

# Risk of Immune Thrombocytopenic Purpura and Autoimmune Hemolytic Anemia Among 120 908 US Veterans With Hepatitis C Virus Infection

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**Background:** There is emerging evidence that hepatitis C virus (HCV) infection play a role in the etiology of immune thrombocytopenia purpura (ITP) and autoimmune hemolytic anemia (AIHA), both of which are severe autoimmune cytopenias.

**Methods:** To determine if HCV infection increases the risk for ITP and AIHA, we calculated the incidence rates of ITP and AIHA among 120 691 HCV-infected and 454 905 matched HCV-uninfected US veterans who received diagnoses during the period 1997 to 2004. After excluding individuals with a prior diagnosis of a lymphoproliferative disease, human immunodeficiency virus, or cirrhosis, we fitted Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) as measures of risks.

**Results:** We found 296 ITP and 90 AIHA cases. Among HCV-infected vs HCV-uninfected persons, the overall in-

cidence rates of ITP were 30.2 and 18.5 per 100 000 person-years, and for AIHA they were 11.4 and 5.0 per 100 000 person-years, respectively. Hepatitis C virus was associated with elevated risks for ITP (HR, 1.8; 95% CI, 1.4-2.3) and AIHA (HR, 2.8; 95% CI, 1.8-4.2). The ITP incidence was increased among both untreated and treated HCV-infected persons (HR, 1.7; 95% CI, 1.3-2.2 and HR, 2.4; 95% CI, 1.5-3.7, respectively), whereas AIHA incidence was elevated only among treated HCV-infected persons (HR, 11.6; 95% CI, 7.0-19.3).

**Conclusions:** Individuals infected with HCV are at an increased risk for ITP, whereas the development of AIHA seems to be associated with HCV treatment. It may be beneficial to test individuals newly diagnosed as having ITP for HCV infection.

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**H**EPATITIS C VIRUS (HCV) IS a chronic viral infection that affects approximately 3% of the world's population.<sup>1</sup> Based on the National Health and Nutrition Examination Survey, HCV is the most common chronic blood-borne infection in the United States, with approximately 1.6% of the US population or 4 million Americans infected.<sup>2,3</sup> Currently, HCV is responsible for substantial morbidity and mortality in the United States resulting from chronic active hepatitis, cirrhosis, and hepatocellular carcinoma. Studies have shown an increase in the incidence of HCV-related liver disease, with HCV infection now the leading cause of liver transplantation in the United States.<sup>4-6</sup>

In addition, HCV infection has been associated with various types of extrahepatic conditions, including lymphoproliferative hematologic malignant neoplasms and related precursors,<sup>7-9</sup> as well as a wide range of immune-related disorders (eg, glomerulonephritis,<sup>7,10</sup> vitiligo,<sup>7</sup> pulmonary fibro-

sis,<sup>10</sup> Sjögren syndrome,<sup>11,12</sup> and cutaneous vasculitis<sup>10</sup>). Recent clinical and molecular research have provided evidence suggesting that HCV infection may play a role in the pathogenesis of immune thrombocytopenia purpura (ITP) and autoimmune hemolytic anemia (AIHA), in which accelerated destruction of platelet and red blood cells occur, respectively.<sup>12-18</sup>

Prior studies<sup>14,16,17,19</sup> suggesting that HCV might be an etiologic risk factor for the development of autoimmune cytopenias have been based on small series of patients from single institutions. Severe autoimmune cytopenias have been attributed to treatment of chronic HCV with interferon alfa therapy in case reports<sup>20,21</sup>; however, AIHA and ITP have been observed to occur among untreated individuals as well.<sup>13,14</sup> To our knowledge, no large study has been conducted. Given that US military veterans have a high prevalence of HCV infection (5%),<sup>22</sup> this population provides a unique opportunity to observe HCV-related phenomena. Thus, we were motivated to ascertain ITP and AIHA incidence rates among a cohort of

