



Original article

Epidemiologic features of a large hepatitis C cohort evaluated in a major health system in the western United States

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ABSTRACT

Introduction and aim: Real-world epidemiologic data to guide hepatitis C virus (HCV)-related public health initiatives are lacking. The aim of this study was to describe the prevalence and epidemiological characteristics of a large cohort of patients with an HCV diagnosis evaluated in one of the largest health systems in the United States.

Materials and methods: De-identified demographic and clinical data were extracted from the electronic health record for patients actively followed within the Providence Health & Services health care system. Rates of HCV prevalence and co-morbid illnesses among HCV-infected patients were determined.

Results: Among 2,735,511 active patients, 23,492 (0.86%) were found to have evidence of HCV infection, the majority of which were Caucasian (78.2%) and born between the years 1945 and 1965 (68.3%). In comparison to Caucasians, higher rates of HCV infection were found among Native Americans (2.5% vs. 0.95%, $p < 0.001$). Compared to HCV-negative patients, a greater proportion of HCV-positive patients had diabetes mellitus (18.7 vs. 8.9%, $p < 0.0001$), chronic kidney disease (4.4 vs. 1.8%, $p < 0.0001$), end-stage renal disease necessitating hemodialysis (2.6 vs. 0.6%, $p < 0.0001$), and HIV co-infection (2.4 vs. 0.2%, $p < 0.0001$). Nearly two-thirds (62.1%) of HCV patients had government-sponsored insurance, and 93.0% of treated patients resided in urban settings.

Conclusion: The prevalence of HCV infection in this large health care system serving the Pacific Northwest, Alaska, and California was lower than prior population-based estimates and may reflect real-world prevalence rates among patients not selected for risk-based screening. Native Americans are disproportionately affected by HCV and may warrant targeted screening.

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Chronic hepatitis C virus (HCV) infection represents a significant public health burden in the United States, affecting approximately 3–5 million Americans [1,2]. Patients with HCV are often asymptomatic, and it is estimated that up to half of individuals with HCV may be unaware of their diagnosis [3]. Left untreated, HCV can lead to the development of advanced fibrosis, decompensated cirrhosis, and hepatocellular carcinoma, often necessitating liver transplantation [4]. Conversely, cure of HCV has been shown to be associated with a reduction in all-cause mortality, liver-related morbidity and mortality, and need for liver transplantation [5].

Well-established risk factors for HCV infection include transfusion of blood products prior to the introduction of sensitive

screening, intravenous drug use, chronic hemodialysis, and having multiple sexual partners [6]. The incidence of HCV infection declined significantly after the introduction of blood donor screening in the 1990s, but began to rise nationally in 2010 and increased by greater than 2-fold by 2014 [7]. In parallel with the opioid epidemic in the U.S., increasing rates of new HCV infection have been observed among young persons (aged ≤ 30 years) who inject drugs [8]. Indeed, 30,500 cases of new HCV infection were reported in 2014 that were largely attributable to injection or snorting of drugs and occurring most commonly among males, persons aged 20–29 years, and American Indians/Alaska Natives [7,9]. However, the majority of individuals with chronic HCV infection likely acquired infection in the remote past, and the most commonly cited estimates of HCV prevalence in the U.S. are derived from serologic data from non-institutionalized participants of the National Health and Nutrition Examination Surveys (NHANES). Based on the most recent update including data collected up to 2010, 1.3%

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of participants had a positive anti-HCV antibody, translating to a HCV prevalence of approximately 3.5 million persons in the U.S. general population [9]. Chronic HCV infection was found to most commonly afflict males, persons born between 1945 and 1965 or the so-called “baby boomer” generation, non-Hispanic Blacks (compared to non-Hispanic whites) and individuals with specific risk factors, particularly injection drug use [9].

There are major variations in HCV burden across different geographic regions and patient populations in the U.S. that are not accounted for in NHANES data or current passive U.S. surveillance programs [7]. As such, targeted state or regional data on HCV prevalence to guide public health initiatives are scarce. Findings from Kaiser Permanente Georgia, a large managed care organization (MCO), showed that while HCV infection was identified in only 0.2% of the entire patient population, they did identify several associations with HCV positivity that paralleled those observed in NHANES [10]. Prevalence of HCV based on NHANES also differed from that observed in another national MCO, the UnitedHealth Group, and the Veterans Health Administration, which reported rates of 0.08% and 5.4%, respectively, among its users [6,11]. Notably, epidemiologic findings based on NHANES are limited by the exclusion of certain at-risk groups from the study population, including individuals who are incarcerated, homeless, nursing home residents, hospitalized, active military personnel, immigrants, long-term hemodialysis patients, and health care workers [2,12].

