

# Patterns of Healthcare Utilization Among Veterans Infected With Hepatitis C Virus (HCV) and Human Immunodeficiency Virus (HIV) and Coinfected With HIV/HCV: Unique Burdens of Disease

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**Background.** Hepatitis C virus (HCV) infection is a leading cause of cirrhosis and the primary cause of liver transplantation in the United States, and coinfection with human immunodeficiency virus (HIV) increases the risk of comorbidities. However, healthcare utilization (HCU) patterns among HIV/HCV-coinfected patients are poorly understood. This study compared the rates of HCU and reasons for hospital admission among HCV-infected, HIV-infected, and HIV/HCV-coinfected veterans.

**Methods.** Hepatitis C virus- and HIV-infected and HIV/HCV-coinfected veterans in care with the Department of Veterans Affairs (VA) from 1998 to 2009 (n = 335 371, n = 28 179, n = 13 471, respectively) were identified by HIV- and HCV-associated *International Classification of Diseases, Ninth Revision* codes from the clinical case registry. We assessed rates of HCU using emergency department (ED) visits, outpatient visits, and hospitalization and primary diagnoses associated with hospitalization. Independent risk factors associated with hospitalization were also examined.

**Results.** Rates of outpatient and ED visits increased over the 11-year study period for all groups, with inpatient admission rates remaining stable. The HCU rates were consistently higher for the coinfecting than other cohorts. The primary reason for hospital admission for all groups was psychiatric disease/substance use, accounting for 44% of all admissions. Nadir CD4 <350 cells/mm<sup>3</sup> was associated with higher rates of hospitalization versus nadir CD4 >500 cells/mm<sup>3</sup>.

**Conclusions.** As the current population of HCV-infected, HIV-infected, and HIV/HCV-coinfected veterans age, they will continue to place a substantial and increasing demand on the US healthcare system, particularly in their utilization of ED and outpatient services. These data suggest the need for an ongoing investment in mental health and primary care within the VA healthcare system.

**Keywords.** coinfection; healthcare utilization; hepatitis C virus; human immunodeficiency virus; veterans.

Hepatitis C is the most common blood-borne infection in the United States, affecting approximately 3 million people [1, 2] and accounting for an estimated \$6.5 billion dollars in healthcare costs [3]. The majority of these costs are due to liver disease associated with chronic infection [4], although the costs of liver transplant and primary liver cancer also contribute. Hepatitis C virus (HCV)-associated mortality has increased in the past decade [5], and modeling studies suggest that the prevalence of HCV-related cirrhosis and hepatocellular carcinoma will peak between 2020 and 2030 [6], leading to an estimated societal cost of \$6.4–\$13.3 billion [3].

It has been previously demonstrated that human immunodeficiency virus (HIV) coinfection is associated with an increased risk of severe liver disease in patients with HCV [7]. Human immunodeficiency virus is an independent risk factor of progression to cirrhosis in these patients, and it leads to shorter survival after hepatic decompensation [8–10]. Highly active antiretroviral therapy (HAART) does not fully mitigate this effect [11, 12]. Analyses from the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, which prospectively evaluated 308 719 person-years of follow-up in HIV-infected persons, suggest that liver disease is a leading cause of death among HIV-infected persons, and that these deaths are largely associated with hepatitis B or C coinfection [13].

Human immunodeficiency virus/HCV coinfection carries morbidity and mortality risks independent of liver disease, and it is associated with a higher risk of insulin resistance, diabetes mellitus, and renal disease than HIV infection alone [14, 15]. Studies examining HIV-infected and HIV/HCV-coinfected patients suggest that these nonliver-related comorbidities, as well as psychiatric/substance use disorders and non-acquired immune deficiency syndrome (AIDS)-associated

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infections, may be major contributors to healthcare utilization (HCU) [16–18].

Descriptive studies suggest that HIV/HCV-coinfected patients are accessing the US healthcare system more frequently than ever before, leading to higher rates of hospitalization, emergency department (ED) visits, and disability days [19, 20]; while other data suggest decreasing hospital admission rates in HIV-infected and -coinfected patients and increasing rates in the HCV monoinfected [21]. The reasons for changes in utilization are poorly understood. The Department of Veterans Affairs (VA) is the single largest provider of care for HCV-infected veterans in the United States, with over 350 000 veterans in this cohort, and is uniquely positioned to address this issue.

Our aim was to compare rates of HCU and reasons for hospital admission among HCV-infected, HIV-infected, and HIV/HCV-coinfected veterans. We were specifically interested in rates of ED and outpatient visits, rates of inpatient admission, and primary discharge diagnoses associated with hospitalization among the 3 groups.

## METHODS

We examined utilization trends from January 1998 through December 2009 using the Clinical Case Registry (CCR). The CCR is a national database of over 60 000 HIV-infected and 320 000 HCV-infected veterans that includes electronic medical record data on diagnosis codes, laboratory results, medications, and procedures. The specifics of identification and validation of HIV- and HCV-infection status have been described previously, and coding is provided in [Supplementary Table 1](#) [22]. Veterans entered cohort with first evidence of any interaction in VA system. Our study period spanned an 11-year period following the widespread availability of HAART. Institutional review board approval was obtained from the local Veterans Administration before accessing CCR data.

