



# Interruption of Antiretroviral Therapy (ART) is Associated with Progression of Liver Fibrosis in HIV/HCV Co-infected Adults

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## Abstract

**Background:** Evidence from randomized trials show that ART interruption increases the risk of non-AIDs clinical (including liver-related) outcomes. We hypothesized that liver disease progression in ART treated co-infected patients may be due, in part, to the consequences of repeated treatment interruptions. Therefore, we examined the impact of ART interruption on fibrosis progression, using AST-to-platelet ratio index (APRI) >1.5 as a surrogate marker of liver fibrosis. **Methods:** Data were analyzed from a Canadian, multi-site prospective cohort of HIV-infected adults receiving ART (n=701) with virologic evidence of HCV infection (n=617) between 2003-2009. Patients with significant fibrosis (n=136), defined as having an APRI score >1.5 at baseline, were excluded. The exposure of interest, ART interruption, was defined as the cessation of all antiretrovirals for at least 14 days after being on ART for at least 30 days, as a time-updated variable. Univariate and multivariate Cox regression models were used to evaluate the association of baseline characteristics and time-varying covariates such as, recent intravenous drug use (IDU), CD4 cell count and HIV viral load, with developing significant fibrosis. **Results:** 481 subjects were followed for a median of 13 months (6-19); 72% were male, 3% were HBsAg positive, 36% reported IDU during followup and 11% interrupted ART. The median age was 45 yrs; HCV duration, 17 yrs, baseline APRI score, 0.54 and nadir CD4 cell count, 161 cells/ $\mu$ l. Univariate analyses revealed that baseline APRI and time-updated CD4 cell count, HIV viral load and ART interruption were associated with fibrosis progression, while nadir CD4 cell count, age, duration of HCV and HIV infections and recent IDU were not. In the multivariate model, baseline lnAPRI (HR 1.61, 95% CI, 1.36-1.90/0.25 increase) and HIV RNA (HR 1.05, 0.95-1.17) were associated with fibrosis progression while a higher current CD4 cell count was protective (HR 0.94, 0.88-1.00/50 cells/ $\mu$ l). After adjustment, the effect of ART interruption was somewhat attenuated (HR 1.80, 0.73-4.40). **Conclusions:** ART interruption appears to be associated with fibrosis progression in HIV-HCV co-infection and was only partially accounted for by HIV viral load and CD4 cell counts. Our findings suggest that some of the liver disease progression observed in ART treated co-infected patients may in fact be due to negative consequences of treatment interruption.

## Background

- Among patients co-infected with HCV, liver disease has emerged as a leading cause of death.
- May be due to ART related hepatotoxicity, irreversibility of hepatic damage, incomplete immune recovery, alcohol use and inconsistent access and/or adherence to ART in a population with high rates of substance use.
- Interruption of ART has been proposed in some situations to reduce toxicities and costs or enhance adherence. However, it has been established that interruptions are potentially quite harmful.
- The SMART study demonstrated that treatment interruption is particularly unsafe for co-infected patients.
- They experienced a much greater risk of mortality due to a variety of non-AIDS, including hepatic, events compared to those with only HIV.
- Despite the evidence that interruptions are harmful, in the clinical setting it is still likely that co-infected patients will discontinue ART for a number of reasons.
- We hypothesized that liver disease progression in ART treated co-infected patients may be due, in part, to the consequences of repeated treatment interruptions.

**Objective:** To determine the impact of ART interruption on fibrosis progression in HIV/HCV co-infected adults, using the AST-to-platelet ratio index (APRI) as a surrogate marker for liver fibrosis.

- An APRI score greater than 1.5 has been shown to be predictive of significant fibrosis.

## Methods

**Setting:** The Canadian HIV/HCV Co-Infection Cohort, a prospective multi-center study enrolling subjects from 16 centers across Canada from 2003-2009. Participants completed questionnaires that collected sociodemographic, medical, drug use and behavioural information and provided blood for routine blood tests every 6 months.

**Subjects:** Eligible participants included HIV positive adults with chronic HCV infection or evidence of HCV exposure. All eligible patients were approached. As of December 2009, 847 subjects were recruited. Participants included in this analysis were HCV RNA positive, had a history of ART and an APRI score <1.5 at baseline.

