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Mortality in HCV-infected Patients with a Diagnosis of AIDS in the Era of Combination Anti-retroviral Therapy

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Summary: Chronic hepatitis C increased mortality about 50% in patients with CDC-defined AIDS, despite the competing mortality risks in these patients. About 20% of the deaths were liver-related, suggesting that greater HCV awareness and treatment could increase survival.

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ABSTRACT

Background: Before the introduction of combination antiretroviral therapy (cART), HIV-positive patients rarely died of liver disease. In resource-rich countries, cART dramatically increased longevity. As patients survived longer, hepatitis C virus (HCV) infection became a leading cause of death; however, because patients with AIDS continue to have five-fold greater mortality than non-AIDS patients, it is unclear whether HCV infection increases mortality in them.

Methods: In this investigation, which is part of the Longitudinal Studies of the Ocular Complications of AIDS, plasma banked at enrollment from 2,025 patients with CDC-defined AIDS were tested for HCV RNA and antibodies.

Results: Three hundred thirty-seven patients had HCV RNA (chronic infection), 91 had HCV antibodies and no HCV RNA (cleared infection), and 1,597 had no HCV markers. Median $CD4^{+}$T cell counts/µL were 200 (chronic), 193 (cleared), and 175 (no markers). There were 558 deaths. At a median follow-up of 6.1 years, patients with chronic HCV had a 50% increased risk of mortality compared to patients with no markers of HCV (relative risk = 1.5, 95% confidence interval =1.2-1.9, p=0.001) in an adjusted model that included known risk factors. Mortality was not increased in patients with cleared infection (relative risk =0.9, 95% confidence interval =0.6-1.5, p=0.82). In patients with chronic HCV, 20.4% of deaths were liver-related versus 3.8% in patients without HCV.

Conclusions: Chronic HCV infection is independently associated with a 50% increase in mortality among patients with a diagnosis of AIDS, despite competing risks. Effective HCV treatment may benefit HIV/HCV co-infected patients with AIDS.

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Introduction

In the early years of the HIV/AIDS epidemic, few patients died of liver disease because they succumbed to other afflictions before progressing to end stage liver disease. In the 17 years of combination antiretroviral therapy (cART), survival of HIV-positive individuals has increased, especially in resource-rich countries, and liver disease has emerged as a major cause of death [1-5]. The majority of liver-related deaths in HIV-positive patients occur in people with chronic hepatitis C virus (HCV) infection [6-7]. HCV infects about 30% of the HIV-positive individuals in the United States and Europe [8]. A recent meta-analysis showed that the overall mortality risk ratio for HIV/HCV co-infected patients compared to HIV mono-infected patients is increased by about 35% [9]. It is unclear whether these results apply to patients with CDC-defined AIDS in the cART era, however, because their mortality rate continues to be approximately five times higher than that of HIV-positive patients without a diagnosis of AIDS [10]. Competing risk factors might eclipse the mortality risk of HCV infection in current patients with AIDS, just as they did in the early years of the epidemic. Outcomes in patients with a diagnosis of AIDS remain an important public health concern. In 2009, almost 35,000 people were diagnosed with AIDS in the United States [11].

To determine the impact of HCV infection on survival, this study compared mortality in a large cohort of AIDS patients. The 2026 study subjects were enrolled in the Longitudinal Studies of the Ocular Complications of AIDS (LSOCA) and were followed prospectively for a median of over six years. LSOCA is one of only a few cohort studies limited to persons diagnosed with AIDS, but without further exclusion criteria. It focuses exclusively on the era following the introduction of cART [12].

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Methods

Study subjects and design

Subjects were 13 years of age or older with a diagnosis of AIDS according to the 1993 CDC definition [13]. The LSOCA population is similar in age, race and sex to the U.S. AIDS population, except it has a lower percentage of patients with a history of injecting drug use (IDU) [14]. At enrollment, demographic information, past medical history, physical and ophthalmologic examinations were performed. Cytomegalovirus retinitis (CMV-R) was diagnosed by a LSOCA-certified ophthalmologist [12,15]. Follow-up occurred every 3 months for patients with an ocular opportunistic infection (e.g., CMV-R) and every six months otherwise. Plasma samples were collected at baseline and every 6 months thereafter. At a baseline structured interview subjects were asked, "Have you ever been diagnosed with hepatitis?" Subjects responding "yes" were then asked to identify the type(s), e.g., hepatitis A virus (HAV), hepatitis B virus (HBV), HCV, or other. One of the original objectives of LSOCA was to collect information about factors associated with mortality. Information on mortality was collected on an ongoing basis. Immediate and contributing causes of death were recorded in death reports. cART was defined as three or more antiretroviral drugs given at therapeutic levels. Most HIV-1 viral load assays were performed using the Roche Amplicor system. For analysis, viral loads below the lower-limit-of-detection were assigned a value of ½ the lower-limit, and values above the assay's upper-limit were assigned the upper-limit. This study was approved by the institutional review board at each center, and all patients gave written informed consent.

