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Race/ethnicity and Other Characteristics Associated with Current Hepatitis C Virus Infection in United States, 2003-2010

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Abstract

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HCV antibody (anti-HCV) test alone will not distinguish current from resolved infection, whether spontaneously or by treatment. Because new antiviral therapies are effective means to reduce HCV viremia, the proportion of persons with current infection will decrease among those tested positive for anti-HCV. The study aim was to describe the percentage of current HCV infection, defined by HCV RNA positivity, among those tested positive for anti-HCV, in a nationally representative sample of adults ≥40 years old in the United States, focusing on racial/ethnic differences over time. Data were from National Health and Nutrition Examination Surveys, collected from 2003–2010. Of 31,034 participants, we identified 304 positive for anti-HCV. Of these, 238 or 75.4% (95% CI 67.5–81.8) had current HCV infection. The percentages of current HCV infection were highest among non-Hispanic blacks (91.1%) and lowest among those with college or more education (57.3%). This percentage was 92.7% among non-Hispanic blacks and 61.9% among non-Hispanic whites in 2009-2010. Among persons with current HCV infection, most had elevated ALT (56.5%) or AST (71.8%) levels, but 35.3% reported having received a diagnosis of "liver condition". Excessive alcohol drinking in the past year was reported by 27.3% of participants with current infection. ***Conclusions:*** Among adults ≥40 years who have ever been infected with HCV, three quarters had current HCV infection. Non-Hispanic blacks were more likely to have current infection compared to all other racial/ethic groups. Among those with current HCV infection, most had abnormal liver function tests and many may benefit from lifestyle modifications, but only a minority received appropriate diagnoses.

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Chapter I. Background

Hepatitis C is an enveloped RNA virus discovered in 1989 (1). The virus has high genetic heterogeneity, with 11 genotypes and many subtypes (2). Genotypes 1 to 3 account for the majority of hepatitis C infections worldwide; genotype 1 alone accounted for about 60% of the infection globally in 2004 (1). While infections with genotypes 1 to 3 occur throughout the world, the other genotypes tend to be endemic to specific regions (1). Genotype 4 infections occur mainly in northern and central Africa and the Middle East, genotype 5 infections are only found in South Africa, and the remaining genotypes are endemic in Asia (2, 3). Estimated global prevalence of HCV infection is 2.2%, although prevalence is considerably higher in certain regions (4). For example, prevalence in Egypt is estimated to be >10% (5). Primary method of transmission for hepatitis C virus (HCV) is parenteral exposure to contaminated blood or blood products (6). The most common risk factor for HCV infection is unsafe percutaneous injection, including medical injections and injection drug use (4, 7).

HCV infection is one of the most common blood-borne diseases in the United States (8). In 2006, Armstrong et al estimated that in 1999 – 2002 approximately 1.6% (1.3 - 1.9%) of National Health and Nutrition Examinations Survey (NHANES) participants tested positive for HCV antibodies (anti-HCV), and of those, approximately 80% was also HCV RNA positive (9). This amounts to an overall current HCV infection prevalence of 1.3% (1.0 - 1.5%) among non-institutionalized civilians living in the U.S. (9). A review estimating the prevalence of HCV infection in populations not included in

NHANES found that prevalence of HCV was 23.1 – 41.2% among incarcerated inmates, 22.0 – 52.5% among homeless or marginally housed people, and 0.48% among active duty military personnel (10). However, because HCV tests were not performed systematically for majority of the inmates and there is a paucity of data on active duty military personnel, the true prevalence among the populations not included in NHANES may also be underestimated (11).

Of note, the data that are available show that the incidence of HCV infection in the United States is declining, though mortality and morbidity related to chronic HCV infection continue to rise (12-14). Since 2007, more people died from illnesses related to HCV than human immunodeficiency virus (13). Rates of HCV-related hepatocellular carcinoma and cirrhosis increased significantly over the last three decades (15, 16). Some studies have found that liver damage among patients with HCV infection is related to the presence of HCV viremia, and that virus clearance is associated with improved liver outcomes (17-19). However, as many studies of HCV infection prevalence do not perform confirmatory HCV RNA tests, the association between HCV viremia and liver damage is not clear among all populations. It is also unknown what proportion of anti-HCV positive cases has active infection in the U.S.

Many factors are associated with the difference in population-level seroprevalence of anti-HCV and HCV RNA. A meta-analysis of 31 longitudinal studies on untreated acute HCV infections found that, on average, 26% of infections resolve in spontaneous viral clearance; though rates of viral clearance in these studies ranged from 0

– 80% (20). Studies of injection drug users found rates of clearance ranged from 18 - 33% (21, 22). Factors associated with spontaneous viral clearance include female sex, high baseline viral load, presence of interleukin 28B (IL-28B) polymorphisms, and symptomatic acute infection (22-26). However, due to the small sample size of many of these studies, researchers often opted to approximate the prevalence of active chronic infection by using the statistics published by Armstrong et al, which estimated that about 80% of anti-HCV positive cases have active infection.