**Exposure of Interest:** ART Interruption, defined as the cessation of all antiretrovirals for at least 14 days after taking ART for 30 days; included as a time-updated variable.

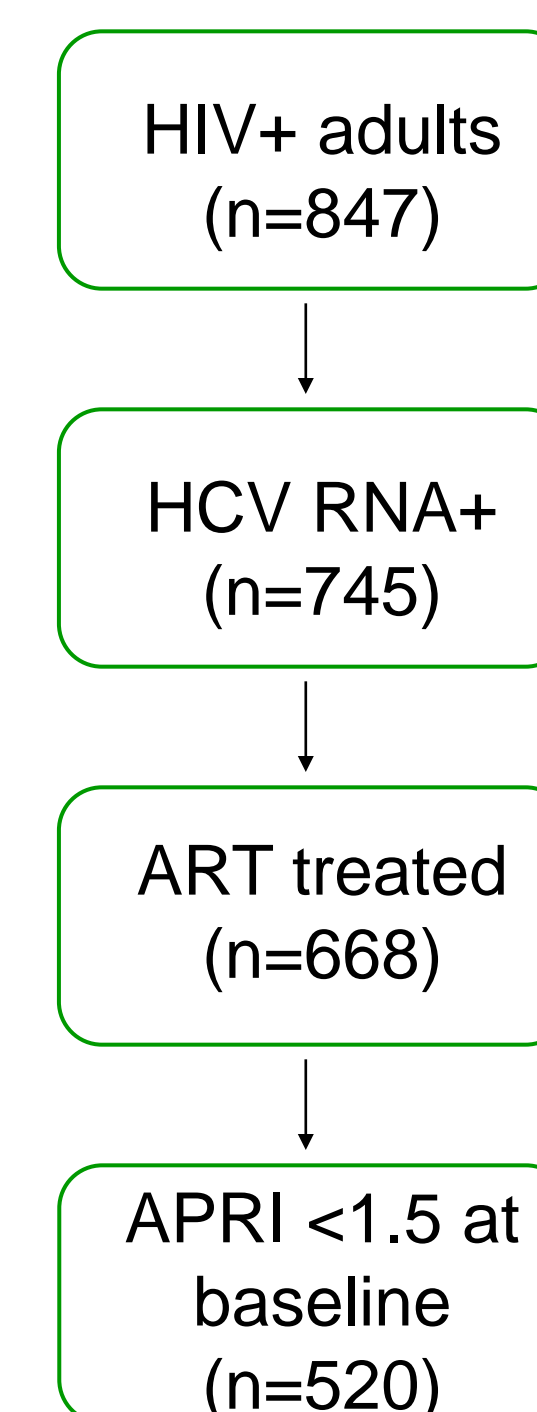
**Covariates:** IDU in the past 6 months or ever, time-updated CD4+ T-cell count (cells/uL), time-updated HIV RNA (log copies/ml), age, gender, duration of HIV and HCV infection, HBV status, nadir CD4+ T-cell count, highest HIV viral load, baseline lnAPRI

**Outcome:** The presence of significant fibrosis, defined as an APRI score greater than or equal to 1.5; assessed for every 6 month interval. Participants were censored when an APRI score greater than or equal to 1.5 was achieved.

$$\text{APRI} = 100 \times [\text{AST (U/L)/upper limit of normal (35 U/L)}] / \text{platelet count (10}^9\text{/L)}$$

**Statistical Methods:** Baseline and time-updated variables were compared between those who had an APRI score greater than 1.5 and those who did not using the chi-squared test for categorical variables and the Wilcoxon rank sum test for continuous variables. Univariate Cox regression models were carried out to estimate the crude hazard ratios (HRs) of developing significant liver fibrosis. A multivariate model was selected that included covariates that had statistically significant HRs in the univariate analyses as well as variables that were determined a priori to be clinically significant. The final multivariate model included ART interruption, time-updated CD4+ T-cell count and HIV RNA, baseline lnAPRI, age and gender.

