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Liesl Hagan Date

INNOVATIONS IN MANAGEMENT OF CHRONIC HEPATITIS C: COST-EFFECTIVENESS ANALYSES AND OVERCOMING BARRIERS TO TREATMENT UPTAKE

BY

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Liesl M. Hagan
M.P.H, Emory University, 2014
B.S., Davidson College, 2005

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An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements of the degree of
Master of Public Health in the Career MPH program
2014

Abstract

INNOVATIONS IN MANAGEMENT OF CHRONIC HEPATITIS C:
COST-EFFECTIVENESS ANALYSES AND
OVERCOMING BARRIERS TO TREATMENT UPTAKE

BY

Liesl M. Hagan

Preliminary study: Cost-effectiveness of interferon-free treatment for chronic hepatitis C. At least 3.2 million people in the United States (US) live with chronic hepatitis C infection (CHC), which progresses largely asymptomatically toward cirrhosis, liver cancer, and premature death when untreated. Interferon-free treatments approved by the FDA in 2013 improve cure rates, eliminate most side effects and eligibility barriers, and simplify treatment administration compared to older interferon-based regimens. However, their added expense will contribute to access challenges. This analysis uses a decision-analytic Markov model with a lifetime horizon and societal perspective to investigate cost-effectiveness of interferon-free treatment compared to the previous standard of care. Results indicate that level of treatment uptake will be an important driver of cost-effectiveness.

Race/ethnicity as a barrier to CHC treatment: NHANES and the Grady Liver Clinic. Although interferon-free regimens will reduce many CHC treatment barriers, additional strategies are needed to overcome those related to socioeconomic status. Black race and Hispanic ethnicity are consistently associated with lack of CHC treatment in the US, and with socioeconomic variables known to impede access to care. A 2013 study of HCV-infected individuals from the National Health and Nutrition Examination Survey (NHANES) found no association between race and treatment, but because NHANES excludes several groups with high CHC prevalence, its generalizability to the overall US HCV-infected population is questionable. This analysis compares the NHANES results to CHC treatment data from the Grady Memorial Hospital Liver Clinic in Atlanta Georgia, which serves a predominantly black and uninsured population. Grady's CHC treatment prevalence was equivalent to NHANES',

even though the Grady sample included an overrepresentation of racial and socioeconomic groups historically difficult to engage and retain in care. In logistic regression analyses, likelihood of treatment was higher among Hispanics than non-Hispanics. Treatment uptake among blacks was mediated by presence of hypertension. These findings indicate that the Grady Liver Clinic is a successful model for treating underserved racial minorities for CHC. Combined with enhanced screening and access to interferon-free regimens that simplify treatment, innovative models like Grady's targeting high-risk, high-prevalence populations can make significant contributions toward reducing CHC-related morbidity and mortality in the US.

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INTRODUCTION

Chronic hepatitis C: Global disease burden and natural history

Hepatitis C virus (HCV) was first identified in 1989 as the principal cause of post-transfusion non-A non-B hepatitis and can take acute or chronic form.[1] An estimated 15-25% of acute infections resolve spontaneously, while the remaining 75-85% progress to chronic hepatitis C (CHC), which affects an estimated 130-170 million people worldwide and 3.2 million in the United States (US).[2, 3] There are six major HCV genotypes and many sub-types that contribute to variable responses to treatment. In the US, genotypes 1, 2 and 3 predominate, with genotype 1 accounting for approximately 73% of infections.[4]

Acute HCV infection can cause non-specific symptoms including fever, fatigue, nausea, vomiting, and jaundice but is usually entirely asymptomatic. As a result, HCV incidence is underestimated despite surveillance efforts. Many individuals whose acute infection resolves spontaneously are unaware that they were ever infected until they test positive for anti-HCV antibodies later in life. For those who develop chronic infection, the lack of definitive symptoms enables a silent progression to advanced liver fibrosis, cirrhosis and/or hepatocellular carcinoma (HCC) over the course of 20-30 years before diagnosis and treatment are likely to occur, maintaining infected individuals as reservoirs for continued transmission [2, 3, 5] Disease progression is measured by degree of liver fibrosis, commonly defined by Metavir score where F0 = no fibrosis, F1 = portal fibrosis without septa, F2 = portal fibrosis with few septa, F3 = numerous septa without cirrhosis, and F4 = compensated cirrhosis.[6]

Individuals with HCV infection face an increased risk of premature death, with all-cause, liver-related, and non liver-related mortality rates reaching 2.4, 26.5, and 1.8 times those of non-infected populations, respectively.[3, 7] Over 350,000 deaths worldwide have been attributed to CHC annually since 2002, most due to cirrhosis and HCC, and approximately 27% of cirrhosis and 25% of HCC cases globally are the result of HCV infection.[8 9]

CHC prevalence in the “baby boomer” generation (those born between 1945 and 1965) is especially high, reaching 4.3% in the United States (US) compared to 1.6% in the general population. High prevalence in this group is due partly to the inability to screen for HCV in blood and solid organ donations prior to 1992, and partly to transmission through injection drug use in the 1960s and 1970s [10]. HCV-related deaths and associated medical costs are expected to rise as infected individuals in this age group, most of whom were initially infected 20-30 years ago, begin to reach end stage liver disease.[11-13] In 2007, HCV-related mortality surpassed mortality from HIV in the US, primarily due to end-stage liver disease among members of this age group.[11] In response to this trend and to the demonstrated cost-effectiveness of birth cohort-based HCV screening,[14] the

Centers for Disease Control and Prevention (CDC) now recommends universal one-time screening for adults in this age group.[15]

HCV transmission

Percutaneous contact with infected blood accounts for most HCV infections worldwide, but primary modes of exposure vary geographically by countries' economic status. With the advent of effective HCV screening in 1992, injection drug use replaced infected blood and tissue donations as the primary source of new infections in developed countries.[9, 16] However, unscreened blood and tissue continue to pose a risk in developing countries without access to screening technology.[9] Injection drug use contributes to transmission in developing countries as well, though most infections in resource-poor areas result from healthcare-related exposures, primarily unsafe injections, which account for an estimated 2 million new infections per year and 40% of total infections globally.[9, 17] Vertical transmission also contributes to overall burden of disease, regardless of geography, with an estimated 4-7% of babies born to HCV-positive mothers becoming infected.[2, 18]

Likelihood of sexual transmission varies based on number of sexual partners, sexual orientation, and relationship duration. Based on retrospective cohort studies, sexual transmission of HCV is relatively rare in monogamous heterosexual relationships, ranging from 0-0.6% per year compared to 0.4-1.8% per year among heterosexual individuals with multiple partners and those at risk for other sexually transmitted infections.[19, 20] Several studies using molecular typing to match viral samples from both infected partners have shown that likelihood of sexual transmission increases with relationship duration.[21-23] However, others have found little or no evidence of sexual transmission and emphasize the likelihood of alternate parenteral household exposures that could account for transmission between sexual partners, such as shared needles, diabetic lancets, syringes, razors, and toothbrushes.[20, 24-27] Exposure to bleeding caused by intimate partner violence has also been associated with HCV infection.[28] Among HIV-infected men who have sex with men, high-risk sexual behaviors have been associated with as much as a 23-fold increase in HCV transmission.[20, 29-31]

Treatment

CHC treatment options have evolved rapidly, bringing progressive improvements in efficacy and reductions in therapy-induced side effects. Cure for CHC is measured by sustained virologic response, or SVR, currently defined as undetectable viral load 12 weeks after treatment completion.[4] The first treatment available for CHC, monotherapy with interferon injected three times per week, became available in 1990 and resulted in SVR for approximately 10% of patients. Side effects from interferon are common and include extreme fatigue,

depression, and flu-like symptoms in addition to the difficulties and discomfort associated with the need for patients to self-inject.[4]

In 1998, the oral, direct-acting antiviral drug ribavirin was added to interferon injections, forming a new standard CHC treatment regimen that increased SVR rates to 40%. Along with ribavirin came additional side effects, chiefly anemia.[32, 33] In 2001, pegylated interferon, a modified interferon molecule with a longer half-life, replaced natural interferon in the combination with ribavirin, further increasing SVR rates to 80% for some genotypes and reducing interferon injections to once per week.[34, 35] SVR rates for individuals with genotype 1 infection remained low until the approval of the protease inhibitors telaprevir and boceprevir in 2011, which when combined with pegylated interferon and ribavirin, brought genotype 1 SVR rates up to approximately 80% as well.[36, 37] However, despite rising SVR rates, the significant side effects of therapy, chiefly induced by interferon, have continued to undermine treatment eligibility, uptake and adherence for many people.[4, 38 39]

In December 2013, the US Food and Drug Administration (FDA) approved the first all-oral, interferon-free CHC treatment regimen, ribavirin plus a second oral, direct-acting antiviral drug developed by Gilead Sciences called sofosbuvir, which has demonstrated SVR rates over 90% in clinical trials and eliminated the need for interferon in most patient subgroups.[40] Recent guidance released by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) has established this and other interferon-free combinations as the new standard of care CHC treatment for most genotypes.[41] Other interferon-free regimens are currently under development with similar SVR rates and are expected to receive FDA approval in 2014 and 2015.

