

# Health Care Utilization in HIV-Infected Patients: Assessing the Burden of Hepatitis C Virus Coinfection

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## Abstract

Health care utilization for HIV-1-infected patients appears to be declining in the United States as a result of highly active antiviral therapy (HAART); yet the opposite appears true in the HIV/hepatitis C virus (HCV) coinfecting population. The reasons for this difference are not well understood. We examined the rates and reasons for emergency department visits and hospital admissions at an academic tertiary care medical center for HIV/HCV coinfecting patients as compared to HIV-1 monoinfected patients, using a retrospective matched cohort study design. HIV/HCV coinfecting patients had higher rates of health care utilization (emergency department visits 43.9 versus 7.1 per 100 person-years; hospital admissions 18.2 versus 6.7 per 100 person-years, for HIV coinfecting and monoinfected, respectively). This increase was not solely due to liver related events. Instead, comorbidities such as diabetes, renal disease, and psychiatric/substance abuse played a larger role in the health-care utilization in the HIV/HCV coinfecting population.

## Introduction

**H**EPATITIS C VIRUS (HCV) chronically infects approximately 170 million people worldwide.<sup>1</sup> In resource-rich countries, HCV is the leading cause of end-stage liver disease (ESLD) and hepatocellular carcinoma (HCC), as well as the primary indication for liver transplantation.<sup>2</sup> In the United States and Europe, HCV affects 15–30% of HIV-infected individuals and is a major cause of morbidity and mortality in the coinfecting population.<sup>3</sup> Coinfecting individuals are reported to have accelerated rates of liver fibrosis, resulting in a higher risk of ESLD and associated complications including HCC, when compared to patients with HCV monoinfection.<sup>3</sup> Multiple studies projections suggest that the aging of current HCV-infected patients, largely driven by the baby-boomer birth cohort, will result in a substantial health and economic burden over the next decade.<sup>4,5</sup> In fact, HCV has surpassed HIV monoinfection as a cause of death in the United States, disproportionately affecting the middle-aged.<sup>6</sup> Given the aging HIV population, the health and economic impact of HIV/HCV coinfecting will likely be substantial.

In the era of highly active antiretroviral therapy (HAART), rates of hospitalization in HIV-1 monoinfected patients first declined and have since reached a plateau.<sup>7</sup> Meanwhile hos-

pitalization rates for HIV/HCV coinfecting patients continue to rise.<sup>5,8</sup> HIV/HCV coinfecting patients are reported to have higher rates of hospital admissions, emergency department visits, and disability days, when compared to their HIV monoinfected counterparts.<sup>5,8</sup> The reasons for these differences in health-care utilization have not been previously reported. While some studies suggest that liver disease remains a primary reason for hospitalization in HIV-infected patients,<sup>7</sup> this remains controversial.<sup>9,10</sup> To better understand the reasons for health care utilization in HIV/HCV coinfecting patients, we sought to determine the risk factors and reasons for hospital admissions and emergency department visits in this high-risk patient population.

## Methods

### *Study population and data abstraction*

Patients were recruited from the Infectious Diseases Clinic at the Duke University Medical Center in Durham, North Carolina. HIV/HCV coinfecting subjects were recruited from July 2006 to March 2007 for a separate prospective study that was approved by the Duke Medical Center Institutional Review Board (IRB). A total of 205 patients were identified as

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HCV/HIV coinfecting during the study period, and patients were approached for participation consecutively as they arrived to their clinic appointments. Almost all patients approached agreed to participate, resulting in a total of 96 coinfecting subjects. Patients were at least 18 years of age and informed consent was obtained from these participants. The definition of chronic hepatitis C included a positive hepatitis C antibody and a positive HCV RNA for greater than 6 months. Thus, patients treated for HCV with a sustained virologic response or who experienced spontaneous clearance were excluded. HIV-1 monoinfected subjects were selected from the active clinic patient population and were matched by age ( $\pm 5$  years), gender, year of HIV diagnosis ( $\pm 2$  years), and year first seen in the Infectious Diseases clinic ( $\pm 2$  years). IRB-approved waiver of consent was obtained for inclusion of the monoinfected participants. We thus created two samples: a coinfecting cohort and a matched HIV-monoinfected cohort.