## Results



**Figure 1: Flow-chart displaying subject selection.** In order to be eligible for inclusion in this analysis patients had to be HCV RNA+, a history of ART and an APRI score <1.5. 520 subjects were included in the analysis.

**Table 1: Baseline characteristics according to outcome**

	APRI <1.5 (471)	APRI >1.5 (49)	P-Value
Duration of follow-up (years)	0.999 (0.5, 1.81)	1.60 (1.32, 2.02)	<0.0001
Age (years)	45 (40, 50)	44 (40, 49)	0.475
Male	348 (74)	38 (76)	0.732
History of IDU	375 (81)	43 (88)	0.156
Greater than high school education	147 (31)	11 (23)	0.601
Interrupted ART	46 (10)	14 (29)	<0.05
Duration of HCV infection (years)	14 (9, 21)	14 (9, 20)	0.459
CD4+ T cell count (cells/uL)	400 (258, 550)	291 (180, 407)	<0.05
HIV viral load (copies/ml)	50 (50, 105)	50 (50, 746)	0.146
Nadir CD4+ T cell count (cells/uL)	160 (66, 252)	158 (82, 280)	0.744
Highest HIV viral load (copies/ml)	95585 (26552, 244515)	102005 (35550, 243210)	0.291
HbsAg+	16 (3)	1 (2)	0.541
APRI score	0.52 (0.36, 0.76)	0.79 (0.50, 1.2)	<0.0001

**Table 2: Univariate and multivariate time-dependent Cox proportional hazards regression**

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Age (per 5 year increase)	0.959 (0.812, 1.13)	0.989 (0.840, 1.16)
Female gender	0.958 (0.479, 1.92)	1.13 (0.547, 2.35)
Active IDU	1.56 (0.882, 2.77)	n/a
Interruption in previous time interval	2.33 (1.08, 4.97)	1.79 (0.776, 4.14)
Duration of HCV infection (per 5 year increase)	1.04 (0.881, 1.22)	n/a
CD4+ T cell count (per 50 cells/uL increase)	0.905 (0.839, 0.966)	0.932 (0.864, 1.00)
HIV viral load (log copies/ml)	1.14 (1.05, 1.23)	1.07 (0.959, 1.19)
Nadir CD4 cell count (per 50 cell/uL increase)	0.975 (0.909, 1.05)	n/a
Highest HIV viral load (log copies/ml)	1.12 (0.996, 1.26)	n/a
HbsAg+	0.799 (0.110, 5.80)	n/a
Baseline ln(APRI)	4.51 (2.47, 8.22)	4.17 (2.28, 7.64)

**Table 2: Univariate and multivariate time-dependent Cox proportional hazards regression.** The crude HRs revealed that ART interruption, baseline APRI, time-updated CD4+ T cell count and HIV viral load were associated with fibrosis progression. After adjusting for age, gender, baseline APRI, time-updated CD4+ T cell count and HIV viral load in the multivariate model, the effect of ART interruption on fibrosis progression was somewhat attenuated, and no longer statistically significant.

\*all results presented include patients added after abstract submission

## Conclusions

- ART interruption appears to be associated with fibrosis progression in HIV/HCV co-infection and was only partially accounted for by HIV viral load and CD4 cell counts.
- Our findings suggest that some of the liver disease progression observed in ART treated co-infected patients may in fact be due to negative consequences of treatment interruption, which may cause increases in pro-fibrogenic inflammatory markers.
- Due to the presence of time-varying confounders that are also affected by prior ART interruption, such as CD4+ T cell count or HIV viral load, using standard survival analyses may result in a biased estimate for the net effect of ART interruption on the development of fibrosis. In order to appropriately adjust for time-varying confounders that are also intermediate causes, further analyses using inverse probability-of-treatment weighting in a marginal structural model would be beneficial.
- Despite evidence that interruption of ART increases the risk of disease progression, in the clinical setting, it is still likely that patients will wish to discontinue ART for a number of reasons. Therefore, further studies on factors associated with ART interruption in the co-infected population would be beneficial and may assist clinicians in preventing treatment discontinuation or in providing alternative solutions for at-risk patients.