10 Aug 97 ± 451 days	<.0001
Age at HAART initiation, years	42 ± 6	37 ± 8	<.0001
BMI immediately prior to HAART initiation	27 ± 7	27 ± 7	.45
CD4 cell count immediately prior to HAART initiation, cells/mm ³	302 ± 236	301 ± 219	.90
HIV RNA level immediately prior to HAART initiation, log ₁₀ copies/mL	3.91 ± 1.31	3.97 ± 1.24	.49

NOTE. Data are no. (%) of patients, unless otherwise indicated. BMI, body mass index; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

interactions between the primary exposure and each secondary exposure.

RESULTS

Characteristics of women who initiated HAART. Table 1 presents characteristics of the 1106 HIV-infected WIHS participants who initiated HAART during the study. The prevalence of HCV antibody positivity among HAART recipients was 41%. HCV-positive women were significantly more likely to be older, to be African-American, and, as expected, to have injection drug use as their HIV transmission risk factor. HCV-

positive women were also more likely to have recently used alcohol and to have used alcohol heavily.

HCV-positive women initiated HAART at a later date than HCV-negative women, but the mean CD4 cell count and HIV RNA level at initiation were almost identical. A majority of women (73%) initiated HAART with a PI/NRTI regimen; 19% initiated HAART with an NNRTI/NRTI regimen. There was no significant difference in receipt of PI-based or NNRTI-based HAART according to HCV status. Nevirapine accounted for 78% of the NNRTI use.

Coinfected women: longitudinal trends in aminotransferase

levels relative to HAART initiation. We first analyzed how often aminotransferase levels were greater than the ULN in all HIV/HCV coinfecting women who initiated HAART. Figure 1 shows trends in aminotransferase values for 312 coinfecting women, who were followed as long as they continued to receive HAART, whether they switched to a different regimen or not. The proportions of coinfecting women with elevated aminotransferase values showed a downward trend in all categories of elevation above the ULN. The proportion of ALT values that were elevated decreased by 0.57%–1.86% per year; however, the trend was statistically significant only for ALT levels >3 times the ULN. AST levels (figure 1B) were greater than the ULN more frequently than were ALT levels. For AST levels, the proportion of women with values greater than the ULN declined significantly in every category of elevation over time (decrease of 2.09%–3.77% per year). The proportion of women with moderate elevation in aminotransferase levels (>3 times the ULN) was low: <7% of women at any time for ALT levels and <12% of women for AST levels. Data for severe elevation are not included in figure 1, because there were few such data,

but aminotransferase values were >5 times the ULN for <4% of coinfecting women at all times, and this proportion declined (nonsignificantly) over time. Of coinfecting women who had moderate or severe elevation in aminotransferase levels while receiving HAART, 36 (57%) of 63 continued to receive HAART within the same category for at least the 2 visits after the last elevated level, 18 (29%) of 63 discontinued HAART within that time frame, and 9 (14%) of 63 had their HAART regimen switched to a different antiretroviral category. Seven (11%) of these women reported having undergone liver biopsy, and 8 (13%) reported having had clinical liver disease at some time subsequent to the elevation in aminotransferase levels, but results of the biopsies and details of the liver disease were not available.

Longitudinal trends in aminotransferase levels stratified by HCV status and antiretroviral category. Figures 2A and 2B show ALT and AST levels during the time patients were receiving HAART for 667 women who started HAART with a PI-only or NNRTI-only regimen (i.e., a PI or NNRTI and nucleoside regimen). Women were included in the analysis as long