**Table 1. Diagnoses and Corresponding ICD-9-CM Codes**

Diagnosis	ICD-9-CM Code
HCV infection	070.41, 070.44, 070.51, 070.54, V02.62
HIV infection	042.0, 042.1, 042.2, 042.9, 043.0, 043.1, 043.2, 043.3, 043.9, 044.0, 044.9, V08, 795.8
Cirrhosis	571.2, 571.5, 571.6
Non-Hodgkin lymphoma	200, 202.0-202.2, 202.8
Chronic lymphocytic leukemia	204.1
Multiple myeloma	203.0-203.1, 238.6
Hodgkin lymphoma	201
Waldenström macroglobulinemia	273.0, 273.3
ITP	287.31
AIHA	283.0
Epistaxis, hemorrhage, or purpura	287, 782.7, 578.0, 578.1, 578.9, 459.0, 431, 432.0, 432.1, 432.9, 362.81, 430, 786.3, 784.7

Abbreviations: AIHA, autoimmune hemolytic anemia; HCV, hepatitis C virus; HIV, human immunodeficiency virus; *ICD-9 CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; ITP, immune thrombocytopenia purpura.

575 596 HCV-infected and matched uninfected veterans to determine the effect of HCV infection and other risk factors associated with ITP and AIHA.

## METHODS

### DATA SOURCES

Methods for establishing the cohort of HCV-infected veterans who used the Veterans Affairs (VA) health system have been previously published.<sup>8</sup> In brief, we used VA administrative inpatient and outpatient records. The patient treatment file (PTF) contains up to 10 *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* codes per hospitalization for all patients hospitalized in more than 150 VA hospitals in the United States from 1981 to the present. We utilized PTF data from fiscal years 1989 through 2004, which correspond to data collected from October 1, 1988, through September 30, 2004. We also collected information from the outpatient clinic file (OPC), which records a primary diagnosis and up to 9 *ICD-9-CM* codes for each outpatient encounter. The OPC data from fiscal year 1997 (the year the OPC was initiated) through 2004 were obtained.

We accessed VA pharmacy data to determine if HCV-infected individuals received HCV treatment. We searched pharmacy records for fiscal years 1997 through 2004 for evidence of at least 1 written (inpatient) or filled (outpatient) prescription for either interferon alfa or ribavirin. Treatment date was defined as the date the prescription was written (for inpatient hospitalizations) or the date the prescription was dispensed (for outpatients).

The institutional review boards of Baylor College of Medicine and Affiliated Hospitals and the National Cancer Institute approved the study. We obtained a waiver of informed consent and release of protected health information.

### STUDY SUBJECTS AND OUTCOMES

The study cohort has been previously described.<sup>8</sup> In brief, the HCV-infected cohort was identified using the *ICD-9-CM* diag-

nosis codes specifying HCV infection (see **Table 1** for *ICD-9-CM* codes). We then identified up to 4 HCV-uninfected individuals matched by age, sex, visit date, and type of visit (inpatient vs outpatient visit) for each HCV-infected person. Because we wanted to ensure that our cohort included only individuals who used the VA system (and were not seen only once), we mandated that both HCV-infected and uninfected individuals have 2 documented encounters in either of the VA databases during fiscal years 1997 to 2004. Matched HCV-uninfected individuals were sampled with replacement. We identified the second of the 2 encounters as the baseline date. To guarantee that ITP or AIHA was not a manifestation of human immunodeficiency virus (HIV) or cirrhosis, we excluded HCV-infected and HCV-uninfected individuals who had a previous diagnosis of HIV infection on or before the baseline date, and we excluded any subject who ever had evidence of cirrhosis. In addition, because ITP and AIHA can be associated with the presentation of lymphoproliferative diseases, we excluded individuals who were diagnosed as having a lymphoproliferative disease up to 6 months after the baseline date, including non-Hodgkin lymphoma, chronic lymphocytic leukemia, multiple myeloma, Hodgkin lymphoma, and Waldenström macroglobulinemia. The initial diagnoses of ITP and AIHA were the outcomes of interest. To allow for possible delays in the diagnosis or reporting of the outcomes, and because a new diagnosis of HCV infection may have facilitated these diagnoses, any outcomes occurring prior to 6 months after the baseline date were excluded. Finally, we utilized *ICD-9-CM* codes for "hemorrhage," "epistaxis," or "purpura" to identify clinically significant events associated with ITP.