Methods to determine HCV sero-status

Plasma samples collected at enrollment were analyzed. All samples were tested for anti-HCV antibodies using the 3rd generation enzyme immunoassay (EIA) version 2.0 (Abbott). HCV

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RNA testing was performed on all samples with anti-HCV antibodies and/or an EIA signal-to-noise ratio ≥ 0.7 and on all samples from IDU, regardless of the HCV antibody test results, using the Roche COBAS AMPLICOR ™ Hepatitis C Virus Test, version 2.0 (lower-limit of detection, 50 IU/ml). Eighteen subjects with HCV antibody-positive plasma were missing HCV RNA results, five were classified as "cleared" HCV because the HCV antibody signal-to-noise ratio was < 3.8 (N=5). HCV serological testing was performed in 2008-2009. Results were sent to participating clinics with the advice that local guidelines be followed for communicating the results to patients. Patients with HCV RNA were considered to have chronic infection, and patients with anti-HCV antibodies and no HCV RNA were considered to have cleared a previous infection. It is possible that some people in the latter group had a false positive antibody test and never had an HCV infection.

Data analysis

Data available as of December 31, 2009 were included. The chi-square test was used for categorical variables and the Kruskal-Wallis test was used for continuous variables. Cox regression was used for factors associated with mortality. Unless otherwise noted, values of samples collected at enrollment were included in the analysis. The variables included: HCV sero-status, self-reported diagnosis of HAV and/or HBV, sex, race, age, birth cohort, education, IDU status, time since AIDS diagnosis, diagnosis of CMV-R, cART, AIDS defining condition, $CD4^+$ T cell count (at enrollment and nadir), $CD8^+$ T cell count, HIV viral load (at enrollment and maximum), platelet count, and year of enrollment. Three adjusted models were developed: (1) forward selection was used and only variables with p-values ≤ 0.05 in the adjusted model were retained; (2) backward selection was used; (3) all the variables were entered into the fully adjusted model. Maximum HIV viral load was excluded from multivariable analyses because

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6% of subjects had missing data. Follow-up time was calculated as the time from study entry to death; to December 31, 2009; or to the date of the last study contact for patients who were lost to follow-up. Univariate and forward selection multiple logistic regression were used to identify factors associated with lack of awareness of chronic infection and HCV clearance. Analyses were performed with SAS [16,17] and Stata software [17].

Results

Baseline characteristics

Among the 2025 subjects, 428 (21%) had evidence of past or current HCV infection. Of these, 337 (79%) were HCV RNA positive, indicating chronic infection, and 91 (21%) had HCV antibodies but no HCV RNA, indicating a past infection. Subjects with HCV infection (combined group of cleared plus chronic) were more likely to be female, black, older at the time of enrollment, part of the 1945-1964 (baby boomer) birth cohort, to have a history of IDU, and to have higher $CD4^{+}$T cell counts (enrollment and nadir) and lower platelets. They were less likely to have a college education, a diagnosis of CMV-R, to use cART, and to enroll during 1998-2000 (Table 1). A $CD4^{+}$T cell count < 200 cells/µL was the AIDS-defining condition in the majority of patients, regardless of HCV sero-status. The rise in $CD4^{+}$ T cells from the nadir did not differ between patients with and without markers of HCV exposure (p=0.91; Table 1). Compared to the group with chronic HCV, the group with past infection had a lower percentage of blacks and IDU, patients were younger, and had higher platelets (Table 1). In an adjusted multiple logistic regression model, failure to clear HCV was associated with black race, IDU, higher nadir $CD4^{+}$T cell counts, and lower platelets (supplemental Table 1).