The advent of highly effective direct-acting antiviral (DAA) therapy has led to a renewed interest in identifying patients with chronic HCV infection and enhancing access to care. To help guide public health efforts, an increased understanding of the burden of disease associated with HCV in real-world clinical practice settings is needed.

The aims of this study were to evaluate the prevalence of chronic HCV infection and describe the epidemiological characteristics in a large cohort of HCV patients within the Providence Health & Services (PHS) health care system, one of the largest not-for-profit health systems in the United States.

1. Materials and methods

1.1. Study design and patient setting

De-identified patient data were extracted from the electronic health record for patients actively being followed within the PHS health care system, a major health care system serving the western United States, including the states of Alaska, California, Montana, Oregon and Washington. The PHS health care system employs more than 82,000 caregivers serving 34 hospitals, 600 physician clinics, 22 long-term care facilities, 19 hospice and home health programmes, and 693 supportive housing units. The PHS health plan currently serves 513,000 members, including its caregivers and other large employer groups. Health care facilities within the PHS health care system also serve patients with alternative insurance plans.

Active patients, defined as those with at least one ambulatory clinic encounter within a two-year period (10/1/2013 to 11/7/2015), were stratified by HCV infection status. Patients with HCV were identified based on the presence of associated ICD 9/10 codes in the patient's problem list or medical history, or a laboratory test showing positive anti-HCV antibody or detectable HCV RNA. Additional aggregate data extracted included patient demographic information (age, gender, race/ethnicity), residential setting (urban vs. rural), insurance status, HCV treatment history, hepatitis A and hepatitis B vaccination history, and diagnosis of cirrhosis or co-morbid illnesses, including HIV coinfection, diabetes mellitus, and

renal disease based on ICD 9/10 codes in the patient's problem list or medical history (Supplementary Table 1).

This study was approved by the Swedish Health Services Institutional Review Board.

1.2. Data analysis

Descriptive statistics (age, gender, race) were used to compare characteristics of groups (i.e., patients with and without HCV). Specifically, continuous variables were summarized with mean and median; categorical variables were summarized with counts and percentages. Differences in proportions of the number of patients were analyzed by chi-square tests of independence. Differences in quantitative values were analyzed by an unpaired, 2-tailed Student's *t* test. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). A significance level of $p = 0.05$ was used.

2. Results

2.1. Prevalence of HCV infection

A total of 2,735,511 active patients were identified, of which 23,492 (0.86%) met criteria for a diagnosis of HCV (Table 1). The diagnosis of HCV infection was supported by HCV testing in 7870 (33.5%) patients, with nearly equal proportions of positive anti-HCV antibody (52.0%) and detectable HCV RNA (48.2%). Patients with HCV had a mean age of 55 years and over half were male (54.9% vs. 43.6% HCV-negative patients, $p < 0.0001$). Patients born between the years 1945 and 1965, the “baby boomer” generation, comprised approximately two-thirds of the HCV cohort (68.3%). Over half of HCV-infected patients had public (Medicaid or Medicare) health insurance coverage. The majority of HCV patients seen in the PHS health care system resided in an urban setting and maintained a home address in the Pacific Northwest (Fig. 1).

2.2. Racial distribution of HCV

The majority of HCV patients were Caucasian (78.2%, Table 1). While white males comprised less than one-third of all patients, they accounted for 43.2% of HCV-infected patients (Fig. 2). Race-specific prevalence rates (Fig. 3) show that in comparison to Caucasians, HCV infection disproportionately affected Native Americans (2.5% vs. 0.95%, $p < 0.001$) and African Americans (1.6% vs. 0.95%, $p = 0.25$). On the other hand, a lower rate of HCV infection was observed among Asian or Hawaiian/Pacific Islanders (API, 0.39% vs. 0.95%, $p = 0.105$).