### STATISTICAL ANALYSIS

The cumulative incidence rate (IR) at 1-year and overall IR per 100 000 person-years for each outcome were calculated for the period from 6 months after the baseline date through the last recorded visit in the VA, death, or as of September 30, 2004. Any HCV-uninfected individuals who subsequently became HCV-positive were censored at their first HCV diagnosis.

A Cox proportional hazards regression model was utilized to obtain hazard ratios (HRs) quantifying the risk for the development of the outcomes and to adjust for any confounding that may be conferred by first the matching variables (age and sex, visit date, and type) and then the matching variables plus race, number of previous inpatient visits, number of previous outpatient visits, and era of military service. In addition, we performed a third Cox proportional hazards regression model including HCV treatment as a time-varying covariate to determine the effect of HCV treatment on the risk of developing the outcome. Only HCV treatments that occurred among eligible patients after the baseline date were included in the analysis. The time receiving treatment was initiated at treatment date and was continued for the entire subsequent follow-up period. Unadjusted and adjusted HRs and 95% confidence intervals (CIs) were estimated as measures of risk. All reported *P* values are 2-sided.

Kaplan-Meier curves were generated to evaluate cumulative incidence of ITP and AIHA among the HCV-infected and HCV-uninfected cohorts. In an analysis to determine if HCV treatment had an effect on outcomes, we repeated the Kaplan-Meier curves, censoring all outcomes occurring anytime after HCV treatment.

In sensitivity analyses, the regression analyses were repeated after deleting the HCV-uninfected controls who subsequently became HCV-infected, rather than censoring them at the time of their HCV diagnosis. A second sensitivity analysis was completed in which those individuals who became HIV-

**Table 2. Baseline Characteristics of HCV-Infected and HCV-Uninfected Veterans<sup>a</sup>**

Characteristic	HCV-Infected Cohort (n=120 691)	HCV-Uninfected Cohort (n= 454 905)
Age, y		
Mean (SD)	52 (8)	52 (9)
Range		
<40	4604 (3.8)	17 841 (3.9)
40-44	15 614 (12.9)	58 855 (12.9)
45-49	33 635 (27.9)	124 456 (27.4)
50-54	37 262 (30.9)	140 033 (30.8)
55-59	15 201 (12.6)	58 360 (12.8)
60-64	4837 (4.0)	18 552 (4.1)
65-69	3662 (3.0)	14 113 (3.1)
70-74	2765 (2.3)	10 667 (2.3)
≥75	3111 (2.6)	12 028 (2.6)
Sex		
Female	4044 (3.4)	15 904 (3.5)
Male	116 647 (96.5)	439 001 (96.5)
Race		
White	60 082 (49.8)	266 410 (58.6)
Black	31 268 (25.9)	94 141 (20.7)
Other <sup>b</sup>	877 (0.7)	44 96 (1.0)
Unknown	28 464 (23.6)	89 858 (19.8)
Fiscal year of baseline date		
1997	3638 (3.0)	13 519 (3.0)
1998	4965 (4.1)	18 613 (4.1)
1999	8217 (6.8)	30 820 (6.8)
2000	13 150 (10.9)	49 385 (10.9)
2001	18 947 (15.7)	71 066 (15.6)
2002	22 234 (18.4)	83 534 (18.4)
2003	24 100 (20.0)	91 076 (20.0)
2004	25 440 (21.1)	96 892 (21.3)
Era of military service		
Pre-Vietnam War	12 281 (10.2)	43 422 (9.6)
Vietnam War	79 290 (65.7)	279 035 (61.3)
Post-Vietnam War	29 120 (24.1)	132 448 (29.1)
Previous inpatient visits within 5 y, mean (SD)	1.1 (2.6)	1.5 (3.3)
Previous outpatient visits within 1 y, mean (SD)	10.7 (24.3)	19.2 (39.5)

Abbreviations: HCV, hepatitis C virus; VA, Department of Veterans Affairs.

<sup>a</sup>Data are shown as number (percentage) unless otherwise specified.

Percentages may not add to 100% because of rounding.

<sup>b</sup>"Other" includes American Indian patients, Asian patients, and individuals whose race was listed as "Other."

positive during follow-up were either censored at the time of the new HIV diagnosis or deleted from the analysis. Statistical analysis was performed using SAS software (version 9.1; SAS Institute Inc, Cary, North Carolina).