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Factors associated with mortality

There were 558 deaths at a median follow-up of 6.1 years (IQR=3.0-8.7). Kaplan-Meier estimates of mortality for patients with chronic hepatitis C, past hepatitis C, and no markers of HCV infection are presented in Figure 1. Cox regression was used to identify factors associated with mortality (Table 2). Three adjusted model were analyzed. All gave similar results concerning the increased mortality risk of HCV infection.

Table 2 presents the model developed using forward selection. Patients with chronic HCV infection had a 50% increased mortality risk (RR= 1.5, 95% CI=1.2-1.9, p=0.001) compared to patients with no markers of HCV infection, whereas patients with prior HCV infection did not have increased risk (RR=0.9, 95% CI=0.6-1.5, p=0.82). In addition to chronic HCV infection, increased risk was associated with a prior diagnosis of HAV, older age at enrollment, a diagnosis of CMV-R, higher HIV viral load, and enrollment during 1998-2000 versus 2006-2009. Decreased risk was associated with higher $CD4^+$ T cell counts and platelets. Neither the time since a diagnosis of AIDS (Table 2), nor the number of interruptions of cART during follow-up (data not shown) were related to mortality in the adjusted model.

In a backward selection model and in a fully adjusted model that included all the variables in the univariate analysis, the RR of chronic HCV infection was 1.5, identical to the RR estimated in the forward selection model. In the backward selection model, the 95% CI was 1.2-1.9, p=0.0007, and in the fully adjusted model, the 95% CI was 1.2-2.0, p=0.003. In all three models, in addition to chronic HCV infection, increased mortality was associated with HAV, CMV-R, higher HIV viral load, and the year of enrollment; and decreased mortality was associated with higher $CD4^+$ T cell counts (Table 2 and data not shown). All three models showed that mortality risk was approximately 50% higher in patients with chronic hepatitis C

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than in patients with prior hepatitis C, but the increase was not statistically significant: 95% confidence intervals were 1.0-1.5 in all three adjusted models and p values were 0.07.

Of the 113 deaths in patients with chronic HCV, 20.4% were liver-related, compared to only 3.8% of the 420 deaths in patients with no markers of HCV exposure. Patients with chronic infection were more than five times more likely to die of liver-related causes than patients with no markers of HCV (p<0.0001). Liver-related deaths contributed to 12.0% of the 25 deaths in patients with cleared HCV. Alcohol use and HBV infection may have contributed to these liver-related deaths. The proportion of deaths related to cardiovascular disease, AIDS, and non-AIDS-related cancer were similar between patients with and without HCV infection (Supplementary Table 2).

Lack of awareness of HCV status

Because HCV infection decreases longevity and is both transmissible and potentially curable, we investigated patient awareness of HCV. Almost one-third (100/337) of the subjects with chronic hepatitis C reported that they had never received a diagnosis of HCV infection. In a logistic regression model, this lack of awareness was positively associated with enrollment during 1998-2000 versus 2006-2009; it was not associated with self-reported HBV infection, and it was negatively associated with self-reported HAV infection (Table 3).

Effectiveness of the approach used to identify cases of chronic HCV

HCV RNA testing was carried out on all samples with HCV antibodies and all samples from subjects with a history of IDU, 25% of the total. This approach identified 337 HCV RNA positive samples. We performed HCV RNA testing on 60 representative samples from low risk patients (non-IDU who self-reported HCV negative status) and used the results to estimate the percentage of HCV RNA positive samples (and cases of chronic infection) that we likely missed

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by not testing all antibody negative samples for HCV RNA. HCV RNA was present in 3 of 60 (5%), two of the three had HCV antibodies. At a 5% positivity rate, the low risk group should contain about 86 chronic cases, but only 61 samples were anti-HCV antibody-positive. This suggests that about 25 cases were missed, and that the actual number of HCV RNA positive samples in the entire study group was about 362. Of these, we identified 337, which is 93% (337/362) of the estimated chronic cases.

Discussion

This study of patients with a diagnosis of AIDS established that chronic HCV infection increased mortality risk by about 50% after adjustment for demographic factors, HIV status, CMV-R, and IDU. It also revealed that almost 30% of the subjects with chronic HCV infection reported that they had never been given a diagnosis of this disease. In addition, and in keeping with previous investigations, this study showed that blacks and patients with a history of IDU were less likely to clear HCV than other patients [18,19].