Cost of treatment

The benefits of interferon-free treatment come with a high price tag. The market entry price for sofosbuvir is $84,000 for a 12-week course of treatment and extends to a possible $150,000 for a 24-week regimen for more difficult to treat individuals. In contrast, prices for interferon-based regimens begin at $23,000 for some viral genotypes. The analysis that follows in the next section investigates the cost-effectiveness of interferon-free treatments, weighing their increased efficacy and improved side effect profile against their increased costs compared to interferon-based regimens. This analysis was published online in the *Journal of Viral Hepatitis* in June 2013 and appeared in the print edition in December 2013.[42]

PART 1: Cost-effectiveness of Novel CHC Treatments

This analysis is published in the *Journal of Viral Hepatitis* and is accessible via the following website: http://onlinelibrary.wiley.com/journal/10.1111/(ISSN)1365-2893

The abstract is available via PubMed:
http://www.ncbi.nlm.nih.gov/pubmed/24304454

Full citation:
Hagan LM, Yang Z, Ehteshami M, Schinazi RF: All-oral, interferon-free treatment for chronic hepatitis C: cost-effectiveness analyses. *J Viral Hepat*. 20(12):847-57, 2013.

LITERATURE REVIEW:
Factors Associated with CHC Treatment Uptake

Importance of treatment uptake

Despite increases in treatment efficacy over time, estimates of treatment uptake with interferon-based regimens have been low, ranging from 10% treated after diagnosis in Canada to 12-25% in the US and 41-44% in parts of Western Europe.[39, 43-47] Estimates as low as 6% have been found among populations of injection drug users (IDU).[48, 49] A 2010 analysis estimates that if current levels of treatment uptake continue in the US, CHC therapy will prevent only 14.5% of HCV-attributable deaths between 2002 and 2030.[50]

In the analysis presented above, treatment uptake emerged as a key variable influencing the cost-effectiveness of interferon-free treatments for CHC. Other researchers have identified treatment uptake as an important variable in the cost-effectiveness of HCV screening and treatment as well. Specifically, a 2013 model by McEwan *et al.* analyzing the cost-effectiveness of one-time, universal HCV screening among the high-prevalence 1945-1965 birth cohort is sensitive to levels of treatment initiation, requiring a certain threshold level of treatment uptake and subsequent cure to generate sufficient cost savings and life expectancy gains to offset screening costs.[51] Similarly, a 2012 study by Coffin *et al.* evaluating the cost-effectiveness of one-time universal screening among the general US population found that the magnitude of screening-derived population benefits was also sensitive to levels of treatment uptake and cure.[52] In 2001, Singer *et al.* found that screening asymptomatic adults for HCV infection was cost-effective when at least 50% of those identified as HCV-positive initiated treatment.[53]

After publishing the above article in the *Journal of Viral Hepatitis*, Hagan and co-authors conducted a follow-up analysis evaluating the cost-effectiveness of all-oral CHC treatment regimens in prison populations, where prevalence is estimated at 17% (much higher than the 1.6% in the general US population).[54] Results were presented at the HEP DART conference in 2013 and the Academic and Health Policy Conference on Correctional Health in 2014. This study used higher estimates for treatment uptake than in the published community model, with the understanding that many incarcerated individuals have greater access to healthcare and lower loss to follow-up inside the prison system than in the community. Results indicated that all-oral CHC regimens could be more cost-effective in a prison model than in the general US population, primarily due to these higher expected levels of treatment access and initiation.[55]

Treatment uptake is expected to increase once interferon-free regimens become widely available, due to improvements in physician confidence in treatment outcomes as well as gradually declining concerns about side effects.[56] Additionally, the simplification of treatment without interferon will allow more

widespread treatment by general practice physicians, reducing the need for specialist referral and the possibility of loss to follow-up at the referral stage.[57]

However, there are many other factors involved in treatment uptake that will need to be addressed to dramatically improve treatment levels for CHC. The literature review that follows explores these barriers to treatment and the potential impact that interferon-free regimens could have on their persistence.

Literature review methods

PubMed was used to identify articles for this literature review. Search terms included "HCV treatment uptake" (196 results), "HCV treatment defer" (17 results), "HCV treatment prescription" (80 results), "HCV treatment barrier" (35 results), and "HCV treatment obstacle" (136 results). After reviewing all results and adding 8 additional articles from reference lists in the articles found on PubMed, 43 articles were included in the literature review.

Overview

Barriers to CHC treatment uptake are often categorized in terms of patient, provider, and system-level factors that can stand alone or interact to influence individuals' likelihood of seeking and receiving CHC care. For example, insurance status may determine an individual's ability to access screening for HCV, but once screened, a healthcare provider has the opportunity to increase that individual's knowledge about the disease, possibilities for further transmission, and options for treatment. That knowledge can then be a determining factor in whether the individual pursues further HCV-related care and treatment, which can be catalyzed by healthcare systems structured to reduce stigma associated with HCV, provide support to maximize treatment adherence, and offer further education to prevent reinfection.

Barriers can arise at numerous points in continuum of care for CHC, including initial access to HCV screening, referral to a specialist, ability to attend specialist visits, eligibility for treatment, and the decision whether or not to pursue treatment that is offered. Some variables can influence treatment uptake on multiple levels and at different points in the continuum of care. For example, black race has been associated with lower levels of referral to a specialist after diagnosis compared to other races (a provider-level barrier),[58] as well as lower acceptance of treatment that is offered (an individual-level barrier),[59, 60] partly due to biological differences in treatment response by race (another individual-level barrier).[61]

Because the primary research question in this thesis analyzes treatment uptake as the dependent variable, the literature review that follows focuses primarily on individual-level factors that impact treatment decisions after diagnosis and

evaluation. However, because many of these variables play a role in winnowing the pool of individuals who ever have the opportunity to make a treatment decision, consideration is also given to their influence on provider and system levels, and as treatment barriers at earlier stages of care.

Healthcare access and insurance status

Summary:
- Lack of health insurance impedes CHC treatment
- Access to routine medical services can predict uptake

Interferon-free impact: Mixed
- \- Increased cost
- \+ Simplified treatment, greater provider capacity

Access to CHC-related medical care can be considered on patient, provider, and system levels. In an analysis of NHANES data from 2005-2008, Stepanova *et al.* found that the HCV-infected population in the US is significantly less likely to have any form of health insurance compared to the non-infected population (61% and 81%, respectively, $p<0.004$). Only 36.3% of the subset of HCV-positive individuals eligible for treatment had insurance coverage, and those with insurance were less likely to have a private plan compared to the non-infected population ($p=0.0002$).[62] Using the same NHANES questionnaires from 2001-2010, Younossi *et al.* demonstrated in univariate analyses that having any form of insurance coverage predicted diagnosis of HCV infection prior to the NHANES survey ($p<0.0001$), as well as treatment uptake after diagnosis ($p=0.09$). Having private insurance had a similar effect on prior knowledge of HCV status ($p=0.0031$).[63] In another US study, Mehta *et al.* found that HCV-positive individuals without health insurance were less likely to have a conversation with their doctor about potential CHC treatment ($p<0.0001$).[49] In these studies, insurance status emerges as a system-level variable affecting HCV treatment (lack of universal access to healthcare in the US), a provider-level variable affecting interactions between patients and their physicians (presence or absence of treatment-related conversations), and an individual level factor influencing treatment uptake decisions.

Although health insurance plays an important role in access, it does not ensure that care and treatment occur. For example, despite universal healthcare in Canada that covers CHC treatment, uptake among Canadians is reported at levels comparable to those in the US, approximately 16-23%.[64, 65] However, treatment levels as low as 6% have been reported among Canadian IDU, who are less likely to engage in medical care overall (see IDU section below),[48] and as high as 48% among HIV/HCV co-infected Canadians, who have more opportunities for integrated care for both conditions.[66] In Australia, government subsidies for CHC treatment were withheld from active IDUs until 2001, contributing to system-level barriers to treatment access for these populations.[67]

The literature reports mixed findings on whether the healthcare setting where HCV-positive individuals receive care can impact treatment uptake. The

NHANES study by Younossi *et al.* found that receiving routine medical care in a doctor's office rather than the emergency room predicted prior knowledge of HCV status, which was itself predictive of treatment uptake (p<0.0001).[63] Similarly, in univariate analyses, Stoove *et al.* found that in Australia, HCV diagnosis by a general practitioner or in a hospital setting (rather than in a drug and alcohol rehabilitation setting), as well as longer consultation at the time of diagnosis, predicted referral to an HCV specialist (p<0.0001 and p=0.002, respectively). In addition, seeing a general practitioner specifically for CHC-related care was an independent predictor of specialist referral (AOR=4.16, 95% CI: 2.73-6.35).[67] In contrast, Alavi *et al.* found that having established access to regular doctor or to nursing care for routine medical needs did not impact HCV treatment uptake among inner-city Canadians with HCV,[48] and Niederau *et al.* found that care in a private practice facility in Germany (as opposed to a hospital setting) was significantly associated with *non*-treatment.[39]

Moving down the continuum of care, seeing a specialist for CHC care has been shown to predict treatment initiation in the US (Kramer *et al.*, AOR=9.34; Morrill *et al*, p<0.0001 in univariate analysis), [46, 60] while missing scheduled CHC-related care appointments has predicted non-treatment in the US and Norway (Morrill *et al.,* AOR=0.005; Toresen *et al.*, AOR=0.13, 95% CI: 0.03-0.52).[46, 68] However, Wagner *et al.* found that missed CHC clinic appointments had no effect on physicians' treatment recommendations among HIV/HCV co-infected individuals in the US.[58]