For all subjects, medical records were retrospectively reviewed and data were abstracted from January 1996 to December 2010, by three chart reviewers (S.N., V.A., B.N.). Data abstraction forms included demographics, comorbidities, CD4 counts, number of and reasons for emergency department visits and hospital admissions. All subjects were considered to have a comorbid condition if it was clearly stated in either the problem list or past medical history of the infectious diseases clinical encounter note. As part of the prospective study, all coinfecting patients completed an interview with research staff for the collection of social history data, such as alcohol and drug use. For the monoinfected subjects this information was abstracted from the problem list and past medical and social histories of the infectious diseases clinic notes. Reasons for emergency department visits were identified by discharge diagnoses documented by the emergency department provider. If there was more than one reason documented, the chart was reviewed and the reason viewed as most related to the chief complaint was used. In the case of difficult reconciliation, the reason listed first by the emergency department provider was used. Reasons for hospital admissions were identified by using only the primary discharge diagnosis reported by the discharging physician on the discharge summary. Outcome categories were defined *a priori* and included (1) HIV associated, (2) non-HIV-associated infections, (3) liver associated, (4) cardiac associated, (5) diabetes associated, (6) renal associated, (7) substance abuse/psychiatric, and (8) other. We used the 1993 Centers for Disease Control and Prevention (CDC) classification system for HIV infection to determine which diagnoses were HIV related. These included AIDS-defining illnesses such as *Pneumocystis jirovecii* pneumonia (PCP) and *Mycobacterium avium* complex (MAC), as well as HIV-related infections such as recurrent pneumonia, herpes zoster, candida, and lymphoma. Liver-associated outcome definitions included decompensated liver disease (encephalopathy, variceal bleeding, peritonitis) and transaminitis. Cardiac-associated outcome definitions included chest pain (unless specifically noted as noncardiac or musculoskeletal), myocardial infarct, congestive heart failure, cardiac arrhythmia, or valvular disease. Diabetes-associated outcomes were defined as hypoglycemic or hyperglycemic episodes. Renal-associated outcomes were defined as acute renal failure, initiation of hemodialysis, missed hemodialysis, and hyperkalemia or volume overload due to acute or chronic renal disease.

Substance/psychiatric associated outcomes included drug overdose, intoxication, psychosis, severe depression/anxiety, and suicide attempts. The "other" category was used to define an emergency department visit or hospital admission that did not clearly fit within the previously described categories. Multiple emergency department visits or hospital admissions by a unique patient were included.

### Statistical analysis

Patient demographic and clinical characteristics were evaluated with counts and percentages in contingency tables or with medians and interquartile ranges. Differences between groups were assessed using the Kruskal-Wallis test for continuous measures and the Fisher's exact test for cross-classifications of categorical data. We compared differences in the reasons for emergency department visits and hospitalizations with counts and percentages and statistical significance was estimated with  $\chi^2$  tests. Differences in health care utilization were evaluated with mean annual rates of emergency department visits and hospitalizations.

We determined the factors that were independently associated with rates of health care utilization with multivariable Poisson models for response variables (1) annual emergency department visit rate and (2) annual hospitalization rate for each patient. Predictor variables included the matching variables (age, gender, years HIV infected, and year first seen at the Duke Infectious Disease clinic) and other factors previously associated with health care use (race, HCV infection status, median CD4 count, drug and alcohol use, diabetes, and renal disease). All analyses were performed using SAS version 9.2 (SAS Inc., Cary, NC).

## Results

### Cohort characteristics

We enrolled 96 patients with HIV/HCV coinfection, matched to 165 HIV-1 monoinfected subjects. The sample was predominantly male with a median age of 50 (Table 1). The HIV monoinfected cohort had a longer duration of HIV infection compared to the coinfecting cohort, with medians of 14 and 12 years, respectively ( $p=0.03$ ). Median CD4 count was slightly lower among the HIV/HCV coinfecting (389 versus 486,  $p=0.04$ ). There were no differences in CD4 nadir, history of AIDS-defining illness, diabetes, or hepatitis B coinfection between the two groups. Coinfecting patients were more likely to be African American, to report active alcohol and illicit drug use, and to have comorbid renal disease. Sixty-five percent of the coinfecting individuals had federal or need-based funding (Medicare, Medicaid, Ryan White funding).

### Health care utilization

Health care utilization metrics included emergency department visits and hospital admissions. Over the course of the study, HIV/HCV coinfecting individuals had a median of 43.9 emergency department visits/100 person-years as compared to 7.1 emergency department visits/100 person-years among the HIV monoinfected ( $p<0.0001$ ) group. HIV/HCV coinfecting also had more hospital admissions over the course of the study as compared to the HIV monoinfected group (18.2/100 person-years versus 6.7/100 person-years,  $p<0.0001$ .)