Strikingly, liver disease was the immediate or contributing cause in 20.4% of the deaths that occurred in patients with chronic hepatitis C. Liver disease was the only cause of death reported more frequently in patients with HCV than in patients without HCV. The negative impact of liver disease on survival emphasizes the need for patients with AIDS to be aware of their HCV status so that they can fully participate in their health care and risk reduction. While current HCV treatments lead to a sustained virological response (SVR) in only 25-50% of HIV/HCV co-infected patients [20-22], SVR rates are expected to rise soon as directing acting antiviral drugs for HCV enter the clinic. SVR increases survival in HIV/HCV co-infected patients [23] and reduces the risk of subsequent antiretroviral-related toxicities [24]. Heightened HCV awareness may increase the proportion of patients seeking treatment and achieving an

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SVR; however, optimizing treatment and managing drug-drug interactions will be significant challenges in the years ahead.

HCV-mediated liver disease was only one of the mortality risks in the patients with chronic HCV infection. AIDS-related conditions were immediate or contributing factors in 58.4% of the deaths. This percentage is similar to that of patients without HCV. We did not find any evidence that HCV increased the immunological deficits caused by HIV. The relationship between HCV infection and immune dysfunction is unresolved in the literature. HCV infection is reported to blunt the $CD4^+$ T cell response to cART, leading to smaller increases in $CD4^+$ T cell counts [1,24-27]; however, maximal viral suppression is reported to mitigate this effect [29]. We did not observe a blunted $CD4^+$ T cell response; however, HCV might have adverse effects on immune function that are not reflected in $CD4^+$ T cell counts. HCV impairs dendritic cell function and alters $CD8^+$ T cell phenotype [30,31]. It is possible that subtle immunological effects of HCV reduced the resilience of patients with chronic infection and rendered them more susceptible to a variety of co-morbid conditions, contributing to their increased overall mortality.

In addition to HCV-mediated liver damage and immune dysfunction, high risk behaviors, including IDU and heavy alcohol consumption, add significantly to excess morbidity and mortality in many groups of HIV/HCV co-infected individuals [5,32,33]. However, none of the three models of mortality risk in our study group showed an association between IDU and mortality. Death due to trauma, which is often a marker of high risk behavior, was not increased in patients with chronic hepatitis C. These results suggest that IDU and accidents did not contribute significantly to the excess mortality we observed in patients with chronic HCV. Although high risk behaviors account for most HCV transmissions, it is significant that past HCV infection was not associated with increased mortality risk in our study group. It thus

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appears that the high risk activities associated with HCV acquisition did not reduce longevity in our cohort.

Considering the impact of end stage liver disease on mortality and the potential benefits of HCV treatment, it is noteworthy that almost one-third of the chronically infected patients said that they had never been given a diagnosis of HCV. Confusion with HAV or HBV did not account for this underreporting. Research is needed to determine whether the failure to accurately report positive HCV status reflected failure of physicians to test for HCV, lack of communication, miscommunication, or denial. We found that lack of HCV awareness was more likely in patients enrolled during the earliest part of the study. Lack of HCV awareness was not associated with race, IDU, or age, in contrast to a previous investigation of HIV-positive women and women at risk for HIV infection. In the women, lack of HCV awareness was associated with black race and younger age [34]. Such disparate results show that the factors contributing to lack of awareness of HCV infection may differ between populations, underscoring the need for broad-based HCV screening. It is estimated that only about half of all the HCV positive individuals in the United States are aware of the infection [35]

The Department of Health and Human Services Guidelines for the prevention of opportunistic infections among HIV-infected persons issued in 2002 advised screening for HCV in all HIV-infected persons [36]. Identifying the most cost-effective screening approach is an important public health objective, but is challenging for several reasons: HIV-seropositive patients with chronic HCV have a significant rate of false-negative anti-HCV antibody test results [37]; the more definitive HCV RNA test is more expensive than the antibody test; and ongoing high risk behaviors may lead to reinfection, resulting in a need for periodic retesting. In this study, HCV RNA tests were performed on about 25% of the study population, with RNA

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testing directed to high risk subjects, e.g., IDU, and to subjects with positive antibody tests. Using this targeted approach, an estimated 93% of HCV RNA positive cases were detected. Our failure to detect all of the cases indicates that HCV RNA testing should be performed on HIV-positive individuals who test HCV antibody negative but have multiple HCV risk factors.