### Outcomes and Endpoints

Measures of utilization included ED visits, outpatient visits, and hospital admission. Reason for admission was identified by *International Classification of Diseases, Ninth Revision* codes for primary discharge diagnoses; only primary diagnoses were used for purposes of analysis. Diagnosis groups were created a priori, including the following: cardiovascular disease (CVD); central nervous system; cancer, not including HIV-associated cancers; diabetes; endocrine; gastrointestinal (GI), not including liver disease; hematologic; hepatitis C infection and associated liver disease (HCV); HIV-associated diagnoses (HIV); infection, not including AIDS-associated infection; other liver disease (including alcoholic, hepatitis B virus [HBV], autoimmune); psychiatric/substance abuse; pulmonary; renal; trauma; and other. We used the 1993 Centers for Disease Control and Prevention classification system for HIV infection to determine

which diagnoses were AIDS-related. These included AIDS-defining illnesses such as *Pneumocystis jiroveci* pneumonia and *Mycobacterium avium* complex, as well as HIV-related infections such as recurrent pneumonia, herpes zoster, candida, tuberculosis, and lymphoma.

### Statistical Analysis

Yearly rates of ED visits, outpatient visits, and hospital admission (per 1000 persons) were calculated for HCV-infected, HIV-infected, and HIV/HCV-coinfected cohorts. To test for temporal trends in admission rates and differences in rates between the HIV and HCV groups, we fit linear trend models for each encounter type, allowing for different intercepts and slopes for HCV-infected, HIV-infected, and HIV/HCV-coinfected patients. For hospital admissions, the proportion of admissions attributable to each prespecified diagnosis group was calculated. Negative binomial regression models were used to assess risk factors independently associated with the outcomes including gender, race, ethnicity, age, body mass index (BMI), calendar year, CD4 nadir, and detectable viral load. These models used a repeated measures formulation by calendar year with the generalized estimating equations method [23, 24] to adjust variance estimates for clustering defined by individual veteran. The 95% confidence intervals (CIs) for rate ratios were constructed using a normal approximation. Due to the large size of the study cohort, *P* values have very limited utility. Reporting of results will focus on clinically meaningful differences rather than statistical significance, and statistical significance, defined as  $P < .05$ , can be assumed for all reported differences unless otherwise noted. Analyses were performed with SAS version 9.4 (Cary, NC).

## RESULTS

### Cohort Description

From 1998 to 2009, the CCR identified 335 371 veterans with HCV infection, 28 179 with HIV infection, and 13 471 with and HIV/HCV coinfection. These cohorts were mutually exclusive. [Table 1](#) demonstrates the demographic characteristics of each group. All 3 cohorts were predominantly male. Cohorts were similar in terms of median age, with highest median age occurring in the HCV cohort. The cohorts differed in terms of race and ethnicity. The coinfecting cohort contained the largest percentage of black veterans (46.8%, compared with 24.0% and 35.3% in the HCV and HIV cohorts). The HIV cohort had more missing data on race (28.2%, compared with 26.2% and 26.1% in the HCV and coinfecting cohorts). Median fibrosis 4 score ranged between 1.3 and 2.0 and was lowest for HIV-monoinfected patients and highest in the coinfecting cohort. CD4 count and nadir CD4 count were similar for the HIV-monoinfected and in the coinfecting cohorts.

### Rates of Healthcare Utilization

[Figure 1](#) demonstrates rates of outpatient visits, inpatient admission, and ED visits among the 3 cohorts. For all cohorts,

**Table 1. Cohort Demographics and Clinical Characteristics<sup>a</sup>**

Patient Characteristic	HCV (N = 335 371)		HIV (N = 28 179)		HIV/HCV (N = 13 471)	
	n	%	n	%	n	%
<b>Sex</b>						
Male	324 956	96.9	27 370	97.1	13 228	98.2
Female	10 414	3.1	809	2.9	243	1.8
Missing	1	0	0	0	0	0
<b>Race</b>						
Black	80 394	24.0	9944	35.3	6304	46.8
White	162 382	48.4	9934	35.3	3552	26.4
Other	4548	1.4	340	1.2	97	0.7
Missing	88 047	26.2	7961	28.2	3518	26.1
<b>Ethnicity</b>						
Hispanic	16 521	4.9	1246	4.4	858	6.4
Non-Hispanic	241 042	71.9	19 196	68.1	9035	67.1
Missing	77 808	23.2	7737	27.5	3578	26.6
Age (years)	59.9 [54.4–62.7]		54.8 [47.4–62.1]		57.2 [53.1–61.1]	
<b>Median [IQR]</b>						
FIB-4	1.8 [2.2–2.9]		1.3 [0.92–1.8]		2.0 [1.4–3.3]	
CD4 (cells/mm <sup>3</sup> ) median [IQR]	NA		291 [59–546]		333 [147–550]	
Nadir CD4 (cells/mm <sup>3</sup> ) median [IQR]	NA		124 [24–300]		140 [41–274]	
HIV viral load (copies/mL)	NA		92.45 [48–9680]		196 [50–13 896]	

Abbreviations: FIB-4, fibrosis-4; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable.