HCV viremia can also be reduced with pharmaceutical therapy. The combination of peginterferon and ribavirin is the current standard treatment for HCV infection (27). Optimal regimen and dosage of peginterferon and ribavirin depends viral genotype and infection characteristics (28-30). Rates of sustained viral response with standard treatment vary depending on the anti-viral regimen, with some studies reported >90% response (31-34). In addition to treatment, factors that are associated with sustained viral response include IL-28B polymorphisms, infections with genotypes 2 or 3, low pre-treatment viremia, treatment in early phases of infection, and attainment of virological response within 4 weeks of beginning treatment (35-41). In the last five years, new treatments involving direct-acting agents have been developed (27). These new therapies, used in combination with standard treatment, are shown to overcome some shortfalls of treating with peginterferon and ribavirin alone (42-44).

Given the increasing number of options for effective antiviral treatment and with the implementation of Centers for Disease Control and Prevention's (CDC)

recommendation on screening and treatment, the proportion of current HCV infection among population with anti-HCV will be increasingly determined by treatment access in the future (45). While the prevalence of anti-HCV may increasingly misrepresent the true health burden of HCV infection, the difference between the two prevalence estimates can be an important factor in monitoring the need and effectiveness of HCV care and treatment over time.

Chapter II. Manuscript

Abstract

HCV antibody (anti-HCV) test alone will not distinguish current from resolved infection, whether spontaneously or by treatment. Because new antiviral therapies are effective means to reduce HCV viremia, the proportion of persons with current infection will decrease among those tested positive for anti-HCV. The study aim was to describe the percentage of current HCV infection, defined by HCV RNA positivity, among those tested positive for anti-HCV, in a nationally representative sample of adults ≥40 years old in the United States, focusing on racial/ethnic differences over time. Data were from National Health and Nutrition Examination Surveys, collected from 2003–2010. Of 31,034 participants, we identified 304 positive for anti-HCV. Of these, 238 or 75.4% (95% CI 67.5–81.8) had current HCV infection. The percentages of current HCV infection were highest among non-Hispanic blacks (91.1%) and lowest among those with college or more education (57.3%). This percentage was 92.7% among non-Hispanic blacks and 61.9% among non-Hispanic whites in 2009-2010. Among persons with current HCV infection, most had elevated ALT (56.5%) or AST (71.8%) levels, but 35.3% reported having received a diagnosis of "liver condition". Excessive alcohol drinking in the past year was reported by 27.3% of participants with current infection. ***Conclusions:*** Among adults ≥40 years who have ever been infected with HCV, three quarters had current HCV infection. Non-Hispanic blacks were more likely to have current infection compared to all other racial/ethic groups. Among those with current HCV infection, most had abnormal liver function tests and many may benefit from lifestyle modifications, but only a minority received appropriate diagnoses.

Introduction

Serosurveys have been one of the best approaches to study the epidemiology of hepatitis C virus infection and to estimate the burden of disease (46). In the United States, data from 1999 – 2002 National Health and Nutrition Examination Surveys (NHANES) showed that approximately 1.6% (1.3 - 1.9) of the non-institutionalized civilians living in the U.S. had serum anti-HCV. Of those tested positive for anti-HCV, 79.7% had HCV viremia, as evidenced by positive results for HCV RNA, which indicated current infection (9). Thus, the prevalence of current HCV infection in 1999 – 2002 was 1.3% (1.0 - 1.5) (9). However, the HCV RNA test to confirm current infection is often not performed in many surveys (46). This is the case for many national level HCV infection surveillance systems, including that of the United States (47, 48). Only 53% of HCV cases reported by enhanced surveillance sites funded by CDC were confirmed with HCV RNA testing (47).

Both spontaneous clearance and successful treatment can lead to resolved HCV infection, defined as disappearance of HCV RNA and having anti-HCV as the only seromarker of past infection. With the implementation of the recommended screening and treatment for HCV infection in the United States, the prevalence gap between anti-HCV and HCV RNA will be increasingly determined by access to and effectiveness of antiviral treatment (45, 49). From the public health perspective, the prevalence of anti-HCV will increasingly misrepresent the true disease burden of HCV infection. In the meantime, because new antiviral therapies are increasingly available and are effective means to reduce HCV viremia, the proportion of persons with current infection will decrease

among those tested positive for anti-HCV (27, 50). This percentage can be an important indicator for monitoring the effectiveness of and access to HCV treatment in different populations over time.