TABLE 1. DIFFERENCES IN DEMOGRAPHIC CHARACTERISTICS AND HEALTH CARE UTILIZATION BETWEEN PATIENTS FROM EACH OF TWO COHORTS

	HCV/HCV <i>coinfected</i> n=96 % (n)	HIV <i>monoinfected</i> n=165 % (n)	p Value
Characteristics			
Age, yrs (median, IQR)	50 (45–52)	50 (46–54)	0.13
Male gender	77.1 (74)	75.2 (124)	0.77
Race			0.003
White	30.2 (29)	46.7 (77)	
Black	67.7 (65)	46.7 (77)	
Other	2.1 (2)	6.7 (11)	
Years with HIV (median, IQR)	12 (9–17)	14 (10–19)	0.03
Hx AIDS defining illness	57.3 (55)	52.7 (87)	0.52
CD4 nadir (median, IQR)	144 (35–287)	208 (53–345)	0.16
CD4 median (median, IQR)	389 (269, 561)	487 (320, 670)	0.04
Active ETOH use	30.2 (29)	15.2 (25)	0.005
Active drug use	26 (25)	13.3 (22)	0.012
Hep BsAg positive	1.3 (1)	3.4 (4)	0.65
Diabetes	10.4 (10)	12.1 (20)	0.84
Renal disease	17.7 (17)	7.3 (12)	0.014
Health care utilization			
Emergency department visits	43.9/100 person-yrs	7.1/100 person-yrs	<0.0001
Hospital admissions	18.2/100 person-yrs	6.7/100 person-yrs	<0.001

IQR, interquartile range, 25–75%; HCV, hepatitis C virus.

In multivariable Poisson models, HCV coinfection was independently associated with a higher rate of emergency department visits (relative risk [RR] 95% confidence interval [CI]; 2.07 [1.49, 2.89]; Table 2). This was not true for hospital admissions, although the trend was toward an increase in admissions (RR [95% CI]; 1.24 [0.73, 2.09]). In this adjusted analysis female gender, drug use, and renal disease were associated with both emergency department visits and hospitalization. In addition black race was independently associated with emergency department visits.

The reasons for health care utilization differed between HIV monoinfected and HIV/HCV coinfecting patients. The primary reasons for emergency department visits in both cohorts were (1) other and (2) non-HIV-associated infections (Table 3). However, renal disease, diabetes, psychiatric/

substance abuse, and liver-related emergency department visits were more common among the HIV/HCV coinfecting group as compared to the monoinfected group ( $p=0.001$ ). The primary reasons for hospital admissions were “other” and HIV-related admissions for the monoinfected, and “other” and non-HIV associated infections for the HIV/HCV coinfecting cohort (Table 3). Renal disease, diabetes, psychiatric/substance abuse, and liver-related causes were again more common among the HIV/HCV coinfecting as compared to HIV monoinfected ( $p<0.0001$ ) patients. The contribution of health care utilization due to liver-related events was greater for the coinfecting as compared to the HIV-1 monoinfected cohort, but liver disease accounted for only a minority of emergency department visits (1.1%) and hospital admissions (2.0%). The combination of hospital admissions attributed to

TABLE 2. PATIENT CHARACTERISTICS RELATED TO THE RISK OF HAVING AN EMERGENCY DEPARTMENT OR HOSPITAL ADMISSION IN MULTIVARIABLE ANALYSIS

Characteristic	Emergency department		Hospital admissions	
	Risk ratio	p Value	Risk ratio	p Value
Age	0.91	0.133	0.95	0.329
Black race	2.97	<0.001	1.64	0.129
Female gender	1.75	0.001	1.83	0.026
CD4 median	1.0	0.171	0.99	0.075
Drug use	3.02	<0.001	2.22	0.008
ETOH use	0.80	0.224	0.57	0.958
Diabetes	0.97	0.932	1.23	0.558
Renal	2.03	0.012	2.97	<0.001
HCV coinfection	2.07	<0.001	1.24	0.430

HCV, hepatitis C virus.

TABLE 3. REASONS FOR HEALTH CARE UTILIZATION BY MONOINFECTED VERSUS COINFECTED COHORTS

Reason for visit	Emergency department		Hospital admissions	
	HIV/HCV	HIV	HIV/HCV	HIV
Total	1134% (#)	658% (#)	345% (#)	329% (#)
Other	57.9 (657)	50.5 (332)	29.3 (101)	38.0 (125)
HIV related	7.0 (79)	11.1 (73)	15.9 (55)	23.4 (77)
Non-HIV infection	13.4 (152)	19.6 (129)	18.6 (64)	13.4 (44)
Cardiac	5.8 (66)	10.2 (67)	7.5 (26)	15.5 (51)
Diabetes	1.3 (15)	0.91 (6)	2.0 (7)	0.3 (1)
Renal	3.3 (37)	1.5 (10)	9.3 (32)	2.1 (7)
Substance/psychiatric	10.2 (116)	6.1 (40)	15.4 (53)	7.0 (23)
Liver related	1.1 (12)	0.15 (1)	2.0 (7)	0.3 (1)
	$p \leq 0.001$		$p < 0.001$	

nonliver-related comorbid conditions including substance/psychiatric disease, renal disease, and diabetes accounted for almost a third (26.7%) of hospitalizations among the coinfecting cohort as compared to only 9.4% among the HIV-1 monoinfected cohort.