<sup>a</sup> Data for repeated measures (FIB-4, CD4, HIV viral load) were taken from the most recent measure available for each patient.

utilization rates of ED and outpatient services increased across the study time period while inpatient admission rates remained relatively steady. The HIV/HCV-coinfected veterans used healthcare services, for all service types, at higher rates than HCV- or HIV-monoinfected veterans. For ED and inpatient services, the HIV cohort had the lowest rates of utilization. Outpatient utilization rates were lowest for the HCV cohort. The median number of admissions was 1, 2, and 4 for HCV, HIV, and coinfecting patients, respectively. Those in the 90th percentile and higher for numbers of admissions (ie, the top 10% of admissions) accounted for 47%, 39%, and 40% of total admissions in these groups, respectively.

In the final year of observation, cohorts used ED services at a rate of 894 visits/1000 persons (HCV), 763 visits/1000 persons (HIV), and 1307 visits/1000 persons (coinfecting); outpatient services at a rate of 8552 visits/1000 persons (HCV), 9118 visits/1000 persons (HIV), and 11 879 visits/1000 persons (coinfecting); and inpatient services at a rate of 391 visits/1000 persons (HCV), 283 visits/1000 persons (HIV), and 572 visits/1000 persons (coinfecting).

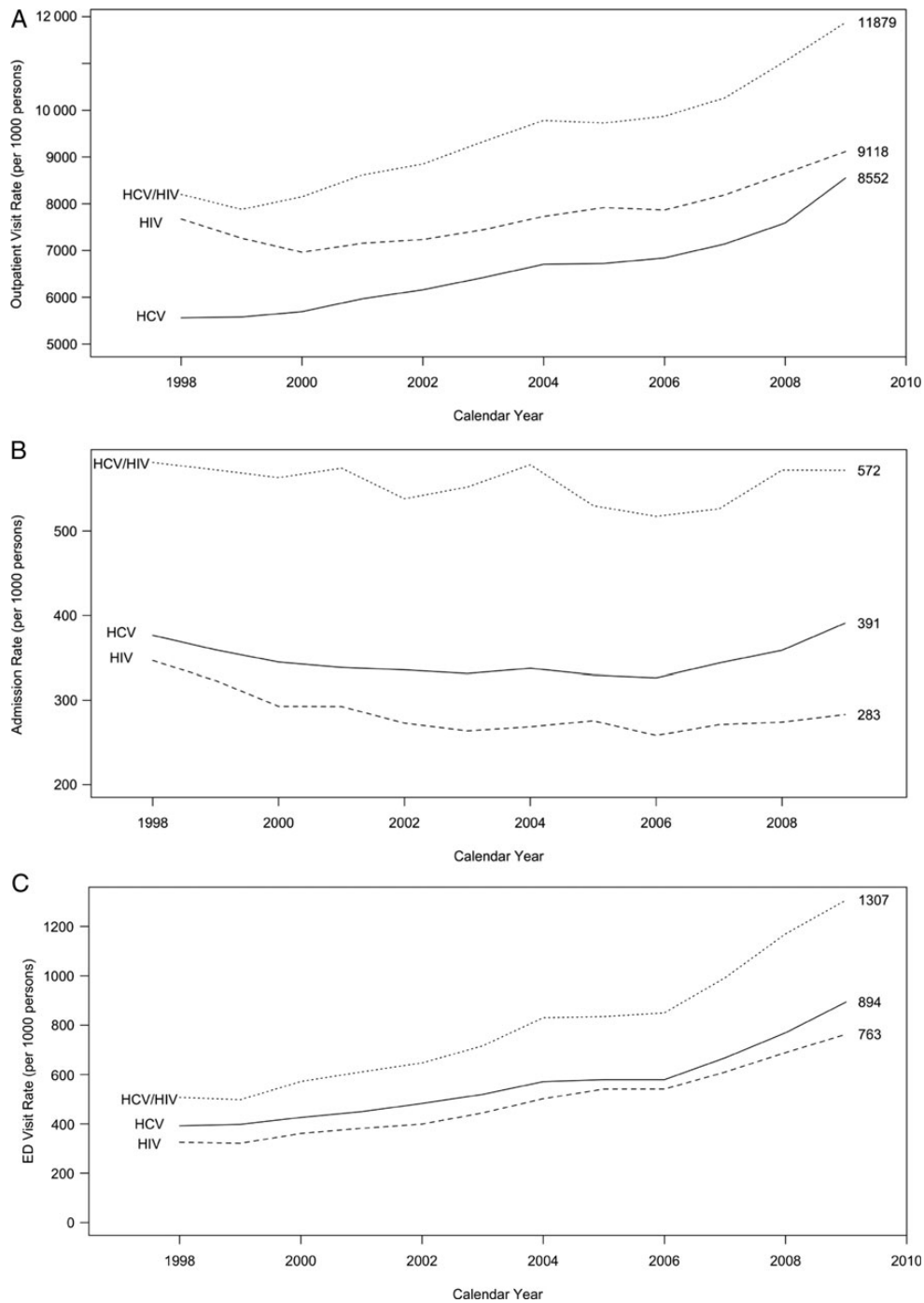
There were significant time trends in utilization over the study period. Emergency department visits increased by 43 per 1000 persons for HCV patients, 41 per 1000 for HIV patients, and 69 per 1000 for coinfecting patients, all were significant ( $P < .05$ ). The rate of increase was statistically different for the coinfecting group compared with the others, whereas the increases were not different comparing HIV and HCV patients. Outpatient visits also increased significantly by 266 (HCV),