With the options for and effectiveness of antiviral therapies for HCV infection increasing in the United States, we sought to describe the percentage of current infection among U.S. non-institutionalized civilians who tested positive for anti-HCV in recent cycles of NHANES from 2003-2010; our analyses focused on whether socio-demographic factors were associated with current infection. We also described results from liver function tests and fibrosis level in persons with current infections as these conditions may be associated with prioritization of patient selection for antiviral treatment and some improvements are expected after successful treatment (37, 51). As the age of 40 years or older has been showed to be an important predictor of HCV viremia in the U.S. population, our analyses were restricted to adults 40 years of age or older (9).

Methods

Data source

NHANES is conducted by the National Center for Health Statistics (NCHS) to assess the health and nutrition status of the U.S. population. Since 1999, this cross-sectional survey has been conducted continuously, with data releases every two years. Data from 4 cycles of NHANES, collected from 2003 – 2010, were used for this analysis. Participants were selected using a multi-stage, cluster sampling design to obtain

nationally representative samples. About 5,000 non-institutionalized civilians living in the 50 states and the District of Columbia were sampled each year. NHANES included interviews as well as a physical examination component. Information on demographics and other characteristics was collected through in-home interviews, and biological specimens were taken for laboratory analyses as part of physical examination, which was conducted in specially designed mobile examination centers.

Laboratory methods

Full descriptions of the laboratory methods used in the analyses of biological specimens of interest to our study are available CDC's website (52-55). Participants 6 years or older were eligible to be tested for hepatitis C virus. Blood samples were tested at the laboratories at Division of Viral Hepatitis at CDC. Specimens were screened for anti-HCV using Ortho HCV enzyme-linked immunosorbent assay version 3.0 (Ortho-Clinical Diagnostics, Inc, Raritan, NJ) in 2003 – 2008 and VITROS anti-HCV assay (VITROS ECi/ECiQ Immunodiagnostic System, Ortho-Clinical Diagnostics, Inc., Raritan, NJ) in 2009 – 2010. The screening procedures were repeated for specimens that were positive. Confirmatory tests for anti-HCV were performed on repeatedly positive specimens using the Chiron RIBA 3.0 strip immunoblot assays (Novartis Vaccines & Diagnostics, Emeryville, CA). HCV RNA quantification was performed on specimens that had a positive or indeterminate RIBA results using COBAS AMPLICOR HCV Monitor Test, version 2.0 (Roche Diagnostics, Indianapolis, IN). Participants with positive RIBA results and positive RNA were considered to have current HCV infection, as were people who have indeterminate RIBA and positive RNA. Those with positive

RIBA and negative RNA were considered to have resolved infections. Those with indeterminate RNA results were excluded from the analyses.

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels were measured using Beckman Synchron LX20 (Beckman Coulter, Brea, CA) and Beckman UniCel DxC800 Synchron (Beckman Coulter, Brea, CA) at Collaborative Laboratory Services. The cutoffs for elevated levels were specified by the manufacturers. For ALT, upper normal limits vary by sex, and is 47 IU/L for males and 30 IU/L for females 20 years or older. Upper normal limits value for AST for both male and female participants ≥20 years old is 33 IU/L. Platelet counts were produced by Beckman Coulter MAXM (Beckman Coulter, Brea, CA) in the Mobile Examination Centers. For 2003 – 2006 participants, platelet counts of $<157 \times 10^3$ cells/μL for males 19 – 65 years old and $<138 \times 10^3$ cells/μL for males 66 years or older were considered abnormal. Platelet counts of $<172 \times 10^3$ cells/μL for females 19 – 65 years old and $<147 \times 10^3$ cells/μL for females 66 years or older were abnormal. In 2007 – 2010, the cutoff values are $<152 \times 10^3$ cells/μL for males 19 – 65 years old, $<124 \times 10^3$ cells/μL for males 66 years or older, $<168 \times 10^3$ cells/μL for females 19 – 65 years old, and $<155 \times 10^3$ cells/μL for females 66 years or older.

Statistical methods

The population of interest for this analysis was participants 40 years or older who were positive for anti-HCV and who were also tested for HCV RNA. Those with indeterminate results were excluded from the analyses. Data management and analyses

were performed according to Analytic and Reporting Guidelines provided by NCHS. Appropriate study design variables and examination weights were used in all analyses to account for the complex probability sampling design and non-response. The examination weights were adjusted for multi-cycle data analyses. The adjusted weights further account for over-sampling of certain subgroups and non-participation in examination portion of the survey.