2.3. Rates of cirrhosis and additional medical co-morbidities

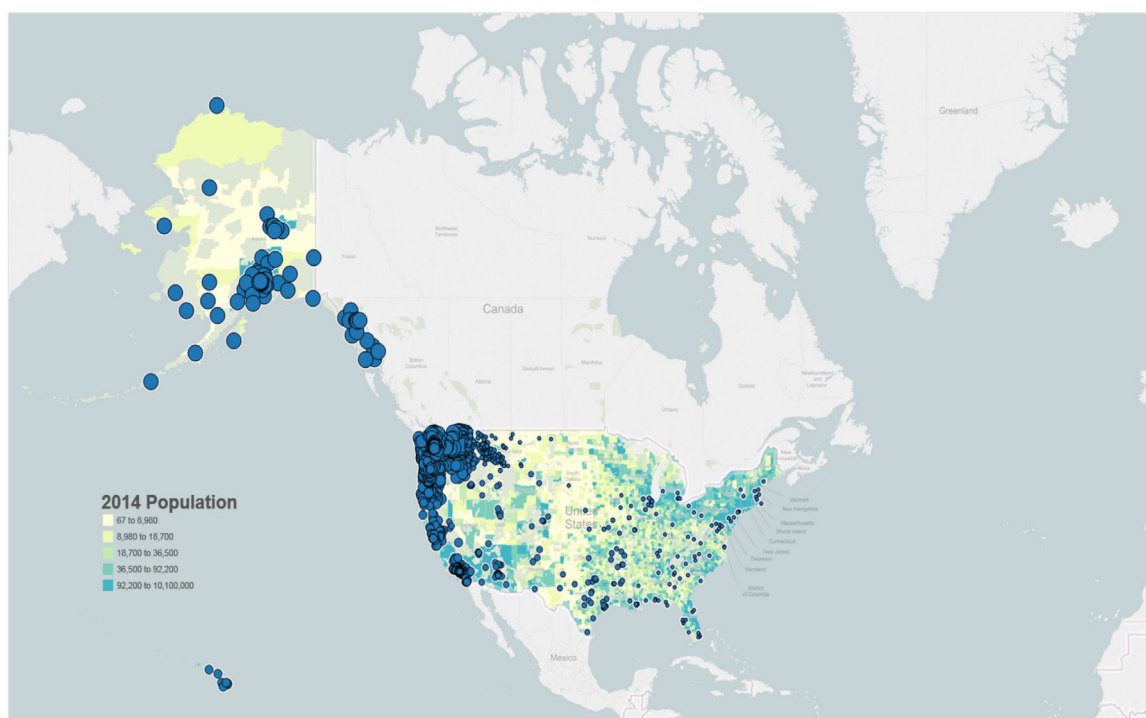
In comparison to HCV-negative patients, HCV-positive patients had higher rates of cirrhosis (20.7 vs. 3.2%, $p < 0.0001$). In addition, compared to HCV-negative patients, a greater proportion of HCV-positive patients had diabetes mellitus (18.7 vs. 8.9%, $p < 0.0001$), chronic kidney disease (4.4 vs. 1.8%, $p < 0.0001$), and end-stage renal disease necessitating hemodialysis (2.6 vs. 0.6%, $p < 0.0001$). Higher rates of HIV (2.4 vs. 0.2, $p < 0.0001$) infection were also observed in HCV-infected patients compared to HCV-negative patients (Fig. 4).

2.4. Management of HCV infection

Only 1475 (6.3%) HCV-infected patients received vaccination against the hepatitis A virus, and only 653 (2.8%) patients received vaccination against the hepatitis B virus. Among this HCV cohort, 1922 (8.2%) patients were prescribed antiviral treatment. The majority of patients prescribed anti-HCV treatment (1802 or 93.8%)

Table 1
Patient characteristics.