234 (HIV), and 355 (coinfecting) per 1000 persons. Again, the coinfecting group had a significantly higher rate of increase than the monoinfected patients. Hospital admissions showed much smaller but significant trends over time, increasing by 2.5 per 1000 persons for HCV patients, but decreasing by 1.5 (HIV) and 1.0 (coinfecting) per 1000 patients per year. After decreasing from 1998 to 2006, the rate of admissions appears to have increased for HCV patients in the last several years of follow-up (Figure 1B).

#### Reasons for Admission

The primary discharge diagnoses associated with inpatient admission for each cohort is summarized in Figure 2. Psychiatric disease and/or substance use was the most common discharge diagnosis for all groups, accounting for 41.0% of total inpatient admissions. Cardiovascular disease, non AIDS-associated infection, and GI disease (excluding liver disease) were all common discharge diagnoses and accounted for an additional 29.3% of total admissions. Hepatitis C virus-associated diagnoses and liver disease accounted for approximately 3.9% of total admissions, whereas AIDS-associated infection was not a common reason for admission and accounted for less than 1% of all admissions.

Within the HCV-infected cohort, leading discharge diagnoses were psychiatric (42.0%), CVD (12.3%), infection (9.9%), GI (7.2%), and trauma (6.2%), with combined liver and HCV diagnoses making up 4.2% of admissions. In the HIV-infected cohort, psychiatric (24.3%), infection (17.7%), cardiovascular