## RESULTS

There were a total of 120 691 HCV-infected and 454 905 HCV-uninfected subjects in the cohort. The median follow-up time from 6 months after baseline for the cohort was 2.5 years. Demographic characteristics of the cohort are shown in **Table 2**. The mean (SD) age of the cohort at baseline was 52 (8) years. The cohort was almost entirely (96.5%) male. Of the HCV-uninfected and HCV-infected cohorts 58.6% and 49.8% were white, respectively. Most patients had baseline dates after fiscal year 2000. Finally, HCV-infected individuals had lower mean inpa-

**Table 3. Risk of ITP and AIHA Among HCV-Infected and Uninfected Veterans**

Incidences and HRs	ITP	AIHA
Incidence per 100 000 person-years (Total No. of events, HCV-uninfected)	18.5 (201)	5.0 (54)
Incidence per 100 000 person-years (Total No. of events, HCV-infected)	30.2 (95)	11.4 (36)
HR of HCV-Infected compared with HCV-uninfected (95% CI) <sup>a</sup>	1.7 (1.3-2.1) <sup>b</sup>	2.3 (1.5-3.6) <sup>b</sup>
Adjusted HR of HCV-infected compared with HCV-uninfected (95% CI) <sup>c</sup>	1.8 (1.4-2.3) <sup>b</sup>	2.7 (1.8-4.2) <sup>b</sup>
Incidence per 100 000 person-years (Total No. of events, untreated HCV-infected)	28.1 (72)	4.3 (11)
Incidence per 100 000 person-years (Total No. of events, treated HCV-infected)	39.3 (23)	42.7 (25)
Adjusted HR of untreated HCV-infected compared with HCV-uninfected (95% CI) <sup>d</sup>	1.7 (1.3-2.2) <sup>b</sup>	1.0 (0.5-2.0) <sup>e</sup>
Adjusted HR of treated HCV-infected compared with HCV-uninfected (95% CI) <sup>d</sup>	2.4 (1.5-3.7) <sup>b</sup>	11.6 (7.0-19.3) <sup>b</sup>

Abbreviations: AIHA, autoimmune hemolytic anemia; CI, confidence interval; HCV, hepatitis C virus; HR, hazard ratio; ITP, immune thrombocytopenia purpura.

<sup>a</sup>Hazard ratio adjusted for matching variables only (age, sex, baseline visit date, and type of visit).

<sup>b</sup> $P < .001$ .

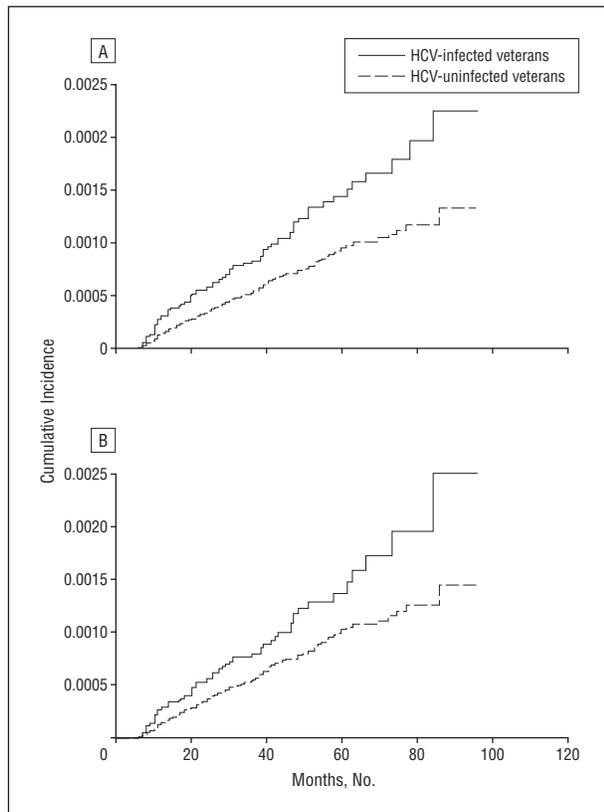
<sup>c</sup>Adjusted HR adjusted for matching variables (age, sex, baseline visit date, and type of visit), race, era of military service, and number of previous visits.