Substance abuse

Injection drug use

Summary:
- Some providers hesitant to treat IDUs – reinfection, adherence
- Integrated CHC and drug treatment models successful

Interferon-free impact: Mixed
+ Shorter treatment duration
+ Less complicated regimen
+ Easier to administer & adhere
- Does not address reinfection

The interactions among access-related variables can be particularly influential in populations less likely overall to engage in medical services, such as IDUs. Injection drug use accounts for the vast majority of HCV incidence and prevalence in developed countries,[9, 16] and IDU populations should arguably be the focus of targeted treatment strategies to reduce the global disease burden [69, 70]. However, these populations with the greatest need for treatment face additional barriers to medical care including fears about confidentiality and stigma, lower likelihood of health insurance, and difficulties keeping scheduled appointments, particularly when enrolled in both CHC treatment and addiction services.[64, 71-76] The research mentioned above by Morrill and Toresen finding that missing CHC care appointments predict non-treatment lends support to recent calls for integrated care for IDU populations.[76] A body of research is growing to support non-

traditional treatment models among IDUs, showing both increased treatment uptake and increased adherence in treatment programs that integrate drug rehabilitation services with CHC care, treatment, and peer support while minimizing the stigma many IDUs feel when accessing medical care in settings unaccustomed to treating people who inject drugs.[57, 64, 71, 72, 74, 75, 77-79]

The literature offers mixed results on whether current or former injection drug use affects treatment uptake. In both a Canadian inner-city population of HCV-positive subjects (primarily injection drug users) and a study of IDUs enrolled in opioid maintenance therapy in Switzerland, treatment uptake was not influenced by former nor current injection drug use.[48, 80] In addition, among numerous non-IDU specific populations including US veterans, the general US population, patients in Norway already referred to a tertiary care facility for CHC treatment, and a study of recently infected individuals in Australia, current and former injection drug use were found to have no impact on whether subjects were ultimately treated for CHC.[63, 68, 77, 81] A study of HIV/HCV co-infected subjects in the US found that history of injection drug use did not affect physicians' decisions to refer HCV-positive individuals to a specialist for further assessment.[58] An Australian study focusing on IDUs enrolled in opioid substitution therapy did not find any difference in the prevalence of on-site HCV assessment among those who had recently injected drugs compared to those who had not.[79]

In contrast, the majority of studies reviewed have found associations between injection drug use and specialist referral, treatment recommendation, or treatment uptake for CHC. In a prospective cohort study among subjects attending HCV clinics in Australia, Gidding *et al.* found that history of injection drug use predicted non-treatment in univariate analysis ($p=0.033$).[56] Similarly, in a population of HIV/HCV co-infected individuals in Canada, Murray *et al.* found that those who had never injected drugs were more likely to be treated for CHC than those with a history of injection drug use (AOR=3.48, 95% CI: 1.37-8.79).[66] In a retrospective cohort study in Germany among HIV/HCV co-infected subjects, a higher proportion of those not receiving treatment had acquired their infection through injection drug use, compared to those who were treated (71% and 48% respectively, $p<0.0001$).[82]

Compared to former injection drug use, current use has an even more consistent effect on CHC care and treatment. Stoove *et al.* found that subjects who had never injected drugs were more likely to be referred to a specialist for further CHC care compared to those currently injecting (AOR=3.38, 95% CI: 1.83-6.23), and the current IDUs who were referred were less likely to be treated ($p<0.0001$).[67] Three studies found that current IDUs were less likely to be treated than those with a history of injection drug use but not currently injecting (Gidding *et al.,* AOR=0.26, 95% CI: 0.08-0.77; Toresen *et al.,* OR=0.32, 0.13-0.82; Moirand *et al.,* AOR=0.02, 0.0-0.16), [56, 68, 73] and two additional studies found that subjects with no current or recent injecting behavior were more likely to be treated than current IDUs (Alavi *et al.,* AOR=3.48, 95% CI: 1.37-8.79; Murray *et*

al., OR=1.86, 95% CI: 1.04-3.32).[57, 66] Recent receptive sharing of injection drug preparation equipment resulted in lower likelihood of treatment among male IDUs in Australia (OR=0.79, 95% CI: 0.63-0.97),[78] and current injection drug use was associated with a lack of willingness to be treated in a study of inner-city HCV-positive individuals in Canada (OR=0.36, 95% CI: 0.16-0.81).[64, 78] Among HIV-co-infected IDUs, current injection drug use has also been associated with lower likelihood of having a consultation with a doctor that included a conversation about potential treatment (69% IDU vs 81% non-IDU, p=0.02).[49]

Other drug use

Aside from a few studies citing no association between non-injecting drug use and referral attendance,[83] CHC treatment uptake,[48, 56, 80] or treatment recommendation by a physician,[58] the bulk of relevant literature cites drug use/abuse as a significant barrier to HCV care and treatment. However, many studies do not differentiate between drug use in general and injection drug use.

Stoove *et al.* found that HCV-positive subjects in an Australian cohort who had not used illicit drugs in the six months prior to assessment were more likely to be referred to a specialist for CHC care than those who had used drugs during the same time period (p<0.05).[67] Similarly, Alavi *et al.* found a specific association between recent abstention from benzodiazepine use and likelihood of specialist referral among current and former Australian IDUs (AOR=2.06, 95% CI: 1.31-3.24).[57] In a US VA study, Bini *et al.* report that ongoing and recent substance abuse are strongly associated with physicians' decisions not to recommend CHC treatment (AOR=17.68, 95% CI: 12.24-25.53),[43] and among HIV/HCV co-infected IDUs, those reporting current non-injection drug use were less likely to have a conversation with their doctor about CHC treatment compared to those not reporting drug use (54% and 70%, respectively, p<0.01).[49]

In numerous populations including IDUs in Australia and Canada, HIV/HCV co-infected individuals in the US, US veterans, and non-IDUs in all three countries, current non-injecting drug use is consistently associated with lower odds of CHC treatment compare to those not using drugs.[46-48, 57, 60, 64, 84-87]

Alcohol

Current and recent alcohol use are contraindications to HCV treatment, as alcohol can blunt the body's natural immune response and result in increased HCV RNA levels, in addition to contributing to liver fibrosis.[72, 85] In the NHANES study mentioned above, Younossi *et al.* found in univariate analysis that excessive alcohol consumption

Summary:
- Alcohol use restricts IFN treatment eligibility
- Impact on treatment uptake is mixed – some studies find reduced uptake, others no effect

Interferon-free impact: Positive
+ Alcohol use does not prohibit treatment with IFN-free regimens

was associated with subjects' lack of awareness of their HCV status prior to the NHANES diagnosis (p<0.0001), which then predicted non-treatment in a multivariate model (AOR=6.14, 95% CI: 2.42-15.6).[63] Among HIV/HCV co-infected subjects, those who reported alcohol use had lower likelihood of having a conversation with their doctor about CHC treatment compared to those not reporting alcohol use (59% vs. 71% respectively, p=0.04),[49] and numerous studies report an association between alcohol use/abuse and non-treatment [46, 47, 56, 60, 68, 73, 84].

Although no studies reviewed found a positive association between alcohol use and CHC treatment, several found that alcohol did not impact subjects' likelihood of treatment in either direction. Examples include a study of recently infected IDUs in Australia,[77] HCV-positive current and former IDUs enrolled in opioid maintenance therapy in Switzerland,[80] a US veteran population,[81] an HIV/HCV co-infected cohort in the US,[87] and prospective cohorts of primarily IDUs in Australia and Canada,[48, 57] which all found no association between alcohol use and treatment for CHC. One US study among HIV/HCV co-infected subjects found no association between alcohol use and physicians' recommendations for treatment.[58]

Demographic variables

Age

Numerous studies reviewed found no association between age and CHC treatment uptake [46, 48, 56, 63, 66, 80-82]. Studies that did find significant associations typically categorized age as "older" versus "younger," though neither the operationalization of these categories nor the direction of the associations is consistent.