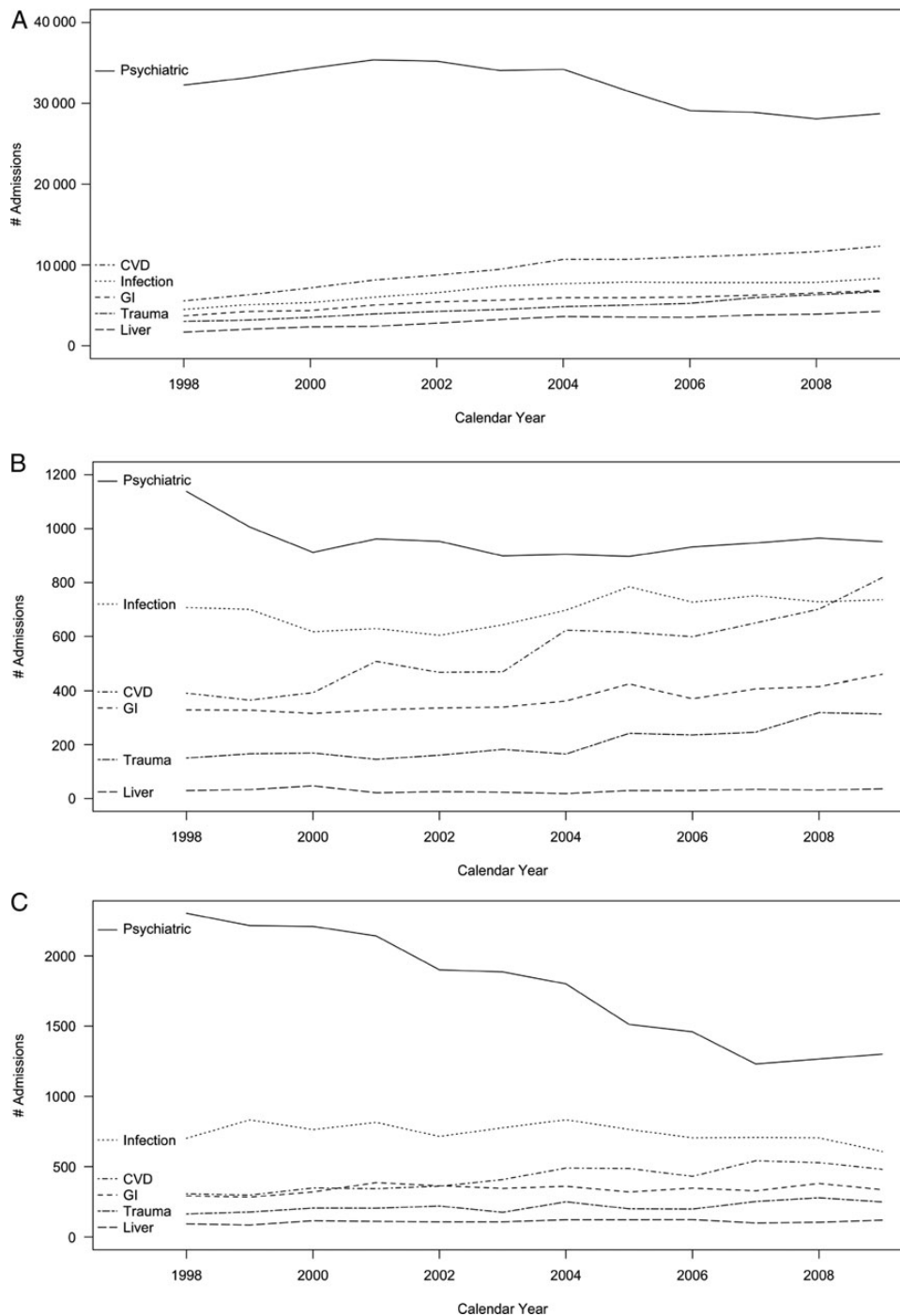


**Figure 1.** National Veterans Affairs healthcare utilization rates (per 1000 persons) from 1998 to 2009 based on (A) outpatient clinic visits, (B) inpatient hospital admissions, (C) emergency department visits in human immunodeficiency virus (HIV) (dashed), hepatitis C virus (HCV) (solid), and HIV/HCV (dotted) cohorts.

(14.0%), GI (9.4%), and AIDS-associated diagnoses (2.5%) were the most frequent reasons for admission. Among coinfecting veterans, psychiatric (39.0%), infection (16.4%), CVD (9.2%), GI (7.5%), and trauma (4.7%) diagnoses made up the majority of admissions. Combined liver/HCV-associated diagnoses and AIDS-associated diagnoses accounted for 3.3% and 1.5% of the coinfecting admissions, respectively.

#### Modeling Risk of Admission

Table 2 shows risk factors associated with inpatient admission, based on negative binomial regression modeling. Before 2004, a large percentage of race and ethnicity data was missing from the CCR database. These data were considered missing at random. To address concerns about missing data, negative binomial models were constructed both for the 2004–2009 time period



**Figure 2.** Primary discharge diagnoses for inpatient hospital admissions from 1998 to 2009 for (A) hepatitis C virus (HCV), (B) human immunodeficiency virus (HIV), and (C) HIV/HCV cohorts. Top reasons for admission: psychiatric (solid), cardiovascular disease ([CVD] dot-dash), infection (dotted), gastrointestinal ([GI] short dash), trauma (2-dash), liver/HCV related (long dash).

(Table 2) as well as for the entire study period (data not shown). Inferences from the 2 sets of models were similar, although the large proportion of missing race/ethnicity data, particularly for those veterans with data only for the 1998–2003 period, caused overestimates of the relative admission rates for calendar year trends.

Female gender was associated with a lower rate of admission in the HCV cohort (adjusted relative rate, 0.83; 95% CI, .79–.87); however, this association was not seen in the HIV and coinfecting cohorts (Table 2). Compared with BMI 20–25 kg/m<sup>2</sup>, BMI less than 20 was associated with a higher relative rate of inpatient admission across all cohorts:

**Table 2. Risk Factors Associated With Inpatient Admission, 2004–2009**

Risk Factor	HCV (N = 335 371)		HIV (N = 28 179)		HIV/HCV (N = 10 599)	
	RR	95% CI	RR	95% CI	RR	95% CI
<b>Sex</b>						
Female sex	0.83	.79–.87	1.08	.92–1.27	0.95	.73–1.23
<b>Race</b>						
Black	1.01	1.00–1.03	1.23	1.15–1.31	1.09	1.01–1.18
<b>Ethnicity</b>						
Hispanic	1.01	.98–1.05	1.00	.87–1.14	1.09	.94–1.27
<b>BMI (kg/m<sup>2</sup>)</b>						
<20	1.35	1.31–1.38	1.57	1.45–1.70	1.29	1.19–1.41
20–24.9	1.00	–	1.00	–	1.00	–
25–29.9	0.82	.81–.83	0.79	.75–.84	0.82	.76–.88
30–34.9	0.75	.73–.76	0.79	.72–.87	0.80	.71–.90
>35	0.79	.77–.81	0.90	.78–1.04	0.87	.73–1.04
<b>Age (years)</b>						
<50	1.00	–	1.00	–	1.00	–
50–54.9	0.98	.96–.99	1.16	1.07–1.24	1.00	.92–1.08
55–59.9	0.94	.92–.96	1.21	1.12–1.31	0.97	.88–1.06
60–64.9	0.95	.93–.98	1.25	1.14–1.38	0.92	.81–1.04
65–69.9	0.83	.80–.87	1.36	1.20–1.54	0.91	.73–1.13
70–74.9	0.82	.79–.86	1.46	1.25–1.71	0.90	.71–1.16
75–79.9	0.82	.78–.86	1.75	1.39–2.20	0.59	.39–.90
>80	0.84	.79–.88	2.20	1.56–3.10	1.40	.87–2.23
<b>Year</b>						
2004	1.00	–	1.00	–	1.00	–
2005	0.98	.97–1.00	1.07	1.00–1.14	0.94	.88–1.00
2006	0.97	.96–.99	1.03	.96–1.11	0.96	.90–1.03
2007	1.02	1.01–1.04	1.11	1.03–1.20	0.95	.88–1.02
2008	1.07	1.05–1.08	1.13	1.13–1.22	1.04	.96–1.12
2009	1.16	1.14–1.18	1.19	1.19–1.29	1.07	.99–1.16
<b>Nadir CD4 (cells/mm<sup>3</sup>)</b>						
<50	–	–	2.45	2.13–2.82	1.51	1.25–1.84
50–99	–	–	2.12	1.80–2.50	1.32	1.08–1.61
100–199	–	–	1.62	1.40–1.88	1.30	1.07–1.58
200–349	–	–	1.30	1.12–1.50	1.05	.86–1.28
350–499	–	–	1.11	.95–1.31	0.95	.75–1.19
>500	–	–	1.00	–	1.00	–
Detectable HIV RNA	–	–	1.99	1.88–2.11	1.78	1.67–1.89

Abbreviations: BMI, body mass index; CI, confidence interval; HCV, hepatitis C virus; HIV, human immunodeficiency virus; RNA, ribonucleic acid; RR, relative risk.