The socio-demographic variables of interest included age, sex, race/ethnicity, education attainment, income poverty ratio, as well as veteran status and current insurance coverage. Age was categorized into at 10-year intervals into 3 groups; participants 60 years or older were put in one group due to the small number of people in each 10-year interval. Income poverty ratio was calculated by NCHS using the federal poverty threshold for the year that income data were collected. As the number of people whose income was >2 times the poverty threshold was small, these people were grouped together. Behavioral risk factors were smoking, alcohol consumption habits in the past year, and ever injected illegal drugs. Participants who currently smoke cigarettes every day or some days were considered current smokers; those who smoked >100 cigarettes in their lifetime but are not currently smoking were considered former smokers; and those who smoked less than 100 cigarettes in their lifetime and were not currently smoking were considered never smokers. Alcohol consumption was dichotomized as excessive drinking or no excessive drinking. Excessive drinking was defined as >21 drinks/week for men and >14 drinks/week for women (56). Degree of liver fibrosis was represented by FIB 4 classes. FIB 4 score was calculated using the formula: [age x AST

(IU/L)]/[platelet (103 /µL) x ALT½ (IU/L)], then categorized into three classes using standard cutoff values: class 1, <1.45; class 2, 1.46 - 3.25; and class 3, >3.25 (57, 58). The degree of fibrosis increased with class.

Univariate analyses were used to obtain unadjusted association between HCV status (current vs. resolved) and socio-demographic, behavioral, and liver biomarker variables. Proportions from univariate analyses of nominal variables were tested using chi-square. These tests were not corrected for multiple comparisons. A logistic regression model was used to determine the independent association between hepatitis C infection status and socio-demographic covariates. Trend tests were performed to assess the pattern of current HCV status across education levels and the trend of prevalence ratios of current infection between non-Hispanic blacks and non-Hispanic whites across survey cycles. A p-value of less than 0.05 was considered statistically significant.

This project does not meet human research criteria, thus, approval from institutional review board was not required All analyses were performed using SUDAAN 11.0 (RTI International, Research Triangle Park, NC) and data management was conducted in SAS 9.3 (SAS Institute, Cary, NC).

Results

The number of participants from the combined 4 cycles of NHANES from 2003 through 2010 was 31,034. Among adults 40 years or older, 304 participants tested positive for anti-HCV and thus, met the inclusion criteria for our analyses. Weighted

mean age in this sample was 50.8 years, and 64.3% of the participants were male. Distribution of self-reported race/ethnicity in this sample was as follows: 65.2% non-Hispanic white, 20.6% non-Hispanic black, 5.6% Mexican American, and 8.61% other race, including other Hispanics, or multi-racial.

Of the 304 participants who tested positive for anti-HCV, 238, or 75.4% (95% confidence interval (CI), 67.5 – 81.8), had current HCV infection, as indicated by positive anti-HCV and HCV RNA tests. The remaining 66 participants (24.7%, 95% CI 18.2 – 32.5) tested positive for anti-HCV and negative for HCV RNA, indicating resolved infection. We examined the percentage of current HCV infection by socio-demographic factors (Table 1). The percentages of current infection were highest among non-Hispanic blacks (91.1%) and lowest in those who had a college degree or higher (57.3%). Although the percentage by age ranged from 72.4% in those aged 40-50 years to 79.2% in those aged 50-60 years, the difference was not statistically significant ($p = 0.48$). Race/ethnicity was significantly associated with HCV status ($p = 0.004$), while the distribution of current HCV status by sex, current insurance coverage, family income, and survey year were not statistically significant (all $p>0.3$).

We used a multivariate logistic regression model to identify factors associated with HCV status. In this model, only race/ethnicity was found to be significantly associated with HCV status ($p = 0.01$). Compared to non-Hispanic whites, adjusted odds ratio (aOR) of having current infection was similar among Mexican Americans, but was significantly higher among non-Hispanic blacks (aOR 3.9, 95% CI 1.6 – 9.2). While the

odds of having an current HCV infection was negatively correlated with education level (p-value for trend = 0.02), education level was not a statistically significant predictor of current versus resolved infection in the multivariate regression model after adjusting for other socio-demographic variables.

The percentages of persons with current HCV infection among those tested positive for anti-HCV were consistently higher among non-Hispanic blacks than those among non-Hispanic whites (Figure 1). The black:white ratio ranging from 1.2 to 1.5, and has an increasing overall trend (p=0.01). In the most recent cycle, 2009-2010, these percentages were 90.4% among non-Hispanic blacks and 60.1% among non-Hispanic whites.

The prevalence of abnormal liver function biomarkers and behavioral factors in persons with current HCV infection and resolved infection are shown in Table 2. Participants with current infection were more likely to have abnormal levels of ALT (56.5%) and AST (71.8%) than those who had resolved infection ($p < 0.0001$ for both ALT and AST). The platelet count was in normal range for most persons with current HCV infection (86.6%). Participant with current infection were more likely to have a FIB 4 score of >3.25 than those with resolved infection (13.6% vs. 2.9%; $p = 0.002$). Only 35.3% of persons with current HCV infection reported having been diagnosed with a liver condition. There was no significant difference between the two groups regarding smoking, excessive drinking, and injection drug use.

