



# Hepatitis C Coinfection Increases Mortality in HIV-Infected Veterans Treated with Highly Active Antiretroviral Therapy

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## ABSTRACT

**Background:** Since the advent of highly active antiretroviral therapy (HAART) for patients with human immunodeficiency virus (HIV), several studies have investigated the effect of hepatitis C virus (HCV) infection on HIV progression, but with conflicting results. Few studies had sufficient events to consider mortality alone and some used data from a single institution. Our objective was to estimate the effect of HCV on mortality using the large cohort of HIV patients cared for by over 100 US Veterans Affairs (VA) facilities and controlling for numerous potentially confounding factors.

**Methods:** Patients were identified from the VA National Immunology Case Registry (ICR) meeting the following criteria: first VA prescription for a HAART-defining potent antiretroviral medication between January 1997 and February 2003, VA results for a baseline CD4 count and HIV viral load in the year prior to that first prescription and VA results for a HCV antibody test at any time. We used the Cox proportional hazard model to estimate the effect of HCV serostatus on mortality. The model included patients' demographic characteristics, baseline CD4 cell count and baseline HIV viral load, psychiatric and substance abuse diagnoses, history of AIDS-defining illness, pre-HAART antiretroviral therapy, receipt of HCV medications, facility size and region and calendar year. For a subset of patients, we also estimated a model controlling for history of injection drug use from reported CDC exposure category.

**Results:** 12,216 patients met inclusion criteria with 4,668 (37%) HCV seropositive. The mean observation time was 3.5 years. 2,087 deaths were reported through 31 March 2003. The unadjusted death rate for HCV seropositive patients was 6.4 deaths per 100 person years compared with 4.0 for HCV seronegatives (p<0.0001). In the multivariate Cox model, the hazard ratio for HCV seropositives relative to HCV seronegatives was 1.52 (95% CI 1.37-1.68, p<0.0001). In the subset analysis additionally controlling for IV drug use, the hazard ratio for HCV seropositive patients was 1.28 (95% CI 1.13-1.45, p<0.0001).

**Conclusions:** After controlling for numerous potentially confounding factors, HCV seropositivity was independently associated with increased risk of death in a large cohort of HIV-infected veterans. Given the success of potent antiretroviral therapy in extending the lives HIV patients, HCV has become an important predictor of mortality in the HIV-infected population.

## BACKGROUND

- Up to 300,000 persons are co-infected with HIV and HCV in the US
- HCV infection has emerged as a potentially important cause of mortality in co-infected persons since HAART use became widespread
- HAART-era studies report conflicting results on effect of HCV on survival or on AIDS-free survival (time to death or an AIDS-defining opportunistic infection (AIDS-OI))

## OBJECTIVE

To determine the effect of HCV infection on mortality for HIV patients receiving HAART in a large cohort of HIV infected veterans receiving care at VA facilities nationwide.

## METHODS

### Population and Measures

- Study cohort consists of VA HIV patients in the ICR with:
  - 1st VA HAART between Jan 1997 and Feb 2003
  - VA CD4 and HIV viral load results within 1 year prior to 1st VA HAART
  - VA HCV antibody test result present

- HCV positive if at least one positive antibody test (HCV seropositive)

- 3 sources of death data: Social Security Administration, VA beneficiary records (BIRLS), and ICR

- Time-dependent measure of HAART exposure: whether patient has a VA prescription for HAART in a given month or is "off HAART"

- Other measures based on ICR data

### Analysis

- Bivariate analyses comparing HCV positive and negative patients
  - Pearson Chi-square and Wilcoxon rank-sum tests (Table 1)

- Time from 1st VA HAART to death for HCV positive and negative patients

- Kaplan Meier survival function (Figure 1)

- Cox proportional hazard "complete" model controlling for: age, sex, race/ethnicity, first period of military service, baseline CD4, baseline HIV viral load, prior AIDS-OI, psychiatric illness, alcohol abuse, hard drug use, NRTI pretreatment, HCV-active medication, region, facility overall caseload and facility HIV caseload

- Cox proportional hazard "parsimonious" model (Table 2)