<sup>d</sup>Hazard ratio adjusted for HCV treatment, matching variables (listed in footnote c), and race, era of military service, and number of previous visits.

<sup>e</sup> $P = .97$ .

tient and outpatient visits compared with the HCV-uninfected cohort. Among the HCV-infected individuals, 20 714 (17%) received at least 1 dose of treatment, and 10 573 (9%) received at least 6 months of treatment.

The number of events, IRs per 100 000 person-years, and HRs of ITP and AIHA are shown in **Table 3**. There were a total of 296 incident cases of ITP and 90 incident cases of AIHA. Among those with ITP, 60% were found to have at least 1 episode of hemorrhage, epistaxis, or purpura during the follow-up period. The incidence of ITP was approximately 3 times higher than AIHA in both the HCV-infected and HCV-uninfected cohorts. The overall IR of ITP was higher among the HCV-infected compared with the HCV-uninfected (30.2 per 100 000 person-years vs 18.5 per 100 000 person-years, respectively). The 1-year cumulative incidence for ITP among the HCV-infected and HCV-uninfected was 27.4 and 12.5, respectively, per 100 000. For AIHA, the IR among the HCV-infected was 11.4 per 100 000 person-years compared with 5.0 per 100 000 person-years among the HCV-uninfected. The 1-year cumulative incidence for AIHA among HCV-infected individuals was 8.7 per 100 000, and for the HCV-uninfected it was 4.6 per 100 000. When we evaluated HRs with adjustment only for the matching variables, we found that the risks for both conditions were significantly increased among the HCV-



**Figure 1.** Cumulative incidence of immune thrombocytopenia purpura (ITP) in hepatitis C virus (HCV)-infected patients compared with HCV-uninfected patients (a total of 574 233 veterans, excluding 1263 individuals with a previous diagnosis of ITP). A, All patients were identified at Department of Veterans Affairs (VA) hospitals from October 1, 1997, to September 30, 2004, with follow-up through September 30, 2004. The difference was statistically significant (log-rank test of equality;  $P < .001$ ). B, Cumulative incidence of ITP in HCV-infected patients compared with HCV-uninfected patients. The HCV-infected patients who received any treatment ( $N=20\,714$ ) during follow-up were censored at their treatment date. All patients were identified at VA hospitals from October 1, 1997, to September 30, 2004, with follow-up through September 30, 2004. The difference was statistically significant (log-rank test;  $P = .002$ ).

infected; the HR for ITP was 1.7 (95% CI, 1.3-2.1), and the HR for AIHA was 2.3 (95% CI, 1.5-3.6). After adjustment for the matching variables as well as race, era of military service, and use of VA services before baseline, the risks for both conditions slightly increased.

We then determined if the receipt of HCV treatment was associated with increased risk of ITP and AIHA. The IR of ITP was slightly higher among treated HCV-infected individuals compared with those who were untreated (39.3 vs 28.1 per 100 000 person-years). Thus, compared with the risk of ITP in the uninfected group, risk was increased among both untreated HCV-infected individuals (adjusted HR, 1.7; 95% CI, 1.3-2.2) as well as treated HCV-infected individuals (adjusted HR, 2.4; 95% CI, 1.5-3.7). Furthermore, the difference in ITP risk between the treated and untreated groups of HCV-infected individuals was not significant (likelihood ratio test,  $P = .06$ ). For AIHA, the IR of treated HCV-infected individuals was 10 times higher than among untreated HCV-infected individuals (42.7 vs 4.3 per 100 000 person-years), and the IR among the HCV-infected untreated group was similar to that of the HCV-

uninfected cohort. In contrast to ITP, we found increased risk for AIHA among treated (adjusted HR, 11.6; 95% CI, 7.0-19.3) but not untreated HCV-infected individuals (Table 3).