Characteristic	All patients (N = 2,735,511)	HCV-positive patients (N = 23,492)	HCV-negative patients (2,712,020)	p-Value
Age, years (Mean, (Median)) (Range, min–max)		55 (57) 4–93		
Birth year 1945–1965 – “Baby Boomer” (N, (%))		16,047 (68.3)		
Male gender (N, (%))	1,195,828 (43.7)	12,897 (54.9)	1,182,931 (43.6)	<0.0001
Race/ethnicity (N, (%))				
Caucasian	1,924,880 (70.4)	18,363 (78.2)	1,906,517 (70.3)	<0.0001
African-American	96,190 (3.5)	1544 (6.6)	94,646 (3.5)	<0.0001
Asian or Hawaiian/Pacific Islander	170,514 (6.2)	667 (2.8)	169,847 (6.3)	<0.0001
Native American	27,153 (1.0)	678 (2.9)	26,475 (1.0)	<0.0001
Unknown/other	516,774 (18.9)	2240 (9.5)	514,534 (19.0)	<0.0001
Location of residence				
Urban		21,840 (93.0)		
Rural		1059 (4.5)		
Unknown		593 (2.5)		
Insurance				
Medicaid		7517 (32.0)		
Medicare		7060 (30.1)		
Other		8915 (37.9)		

**Fig. 1.** Geographic distribution of hepatitis C patients within the Providence Health & Services health care system.

resided in urban settings. The most commonly prescribed treatment regimens included the combinations of ledipasvir with sofosbuvir (930 prescriptions), sofosbuvir with ribavirin (434 prescriptions), and pegylated interferon with ribavirin (321 prescriptions).

3. Discussion

We report on the epidemiologic characteristics of a cohort of over 23,000 patients with a history of HCV seen within one of the largest health care systems in the United States. In this cohort of patients largely residing in the Pacific Northwest, Alaska, and California, we observed that the prevalence rate of HCV was 0.86%. Our findings suggest that HCV disproportionately affects males, Native Americans, and African Americans, while API populations have

proportionately lower HCV prevalence. The majority of patients with an HCV diagnosis used government-sponsored health coverage, and treatment of HCV appears to be more common in urban versus rural areas.

The NHANES dataset suggest that 1.3% of persons in the general U.S. population have evidence of past or current HCV infection (positive anti-HCV antibody) and 1.0% of persons have chronic HCV infection (detectable HCV RNA) [13]. It has been suggested that NHANES may not reflect actual HCV prevalence rates because it was based on a largely non-institutionalized, civilian population that did not include certain high-risk groups [2]. Recently, HCV prevalence has been shown to vary considerably by state and region, and the Pacific Northwest was identified as an area of highest anti-HCV positivity, estimated at 2.3% of the population [7]. However, the observed HCV prevalence rate of 0.86% in this HCV cohort largely

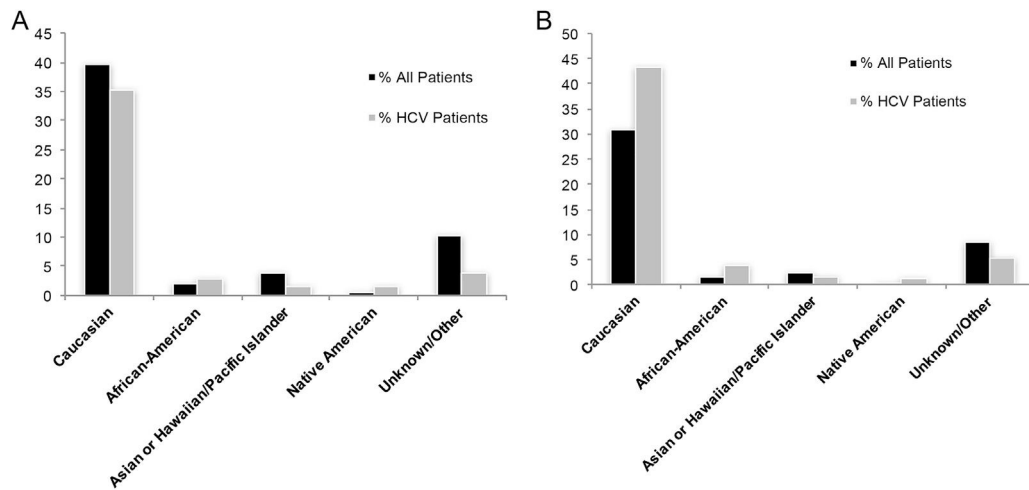


Fig. 2. (A) Race/ethnicity of female patients by hepatitis C virus (HCV) status. (B) Race/ethnicity of male patients stratified by hepatitis C virus (HCV) status.