Discussion

In this study, which was limited to adults ≥40 years of age, the percentage of current HCV infection among those tested positive for anti-HCV was 75.4%, with the upper limit of the 95% CI at 81.8%. While the overall percentage of current HCV infection among NHANES 1999 – 2002 was 79.7%, the percentage among those who were ≥40 years old was 89.6% (9). The above estimates were based on small sample sizes. Nonetheless, broadly comparing NHANES 2003 – 2010 estimate to the earlier estimate suggests a small decrease (14.2%) in the percentage of HCV RNA positivity among people who had ever been infected with HCV in the general household population in the United States.

Our analysis showed that the percentage of current HCV infection varied by demographic factors and possibly by time. There was a large racial difference in the percentages of current HCV infection, with Non-Hispanic blacks more likely to have current infection. This pattern of racial differences had been observed in previous studies before the development of effective treatments, including NHANES 1988 – 1994 (7, 59). However, the trend of black:white ratio across the four recent cycles of NHANES is consistent with a possible increasing gap. The large difference in the percentage of current HCV infection between non-Hispanic blacks and non-Hispanic whites warrants further attention. The black:white ratio may be considered as one of the population-based indicators in monitoring disparities in uptake and/or effectiveness of antiviral treatment.

Studies have found that African Americans were less likely to spontaneously clear HCV virus compared to their white and Hispanic counterparts (21, 60). The underlying reasons for lower spontaneous clearance rate among black patients are not well understood, but viral factors and host factors certainly have played a role. Rate of spontaneous viral clearance is comparatively lower among genotype 1 infections, which occur more frequently in African Americans (59, 61). In addition, spontaneous resolution of HCV infection differs depending on the nucleotide sequence near the host gene for IL-28B or lambda interferon 3 (62). Since genotype CC at IL-28B is least likely to be present in African Americans, compared to Asians, Caucasians, and Hispanics, different percentages of current HCV infection could be partially explained by the unequal distribution of this allele across these racial/ethnic groups (62, 63). It should be noted that the percentage of current HCV infection among Mexican Americans is the lowest compared to all other groups in this our study. However, due to the small number of Mexican Americans represented in the sample, this data should be interpreted with caution.

Differences in antiviral treatment access, uptake, and response may further increase the racial gap in the percentage of current infection over time. One of the greatest contributors to the racial disparities in healthcare access is health insurance coverage (64). Compared to whites, African Americans are twice as likely to be uninsured, and spend more of their lifetime without some form of health insurance even though they have more unhealthy years (65, 66). In addition to race, a factor that impacts both the ability to access care and to obtain health insurance is socioeconomic position;

people at the lowest end of the socioeconomic spectrum least likely to be healthy and have health insurance (66, 67). Even when they have health insurance, African Americans receive lower quality of care and are less likely to use health services than whites (65, 68). Thus, African Americans, at the intersection of both racial and socioeconomic disparities in health, are at a great disadvantage.

African Americans are more often to be ineligible for treatment than their non-black counterparts due to presence of other conditions, such as uncontrolled diabetes mellitus and abnormal hematology (69). Even when there are no contraindications for therapy, African Americans are less likely to complete the required pre-treatment laboratory evaluations (69, 70). Rousseau et al found significantly low treatment uptake among black veterans compared to white veterans even after adjusting for socioeconomic and clinical factors (70). The decision to not to seek treatment, perhaps at the providers' recommendation, could be influenced by the research findings that African Americans have lower response rate to therapy and lower rates of sustained virologic response at the end of therapy (71-73).

The underlying reasons for the low treatment response rate among black patients are not well understood. Among those who received treatment, Brau et al found that African Americans required higher frequency of dose reduction due to adverse events associated with low hemoglobin level and neutrophil count, and that African Americans had lower response rate even when they completed the entire course of therapy at full dose (74). Moreover, treatment response rates vary depending on HCV genotype.

Genotype 1 infected patients have lower sustained virologic response than those infected with genotypes 2, 3, or 4 (29, 30, 32, 75, 76); and African Americans are more likely to be infected with genotype 1 virus than other racial/ethnic groups (59, 74). However, genotype does not fully explain the racial disparity. In a study of patients infected by genotype 1, African Americans were found to have reduced response rate regardless of treatment regimen, clinical features of their infection, and disease severity (77). In addition to its involvement in spontaneous viral clearance of HCV, the CC allele at the IL-28B gene is also significantly associated with sustained virologic response (22, 37, 62, 63, 78-81). Given the severity of the side effects of HCV therapy and low response rates, some African American patients may decide that adverse effects outweigh the benefit of treatment (29, 30, 50, 74).