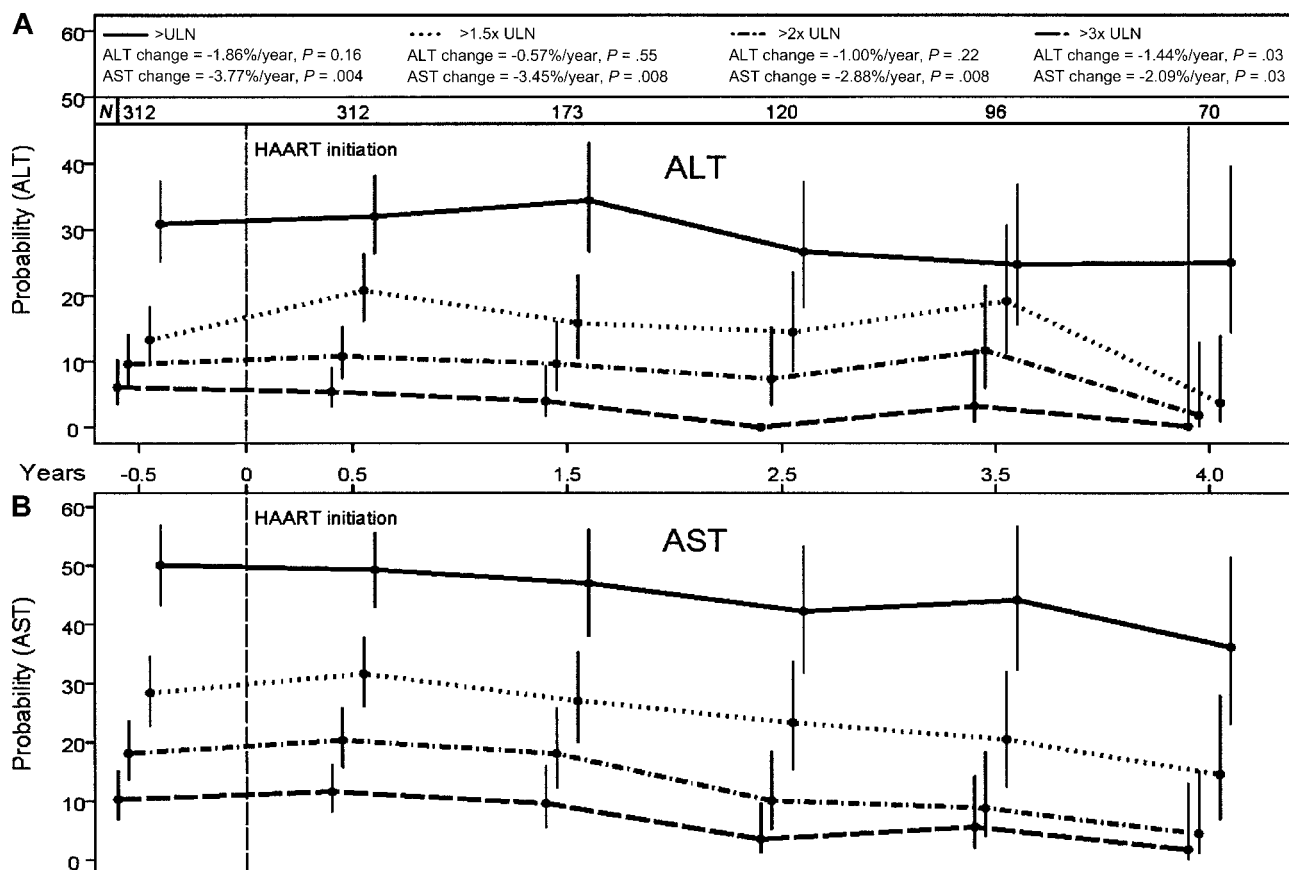


Figure 1. Proportion of 312 HIV and hepatitis C (HCV) coinfecting women exposed to HAART who had alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels greater than the upper limit of normal (ULN) while receiving HAART. The 95% CIs are displayed for each data point (vertical lines); data points for each time point are concurrent but are offset horizontally to display the 95% CI. Time 0, HAART initiation.