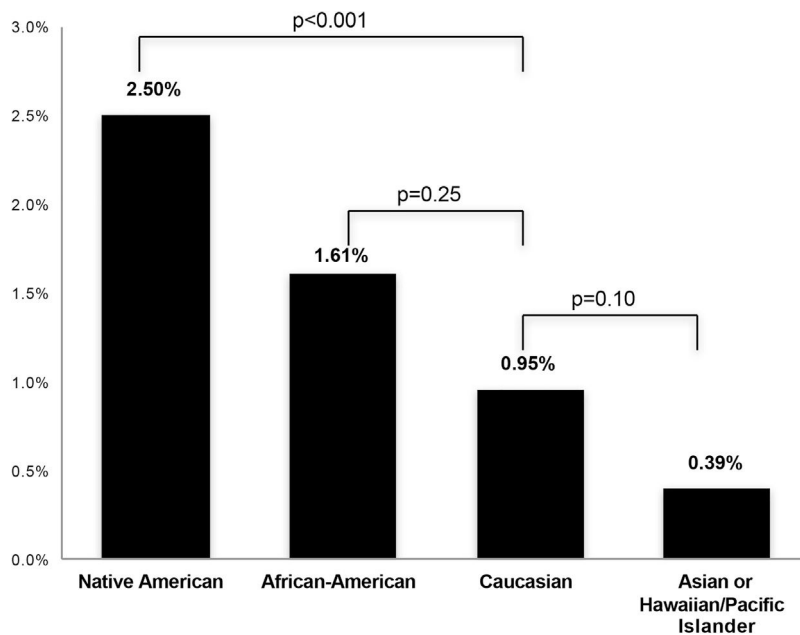


Fig. 3. Rates of hepatitis C infection among various racial/ethnic groups.

residing in the Pacific Northwest is lower than both of these estimates. While this observed rate may represent the true prevalence of HCV in this region or be the result of inadequate sampling of high-risk HCV populations in our cohort, we suspect that this lower-than-expected rate may reflect suboptimal HCV screening.

Real-world HCV epidemiologic data are lacking. In this study based on electronic health record review of over 2.7 million patients, we found that while the majority of HCV-infected individuals in this cohort were Caucasian, Native Americans and African Americans were disproportionately affected by HCV. In contrast, API patients had the lowest prevalence of HCV infection. The reasons for this disparity are unclear, though higher rates of acute HCV infection have similarly been described among Native and African Americans [14], and the NHANES dataset showed that non-Hispanic blacks had the greatest burden of HCV infection in the U.S. [9]. Given the observed health disparities among minority groups with HCV, including higher mortality rates among African Americans with HCV, screening and treatment programmes targeting these populations are warranted [15]. The findings of this study also confirm several established observations regarding

HCV epidemiology, including higher rates of HCV among males and persons born between the years 1945 and 1965, the so-called “baby boomer” generation that has been shown to have a five-fold higher risk of HCV infection than other adults and the highest risk for HCV-related morbidity and mortality [15,16].

Chronic HCV infection is associated with significant morbidity and mortality, and it has been implicated in the development of several extrahepatic conditions, including mixed cryoglobulinemia, porphyria cutanea tarda, and hypothyroidism [17,18]. In addition to higher rates of cirrhosis, we observed significantly higher rates of diabetes mellitus among patients with HCV compared to non-infected persons in this cohort. This is consistent with prior epidemiologic findings that suggest a strong association between HCV and diabetes [18]. Higher rates of chronic kidney disease (4.4%) and end-stage renal disease (2.6%) among HCV-infected patients compared to non-infected patients were also observed. Given that renal disease in the setting of HCV infection has been associated with increased morbidity, greater likelihood of negative health outcomes, and higher health care utilization and costs, this represents an additional target population for HCV treatment [19].