The strengths of this study include the large number of AIDS patients (2025), the large number of HIV/HCV co-infected non-IDU (179), the prospective collection of data and plasma, the long duration of follow up (median of 6.1 years), the use of HCV RNA testing to distinguish chronic from previous HCV infection, and the use of a testing algorithm that identified an estimated 93% of the cases of chronic infection. The limitations include the use of baseline data to analyze factors associated with mortality and the lack of data about alcohol use.

Our results underscore the urgency of efforts to screen AIDS patients for HCV and to make sure that the test results and their implications are clearly communicated. A new era of HCV treatment with direct acting antiviral drugs has just begun. More effective treatments for both HIV and HCV will undoubtedly decrease mortality in HCV-positive patients with a diagnosis of AIDS. Early cure of HCV may avoid the costs of liver transplantation, which exceeds $123,000 per patient [38]. Broader screening and more patient education are needed to maximize the benefits of new treatments and to lower liver-related mortality.

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Notes

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Conflicts of interest: Dr. Jabs has acted as a consultant for Ciba Vision, Bayer Corporation, Centocor, Inc., and SmithKline Beecham. Currently, Dr. Jabs is a consultant for Allergan Pharmaceutical Corporation, Genzyme Corporation, Abbott Laboratories, Novartis Pharmaceutical Corp., Roche Pharmaceuticals, GlaxoSmithKline, Alcon Laboratories, Corcept Therapeutics and GenenTech. Research support has been provided from Roche Laboratories, Inc. in the past. He also currently acts as a Data and Safety Monitoring Board (DSMB) member for Applied Genetic Technologies Corporation (AGTC). All other authors: no other reported conflicts.

Writing assistance: The writing was performed by the authors, with no outside assistance.

Figure Legends

Figure 1. Kaplan-Meier survival curves.

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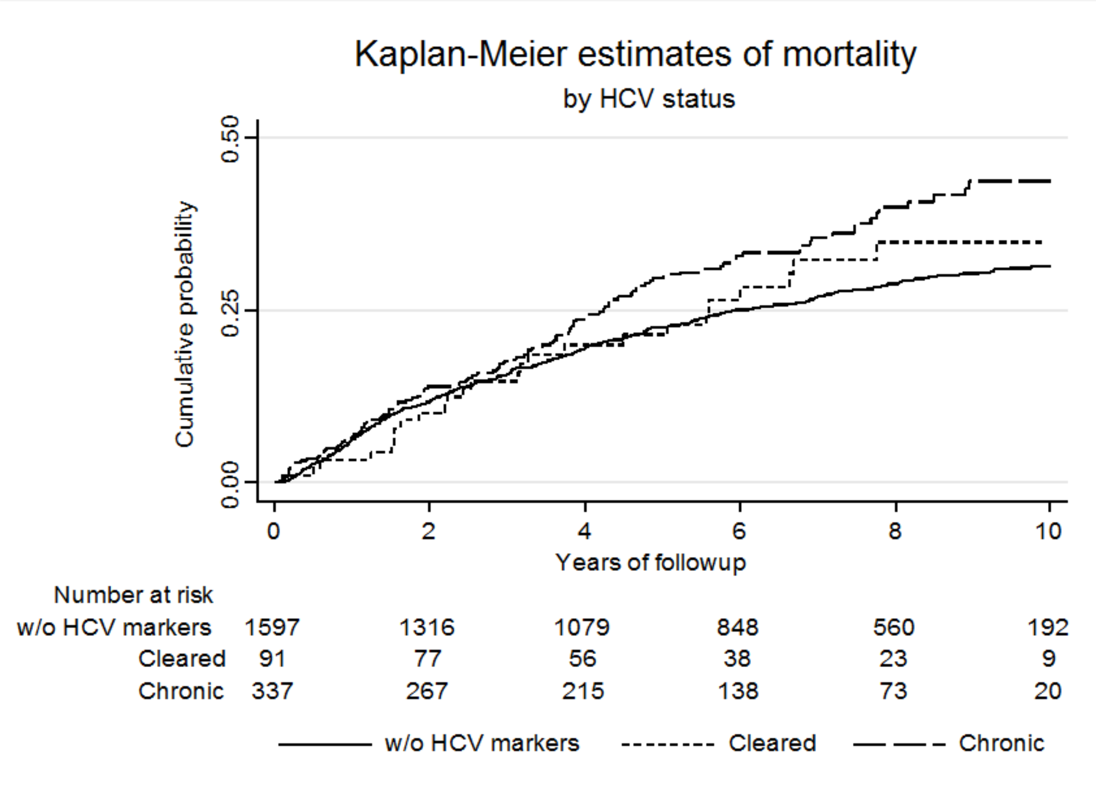