HCV-infected (adjusted relative rate, 1.35; 95% CI, 1.31–1.38), HIV-infected (adjusted relative rate, 1.57; 95% CI, 1.45–1.70), and coinfecting (adjusted relative rate, 1.29; 95% CI, 1.19–1.41). Older age was negatively correlated with admission rate in the HCV cohort, positively correlated in the HIV cohort, and was not associated in the coinfecting cohort. Black race was associated with increased rate of hospitalization among the HIV-infected (adjusted relative rate, 1.23; 95% CI, 1.15–1.31) and coinfecting cohorts (adjusted relative rate, 1.09; 95% CI, 1.01–1.18), although not in the HCV-infected cohort. In the HCV and HIV groups, the rates of inpatient admission showed a small but significant correlation with later year in the study period, adjusted for aging.

Among HIV-infected and coinfecting veterans, low nadir CD4 count and detectable viral load were both associated with increased inpatient admissions. In the HIV-infected cohort, relative to nadir CD4 count  $\geq 500$  cells/mm<sup>3</sup>, nadir CD4 counts of <50 were associated with the greatest increase in relative admission rate (adjusted relative rate, 2.45; 95% CI, 2.13–2.82), and nadir CD4 counts of 50–99 (adjusted relative rate, 2.12; 95% CI, 1.80–2.50), 100–199 (adjusted relative rate, 1.62; 95% CI, 1.40–1.88), and 200–349 (adjusted relative rate, 1.30; 95% CI, 1.12–1.50) were also associated with increased rate of hospitalization. Among coinfecting veterans, nadir counts of <50 (adjusted relative rate, 1.51; 95% CI, 1.25–1.84), 50–99 (adjusted relative rate, 1.32; 95% CI, 1.08–1.61), and 100–199

(adjusted relative rate, 1.30; 95% CI, 1.07–1.58) were associated with increased rates of hospitalization.

## DISCUSSION

It has previously been demonstrated that HIV/HCV-coinfected persons utilize the healthcare system at a higher rate than either HCV- or HIV-monoinfected veterans. This study sought (1) to quantify rates of HCU of ED, outpatient, and inpatient services in a large-scale health system over a period of 11 years and (2) to determine the medical diagnoses and independent risk factors that drive inpatient admissions in these high-risk veteran populations. We found (1) that HCU in the VA healthcare system is increasing for all chronically infected groups and (2) that the primary reason for inpatient utilization is related to psychiatric disease and substance use.

Although ED and outpatient utilization rates are increasing for all groups, the HIV/HCV-coinfected cohort had the highest rates of HCU for all locations throughout the study. This comes in contrast to a recently published study looking at outpatient HCU using data from 2005 to 2010 US National Hospital Ambulatory Medical Care Surveys (NHAMCS), which found that outpatient visit rates were highest among HIV-monoinfected patients, followed by coinfecting, and then HCV-infected [25]. The NHAMCS study is based on a sample of ambulatory care centers that excludes federal, veteran affairs, and institutional hospital clinics, and their findings may reflect differences in retention of care among HIV-infected patients within the VA system, which provide comprehensive HIV treatment with few out-of-pocket costs to the patient. Our study also demonstrated that utilization rates for the outpatient visit, by far the most common healthcare service accessed by veterans, were lowest for the HCV cohort, in keeping with previous observations [25]. It is possible HCV-infected veterans are less likely to be engaged in regular outpatient follow-up, have fewer comorbidities requiring additional follow-up, or are more medically stable thus requiring fewer frequent visits. For ED and inpatient services, the HIV cohort had the lowest rates of utilization, perhaps reflecting access to comprehensive HIV treatment and care provided by the VA system. Our findings demonstrate stability of inpatient admission rates across the study period, for all cohorts. This could be related to the changing epidemiology of morbidity in HIV-infected persons in particular but also may reflect better access to outpatient services, including outpatient mental health services and antiretrovirals [26]. It is worth noting that despite increased access to outpatient care in this population, hospitalization rates did not decline during the period of study follow-up.

Factors independently associated with inpatient admission included BMI of less than 20, black race (HIV and coinfecting cohorts), detectable HIV viral load, CD4 nadir <350 (HIV infected) and <200 (HIV/HCV coinfecting), and older age (HIV infected). Female sex and older age were both negatively

associated with risk of hospitalization in the HCV-infected cohort. The association between age and decreased risk of hospitalization in the HCV-infected cohort is intriguing, and it could reflect care received outside the VA system due to availability of Medicare in older veterans. Hispanic ethnicity was not an independent risk factor for admission, consistent with prior reports from the Veterans Aging Cohort Study [27].