We further evaluated the effect of HCV treatment by examining Kaplan-Meier curves of the cumulative incidence of each of the outcomes. We compared the Kaplan-Meier curves of the HCV-infected and uninfected cohorts, and then demonstrated the effect of HCV treatment by censoring HCV-infected individuals at the time of HCV-treatment (**Figure 1** and **Figure 2**). As shown in Figure 1A, the cumulative incidence of ITP was significantly higher ( $P < .001$ ) among HCV-infected individuals compared with the HCV-uninfected individuals. Figure 1B shows that despite censoring HCV-infected individuals at the time of treatment, the difference in the cumulative incidence of ITP between the HCV-positive and uninfected individuals remained significant (log-rank test;  $P = .002$ ). In contrast, although the cumulative incidence of AIHA was significantly higher ( $P < .001$ ) among the HCV-infected individuals compared with HCV-uninfected individuals (Figure 2A), when all HCV-infected individuals were censored at the time of treatment (Figure 2B), the difference between HCV-positive and uninfected individuals was no longer significant (log-rank test;  $P = .84$ ).

In addition to these analyses, we conducted 2 sensitivity analyses, as described in "Statistical Analysis" subsection of the "Methods" section, to test the robustness of the results. Neither analysis demonstrated materially different results than those presented (data not shown).

## COMMENT

In this large national cohort study including over half a million US veterans, we observed HCV-infected persons to be at increased risk of ITP and AIHA. Because both ITP and AIHA have been previously associated with interferon alfa use, we were also interested in assessing pharmacy data to account for the effects of HCV treatment. We found that both treated and untreated HCV-infected individuals were at higher risk for ITP, with a suggestion that ITP risk was higher in the treated subjects than the untreated subjects. In contrast, we found that HCV-infected individuals who received interferon alfa therapy were at increased risk for AIHA, whereas untreated HCV-infected individuals were not. Based on our findings, it seems that both HCV infection and HCV treatment independently increase the risk for ITP, whereas the observed increased risk of AIHA among HCV-infected individuals is solely due to interferon alfa therapy and not HCV infection.

The initially observed excess risk of AIHA among HCV-infected individuals was explained by the use of interferon alfa therapy. Among the subset of HCV-infected subjects who had not received interferon alfa therapy, there was no evidence of an association between HCV infection and risk of developing AIHA (HR, 1.0). Our findings are consistent with prior small case series.<sup>21,23,24</sup> Although underlying mechanisms for this association remain unclear, a few models have been proposed. One

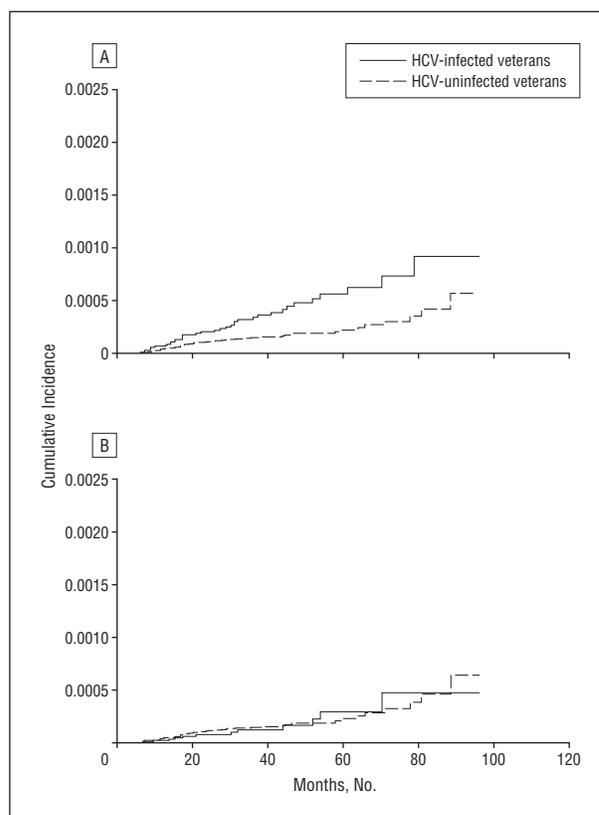
hypothesis is that interferon alfa alters the red blood cell membrane in a fashion similar to alpha-methyl-dopa, causing autoimmunity that leads to accelerated destruction of red blood cells.<sup>25</sup> Alternatively, it has been suggested that interferon alfa might exacerbate autoimmune phenomena by virtue of its immunomodulatory effects.<sup>26,27</sup>