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Table 1. Characteristics of the population at enrollment by sero-HCV status

	Sero-HCV status*				P-value[a]	
		With HCV markers				
	Without HCV markers (n=1597)	Cleared[b] (n=91)	Chronic[c] (n=337)	Total (n=2025)	With vs. without HCV markers	Cleared vs. Chronic
Demographics						
Female (%)	17	30	26	19	<0.0001	0.53
Black race (%)	30	40	55	35	<0.0001	0.01
Age - yrs (median±SD[d])	42	43	45	43±9	<0.0001	0.03
Birth cohort (%)					<0.0001	0.60
< 1945	6	7	5	6		
1945 - 1964	68	76	80	71		
≥ 1965	25	18	15	23		
College graduate (%)	36	16	12	31	<0.0001	0.28
HIV / AIDS history						
Intravenous drug user (%)	4	33	47	13	<0.0001	0.02
Time since AIDS dx- yrs (median±SD)	4.4	4.9	4.3	4.4±4.1	0.79	0.48
Dx with CMV retinitis (%)	22	12	12	20	<0.0001	0.92
Currently on cART (%)	84	84	80	84	0.05	0.40
CD4+ T-cell count < 200µL as AIDS defining illness (%)	62	63	66	63	0.17	0.64
Self-reported hepatitis history						
HCV exposed (%)	3	35	71	16	<0.0001	<0.0001
HBV exposed (%)	16	21	19	16	0.08	0.64
HAV exposed (%)	8	9	9	8	0.37	0.97
Exposed - type unknown (%)	8	8	5	7	0.12	0.33
Immunology / virology						
CD4+ T-cells - /µL	175	193	200	182±207	0.03	0.80

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(median±SD)						
Nadir CD4+ T-cells - /µL (median±SD)	30	24	57	32±62	<0.0001	0.003
Change from nadir CD4+ T-cells - /µL (median±SD)	114	128	130	117±177	0.91	0.60
CD8+ T-cells - /µL (median±SD)	736	800	734	739±473	0.47	0.38
HIV viral load - log copies/mL (median±SD)	2.8	2.8	2.6	2.8±2.0	0.25	0.50
Max HIV viral load - log copies/mL (median±SD)	5.3	5.4	5.3	5.3±0.8	0.57	0.27
Hematology						
Platelets - 100,000 cells/mL (median±SD)	2.14	2.18	1.96	2.12±0.68	<0.0001	0.01
Year of enrollment (%)					0.02	0.86
1998 - 2000	43	37	35	41		
2001 - 2005	38	42	45	40		
2006 - 2009	19	21	20	19		

*18 observations with positive HCV antibody and missing HCV RNA results were imputed to cleared HCV if HCV antibody signal to noise cutoff < 3.8 (n=5), otherwise imputed to chronic (n=13)

[a] P-value based on chi-square test for categorical variables or Kruskal-Wallis test for continuous variables

[b] Cleared defined as positive HCV antibody and undetectable HCV RNA

[c] Chronic defined as detectable HCV RNA

[d]SD estimated using pseudo-sigma

Note: There were no statistically significant (p<0.01) interactions of characteristics of the population with HCV status by IDU status

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Table 2. Cox regression analysis of factors associated with mortality among 2,025 patients