Our finding that current HCV infection is positively associated with more severe liver damage is consistent with previous research (17-19, 82). The majority of the participants with current infection have elevated ALT and AST in our sample, and 13.6%, or 1 in 7, had a FIB4 score suggestive of advance fibrosis or cirrhosis (57, 58). However, relative small number of participants reported having ever received a diagnosis of liver condition. These findings, plus the average age of 50.8 years in this population, support CDC's recent recommendations for testing the cohort born between 1945 – 1965 and increase the number of HCV-infected persons who are tested and appropriately referred to care (45). Previous studies have shown that only about half of anti-HCV positive participants identified by NHNAES were aware of their infection status (83). We show that moderate, not insubstantial, number of persons with current HCV infection are

smokers and consume an excessive amount of alcohol. This speaks for the importance of behavioral modifications as effective interventions to reduce liver complications (84-87). It has been shown that the interaction between excessive alcohol consumption and HCV infection and smoking and HCV infection have multiplicative, synergistic effect on liver diseases, such as cirrhosis and hepatocellular carcinoma (85, 87-89). Although excessive alcohol consumption and smoking were not significantly different between participants with current infection and those with resolved infection in our sample, biomarkers of liver damage were worse off in those with current HCV infection. These findings indicate that current infection in the setting of the same amount of alcohol consumption and smoking is associated with more severe liver damage. Given the high prevalence of alcohol consumption and smoking, non-medical interventions also warrant urgent attention.

One major limitation of this study is its sample size. Due to the small number of eligible participants, the estimates have wide confidence intervals and the statistical power to do potential hypothesis testing was limited. Some essential information, such as treatment history, HCV genotype and IL28B allele, was not available from the survey. Additionally, we were unable to determine the effect of HIV or hepatitis B virus co-infection on HCV persistence and liver fibrosis because of a lack of data on these infections. As co-infection with HIV or HBV changes the characteristics of HCV infection and liver-related morbidity, availability of such data would have important public health implications (90, 91). Another important limitation to this study is the cross-sectional nature of NHANES interviews and examinations. The pattern of viral

clearance, whether spontaneous or treatment-induced, in participants with resolved infection cannot be determined. Some subgroups of the U.S. population were not included in the sampling frame by design. As pointed out by Chak et al, the excluded subgroups, such as incarcerated or homeless persons, are ones who have the highest prevalence of HCV infection (10). The correctional population alone represents 28.5 – 32.8% of the U.S. hepatitis C epidemic (Varan et al, 2013, unpublished). As black men are disproportionately more likely to be incarcerated, inclusion of the prison population may yield an even greater racial gap in proportion of current HCV infection in the U.S. (92). Investigations into the trend of HCV infection in populations not included in NHANES are needed and would help to understand HCV treatment and care in these populations.

Rapid improvement of anti-viral treatments is likely to further reduce the percentage of current HCV infection among those tested positive for anti-HCV. Our findings highlight the need for robust data systems in monitoring access to and uptake of HCV treatment in different populations. As more effective direct-acting antiviral agents are developed, existing host characteristics and virologic challenges that disproportionally affect African Americans may become less important (42-44). The reach of treatment and treatment outcomes are likely to become the more accurate predictors of current infections in the future.

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Tables

Table 1. Comparison of participants with current versus resolved HCV infection by socio-demographic factors, NHANES 2003 - 2010

	Current infection		Resolved infection		
	n	% (95% CI)	n	% (95% CI)	**p-value**
Overall	238	75.3% (67.8 - 81.5)	66	24.74% (18.6 - 32.2)	
Age					0.4820
40 - 50 years old	89	72.2% (62.0 - 80.6)	31	27.8% (19.4 – 38.0)	
50 - 60 years old	93	79.2% (67.9 - 87.2)	20	20.8% (12.8 - 32.1)	
60+ years old	56	74.9% (56.3 - 87.4)	15	25.1% (12.6 - 43.7)	
Race/Ethnicity					0.0037
Mexican American	27	66.2% (47.0 - 81.2)	13	33.8% (18.8 – 53.0)	
Non-Hispanic Black	95	91.1% (84.4 - 95.1)	11	8.9% (4.9 - 15.6)	
Other/Multi-Racial	23	74.9% (49.2 - 90.2)	9	25.1% (9.8 - 50.8)	
Non-Hispanic White	93	71.2% (59.5 - 80.6)	33	28.8% (19.4 - 40.5)	
Gender					0.4737
Male	147	77.0% (66.8 - 84.8)	39	23.0% (15.2 - 33.2)	
Female	91	72.4% (61.3 - 81.3)	27	27.6% (18.7 - 38.7)	
Education Level					0.0880
< High school, no diploma	90	84.8% (77.3 - 90.1)	19	15.2% (9.9 - 22.7)	
High school graduate or equivalent	68	75.7% (62.6 - 85.3)	21	24.3% (14.7 - 37.4)	
Some college	64	74.4% (61.9 - 83.9)	19	25.6% (16.1 - 38.1)	
College graduate or above	15	57.3% (36.4 - 76.0)	7	42.7% (24.0 - 63.6)	
Current Insurance coverage					0.5143
Yes	162	73.7% (64.1 - 81.5)	45	26.3% (18.5 - 35.9)	
No	75	78.0% (65.6 - 86.9)	21	22.0% (13.1 - 34.4)	