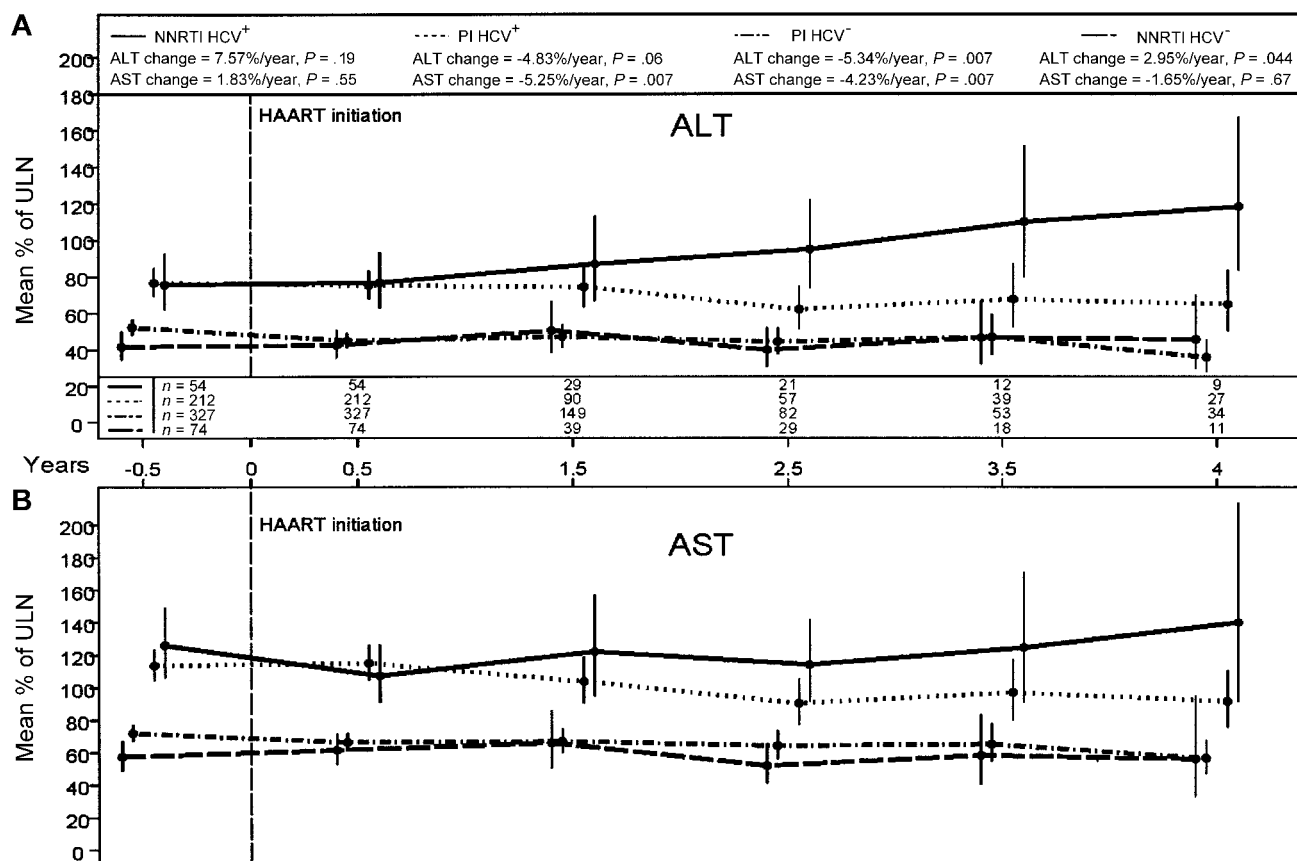


Figure 2. Trends in alanine aminotransferase (ALT) levels (A) and aspartate aminotransferase (AST) levels (B) among 657 women receiving HAART, stratified by hepatitis C virus (HCV) status and type of antiretroviral therapy received. The 95% CIs are displayed for each data point (vertical lines); data points for each time point are concurrent but are offset horizontally to display the 95% CI. Time 0, HAART initiation. NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

as they continued to receive a HAART regimen within the original category. The same inferences were obtained from GEEs and random coefficient analysis. GEE results are shown in figure 2. HCV-positive women had significantly higher aminotransferase levels at all time points. There was little difference between values before and immediately after HAART initiation in any category. However, during the time they were receiving HAART, women who continued to receive PIs had declines in ALT and AST values (decreases of 4.23%–5.34% of the ULN per year). These declines were statistically significant for AST levels for HCV-infected and -uninfected women ($P = .007$) and for ALT levels for HCV-negative women ($P = .007$) and approached significance for HCV-positive women ($P = .06$). Aminotransferase levels increased among women who continued to receive NNRTIs (1.83% to 7.57% of the ULN per year), except for AST levels among HCV-negative women (decreases of 1.65% of the ULN per year); none of these trends was significant.