A principle finding of this study relates to reasons for inpatient admission among HCV-infected, HIV-infected, and coinfecting patients. Prior studies have not been consistent in demonstrating the primary diagnoses that drive inpatient utilization. One cohort study of HIV-infected military personnel between 2000 and 2013 found that non-AIDS-defining infections were the most common cause of hospital admission [16]. Other studies suggest that AID-related diagnoses, non-AIDS-related cancers, and liver disease account for the majority of deaths in HIV-infected persons during a similar time period [13]. Among HCV-infected persons, a longitudinal study that examined trends in inpatient utilization among HCV-infected patients from 2004 to 2011 found that HCV-infected patients hospitalized for any cause had a higher prevalence of mental illness, substance use disorder, chronic kidney disease, pneumonia, HBV infection, and HIV infection than those without HCV infection [18]. Our findings demonstrate that the majority of inpatient admissions, among all cohorts, are due to conditions other than liver disease. It is worth noting that liver disease accounted for less than 4% of admissions in the HCV-monoinfected veterans and 3% in HIV/HCV-coinfected veterans. For all groups the primary indications for inpatient admission were psychiatric and substance abuse disorders. Recognizing the high rates of psychiatric disease including posttraumatic stress disorder in veterans, this may explain the differences in reporting with other large cohorts. This finding is relevant to resource allocation within the VA system, including confirming the need to increase access to mental health services. It is also worth noting that clinicians often wait for stabilization of psychiatric disease before treatment of HIV and HCV, which may result in a delay in access to therapies for these diseases, including direct-acting antivirals.

Other major contributors to inpatient admission, for both HCV- and HIV-infected veterans, included CVD and non-AIDS-associated infection, not dissimilar from the diagnoses driving admissions in the general population [28]. This finding supports the need for good access to primary care in the HCV and HIV populations, with attention to appropriate age-based preventative care. This is particularly important in light of the recent data suggesting these veterans are less likely to receive appropriate guideline-recommended therapy for primary CVD prevention [29].

The present study has multiple strengths, including the large size of its cohort, the quantification of ED, outpatient, and inpatient services over 11 years, and the novel findings related to

inpatient-associated diagnoses. However, our study also has several limitations. Due to the size of the dataset, we were unable to adjudicate the primary diagnosis for hospitalization. We were unable to capture veterans' pre-existing medical conditions, nor did we capture social and behavioral factors such as income, housing, amount/pattern of alcohol use, or intravenous drug use. In the model we were unable to control for length of time with HCV or HIV, nor could we examine risk related to calendar year across the entire study period. We were also unable to control for any subjects who may have received HCV therapy and cleared the infection during the study period. Future work should include capturing medical comorbidities as they relate to HCU and implementing policies that increase access to psychiatric care and limit the use of the ED for chronic care [30].

## CONCLUSIONS

Hepatitis C is a growing stress on the healthcare system, particularly affecting our nation's veterans. Coinfection with HIV exacerbates the morbidities of HCV. With the aging of the HCV cohort, understanding patterns of HCU in this population is critical. This study provides evidence that utilization of ED and outpatient services is growing among HCV-infected, HIV-infected, and coinfecting veterans; that coinfecting veterans are using healthcare services at higher rates than the other groups. Psychiatric disease, CVD, and non HIV-associated infection are the primary drivers of inpatient admission for all groups, emphasizing the importance of investing in mental health and primary care services for veterans. The emergence of effective HCV therapies may shift utilization patterns, and ongoing longitudinal follow-up is needed to understand utilization in an era where HCV cure is a possibility. Thoughtful healthcare planning, which incorporates our evolving knowledge of utilization patterns, will facilitate improved healthcare for US veterans.

## Supplementary Data

Supplementary material is available online at *Open Forum Infectious Diseases online* (<http://OpenForumInfectiousDiseases.oxfordjournals.org/>).