	Current infection		Resolved infection		
	n	% (95% CI)	n	% (95% CI)	**p-value**
Family income					0.7116
At or below poverty threshold	76	77.8% (65.3 - 86.7)	18	22.2% (13.3 - 34.7)	
Up to 2 times poverty threshold	68	77.9% (65.1 - 87.0)	18	22.1% (13.0 - 34.9)	
>2 times poverty threshold	78	72.6% (59.4 - 82.7)	24	27.4% (17.3 - 40.6)	
Veteran/military status					0.6331
Yes	37	71.3% (50.5 - 85.9)	12	28.7% (14.1 - 49.5)	
No	201	76.1% (67.6 - 82.9)	54	23.9% (17.1 - 32.4)	
Year of survey					0.3423
2003 - 2004	58	82.5% (69.9 - 90.5)	10	17.5% (9.5 - 30.1)	
2005 - 2006	45	70.4% (53.1 - 83.3)	17	29.6% (16.7 - 46.9)	
2007 - 2008	72	81.2% (66.2 - 90.4)	17	18.9% (9.6 - 33.8)	
2009 - 2010	63	67.3% (47.1 - 82.6)	22	32.8% (17.4 - 52.9)	

HCV, hepatitis C virus; CI, Confidence interval.

Table 2. Prevalence of selected liver conditions and behavioral factors in participants with current versus resolved HCV infection, NHANES 2003 - 2010.

	Active infection		Past infection		
	n%	(95% CI)	n	% (95% CI)	p-value
Liver conditions					
Alanine aminotransferase (ALT) level (IU/L)					<0.0001
Elevated*	133	56.5% (47.9 - 64.7)	7	8.9% (3.5 - 21.2)	
Normal	101	43.5% (35.3 - 52.1)	58	91.1% (78.8 - 96.5)	
Aspartate aminotransferase (AST) level (IU/L)					<0.0001
Elevated (>33 IU/L)	172	71.8% (63.3 - 79.0)	10	13.7% (6.8 - 25.5)	
Normal (≤33 IU/L)	62	28.2% (21.0 - 36.7)	55	86.3% (74.5 - 93.2)	
Platelet count (x10^3µL)					0.5125
Low**	31	13.4% (8.9 - 19.8)	9	18.2% (8.3 - 35.6)	
Normal	148	86.6% (80.2 - 91.1)	46	81.8% (64.4 - 91.7)	
FIB-4 classes					0.0016
Class I (≤1.45)	114	55.2% (47.4 - 62.7)	47	73.6% (57.1 - 85.4)	
Class II (1.45 < Fib4 ≤ 3.25)	81	31.2% (23.6 - 40.1)	14	23.5% (11.8 - 41.4)	
Class III (>3.25)	43	13.6% (8.6 - 20.8)	5	2.9% (1.1 - 7.5)	
Ever diagnosed with liver condition					0.5203
Yes	84	35.3% (28.3 - 43.1)	28	41.4% (26.5 - 58.1)	
No	153	64.7% (56.9 - 71.7)	38	58.6% (41.9 - 73.5)	
Still have liver condition (among those who were diagnosed)					0.0074
Yes	70	92.7% (82.1 - 97.2)	15	44.5% (21.0 - 70.8)	
No	7	7.3% (2.8 - 17.9)	12	55.5% (29.2 - 79.0)	
Smoking					0.3687
Current smokers	135	58.3% (50.9 - 65.4)	32	46.8% (33.3 - 60.8)	
Previous smokers	62	25.4% (19.7 - 32.2)	22	29.0% (16.6 - 45.7)	
Never smokers	41	16.3% (10.8 - 23.9)	12	24.2% (12.3 - 42.0)	

	Active infection		Past infection		
	n%	(95% CI)	n	% (95% CI)	p-value
Excessive alcohol consumption					0.9771
Yes***	67	27.3% (20.3 - 35.6)	15	24.1% (12.8 - 40.7)	
No	170	72.7% (64.4 - 79.7)	51	75.9% (59.3 - 87.2)	
Ever use a needle to inject illegal drug					0.6765
Yes	60	45.3% (35.9 - 55.0)	27	45.6% (28.9 - 63.3)	
No	83	54.7% (45.0 - 64.1)	23	54.4% (36.7 - 71.1)	