## Discussion

With the advent of HAART, persons with HIV are living longer.<sup>11,12</sup> A decline in AIDS related events and opportunistic infections has led to an increased role for comorbidities and coinfections in HIV disease burden and health care utilization.<sup>12</sup> This study adds to the growing body of evidence that, when compared to HIV-1 monoinfected individuals, health care resource utilization is greater for the HIV/HCV coinfecting population. This study also suggests that the reasons for increased health care utilization in this high-risk group is not solely related to their underlying liver disease, but is also related to other comorbidities including psychiatric disease, substance abuse, renal disease, and diabetes.

Previous studies have suggested that liver-related morbidity and mortality have been on the rise in the HIV population and that this is primarily driven by chronic HCV co-infection.<sup>13</sup> The D:A:D study identified liver-related deaths as the most common cause of non-HIV-related mortality.<sup>14</sup> In contrast, other studies have reported a reduction in liver-related mortality among HIV-infected individuals during the era of HAART, possibly due to improved immune function attenuating the progression of viral hepatitis.<sup>10,15</sup> This study suggests that the reason for health care utilization among a coinfecting population is not exclusively related to liver morbidity, which comprises 2% or less of emergency department visits and hospitalizations. This finding is similar to that reported in the SMART study,<sup>16</sup> although the HIV/HCV coinfecting subjects constituted a high proportion of the nonopportunistic disease death, liver-related mortality was uncommon. Instead, substance abuse, non-AIDS cancers, and renal disease comprised a higher proportion of the reasons for death among this group.<sup>16</sup> Here we report that this disparity is true in health care utilization metrics as well. Although HIV and other infections were a leading cause of health care utilization in both groups, comorbidities contributed toward a larger proportion of resource utilization for the HIV/HCV coinfecting patients.

This study has limitations. This is a retrospective chart review and thus only emergency department visits and hospital admissions occurring at our site would be included. This may have resulted in an underestimate of utilization in both groups. The retrospective nature of the study may also result in bias due to incomplete data collection; as unidentified confounders may be more common in those with poor health care follow-up and thus incomplete medical records. The lack of a reviewer validation process for data abstraction may have resulted in reviewer specific variations in the classification of reasons for health care utilization. However, all reviewers followed definitions outlined *a priori* when abstracting data, decreasing the risk of significant variability. Due to the tertiary care structure of our center, the patient population may include individuals who have more complex health problems than those seen at community hospitals; thus the results may not be generalizable to the overall population. On the other hand, given the patient level data collection, we were able

assess specific reasons for health care utilization and to classify our HIV/HCV coinfecting cohort by evidence of HCV viremia, establishing an accurate cohort of patients with chronic hepatitis. Prior studies assessing health care utilization have used hepatitis C antibody to identify the HCV-infected cohort that could result in mischaracterization in up to 30% of persons who have spontaneously cleared their infection.

In conclusion, HCV coinfection is a risk factor for increased health care resource utilization in HIV-infected persons. The increasing demand of health care resources by this high-risk group of patients warrants further attention to improve our knowledge of the reasons for this trend and to consider interventions that may improve long-term clinical outcomes. This study suggests that comorbid illnesses, in addition to liver disease, may be contributing to the increased utilization in HIV/HCV coinfecting patients, as compared to their HIV-1 monoinfected counterparts. While larger multicenter studies are needed to confirm these findings, resource allocation to address psychiatric disease, substance abuse, and HCV related medical complications such as diabetes and renal disease may be helpful to prevent emergency department and hospital admissions. Access to improved HCV therapies may improve rates of liver disease, diabetes and renal disease, but with the prevalence of uncontrolled psychiatric disease and active substance use noted in this population, it is unlikely these patients will be viewed as candidates for therapeutic regimens.<sup>17-19</sup> These findings are important to policymakers and clinicians to determine where we must allocate our time and resources to be most effective in aiding this unique and growing population.

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## Author Disclosure Statement

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