Two studies defined age as a continuous variable and found positive associations between older age and CHC care or treatment. In a retrospective observational study of former IDUs in China, Wong *et al.* report that those attending a CHC referral visit were older on average than those who chose not to attend (69 versus 42 years old, p=0.022).[83] In a retrospective chart review of US veterans, Butt *et al.* found that those who were treated for HCV were also older on average compared to those who were not treated (48.6 vs. 47.4 years old, p<0.0001).[84]

Summary:
- Inconsistent associations between older age and treatment eligibility and uptake – some find greater likelihood, some lower
- 1997 NIH Consensus Statement advised caution in treating those > 60 years
- Older age coincides with comorbid conditions and advanced liver disease

Interferon-free impact: Positive
+ Fewer complications and drug-drug interactions make treatment more tolerable for those with comorbidities
+ Treatment successful in those with advanced liver disease

Two more studies defined age categorically and also found positive associations with treatment uptake. Alavi *et al.* categorized age as less than 35 years, 35-45, and more than 45 years old and found increasingly positive associations with treatment as age increased compared to the <35 reference group (OR=1.98, 95% CI: 1.02-3.81 for 35-45 years old; OR=2.07, 95% CI: 1.05-4.08 for >45 years old).[57] Iversen *et al*. found a similar trend among male IDUs in Australia, with odds of treatment increasing gradually with age compared to the <30 year-old reference category, from 1.42 (95% CI:1.99-2.01, p=0.047) among those between 30 and 34 years old, up to 2.39 (95% CI: 1.62-3.52, p<0.001) among those 50 years of age or older.[78]

All other studies reviewed found negative associations between HCV treatment and older age, defined in a variety of ways. These results could be explained by clinical consensus in the 1990s and 2000s against treating older individuals, guided by a 1997 National Institutes of Health consensus statement advising caution in treating those age 60 and older.[88]

In a US veteran population, Bini *et al.* report that those age 50 and over were more likely to decline treatment compared to their younger counterparts (AOR=1.37, 95% CI: 1.07-1.76, p=0.014), with a similar association between age and treatment recommendation by a physician (AOR=1.33, 95% CI: 1.07-1.76, p=0.004).[43] In a study of HCV-positive subjects in Norway referred to a tertiary care facility for treatment, Toresen *et al.* found that those age 50 and older were more likely to be treated compared to the <30 reference group (AOR=0.06, 95% CI: 0.00-0.81).[68]

Moirand *et al.* report that, in a retrospective chart review of HCV-positive subjects treated in Canadian outpatient facilities, those over age 45 were less likely than those 45 or younger to be eligible for treatment (AOR=0.61, 95% CI: 0.4-0.9) and to accept treatment that was offered (AOR=0.47, 95% CI: 0.27-0.83).[73] In a US VA population, Kramer *et al.* found that veterans age 65 and older were less likely to be treated compared to those in the age 45-54 reference category (AOR=0.32, 95% CI: 0.24-0.41, p<0.0001) [60], and in another VA study Butt *et al.* report decreased odds of treatment with each 5-year increase in age (AOR=0.77, 95% CI: 0.76-0.78).[47] In a retrospective chart review among HIV/HCV co-infected individuals in the US, Osilla *et al.* found that the mean age of those accepting treatment that was offered was younger than those who declined a treatment offer (48.1 vs. 51.2 years old, AOR=0.95, 95% CI: 0.91-0.99, p=0.05).[87]

In general, age has been cited as a barrier to treatment, often because it coincides with later stages of liver fibrosis including cirrhosis, or other comorbid conditions that make CHC treatment less effective and less tolerable.[74] On the other hand, CHC treatment is often delayed for those with early stages of fibrosis (F0 or F1), who tend to be younger and healthier.[60] Thus, depending on how age is defined, it could be a proxy for severity of liver disease, with low likelihood of

treatment for younger individuals (with less fibrosis), progressively higher likelihood for those in middle age (coinciding with moderate fibrosis stages considered optimal for treatment), and decreasing likelihood for older age groups (coinciding with cirrhosis and comorbid disease).

Gender

Summary:
- Mixed results on gender-treatment association
- Female IDU more likely to report stigmatization in traditional clinic settings

Interferon-free impact: Neutral
- ± No difference in efficacy by gender
- \+ Simplified regimens easier to administer in integrated drug treatment settings – addresses stigmatization

Reported associations between treatment and gender are entirely mixed, with roughly half of studies reviewed finding no association,[46, 48, 56, 57, 66, 67, 79-82] and the other half reporting significant associations with treatment or non-treatment by gender.

In the US general population, Younossi *et al.* report an association between male gender and lack of awareness of HCV status, which is a factor associated with non-treatment (see above).[63] Similar results associating male gender with lower likelihood of treatment come from a US VA population (Kramer *et al.,* AOR=0.53, 95% CI: 0.44-0.63, p<0.0001) and the previously mentioned Norwegian cohort of HCV-positive individuals referred to treatment (Toresen *et al.*, OR=0.49, 95% CI: 0.27-0.89). The association found in the Norwegian study does not remain significant in adjusted analysis.[68] On the other hand, positive associations between male gender and CHC treatment are reported among Canadian IDUs (Charlebois *et al.,* p=0.07, trend only),[86] Australian IDUs (Iversen *et al.,* p=0.002),[78] and HIV/HCV co-infected subjects in the US (Osilla *et al.,* p<0.05).[87]

Female gender has been associated with greater likelihood of referral to a specialist in a community-based sample of HCV-positive individuals in Australia (Stoove *et al.,* p<0.0001 in univariate analysis).[67] However, females in a US community-based sample were less likely to be treated than their male counterparts (Morrill *et al.,* AOR=0.31, 95% CI: 0.12-0.79, p=0.01),[46] with similar results from a prospective cohort of CHC patients in Germany (Niederau *et al.,* p<0.001).[39] In addition, two studies discuss gender differences in experiences of stigma related to HCV and injection drug use, with female IDUs more likely to report stigmatization in healthcare settings, potentially impeding CHC care and treatment.[86, 89]

Race/Ethnicity

In the US studies reviewed, black race consistently reduces the likelihood of CHC care and treatment. Adjusted odds ratios for treatment among black

subjects range from 0.44 (95% CI: 0.28-0.7) compared to white reference groups[43] to 0.64 (95% CI: 0.6-0.68),[47] with additional studies reporting results within that range. [43, 60, 84, 87] Several studies also found reduced odds of a physician's treatment recommendation among black subjects. In a VA cohort, Butt *et al.* found that only 13.6% of those recommended for treatment were black, compared to 23.1% of those for whom treatment was not recommended, ($p<0.001$).[47] In a cohort of HCV-positive subjects receiving care in academic medical centers in the US, authors found similar results, with black subjects less likely than whites to receive treatment recommendations from their physicians (AOR=0.44, 95% CI: 0.28-0.7). This study also found that the effect of black race is amplified by co-infection with HIV, with odds of treatment recommendation for HIV/HCV co-infected black subjects even lower compared to their white counterparts (AOR=0.28, 95% CI: 0.12-0.68).[59]

Summary:
- In US, black race a consistent barrier to eligibility, referral, and treatment for CHC (related in part to higher genotype 1 prevalence, lower SES, and lower healthcare access)
- Hispanic ethnicity also associated with lower likelihood of treatment
- Amplified by HIV co-infection
- Aboriginal identity in Australia associated with lower treatment uptake

Interferon-free impact: Mixed
+ Unfavorable IL-28B genotype (more prevalent among blacks) no longer predictor of poor treatment response
- More expensive - does not address issue of access for racial groups with lower SES

Hispanic ethnicity is also associated with lower likelihood of HCV treatment, with adjusted odds ratios reported between 0.56 (95% CI: 0.38-0.82)[84] and 0.88 (95% CI: 0.8-0.96).[47] In a study among HIV/HCV co-infected subjects, Wagner *et al.* found that both black and Hispanic subjects were less likely to receive a treatment recommendation from their physician compared to the white reference group (AOR=0.32, 95% CI: 0.15-0.70, $p<0.01$).[58]

In Australia and Canada, Aboriginal identity has also been associated with lower likelihood of CHC specialist assessment and treatment,[48, 57] with the exception of female IDUs in a prospective observational cohort of subjects using a needle exchange program. In this study, Iversen *et al.* found that indigenous Australian identity was associated with treatment uptake among female IDUs (OR=1.6, 95% CI: 1.07-2.37, $p<0.005$), but this association did not remain significant in multivariate analyses.[78]

Although no studies reviewed showed positive associations between minority race and CHC treatment (other than the exception mentioned above), several did report a lack of association in either direction. [46, 56, 63, 66, 74, 79, 81]

Socioeconomic status

Summary:
- Higher education consistently associated with CHC treatment uptake
- Employment as positive predictor of treatment in half of studies; other half find no association
- Higher income associated with knowledge of HCV status and subsequent treatment; poverty reduces treatment rates
- Financial barriers (transportation, time away from work, child care) cited as reasons for non-treatment
- Lack of stable housing a barrier to treatment, particularly for IDUs

Interferon-free impact: Mixed
+ Shortened treatment duration – fewer doctor's appointments
+ Refrigeration of oral medications not required
- More expensive – does not improve access to populations already underserved
- Public assistance with treatment costs only available for HIV/HCV co-infected

Education

Aside from three studies that reported no association between CHC treatment and education level,[48, 57, 81] higher levels of education are consistently associated with greater odds of CHC care and treatment. In a US veteran cohort, Bini *et al.* found that having a high school education or less is associated with lack of treatment recommendation by a physician (AOR=1.24, 95% CI: 1.03-1.50, p=0.027).[43] Using data from NHANES, Younossi *et al.* report that having a college degree is associated with treatment uptake in univariate analysis (p=0.02).[63]

In Australia, Grebely *et al.* found that lack of tertiary education is associated with non-treatment (AOR=0.43, 95% CI: 0.17-1.08, p=0.071),[77] and Treloar *et al.* found that having a high school education or more is associated with CHC treatment assessment among opioid substitution therapy clients (AOR=7.81, 95% CI: 1.62-37.72, p=0.01).[79] In a retrospective study of former IDUs in China, Wong *et al.* reports that having secondary education or above is a positive predictor for CHC referral attendance in univariate analysis (p=0.039).[83]