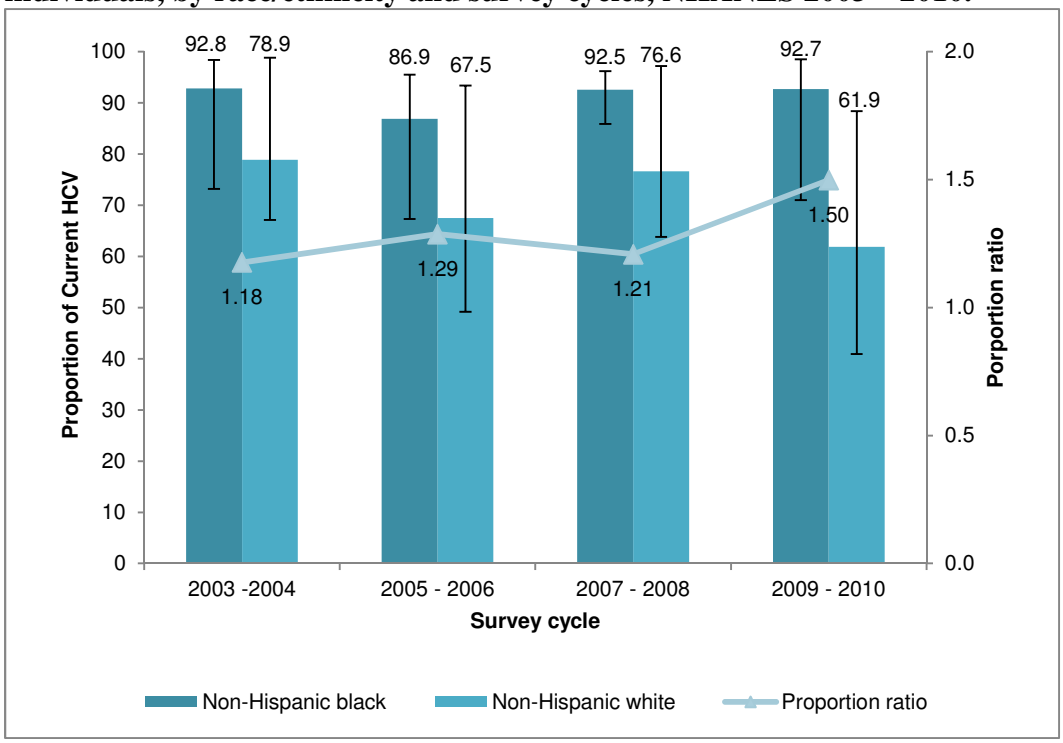
* >47 IU/L for males or >30 IU/L for females

** For the 2005-2006 cycle, lower limit of normal (LLN) is 157 x10^3 µL for males ≤65 years old and 172x10^3 µL for females ≤65 years old. In the same cycle, the LLN for males >65 is 138 x10^3 µL and for females >65 is 147 x10^3 µL. In 2007-2010 cycles, the LLN for males ≤65 years old is 152 x10^3 µL and for females ≤65 years old is 168 x10^3 µL. The LLN for males >65 years old is 124 x10^3 µL and for females >65 years old is 155x10^3 µL.

*** had on average >21 drinks/week for men or >14 drinks/week for women in the past year

Figure

Figure 1. Proportion of current HCV infections among anti-HCV positive individuals, by race/ethnicity and survey cycles, NHANES 2003 – 2010.



Chapter III. Summary

Incidence of HCV infection in the United States has been declining in recent years. However, morbidity and mortality caused by liver diseases associated with current HCV infection continues to rise. Presence of HCV viremia is detrimental to liver functions, and high prevalence of alcohol consumption and smoking may compound the adverse effect of HCV infection on the liver. While improvements in drug therapies may help reduce the manifestations of HCV infection in the future, the existence of racial disparities in the proportion of HCV viremia among anti-HCV positive individuals is of particular concern. Specifically, African Americans are disproportionally affected by current HCV infection. Factors associated with this disparity include host characteristics, viral factors, and treatment access. The newly developed anti-viral treatments involving direct-acting agents show promising abilities to overcome the difficulties presented by some viral and host factors. However, the relatively lower health insurance coverage among African Americans may continue to be a problem in their ability to obtain these new treatments. Thus treatment access may become the most important factor in determining proportion of current HCV infection and liver-related conditions caused by HCV among African Americans and U.S. population in general. Public health resources should be devoted to increase access to the new and effective HCV treatments.