Figure 3 demonstrates the proportion of women with ALT (figure 3A) or AST (figure 3B) levels greater than the ULN

before and after HAART initiation, stratified by HCV status and HAART category. We found similar trends to those shown in figure 2, with HCV-infected women who received PIs having decreasing proportions of values greater than the ULN over time (ALT, decrease of 4.67% of the ULN per year [$P = .02$]; and AST, decrease of 3.85% per year [$P = .06$]). There were no significant trends over time among patients receiving other categories of HAART, although, again, NNRTI recipients had nonsignificant increases in the proportion of values greater than the ULN (1.14%–2.76% per year).

When we analyzed trends for specific NNRTIs, the small number of evaluable women receiving efavirenz ($n = 26$) precluded meaningful comparison of trends in aminotransferase levels between treatment with nevirapine and treatment with efavirenz.

Trends in aminotransferase levels stratified by pre-HAART values. To better understand trends in aminotransferase values in HCV-positive women, we stratified results by pre-HAART aminotransferase levels. Figure 4 compares trends in ALT and AST values between women whose pre-HAART levels

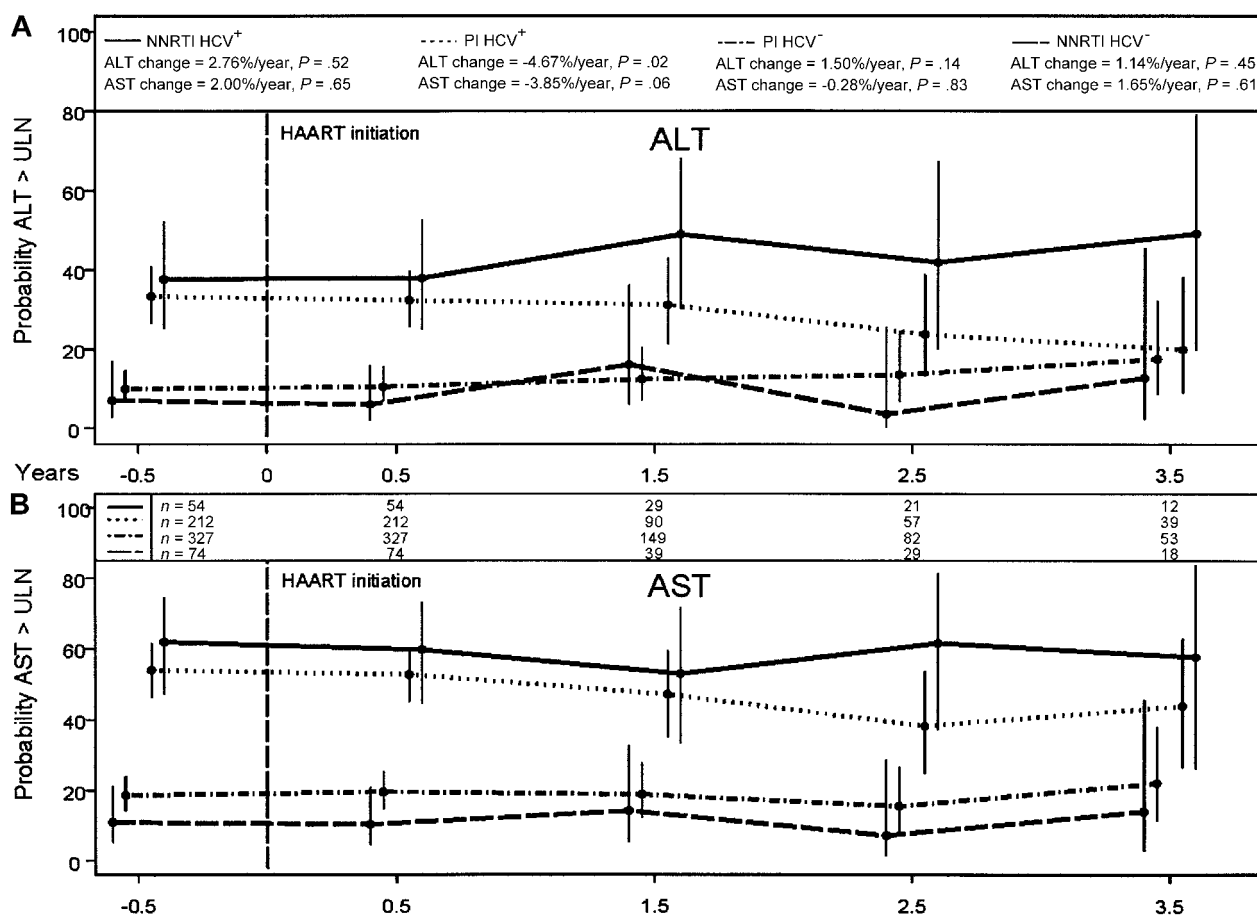


Figure 3. Proportion of 657 women receiving HAART who had alanine aminotransferase (ALT) levels (A) and aspartate aminotransferase (AST) levels (B) greater than the upper limit of normal, stratified by hepatitis C virus status and type of antiretroviral therapy received. The 95% CIs are displayed for each data point (vertical lines); data points for each time point are concurrent but are offset horizontally to display the 95% CI. Time 0, HAART initiation. ULN, upper limit of normal.