Employment

Approximately half of the studies reviewed that assessed employment status found no association with CHC care and treatment.[46, 48, 80, 87] The rest consistently identified employment as a positive predictor of treatment. In Australian studies among IDU, Alavi *et al.* found that full or part-time employment was associated with treatment (OR=2.55, 95% CI: 1.24-5.25),[57] though this

association did not remain significant in multivariate analysis, and Grebely *et al*. found that unemployment predicted non-treatment (AOR=0.44, 95% CI: 0.18-1.10, p=0.08).[77] In a study among subjects in an out-patient liver clinic in Canada, Moirand *et al.* report that a categorization encompassing employment, being in school, and raising children at home is associated with higher likelihood of treatment uptake compared to unemployed subjects (OR=1.75, 95% CI: 1.1-2.8).[73] A US study of subjects in several specialty liver clinics also found that employment is associated with treatment (p=0.02 in univariate analysis).[90] In studies among clinical populations in both Germany and Norway, unemployment was associated with non-treatment (p=0.05)[39] and (AOR=0.06, 95% CI: 0.01-0.29, p<0.05), respectively.[68]

Income

Only two reviewed studies address income as a quantitative predictor of CHC care or treatment, and both come from the US. In a US veteran population, Bini *et al.* report that having a yearly household income less than $10,000 is a predictor of non-treatment in univariate analysis (OR=1.31, 95% CI: 1.03-1.68, p=0.029) .[43] Using NHANES data, Younossi *et al.* found that HCV-positive individuals who report CHC treatment have a higher average income-to-poverty ratio compared to those who do not report treatment (2.25 vs. 1.89, p=0.14). They also note that those who were aware of their HCV infection prior to NHANES diagnosis had a higher income-to-poverty ratio than those who were unaware (2.17 vs. 1.73, p=0.036), demonstrating a link between income and healthcare access in the US.[63] In another study of US veterans, Seal *et al.* found no association between income and HCV treatment.[81]

Other studies note that the cost of transportation to medical visits (and paid work hours lost while receiving care) can become barriers to treatment, particularly among IDUs enrolled in addiction services as well. These authors advocate for co-located services for HCV care and drug rehabilitation to ameliorate this problem.[72, 76, 91]

Housing

Two studies addressed housing status as a quantitative predictor of HCV treatment, both conducted in Canada. Charlebois *et al.* report that IDUs with stable housing have 6.22 times the odds of being treated for HCV compared to those without stable housing (95% CI: 1.54-25.11, p<0.05),[86] and Moirand *et al.* found that patients in an outpatient liver clinic who had a precarious housing situation had 0.22 times the odds of treatment of those who lived with others (95% CI: 0.1-0.6).[73] In a review of treatment barriers among IDUs, Cooper *et al.* explain this association by nothing that lack of stable housing makes CHC treatment and adherence particularly difficult due to the need to refrigerate interferon.[72]

Three studies found no association between housing status and CHC treatment.[48, 68, 80]

Social support

Summary:
- Social support (family, peers) associated with higher likelihood of treatment uptake
- Mixed results on marriage as predictor of treatment

Interferon-free impact: Neutral
± Simplified regimens may increase treatment in supportive, interconnected care settings

Two community-based studies found that HCV-positive individuals who were married were more likely to be treated than those who were unmarried. Moirand *et al.* reported an odds ratio of 1.81 in Canada (95% CI: 1.2-2.8),[73] and Morrill *et al.* reported odds of 2.79 (95% CI: 1.15-6.76, p=0.02) in the US.[46] A third study by Evon *et al*., also in the US, reported that those treated for CHC were more likely to be married than those not treated (60% vs. 41%, p=0.05).[90] Moirand *et al.* also found that family support in general predicted CHC treatment (OR=2.04, 95% CI: 1.3-3.2),[73] and Alavi *et al.* found similar results among IDUs in Australia, where those who had social support from friends and family had 2.15 times the odds of being treated for CHC compared to those without social support (95% CI: 1.25-3.71, p=0.006).[57]

In contrast, Younossi *et al.* found the opposite association in univariate analysis of NHANES data, where those treated for CHC were less likely to be married compared to those who were not treated (17% vs. 61%, p=0.14), though the significance level in this study was higher than those reporting a positive association between marriage and treatment.[63] Among former IDUs in China, Wong *et al.* report that marital status had no effect on CHC referral attendance.[83]

Sexual identity/Sexual history

Summary:
- Mixed results on number of sexual partners and likelihood of treatment
- MSM more likely to be treated

Interferon-free impact: Neutral

Two studies reported findings related to sexual history, both in US veteran populations. Although Seal *et al.* report no association between CHC treatment and number of lifetime sexual partners or reported sex with a sex worker,[81] Bini *et al.* found that subjects with more than 50 lifetime sexual partners had 1.44 times the odds of non-treatment compared to those with fewer partners (95% CI: 1.08-1.93, p=0.013).[43]

Two studies reported that men who have sex with men (MSM) were more likely to be treated than those without MSM identification (Grint *et al.* RR=1.36, 95%

CI:1.0.-1.83, p=0.046; Murray *et al.* 67.5% MSM treated vs. 32.5% non-MSM treated, p=0.008).[66, 92] In a study of IDUs in Australia, Iversen *et al.* found that both male and female IDUs identifying as homosexual had greater odds of CHC treatment compared to their heterosexual counterparts (male OR=2.58, 95% CI: 1.70-3.93, p<0.0001; female OR=1.87, 95% CI: 1.06-3.30, p=0.03).[78]

Incarceration history

Associations between history of incarceration and HCV treatment are more sparsely reported. Among Australian IDUs, Iversen *et al.* found that past incarceration was associated with higher odds of treatment among women (OR=1.41, 95% CI: 1.0-1.98) but lower odds of treatment among men (OR=0.76, 95% CI: 0.6-0.97).[78] Three studies – a second study of Australian IDUs,[57] one involving a sample of US veterans,[81] and one studying a community-based US sample[46] – found no association between history of incarceration and HCV treatment.

HCV-specific variables

Summary:

- Genotype 1-infected individuals less likely to be treated for CHC (lower SVR rates, and treatment is longer, more complicated, and has more side effects)
- Liver biopsy predictive of treatment (though biopsy could be interpreted as an outcome itself, as an immediate precursor to treatment)
- Advanced liver fibrosis and high ALT levels predict treatment in some studies
- Asymptomatic disease associated with non-treatment
- Mixed results on duration of disease/time since diagnosis and HCV viral load

Interferon-free impact: Mixed

+ Some IFN-free combinations are pangenotypic; however, genotype 1 infections are still more difficult to treat and require longer treatment courses, sometimes with IFN
+ Successful in early and late stage fibrosis and compensated cirrhosis
- Does not address identification of infections/screening in absence of symptoms
- High cost may drive payers to cover only those with late stage disease, preserving early stage individuals as reservoirs for continued transmission

Genotype

Approximately half of reviewed studies that considered HCV genotype as a possible predictor of treatment found no association.[56, 58, 77, 81, 83, 87, 92] Those that did find a relationship involving genotype reported greater likelihood of CHC care and treatment among subjects with genotypes other than 1. These associations

are not unexpected, considering that genotype 1 is the most difficult to treat, with the lowest SVR rates.

Alavi *et al.* found that non-genotype 1 individuals had 2.13 times the odds of specialist assessment (95% CI: 1.32-3.43, p=0.002) and 3.07 times the odds of treatment (95% CI: 1.67-5.64, p=0.001) compared to those with genotype 1.[57] Two studies reported that subjects with genotypes 1 or 4 had lower odds of treatment compared to those with genotypes 2 or 3 (AOR= 0.6, 95% CI: 0.55-0.65, p<0.0001)[60] and (AOR=0.03, 95% CI: 0.01-0.28)[68]. A German study found that those with genotypes 1, 4, 5, or 6 were less likely to be treated compared to subjects with genotypes 2 or 3 (p<0.05),[39] and a Canadian study reported a trend toward higher odds of treatment among those with genotypes 2 or 3 (p=0.09).[66]

Liver biopsy

Two studies found no association between liver biopsy and HCV care or treatment.[56, 66] All studies that found a relationship between these variables reported that having a liver biopsy is a predictor of HCV treatment or care. Two studies reported univariate findings showing that a greater proportion of treated subjects had undergone a biopsy compared to untreated subjects (Butt *et al.* 71.4% vs. 43.7%, p<0.001; Younossi *et al.* 82.4% vs. 9.5%, p<0.0001).[59, 63] Two studies found a positive association between biopsy and treatment (Moirand *et al.* OR=4.72, 95% CI: 3.0-7.4; Niederau *et al.*, p<0.05),[39, 73] and one study reported that subjects who did *not* undergo a liver biopsy had 0.11 times the odds of treatment of those who had a biopsy (95% CI: 0.02-0.83).[68] Mehta *et al.* found that a greater proportion of subjects who had a biopsy reported having a conversation with a doctor about treatment, compared to those who had not had a biopsy (66% vs. 35%, p<0.0001).[49]

It is possible that liver biopsy could serve as a proxy for engagement in medical care, since it is an invasive procedure that requires commitment from the patient. It could also be a correlate of access to medical care and could therefore be related to issues surrounding insurance and socioeconomic status. Another interpretation of these results is that liver biopsy can be considered an outcome in itself, an immediate precursor to treatment.