- Selected with backward stepwise procedure, threshold P < 0.05

- Include / exclude HAART exposure to bound estimate of HCV impact (Table 3)

- If include, may underestimate impact since HCV affects HAART exposure
- If exclude, may overstate impact since events correlated with HCV (e.g., alcoholism) also affect HAART exposure

## RESULTS

Table 1: Patient Characteristics

	HCV negative (n=4,668)	HCV positive (n=7,548)	
<b>Baseline:</b>			
Mean age in years	45.5	47.4	**
Male	97.8%	98.5%	
White	40.6%	22.5%	φφ
1 <sup>st</sup> period of service: Vietnam	40.3%	67.6%	φφ
Mean CD4 count (cells/ml)	293.4	285.4	**
Median HIV viral load (copies/ml)	25,916	19,200	**
AIDS-OI pre-HAART	21.4%	20.5%	
<b>Diagnosis of:</b>			
Psychiatric illness	59.3%	71.9%	**
Alcohol abuse	29.5%	63.0%	**
Hard drug use	20.7%	62.1%	**
<b>Treatment:</b>			
NRTI pretreatment	38.8%	48.8%	**
Mean date 1 <sup>st</sup> VA HAART	June 99	April 99	**
Mean months HAART exposure	24.9	21.3	**
HCV-active medication	0.3%	3.0%	**
<b>Follow-up</b>			
Mean length of follow-up (yrs)	3.5	3.5	
<b>Outcome</b>			
Death	13.9%	22.2%	**

\*\* P < .0001, difference between positive and negative groups

φφ P < .0001, difference in distributions for positive and negative groups

Figure 1: Unadjusted Survival

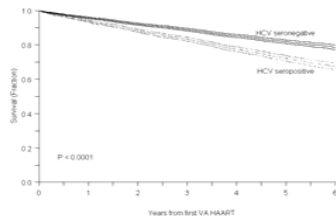


Table 2: Parsimonious Cox Proportional Hazard Model, Including HAART

Covariate	Hazard Ratio	(95% CI)
HCV positive	1.38	(1.26-1.51) **
Being off HAART	3.91	(3.53-4.33) **
Age at 1st HAART (per decade)	1.65	(1.57-1.73) **
Baseline HIV viral load		
50,000-99,999	1.09	(0.94-1.26)
≥100,000	1.45	(1.30-1.62) **
AIDS-OI pre-HAART	1.29	(1.16-1.42) **
NRTI pretreatment	1.28	(1.17-1.41) **

Model was stratified by baseline CD4 count.

\*\* P < .0001, difference between positive and negative groups

Table 3: Summary of Cox Model Estimates Impact of Being HCV Positive

	Hazard Ratio	(95% CI)
<b>Parsimonious Model</b>		
No HCV exposure		
HCV positive	1.56	(1.42-1.70) **
With HAART exposure		
HCV positive	1.38	(1.26-1.51) **
<b>Complete Model</b>		
No HAART exposure		
HCV positive	1.52	(1.37-1.68) **
With HAART exposure		
HCV positive	1.43	(1.29-1.58) **

\*\* P < .0001, difference between positive and negative groups

## DISCUSSION

- Previous studies of the impact of HCV in HIV patients have conflicting results. These studies differ on:

- Definition of time origin for calculation of survival time
- Whether and how to control for HAART exposure
- Outcome measure: survival vs. AIDS-free survival

- 4 studies with large enough number of outcome events per HCV group to be confident in results

- HCV impact found in present study and one other.<sup>1</sup> In these:

- Time origin for model = receipt of first HAART
- All patients in cohort received HAART

- No HCV impact found in 2 studies.<sup>2,3</sup> In these:

- Time origin for model = date of clinic entry
- Patients never on HAART included
- Counted survival time beginning before HAART

## CONCLUSION

HCV infection increased risk of death in HIV patients who received HAART controlling for numerous demographic and clinical factors.

Increased risk of death is between 40% and 60% higher for those with HCV infection.

Can HCV treatment be improved to reduce this risk?

While awaiting improved pharmacologic treatment, greater emphasis on treatment of alcohol abuse may be warranted as many patients in study cohort were triply diagnosed with HIV, HCV, and alcohol abuse.

## REFERENCES

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