Characteristics at enrollment	Crude RR	Crude 95% CI	Crude p	Adjusted[a] RR	Adjusted[a] 95% CI	Adjusted[a] p
HCV sero-status			0.008			0.004
Cleared vs. without HCV markers	1.1	0.7 - 1.6	0.68	0.9	0.6 - 1.5	0.82
Chronic vs. without HCV markers	1.4	1.1 - 1.7	0.002	1.5	1.2 - 1.9	0.001
Self-reported hepatitis						
HBV (yes vs. no)	0.8	0.6 – 1.0	0.04			
HAV (yes vs. no)	1.1	0.8 – 1.5	0.46	1.5	1.1 – 2.1	0.02
Demographics						
Female vs. male	1.2	1.0 - 1.4	0.12			
Black vs. non-black	1.3	1.1 - 1.5	0.002			
Age (per yr)	1.00	0.99 - 1.01	0.97	1.01	1.00- 1.02	0.02
Birth cohort			0.35			
< 1945 vs. ≥1965	1.2	0.9 - 1.7	[b]			
1945-1964 vs. ≥ 1965	1.0	0.8 - 1.2	[b]			
Not college grad vs. college grad	1.3	1.0 - 1.5	0.02			
HIV/AIDS history						
IDU vs. No IDU	1.3	1.0 - 1.6	0.05			
Time since AIDS dx (per yr)	1.01	0.99 - 1.03	0.48	1.02	1.00 - 1.05	0.04
Dx vs. not dx with CMV retinitis	1.8	1.5 - 2.2	<0.0001	1.9	1.6 - 2.3	<0.0001
On vs. not on cART	0.5	0.4 - 0.6	<0.0001			
CD4+ T-cells count < 200 µL vs. other AIDS defining illness	1.0	0.8 – 1.1	0.65			
Immunology / Virology						
$CD4^+$ T-cells (per 100 cells /µL)	0.70	0.66 - 0.74	<0.0001	0.82	0.77 - 0.88	
<0.0001						
Nadir $CD4^+$ T-cells (per 100 cells /µL)	0.71	0.62 - 0.82	<0.0001			
$CD8^+$ T-cells (per 100 cells /µL)	0.93	0.91 - 0.94	<0.0001			
HIV viral load (per log copies/mL)	1.63	1.53 - 1.74	<0.0001	1.47	1.37 - 1.58	
<0.0001						
Max HIV viral load (per log copies/mL)	1.51	1.35 - 1.70	<0.0001			
Hematology						
Platelet count (per 100K cells/mL)	0.67	0.60 - 0.76	<0.0001	0.87	0.77 - 0.99	0.04
Year of enrollment			0.0007			0.008
1998-2000 vs. 2006-2009	1.7	1.2 - 2.3	0.002	1.5	1.0 – 2.1	0.03
2001-2005 vs. 2006-2009	1.3	0.9 - 1.8	0.12	1.1	0.8 – 1.6	0.47

[a]Variables selected from multiple Cox regression model regressing time to death on all variables listed above (except max HIV viral load due to 6% with missing data) using forward selection entry criterion p<0.05. There were 1833 complete cases.

[b]Not shown since overall p-value is not significant.

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Table 3. Logistic regression analysis of factors associated with failure to accurately self-report positive HCV status among 337 patients with chronic HCV infection

Characteristics at enrollment	Crude OR	Crude 95% CI	Crude p	Adjusted[a] OR	Adjusted[a] 95% CI	Adjusted[a] p
Demographics						
Female vs. male	0.8	0.5 - 1.4	0.39			
Black vs. non-black	1.1	0.7 - 1.7	0.82			
Age (per yr)	0.97	0.94 - 1.00	0.05			
Birth cohort			0.39			
< 1945 vs. ≥1965	0.7	0.2 - 3.0	[b]			
1945-1964 vs. ≥ 1965	1.4	0.7 - 2.9	[b]			
Not college grad vs. college grad	0.6	0.3 - 1.2	0.15			
Self-reported hepatitis						
HBV (yes vs. no)	0.6	0.3 – 1.1	0.09			
HAV (yes vs. no)	0.2	0.1 – 0.8	0.02	0.3	0.1 - 0.9	0.03
HIV/AIDS history						
IDU vs. No IDU	0.6	0.4 - 1.0	0.08			
Time since AIDS dx (per yr)	0.99	0.93 - 1.04	0.63			
On vs. not on cART	0.9	0.5 - 1.5	0.61			
Year of enrollment			0.0001			0.0002
1998-2000 vs. 2006-2009	3.7	1.8 - 7.6	0.0004	3.2	1.6 - 6.8	0.002
2001-2005 vs. 2006-2009	1.5	0.7 - 3.1	0.28	1.3	0.6 - 2.7	0.48

[a]Multiple logistic regression model regressing probability of self-reported negative HCV on all variables listed above using forward selection entry criterion p<0.05. There were 329 complete cases.

[b]Not shown since overall p-value is not significant

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