were always ≤ 1.5 times the ULN and women who ever had a pre-HAART level of >1.5 times the ULN. Of interest, women who started with lower aminotransferase values had stable mean ALT and AST values over time, whereas women who had elevated values prior to HAART had significant decreases in mean values over time.

When we further stratified results for women with high pre-HAART aminotransferase values by the degree to which aminotransferase levels exceeded the upper limit of normal, we found that those starting HAART with the highest values had the largest decreases in mean values (data not shown).

Secondary exposures. For each analysis, we tested for interactions between the primary exposure, time receiving HAART, and age, alcohol use, and BMI. Although there were instances of associations between secondary exposures and absolute aminotransferase level, there were no statistically significant interactions between secondary exposures and trends in aminotransferase values.

DISCUSSION

Hepatotoxicity is a potentially serious complication of HIV treatment, and elevation of serum aminotransferase levels is often the first sign of hepatotoxicity. We observed a large cohort of women before and after HAART initiation to characterize patterns of elevation in ALT and AST levels. It is not a surprise that we found that HCV antibody-positive women had higher ALT and AST levels before and after HAART initiation than did HCV antibody-negative women. With a mean follow-up of 1.8 years, we found no increase in aminotransferase values with HAART initiation and found improvement over time in aminotransferase values in many of the analyses performed; improvement was most marked among those women who had elevated aminotransferase levels prior to the beginning of HAART therapy.

When trends in aminotransferase levels were stratified by type of ART, our data showed that, among women who con-