Interferon alfa has been associated with ITP as well as AIHA,<sup>20,21,24</sup> and in our cohort, an increased risk of both conditions was shown with prior interferon alfa therapy. We found interferon alfa-treated vs untreated HCV-infected individuals to be at 2.4- and 1.7-fold increased risk of developing ITP, respectively. The difference in risk was not significant, indicating that interferon alfa increases the risk for ITP beyond HCV-infection alone ( $P = .06$ ). Thus, our study supports the theory that the observed increased risk for autoimmune cytopenias associated with interferon alfa might be due to immunomodulatory effects of the drug.<sup>26,27</sup>

Simultaneously, consistent with prior smaller clinical studies, our results in untreated HCV-infected patients implicate a role for chronic HCV infection in the development of ITP. For example, based on 151 cases of ITP among 368 individuals infected with HCV, Nagamine et al<sup>13</sup> showed a higher incidence of ITP among HCV-infected patients compared with patients infected with hepatitis B. Others<sup>16,28-30</sup> have found a higher prevalence of HCV infection among patients with ITP compared with the general population. Improvement of thrombocytopenia has also been observed with the disappearance of HCV RNA in HCV-positive patients with ITP receiving HCV therapy.<sup>30-32</sup> Similar to studies<sup>30,31</sup> that showed resolution of ITP with clearance of HCV RNA, antibiotic treatment leading to the eradication of *Helicobacter pylori*, another infectious agent associated with ITP, has also been associated with a better platelet response.<sup>33,34</sup>

Several biological mechanisms have been proposed for the role of HCV infection in the etiology of ITP. First, HCV infection causes other autoimmune processes and therefore may dysregulate the immune system, thus stimulating nonspecific autoimmunity and autoantibody production.<sup>35</sup> Second, HCV may specifically bind to the human CD81 receptor on the platelet membrane, thus causing autoantibody production against HCV-bound platelets.<sup>36,37</sup> Third, there has been evidence that HCV can infect and replicate in megakaryocytes, leading to their depletion.<sup>38,39</sup> The fact that AIHA and ITP are both autoimmune cytopenias, but HCV infection seems to be associated with only ITP, supports the hypothesis that beyond a mechanism of generalized autoimmunity, chronic HCV infection may also cause ITP through a platelet-specific mechanism. Of note, ITP is formally defined by the presence of isolated thrombocytopenia without another identifiable etiology or associated condition.<sup>40</sup> Because we found HCV infection to be associated with clinically significant thrombocytopenia, one might suggest that the term "HCV-associated thrombocytopenia" (analogous to HIV-associated thrombocytopenia) should be applied in future studies.

The major strength of this study is the size of the cohort. We were able to evaluate the incidence rates of ITP and AIHA in over 100 000 individuals with HCV and over



**Figure 2.** Cumulative incidence of autoimmune hemolytic anemia (AIHA) in hepatitis C virus (HCV)-infected patients compared with HCV-uninfected patients (a total of 574 333 veterans, excluding 1173 individuals with a previous diagnosis of AIHA). A, All patients were identified at Department of Veterans Affairs (VA) hospitals from October 1, 1997, to September 30, 2004, with follow-up through September 30, 2004. The difference was statistically significant (log-rank test;  $P < .001$ ). B, Cumulative incidence of AIHA in HCV-infected patients compared with HCV-uninfected patients. The HCV-infected patients who received any treatment ( $N = 20\,714$ ) during follow-up were censored at their treatment date. All patients were identified at VA hospitals from October 1, 1997, to September 30, 2004, with follow-up through September 30, 2004. The difference was not statistically significant (log-rank test;  $P = .84$ ).

400 000 matched uninfected subjects, resulting in over 1 000 000 person years of follow-up. To our knowledge, this is the first large cohort study evaluating the effect of HCV-infection on autoimmune cytopenias. Other strengths of our study include the availability of data on cirrhosis, HIV disease, and lymphoproliferative diseases, which allowed us to control for possible confounding. We also had access to pharmacy records and were able to determine whether the HCV-positive patients had received HCV treatment.