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## References

- Denniston MM, Jiles RB, Drobeniuc J, et al. Chronic hepatitis C virus infection in the United States, National Health and Nutrition Examination Survey 2003 to 2010. *Ann Intern Med* **2014**; 160:293–300.
- Messina JP, Humphreys I, Flaxman A, et al. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* **2015**; 61:77–87.
- Razavi H, Elkhoury AC, Elbasha E, et al. Chronic hepatitis C virus (HCV) disease burden and cost in the United States. *Hepatology* **2013**; 57:2164–70.
- Leigh JP, Bowler CL, Leistikow BN, Schenker M. Costs of hepatitis C. *Arch Intern Med* **2001**; 161:2231–7.
- Ly KN, Hughes EM, Jiles RB, Holmberg SD. Rising mortality associated with hepatitis C virus in the United States, 2003–2013. *Clin Infect Dis* **2016**; 62:1287–8.
- Davis GL, Alter MJ, El-Serag H, et al. Aging of hepatitis C virus (HCV)-infected persons in the United States: a multiple cohort model of HCV prevalence and disease progression. *Gastroenterology* **2010**; 138:513–21.
- Graham CS, Baden LR, Yu E, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. *Clin Infect Dis* **2001**; 33:562–9.
- Vallet-Pichard A, Pol S. Natural history and predictors of severity of chronic hepatitis C virus (HCV) and human immunodeficiency virus (HIV) co-infection. *J Hepatol* **2006**; 44(1 Suppl):S28–34.
- Bierhoff E, Fischer HP, Willsch E, et al. Liver histopathology in patients with concurrent chronic hepatitis C and HIV infection. *Virchows Arch* **1997**; 430:271–7.
- Soto B, Sánchez-Quijano A, Rodrigo L, et al. Human immunodeficiency virus infection modifies the natural history of chronic parenterally-acquired hepatitis C with an unusually rapid progression to cirrhosis. *J Hepatol* **1997**; 26:1–5.
- Thein HH, Yi Q, Dore GJ, Krahn MD. Natural history of hepatitis C virus infection in HIV-infected individuals and the impact of HIV in the era of highly active antiretroviral therapy: a meta-analysis. *AIDS* **2008**; 22:1979–91.
- de Ledinghen V, Barreiro P, Foucher J, et al. Liver fibrosis on account of chronic hepatitis C is more severe in HIV-positive than HIV-negative patients despite antiretroviral therapy. *J Viral Hepat* **2008**; 15:427–33.
- Smith CJ, Ryom L, Weber R, et al. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet* **2014**; 384:241–8.
- Caronia S, Taylor K, Pagliaro L, et al. Further evidence for an association between non-insulin-dependent diabetes mellitus and chronic hepatitis C virus infection. *Hepatology* **1999**; 30:1059–63.
- Visnegarwala F, Chen L, Raghavan S, Tedaldi E. Prevalence of diabetes mellitus and dyslipidemia among antiretroviral naive patients co-infected with hepatitis C virus (HCV) and HIV-1 compared to patients without co-infection. *J Infect* **2005**; 50:331–7.
- Crowell TA, Ganesan A, Berry SA, et al. Hospitalizations among HIV controllers and persons with medically controlled HIV in the U.S. Military HIV Natural History Study. *J Int AIDS Soc* **2016**; 19:20524.
- Norton BL, Park L, McGrath LJ, et al. Health care utilization in HIV-infected patients: assessing the burden of hepatitis C virus coinfection. *AIDS Patient Care STDS* **2012**; 26:541–5.
- Tong X, Spradling PR. Increase in nonhepatic diagnoses among persons with hepatitis C hospitalized for any cause, United States, 2004–2011. *J Viral Hepat* **2015**; 22:906–13.
- Grant WC, Jhaveri RR, McHutchison JG, et al. Trends in health care resource use for hepatitis C virus infection in the United States. *Hepatology* **2005**; 42:1406–13.
- Linas BP, Wang B, Smurzynski M, et al. The impact of HIV/HCV co-infection on health care utilization and disability: results of the ACTG Longitudinal Linked Randomized Trials (ALLRT) Cohort. *J Viral Hepat* **2011**; 18:506–12.
- Oramasionwu CU, Toliver JC, Johnson TL, et al. National trends in hospitalization and mortality rates for patients with HIV, HCV, or HIV/HCV coinfection from 1996–2010 in the United States: a cross-sectional study. *BMC Infect Dis* **2014**; 14:536.
- Backus LI, Gavrillov S, Loomis TP, et al. Clinical Case Registries: simultaneous local and national disease registries for population quality management. *J Am Med Inform Assoc* **2009**; 16:775–83.
- Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* **1986**; 42:121–30.
- Liang KY, Zeger SL. Longitudinal data analysis using generalized linear models. *Biometrika* **1986**; 73:13–22.
- Johnson TL, Toliver JC, Mao L, Oramasionwu CU. Differences in outpatient care and treatment utilization for patients with HIV/HCV coinfection, HIV, and HCV mono-infection, a cross-sectional study. *BMC Infect Dis* **2014**; 14:217.
- Godleski L, Darkins A, Peters J. Outcomes of 98,609 U.S. Department of Veterans Affairs patients enrolled in telemental health services, 2006–2010. *Psychiatr Serv* **2012**; 63:383–5.
- Akgün KM, Gordon K, Pisani M, et al. Risk factors for hospitalization and medical intensive care unit (MICU) admission among HIV-infected Veterans. *J Acquir Immune Defic Syndr* **2013**; 62:52–9.
- Pfunter A, Wier LM, Stocks C. Most frequent conditions in U.S. Hospitals, 2011. Healthcare cost and utilization project, **2013**. Available at: <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf>. Accessed 15 December 2014.
- Clement ME, Park LP, Navar-Boggan AM, Okeke L, Pecina M, Douglas P, Naggie S. HIV-infected Veterans and the New ACC/AHA Cholesterol Guidelines: Got Statins? Poster presented at: Conference on Retroviruses and Opportunistic Infections (CROI); 23–25 February 2015; Seattle, WA.
- Taylor LE, Swan T, Matthews GV. Management of hepatitis C virus/HIV coinfection among people who use drugs in the era of direct-acting antiviral-based therapy. *Clin Infect Dis* **2013**; 57(Suppl 2):S118–24.