Measures of HCV disease severity

Fibrosis stage and cirrhosis

Three studies reported no association between fibrosis stage and CHC treatment. [66, 68, 81] Among studies that did find an association, most reported that later fibrosis stages and cirrhosis were predictive of CHC care and treatment. Six found that cirrhosis was associated with either greater likelihood of treatment (Butt *et al.* 2007 AOR=1.6, 95% CI: 1.5-1.7; Kramer *et al.* AOR=2.11, 95% CI:

1.87-2.38, p<0.0001; Bini *et al.* AOR=2.57, 95% CI: 1.47-4.49, p<0.0001; Butt *et al.* 2006 10.9% of subjects treated had cirrhosis vs. 7.4% untreated, p=0.007), [43, 47, 60, 84] lower likelihood of treatment deferral (Gidding *et al.* AOR=0.059, 95% CI: 0.031-1.09, p=0.059),[56] or higher likelihood of referral attendance (Wong *et al.*, higher average liver stiffness measurement among those attending referral than those not attending, p=0.02).[83] In addition, fibrosis stages F2 and above have been associated with greater likelihood of treatment compared to lower fibrosis scores in a study across numerous European countries (IRR=1.6, 95% CI: 1.14, 2.25, p=0.0065),[92] and subjects with F4 fibrosis were found to have 2.6 times the odds treatment compared to those with F2 in a Canadian study (95% CI: 1.2-5.6).[73] The only study in which earlier fibrosis stages were associated with treatment was a German study of HIV/HCV co-infected subjects, in which the average fibrosis score among treated subjects was F2, compared to F4 among those not treated (p<0.0001).[82]

Two additional studies found no association between CHC treatment and APRI score, a value calculated using common serologic measures and often used as an indicator of cirrhosis in the absence of biopsy results.[56, 92]

Asymptomatic disease

Of the two studies that considered HCV symptoms as a possible predictor of treatment, one found no association with treatment but a positive association between symptoms and referral (p<0.0001),[67] and the other found that asymptomatic disease was associated with non-treatment (p<0.05).[39]

Infection length

Associations between duration of infection and CHC treatment are mixed. In a study of recently infected Australian IDUs, Grebely *et al.* report that odds of treatment increase by 1.03 times per week of infection (95% CI: 1.0-1.36, p=0.035).[77] A diagnosis 5 or more years prior to data collection predicted referral to a specialist in another study of Australian IDUs (AOR=1.88, 95% CI: 1.23-2.85),[67] whereas infection duration of 20 years or more predicted non-treatment in study of clinic-based HCV patients in Australia (OR=1.77, 95% CI: 1.07-2.94, p=0.027), though the latter association does not persist in multivariate analyses.[56] In a German study, duration of infection greater than 12.5 years also predicted non-treatment (p<0.05).[39] Two studies found no association between treatment duration/time since diagnosis and HCV treatment.[66, 67]

ALT and AST levels

Elevated levels of the enzymes alanine-amino transferase (ALT) or aspartate

aminotransferase (AST) in the blood can be indicators of liver fibrosis and are often used to estimate severity of liver disease.

Numerous studies reviewed measured differences in ALT levels for treated versus untreated subjects. Four of these studies found no association between ALT levels and HCV treatment,[56, 63, 77, 81] and only one found that elevated ALT levels were more common among untreated subjects compared to those who were treated (72.7% and 52% respectively, p=0.05).[46] Two reported that normal ALT levels predicted non-treatment,[39, 68] and the remaining studies reported significant associations between higher ALT levels and CHC treatment (Murray *et al.*, 56% treated had high ALT compared to 44% untreated, p=0.003; Kramer *et al.,* AOR=1.98, 95% CI 1.84-2.13, p<0.0003; Grint *et al.,* IRR=2.33, 95% CI 1.83-2.96, p<0.0001; Reiberger *et a.*, AOR=4.04, 95% CI 2.69-6.06, p<0.0001). One study reported higher ALT levels as predictive of specialist referral attendance (p=0.001).[83]

Only three studies considered AST levels, and none found associations with CHC care or treatment.[58, 63, 77]

HCV viral load

Four studies found no association between viral load and CHC care or treatment.[56, 58, 81, 87] Two reported higher likelihood of treatment among subjects with higher viral load (Grint *et al.*, IRR=1.21, 95% CI: 1.0-1.47, p=0.049; Grebely *et al.,* AOR=1.92 per log increase in viral load, 95% CI: 1.36-2.73, p<0.001).[77, 92] In addition, Wong *et al.* reported higher mean viral load measurements among subjects who attended a specialist referral compared to those who did not (p=0.001).[83]

In contrast, Morrill *et al.* found lower average viral load measurements among treated subjects compared to untreated (p<0.0001),[46] and Niederau *et al.* reported lower odds of treatment among those with lower average HCV viral load (p<0.05).[39]

Co-morbidities

Medical comorbidities

Summary:
- Many medical comorbidities reduce eligibility for treatment as well as uptake
- Mixed results on weight/obesity, diabetes, coronary artery disease, stroke, and anemia as predictors of treatment or non-treatment
- Co-infection with HIV or HBV predicts treatment in some populations, non-treatment in others. Severity of HIV disease impacts treatment uptake in some studies

Interferon-free impact: Mixed
+ More tolerable treatments with fewer adverse events and drug-drug interactions could reduce or remove medical barriers to eligibility and treatment
- High cost adds to medical bills for those with pre-existing comorbid conditions

Comorbid medical disease in general has been associated with lack of treatment recommendation by a doctor (Bini *et al.,* AOR=8.43), reduced treatment willingness among patients (Grebely *et al.,* p=0.02), and lower likelihood of treatment uptake for CHC (Bini *et al.,* OR=0.46; Nederau *et al.,* p,0.05).[39, 64, 71] However, some specific comorbidities have a greater effect on treatment uptake than others.

Weight/Obesity

Only two studies reviewed included weight as a possible predictor of CHC treatment uptake. Reiberger *et al.* found no significant relationship,[82] while Younossi *et al.* found that obesity (body mass index>30) was associated with treatment uptake in univariate analysis (p=0.0687).[63]

HIV and HBV co-infection

Partly due to shared modes of transmission, particularly injection drug use, an estimated 25% of HIV-infected individuals and up to 90% of HIV-infected IDU are co-infected with HCV.[93, 94]

The increased availability of antiretroviral therapy against HIV in developed countries now allows HIV-positive individuals to live longer lives. As a result, those who are co-infected with HCV now have time to develop the long-term complications associated with HCV infection, and liver disease from CHC is the leading non-AIDS cause of death among co-infected individuals in the US.[93, 95] In addition, co-infection has been shown to speed disease progression for both infections.[93, 94, 96]

Results are mixed on whether co-infection with HIV affects CHC treatment uptake. Seven studies found no relationship. [48, 56, 63, 77, 80, 81, 83] Of the four studies that reported an association, three found that HIV/HCV co-infected individuals were less likely to be treated for CHC compared to mono-infected individuals (Butt *et al.*, AOR=0.33, p<0.001; Grebely *et al.,* AOR=0.22, 95% CI: 0.05-0.96; Niederau *et al.* p<0.05),[39, 59, 77] and one study found lower willingness to be treated among those with HIV/HCV co-infection (Grebely *et al.,* p=0.008).[77] One study reported that co-infected individuals were more likely to be treated (Iversen *et al.,* OR=0.23, 95% CI: 1.17-4.25).[78]

Among co-infected individuals, those with well-controlled HIV (defined by viral suppression, being on antiretroviral medications, or having higher baseline CD4 counts) were more likely to be treated for CHC[82, 87, 92] or to receive a treatment recommendation from a doctor.[58] However, one study reported no relationship between severity of HIV and likelihood of CHC treatment.[66]

Similar trends exist for HBV co-infection, with most studies reporting no relationship with treatment probability,[63] with the exception of one that found an association between HBV and non-treatment for CHC (Butt *et al.,* AOR=0.72, p=0.02).[47]

Serological markers

Numerous studies tested the relationships between serological markers and CHC treatment, and in general, abnormal values were associated with lower likelihood of treatment uptake.