Our study has limitations that need to be taken into account when interpreting the results. First, we obtained the diagnoses of AIHA and ITP through ICD-9-CM coding only and were not able to confirm these through medical record review. The diagnosis of HCV infection, however, has been previously validated using this cohort.<sup>8</sup> In addition, previous studies within the VA have validated the diagnoses of HIV and cirrhosis, indicating a positive predictive value of more than 89% for HIV and 90% for cirrhosis.<sup>41</sup> The diagnosis of ITP is primarily a clinical one, making a definitive diagnosis difficult to ascertain. However, we attempted to eliminate

possible bias from conditions that are associated with thrombocytopenia, including hematologic malignant neoplasms and cirrhosis. Also, we found that 60% of the ITP cases had epistaxis, hemorrhage, or purpura, providing validation that the ICD-9-CM code for ITP was associated with clinically significant disease. Although misclassification of ITP may still occur, it is unlikely that HCV status would cause a differential misclassification of ITP, especially because we attempted to ensure that both cohorts were equally likely to utilize the VA.

Second, the methods we used to calculate the cumulative incidence of ITP and AIHA (Kaplan-Meier) did not account for all other competing risks (such as liver disease and HCV-related mortality), which could have biased these estimates. However, we eliminated individuals with cirrhosis (the most likely cause of differential mortality in these cohorts), and, consequently, mortality was similar among the 2 cohorts (6.3% in both cohorts at 2 years), suggesting a minimal impact of competing risks. Furthermore, our proportional hazards regression models, which demonstrated associations between HCV and these conditions, depend on comparisons of instantaneous risk and are less affected than the Kaplan-Meier method by issues arising from competing mortality.

Third, because of the relatively short median follow-up (compared with the life expectancy of HCV-infected patients), we had fewer ITP and AIHA events than we would have had with a longer follow-up. Because we had fewer events, we may not have had the power to detect differences, particularly for AIHA.

Fourth, the incidence rates of ITP and AIHA were both higher than previously reported in the general population. Population-based reports from Denmark and the United Kingdom have found much lower rates of ITP in the population (2.7 and 1.6 cases per 100 000 population per year, respectively).<sup>42,43</sup> Because our patient cohort was accumulated from active users of the VA medical system, our incidence rates among both HCV-infected and HCV-uninfected persons reflect a more chronically ill population, who do not represent the general population. Thus, compared with the general population, the VA users (both cases and controls) were probably more likely to be diagnosed as having ITP or AIHA. However, because the bias occurs in both groups, the HR remains accurate. The effect of the chronically ill HCV-uninfected population was also exemplified by the fact that these individuals had a higher number of visits compared with the HCV-infected individuals. Active users (who probably had more medical problems) were more likely to be picked as controls because our control group was matched not only by age and sex, but also visit date, and were sampled with replacement.

Fifth, we did not have laboratory data to confirm HCV genotype or a sustained virologic response after treatment. We were able to determine the initiation of treatment and that over 50% of our treated study subjects had received at least 6 months of therapy. Although we had no access to clinical outcomes, previous studies of treatment outcomes among HCV-infected veterans have shown a clinically sustained virologic response of 20%, 52%, and 43% for genotypes 1 (the most common HCV genotype in the United States), 2, and 3, respectively.<sup>44</sup> Therefore, it is likely that most HCV-infected treated veterans in our

cohort did not attain a sustained virologic response despite treatment.

Sixth, we attempted to adjust for confounding factors that may have an impact on the ability of the HCV-infected individual to receive treatment (age, race, sex, and year of diagnosis). However, we were probably unable to completely account for the bias introduced by other factors affecting the physician's decision to offer or the patient's decision to accept treatment. Finally, because our data were obtained from veterans only, there were few women included in the study, and our data may not be generalizable.

In conclusion, our study is the first, to our knowledge, to provide an estimate of risk for autoimmune cytopenias among HCV-infected individuals. Compared with HCV-uninfected persons, we found that untreated and treated HCV-infected individuals have an increased risk of ITP. Our observation that interferon alfa treatment increased the risk of ITP beyond the influence of HCV infection alone indicates that HCV infection and interferon alfa treatment are both independently associated with increased risk of ITP. We also found that interferon alfa treatment (but not HCV infection per se) markedly increased the risk of AIHA. Future research is needed to clarify the underlying mechanisms and implications of our findings. Because HCV is a treatable and transmissible disease, our results indicate that HCV testing may have a role in clinical practice when evaluating newly diagnosed ITP patients.

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