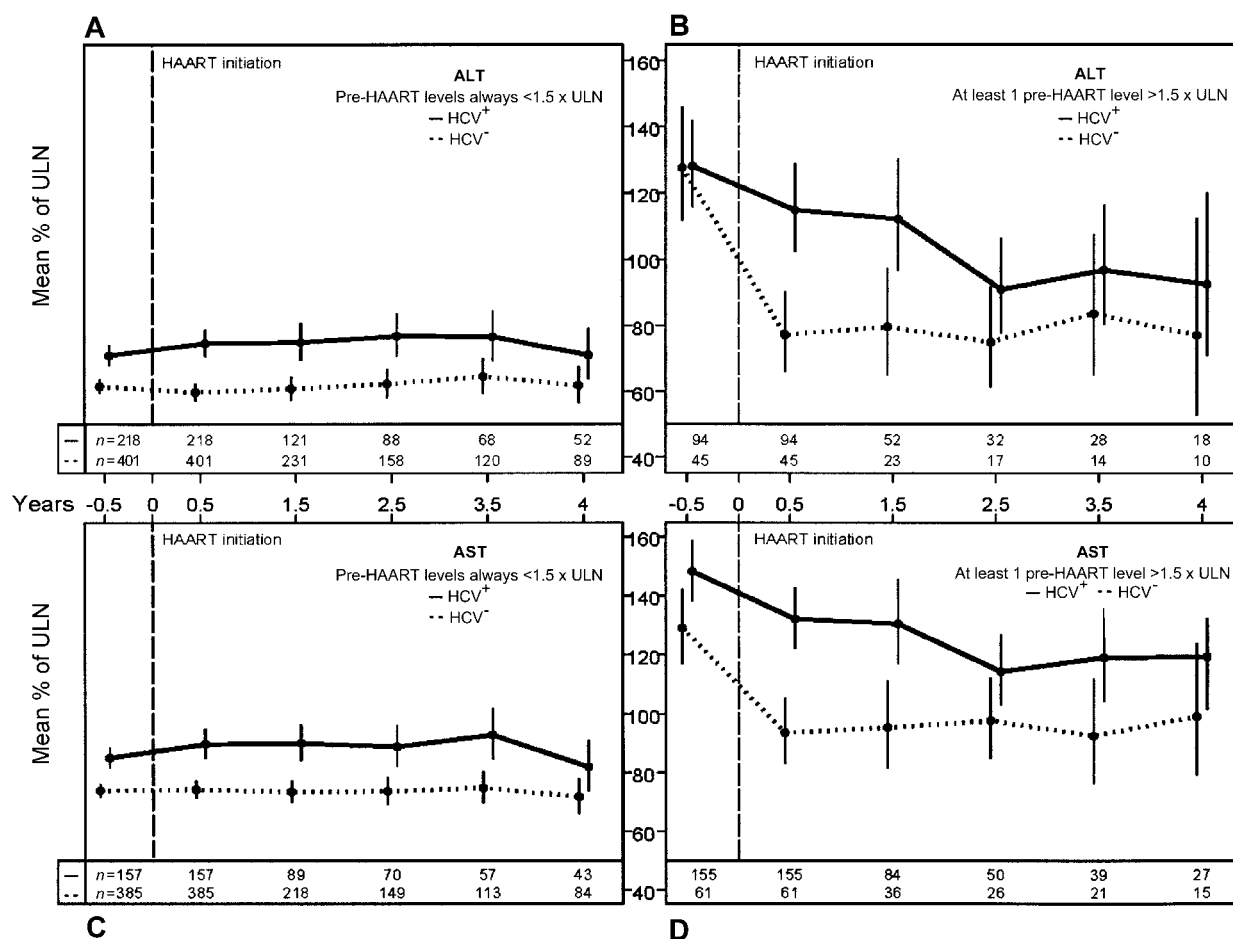


Figure 4. Trends in aminotransferase levels over time receiving HAART, stratified by hepatitis C virus status and aminotransferase level status before HAART initiation. *Top*, Trends in alanine aminotransferase (ALT) levels in women who, when they initiated HAART, had always had an ALT level of ≤ 1.5 times the upper limit of normal (ULN) (A) or had had at least 1 ALT level of > 1.5 times the ULN (B). *Bottom*, Trends in aspartate aminotransferase (AST) levels in women who, when they initiated HAART, had always had an AST level of ≤ 1.5 times the ULN (C) or had had at least 1 AST level of > 1.5 times the ULN (D). The 95% CIs are displayed for each data point (vertical lines); data points for each time point are concurrent but are offset horizontally to display the 95% CI. Time 0, HAART initiation.

tinued to receive PIs, there were decreases in aminotransferase values; these changes were statistically significant in the majority of analyses. Women who continued to receive NNRTIs had no significant changes in aminotransferase values over time, although, in several analyses, there were nonsignificant upward trends.

The majority of published hepatotoxicity studies have included mostly or only patients receiving PI therapy and were unable to compare the effects of different regimens on aminotransferase levels. In the largest published study comparing regimens, Nunez et al. [9] reported that, among 225 persons who initiated HAART, there was no difference between recipients of PI and recipients of NNRTI in incidence of severe hepatic enzyme elevation (defined as > 5 times the ULN). Our study measured trends over time and did reveal a difference in trends in aminotransferase levels between recipients of NNRTIs and recipients of PIs. This difference in the trajectory of ami-

notransferase levels in women receiving different classes of antiretrovirals suggests that PIs may have less longitudinal hepatic toxicity than do NNRTIs.