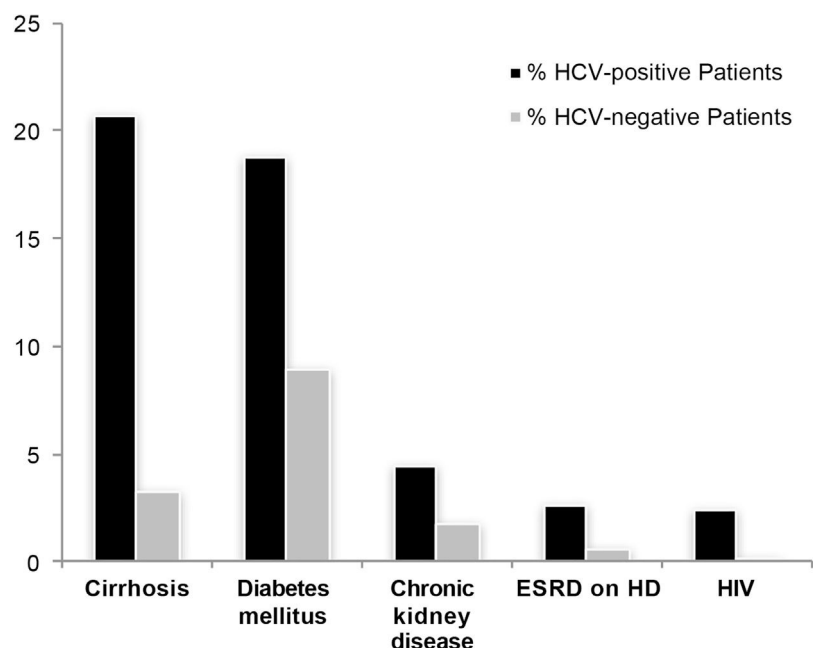


Fig. 4. Rates of cirrhosis and comorbid illnesses among patients with and without hepatitis C virus (HCV) infection.

There can be considerable geographic variation in HCV prevalence and demographics across the U.S., and geographic factors likely influence management practices. In this population, we observed that the majority of HCV-infected individuals lived in an urban setting. This is consistent with the recent observation that states with high estimated HCV prevalence contain highly urban populations [7]. While these data were gathered only shortly after the availability of direct-acting antiviral therapy and there are likely greater numbers of patients receiving treatment currently, it is important to note that fewer prescriptions for antiviral treatment were issued to patients living in rural areas compared to patients in urban residences. To work towards the eradication of HCV, it will be important for health care organizations to establish screening and treatment pathways, and patients in rural areas may represent a vulnerable population that warrants special attention in their implementation. In particular, increasing resources may be needed to address the recent surge in new HCV infections among young adults in rural settings with a history of opioid abuse [20]. Given limited access to specialty care in rural settings, primary care providers may need to be at the forefront of HCV treatment, and remote hepatology video consultation services such as Project Echo may help facilitate this [21].

There remains a need for accurate data describing HCV epidemiology and HCV-related morbidity and mortality, and the findings of this study provide novel and significant information on demographics of HCV infection in a large portion of the western U.S. However, these findings may not be reflective of the burden of disease across the entire nation, and there are several limitations. In this study, we did not assess the rate of HCV screening among at-risk populations, and HCV prevalence was based on either a chart diagnosis of HCV or positive HCV testing (anti-HCV antibody positivity or detectable HCV RNA), so active infection or spontaneous clearance of HCV could not be assessed. Additional data extracted from patient electronic health records, including rates of cirrhosis and co-morbid illnesses, may also be subject to error and under-represented if ICD9/10 codes were not appropriately entered. However, prior studies support the validity of our findings, showing that there is good agreement between ICD 9/10 codes and chart data for liver disease as a whole, and the presence of a HCV code has excellent positive predictive value for the diagnosis of HCV

infection [22,23]. In addition to limited serologic data, our assessment of HCV management is limited by the fact that the PHS health care system is not a MCO, so clinical management of patients receiving care from additional providers or facilities outside the system may not be captured.

With the advent of highly efficacious, short-duration treatments for HCV offering the prospect of a cure for the majority of patients, the eradication of HCV has become a possibility with increased emphasis on screening and linkage to care. The findings of this study may help address gaps in screening and access to care and inform targeted clinical pathways to address the high burden of HCV in this region of the country. In particular, our findings highlight the need for greater screening of at-risk patients, particularly Native and African Americans, assessment of diabetes and renal insufficiency among HCV-infected patients, and concentrated efforts to provide access to HCV care for patients in rural settings.

Abbreviations

HCV	hepatitis C virus
NHANES	National Health and Nutrition Examination Surveys
MCO	managed care organization
DAA	direct-acting antiviral
PHS	Providence Health & Services
API	Asian or Hawaiian/Pacific Islanders
HIV	human immunodeficiency virus

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.aohp.2018.12.003](https://doi.org/10.1016/j.aohp.2018.12.003).

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