Two studies looked at creatinine levels; one found no association with CH treatment uptake,[66] and the other found that people with higher levels have lower odds of being treated compared to those with normal creatinine levels.[60]

Four studies investigated hemoglobin levels. One found no association between hemoglobin and treatment recommendation by a doctor,[58] and two found that either normal or high hemoglobin levels are predictive of HCV treatment.[60, 66]

Of two studies reporting on platelet count, one found no association with treatment,[66] and the other found that low platelet counts were predictive of non-treatment.[39] Another study reported no association between referral attendance and either albumin or bilirubin levels.[83]

Miscellaneous

Results regarding anemia vary; it has been cited generally as a contraindication to treatment,[85] but also as a predictor of treatment in a sample of US academic

medical centers (Butt *et al.* AOR=2.16)[59] and a predictor of non-treatment in a US veteran population (Butt *et al.*, AOR=0.18).[47]

Coronary heart disease, congestive heart failure, and ischaemic heart disease have been cited consistently as factors related to non-treament for CHC. [47, 63, 84, 85] The one study reviewed that investigated pulmonary disease as a possible predictor in a US VA population found that it was associated with non-treatment as well.[84]

Two studies reviewed considered stroke as a possible predictor; one found no association with CHC treatment, and the other found that it predicted non-treatment.[47, 63] Of three that tested diabetes, two found no association,[56, 63] and the third cited diabetes as a predictor of non-treatment.[47]

Mental health/Psychiatric comorbidities

Summary:

- Past and current psychiatric disease sometimes associated with non-treatment, but results are mixed
- Diagnosis with bipolar disorder, schizophrenia, PTSD or personality disorder predictive of non-treatment in some studies
- 60% of CHC patients report depressive symptomology; depression is a contraindication to interferon-based treatment regimens and can amplify other perceived barriers to medical care in general and to CHC treatment in particular

Interferon-free impact: Mixed

+ Elimination of interferon expands eligibility to people with depression and removes risk of treatment-induced depression
- Individuals with psychiatric illness face other barriers to treatment related to social support, financial barriers, and continuity of care that are not addressed by new drug regimens

The studies reviewed offer mixed results on the association between psychiatric disease and CHC treatment. While one study found no association with unspecified psychiatric comorbidity,[80] two studies report that it is predictive of non-treatment (Morrill *et al.,* p=0.02)[46] or lack of treatment recommendation from a doctor (Bini *et al.*, AOR=9.05).[43]

Results are similarly mixed when considering current or past psychiatric disease specifically. One study reports no association between current psychiatric disease and CHC treatment,[57] and two report no association with past psychiatric disease.[56, 57] One study found that admission to a psychiatric ward within 6 months of evaluation for CHC treatment predicted non-treatment (Torsen *et al.,*

OR=0.44, 95% CI: 0.21-0.93),[68] and one found that past psychiatric disorder predicted treatment (Moirand *et al.,* OR=2.37).[73]

Several studies have reported that diagnosis with bipolar disorder, schizophrenia, PTSD, or a personality disorder was associated with lower odds of treatment compared to those without these diagnoses.[47, 73, 84]

Most studies considering depression as a possible factor influencing treatment uptake for CHC report that major or mild depression is associated with non-treatment.[47, 60, 77, 84] However, one study reports higher odds for treatment among those with current depression compared to those without a depression diagnosis (OR=3.86),[73] and two studies found no association.[63, 87] One study found that among those with a depression diagnosis, odds of a physician recommending treatment were greater when individuals were on medication for depression ($p<0.05$),[58] though in another study access to depression medication did not affect the likelihood of treatment.[48] In a study of treatment specifically among depressed individuals, Evon *et al.* note that 25% of HCV patients meet DSM V criteria for major depression, and 60% report depressive symptomology. Depression can reduce individuals' motivation to seek medical services in general, as well as their optimism about possible outcomes. In this sample, depression served to amplify patients' perceptions about barriers to CHC treatment, with higher depression scores accounting for 7-18% of the variance in these perceived barriers. Their study also reports that subjects with lower depression scores were more likely to be treated for CHC than those with higher scores ($p<0.01$).[90]

PART 2:
Is race as a barrier to CHC treatment?
A Comparison of NHANES and the Grady Liver Clinic

Racial and socioeconomic barriers to CHC treatment

In coming years, the availability of interferon-free drug regimens will help overcome many of the barriers to CHC treatment reviewed above. Their improved SVR rates, even for genotype 1-infected individuals who have historically had the lowest response rates, will increase the number of people who can be cured. Their improved side effect profiles compared to interferon-based regimens will increase both eligibility for and tolerance of treatment, and their shorter duration will improve adherence and simplify treatment administration for providers. However, novel interferon-free drug treatments have not addressed barriers to treatment that are related to socioeconomic status and access to care. In fact, the increased costs of these drugs compared to the previous standard of care may exacerbate these issues.

Many socioeconomic factors impacting CHC treatment uptake are intertwined with race, particularly with black race in the United States. Compared to people of white race, those of black race on average have lower incomes, less education, and are less likely to have health insurance or utilize medical services. More black individuals are unemployed, use drugs, live in unstable housing arrangements, or are incarcerated.[61,97-99] Because each of these factors is individually associated with lower likelihood of treatment for CHC, they combine to make access to CHC care especially difficult for people of black race.

In the studies reviewed above, black race consistently reduces the likelihood of CHC care in the US, with odds of treatment ranging from 0.44 to 0.64 compared to whites.[43,47,43, 60, 84, 87] Combined with higher genotype 1 prevalence and faster progression to late stage liver disease, difficulty accessing treatment has contributed to higher HCV-related mortality rates among blacks (6.5-7.8 per 1,000 compared to 2.7-3.8 per 1,000 among whites).[100]

Though less thoroughly documented, Hispanic ethnicity is associated with many of the same socioeconomic barriers to CHC care, also resulting in lower likelihood of treatment, with odds ranging from 0.56 to 0.88 times the likelihood of treatment seen among whites.[47, 84]

Race, ethnicity and CHC treatment in NHANES

In a 2013 study, Younossi *et al.* analyzed data from HCV-infected subjects participating in the CDC National Health and Nutrition Examination Survey (NHANES), the primary surveillance system for HCV in the US. In this study, the

authors found no association between race/ethnicity and treatment for CHC.[63] Considering the body of evidence identifying race and ethnicity as barriers to treatment in numerous US samples, the lack of association in this dataset is surprising and could stem from systematic differences between the NHANES sample and the overall HCV-infected population in the US.

Although the NHANES sample overall is weighted to accurately represent the US civilian non-institutionalized population,[101] CDC recommends against using sample weights when analyzing NHANES HCV-related data because the small sample size (only 203 respondents in 10 years) and potential response bias impede their generalizability to the larger US population that the weights were designed to represent. In addition, recent research has highlighted NHANES' exclusion of certain groups with extremely high HCV prevalence, calling into question whether the NHANES HCV sample is an accurate representation of the overall HCV-infected population in the US.[102] Among those excluded are US prison populations (where seroprevalence has been estimated at 17.4% and represents 29-33% of the national disease burden) as well as homeless populations (where prevalence estimates range from 19-69%).[10,54,102] Chak *et al.* estimate that including these groups would nearly double the 1.6% national HCV prevalence figure measured in NHANES.[102]

In subgroups excluded from NHANES, HCV prevalence is not the only factor that differs systematically from the general US population. In fact, some of the same factors that have proven important in predicting treatment uptake and response – race/ethnicity, socioeconomic status, and access to healthcare – also deviate from national averages in prison and homeless populations specifically. For example, black and Hispanic individuals are more likely than whites to be infected with HCV,[61,103,104] cirrhosis develops more quickly among men and heavy alcohol users,[105] and blacks are less likely than other racial groups to respond to treatment.[61] Men, black and Hispanic individuals, and heavy alcohol users are overrepresented in homeless and incarcerated populations,[106,107] making these groups not only more likely to be HCV-positive, but also less able to access and complete treatment successfully compared to the population represented by NHANES data. Thus, although the NHANES sample is designed to reflect the racial distribution of the overall US population, it does not include representation from the subset of non-white individuals experiencing some of the highest barriers to CHC care and treatment. As a result, treatment barriers identified from this sample may not reflect the experience of the overall HCV-positive population in the US.

Race/ethnicity as a treatment barrier in clinical models

Numerous clinical models have been developed to increase access to CHC treatment for underserved populations, including the groups mentioned above. One example is the Grady Liver Clinic, housed within the Grady Memorial Hospital, an urban safety-net teaching hospital in Atlanta. The Grady Liver Clinic

treats HCV-positive individuals referred from Grady's Primary Care Center, satellite clinics, Georgia's state correctional health system, and a state psychiatric hospital and serves a population that is predominantly black (76%) and uninsured (59%).[108]

The analysis that follows replicates Younossi's findings from NHANES, where there was no race-CHC treatment association, and compares them to a dataset from the Grady Liver Clinic. The primary research question is whether the same lack of association between race and CHC treatment is also valid in the Grady Liver Clinic, a program specifically designed to reach underserved individuals of low socioeconomic status, most of whom are non-white and many of whom would not be eligible for inclusion in an NHANES sample. The answer to this question will contribute to the discussion of how clinical models can be designed to increase CHC treatment among racial and ethnic groups traditionally unable to access care.

Methods

Data Sources

This analysis models predictors of CHC treatment uptake in samples of mono-infected HCV-positive individuals derived from two sources, NHANES between 2001 and 2010, and Grady Memorial Hospital's Liver Clinic in Atlanta, Georgia between 2002 and 2007.

NHANES

Subjects participating in NHANES undergo an in-person interview, medical examination, laboratory tests, and follow-up interviews to assess overall health as well as presence of specific medical conditions. Beginning in 2001, NHANES staff have followed up with subjects who test positive for anti-HCV antibodies to administer a phone-based follow-up questionnaire asking additional questions pertinent to HCV including prior awareness of infection, follow-up with a physician after diagnosis, treatment status, and knowledge about transmission risks and the health consequences of infection. This analysis uses all NHANES data available since CDC incorporated the HCV follow-up questionnaire (2001-2010).

CDC releases NHANES data in 2-year increments. To combine data from 2001-2010, demographic files, medical examination results, laboratory results, behavioral and medical questionnaire results, and HCV follow-up questionnaire results for each 2-year data release were downloaded form the NHANES website. For each of the five data releases, these files were merged, and the resulting five merged files were appended to create one dataset including demographics, medical examination results, laboratory results, behavioral and

medical questionnaire results, and HCV follow-up data for all NHANES respondents from 2001-2010.