Nevirapine, which was the NNRTI used by the majority of this cohort, has been associated with 2 types of hepatotoxicity syndromes. There is a syndrome of early hepatotoxicity, often occurring with a rash, which is thought to be allergic in origin [17]. A second mechanism, which has delayed onset, represents the intrinsic toxic effect of the drug [17]. Several recent studies have demonstrated that nevirapine has greater hepatotoxicity than does efavirenz. Sulkowski et al. [6] and Martin-Carbonero et al. [18] reported that severe hepatic enzyme elevation (defined as ≥ 5 times the ULN) was 2 times and 3 times more common, respectively, with nevirapine than with efavirenz therapy in retrospective clinical cohorts. The randomized “2NN” study showed that nevirapine was associated with more hepatic adverse events overall than was efavirenz [19].

Several of the published studies on hepatotoxicity report that a significant proportion of patients with severe enzyme elevations (defined as ≥ 5 times the ULN) who continued to receive the same antiretroviral regimen had improvement in or normalization of their enzyme levels and were able to continue therapy [2, 4, 18, 20, 21]. Our findings that, among patients who continued to receive HAART, there was no significant increase and, in some cases, there was a decrease in ALT or AST levels while receiving therapy support the observation that continued ART does not lead to continued elevation of aminotransferase levels in persons for whom clinicians have chosen to continue ART.

The question about the relationship between HIV therapy and HCV disease progression is extremely complex. Some studies have reported more-frequent elevation in hepatic enzyme levels among coinfecting persons who experience good immunologic response and postulated that immune reconstitution had induced hepatic inflammation [21–23]. Others have found that coinfecting persons who did not respond to antiretroviral therapy had more hepatotoxicity [1]. Investigators exploring the relationship between HCV load and HAART have found an initial increase in HCV load, followed by a decrease to below-baseline levels after several months of therapy [18, 24]. Torre et al. [21], in a cohort of 323 coinfecting patients initiating HAART, found that aminotransferase levels increased in the first 6 months of HAART, then decreased to levels lower than at baseline, later in therapy. Torre and colleagues [21] also found, as we did, that those beginning HAART with elevated aminotransferase levels had significant decreases while receiving HAART. They postulated that HAART leads to restoration of cytotoxic T lymphocyte responses to HCV, thus improving HCV disease status over time. Our findings that HCV-infected women who received HAART had either a decrease in or no change in aminotransferase levels over time imply that continued HAART does not worsen HCV-induced liver injury.

Some investigators have found that persons with HCV infection are less likely to receive ART [25]. We found that the median date of HAART initiation was later for HCV-infected women, but that the mean CD4 cell counts and HIV RNA levels at initiation were similar for HCV-positive and HCV-negative women, which implies that clinical thresholds for starting therapy were similar for HCV-positive and HCV-negative women in this cohort.

Limitations. Our study needs to be evaluated with the limitations of the data in mind. Aminotransferase levels were determined on an annual basis only for the majority of the study period; much of the incidence of early antiretroviral hepatotoxicity may have been missed because of infrequent observation. We do not have data regarding the reason for discontinuation for women who stopped HAART; we assume, but cannot prove, that clinicians quickly discontinued therapy

for women who had significant hepatic enzyme elevation and that these elevations in enzyme levels will not be ascertained. HCV antibody status rather than HCV viremia was used as the predictor. According to the literature, 10%–15% of HCV antibody-positive persons actually had viremia that has cleared, so some HCV antibody-positive women in our study were likely not chronically infected [26, 27]. This misclassification bias is unlikely to have had affected trends in aminotransferase levels over time within groups. We were unable to provide complete clinical data regarding women who had moderately or severely elevated aminotransferase levels while receiving HAART, and thus we were unable to report the cause or outcome of elevation of aminotransferase levels for these patients.

Conclusion. In this large study of the effects of antiretroviral therapy on serum aminotransferase levels in clinical practice, we found that mean levels did not increase with HAART initiation and actually decreased while receiving HAART in many women who continued to receive potent therapy. We found that the proportion of women who had moderately or severely elevated aminotransferase levels while receiving HAART, even among those with hepatitis C coinfection, was low and decreased over time. Among women receiving PI-based HAART, there was more likely to be a decrease in prevalence of elevated aminotransferase levels than among women receiving NNRTI-based HAART. Our findings support assertions that antiretroviral therapy is safe for women with hepatitis C infection; further study is required to determine whether anti-HIV therapy has an overall salutary effect on HCV disease in coinfecting persons.

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Conflict of interest. All authors: No conflict.

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