Grady Liver Clinic

The Grady Liver Clinic is housed within Grady Memorial Hospital's Primary Care Center and is staffed by general internists who have received training from a hepatologist and psychiatrist in treating CHC. The clinic began in 2002 and has been operated solely by general internists since 2003. Patients attending the Liver Clinic for CHC care are referred from Grady's Primary Care Center, satellite clinics, gastrointestinal, surgical, and obstetric/gynecologic clinics, and its inpatient service, as well as Georgia's correctional health system and a state forensic psychiatric hospital. Patients who are HIV-positive are referred to a separate facility for treatment of both HIV and CHC.

Grady Liver Clinic physicians performed a retrospective chart review of all individuals who attended at least one visit between 2002 and 2007 and compiled these data into the Grady Legacy database.[108] The Legacy database was provided for this analysis in de-identified form by the Liver Clinic's Director.

This study was approved by the Emory University Institutional Review Board and was deemed secondary data analysis, exempt from review. The IRB determination letter is available in the Appendix.

Variable definitions

Some variables were unavailable in either the NHANES and Grady Legacy databases, and some variables available in both datasets were defined differently. Table 1 lists all variables included from each data source and describes how they were operationalized for analysis.

Statistical analysis

All statistical analyses were conducted using SAS 9.3 (SAS Institute, Inc., Cary, North Carolina, USA). For each of the two datasets, univariate comparisons were made between treated and untreated subjects based on demographic, socioeconomic, HCV-specific, health-related, and drug-related variables. Chi-square tests were used for categorical variables, or Fisher's exact tests for those with cell sizes ≤5. The Wilcoxon two-sample test was used for continuous variables.

Logistic regression analysis was used to evaluate the impact of race/ethnicity on treatment uptake, with race defined categorically (white/black/Hispanic) and dichotomously (white vs. non-white, black vs. non-black, and Hispanic vs. non-

Hispanic) in different models. Variables with univariate comparisons between treated and untreated subjects that returned p-values ≤0.2 were included in initial logistic regression models as potential confounders of a race/ethnicity-treatment relationship. All two-way interaction terms between race and potential confounders were included in initial models. Variables missing more than 10% of observations were excluded. These included genotype, depression, injection drug use, and alcohol use for both samples and age for the Grady sample only.

Models were reduced using backward elimination, with the prevalence odds ratio as the measure of effect. Interaction terms were removed from models when they were not significant at $p<0.05$, and confounders were removed when they did not impact the main effect odds ratio by more than 10% in either direction. Final models were assessed for fit using the Hosmer-Lemeshow test, with a p-value >0.05 indicating model fit. Variables in final models were also assessed for collinearity. Because treatment for CHC is not a "rare" event, the odds ratio may overstate associations in logistic regression models. Therefore, prevalence ratios were generated for all final models for comparison. All p-values are two-sided.

Results

The full NHANES sample from 2001-2010 included 52,195 respondents who participated in both the NHANES in-person interview and the medical examination that included the HCV laboratory test. The subset that tested positive for HCV included 500 subjects, 203 of whom completed the HCV follow-up questionnaire. Of those 203 subjects, 3 were excluded due to a positive HIV test. (HIV-positive subjects were excluded for comparability to the Grady Legacy database, which includes only HIV-negative subjects.) The final NHANES sample used for analysis contained 200 subjects. The Grady Legacy database included 810 subjects, all of whom were included in analyses.

Descriptive statistics

Results of descriptive analyses for both the NHANES and Grady samples are displayed in Table 2. Compared to the Grady sample, the NHANES sample included a greater proportion of males, whites, Hispanics, those with private insurance, chronic pain, heart disease, lung disease, history of injection drug use, and current alcohol use. The Grady sample included a greater proportion of blacks, individuals with no insurance or public insurance, as well as those with genotype 1 infection, cirrhosis (determined by an APRI score >1.5), current depression, diabetes, and hypertension. Grady subjects had a higher mean APRI score (composite score indicating level of liver fibrosis), weight, and number of comorbidities compared to NHANES subjects. Samples were comparable in terms of mean age and proportion of subjects who had undergone a liver biopsy.

Univariate analyses

Treatment uptake

Univariate comparisons between subjects in each sample who were treated for CHC and those who were not treated are displayed in Tables 3a and 3b. In the NHANES sample, a total of 34 subjects (17%) reported being treated, and the remaining 166 reported no treatment. In the Grady Liver Clinic sample, 138 subjects (17%) initiated treatment, and 656 were not treated.

Race

In univariate analyses of NHANES data, there were no significant associations between race/ethnicity and treatment status. However, black and Hispanic individuals who were treated were more likely to be insured ($p=0.1072$), to have completed high school ($p=0.1618$), and to have prior knowledge of their HCV-positive status ($p=0.0219$) compared to those of the same race/ethnicity who were not treated.

In univariate analyses of Grady data, there was an overall association between race and treatment, significant at the $p<0.1$ level. When broken down by individual race, black race was associated with non-treatment ($p=0.013$ and $p=0.0377$, respectively). However, this association did not persist in adjusted models controlling for other variables.

Other associations

In the NHANES sample at the $p<0.05$ level, treated subjects were more likely than those untreated to have prior awareness of their HCV infection and to have had a liver biopsy. Treated subjects also had higher mean weight and were more likely to be obese. Untreated subjects were more likely than treated subjects to currently drink alcohol. At the $p<0.1$ level, treated subjects were more likely to have hypertension. Untreated subjects were more likely to have no form of health insurance and to have heart disease.

In the Grady sample at the $p<0.05$ level, subjects who were treated were more likely than those untreated to be under age 60, to have undergone a liver biopsy, to have later stages of fibrosis (F2 or F3), and to have cirrhosis (determined by both chart review and APRI score). Mean APRI score was also higher among those who were treated. Untreated subjects were more likely to currently use drugs or alcohol. At the $p<0.1$ level, subjects who were treated were more likely than those untreated to have no form of health insurance coverage and to have a current depression diagnosis. Untreated subjects were more likely to have public insurance and to have genotype 1 infection.

Multivariate logistic regression (race/ethnicity-treatment associations)

In the NHANES sample, race/ethnicity was not significantly associated with treatment in any model (Tables 4a and 4b). These results confirm the findings from Younossi *et al.*

In the Grady sample, Hispanic subjects were more likely than whites to be treated, controlling for presence of cirrhosis (AOR=3.506, p=0.0442). When Hispanic subjects were compared to all non-Hispanic subjects, ethnicity was not significantly associated with likelihood of treatment.

There was a significant interaction between black race and hypertension, with black hypertensive subjects less likely to be treated compared to whites (adjusted OR=0.321, p=0.0088). This interaction also held in a comparison of black subjects to all non-black subjects (adjusted OR=0.318, p=0.021). A race-hypertension interaction was also present among whites but in the opposite direction; white subjects with hypertension were more likely to be treated than non-whites (adjusted OR=3.356, p=0.0033). These interactions remained significant when controlling for gender, drug and alcohol use, medical comorbidities, insurance status, and presence of cirrhosis.

All Hosmer-Lemeshow p-values were >0.05, indicating good model fit. There was no evidence of collinearity in any of the models. When prevalence ratios were calculated for all final models, associations between race/ethnicity and treatment remained valid, though the odds ratios did somewhat overstate the strength of these associations.

Discussion

General findings

Descriptive results confirmed expectations that HCV-infected subjects from NHANES would be predominantly white and of higher socioeconomic status compared to Grady subjects, who were predominantly black. Grady subjects also had a higher mean number of medical comorbidities and greater prevalence of cirrhosis than NHANES subjects. These differences in overall health and CHC disease progression could be due to sample composition (clinical vs. household), or to lack of access to regular medical care among a majority of Grady subjects (59% without health insurance compared to 27% in NHANES).

A higher proportion of Grady subjects had genotype 1 infection, possibly because of the high proportion of black subjects, among whom genotype 1 HCV is more prevalent. In both samples, genotype 1 was more common among untreated subjects than treated subjects. Interferon-free regimens with SVR rates exceeding 90% for genotype 1 individuals can be expected to reduce this disparity in treatment uptake.[57, 60, 68]

The equivalence of treatment uptake between NHANES and Grady (17% in both samples) is noteworthy, given that Grady serves a population in which the majority of patients are uninsured, infected with genotype 1 HCV, and members of racial and socioeconomic groups known to be difficult to engage and retain in care.

It is also notable that uninsured subjects comprise 65% of those who were treated for CHC at Grady, compared to only 15% in the NHANES sample. This difference could be explained by Grady's policy to treat regardless of financial means, or by the possibility that those with insurance chose to seek treatment from a different provider after their initial visit to the Liver Clinic. Regardless of the reason however, these data indicate that the Grady Liver Clinic has established itself as a route to CHC care for those without insurance.

Despite literature consistently demonstrating lower likelihood of CHC treatment uptake among individuals with a current depression diagnosis, depression was reported in a higher proportion of treated subjects at Grady compared to untreated subjects. (Depression diagnosis was made prior to treatment initiation, eliminating the possibility that it was treatment-induced.) In the first year of the Liver Clinic's operation, a co-located psychiatrist provided training to assist internists in treating CHC patients with comorbid psychiatric illnesses. In subsequent years, the Liver Clinic has worked closely with Grady's psychiatry department to determine interferon eligibility for depressed individuals and to support their progress through CHC treatment. These practices have allowed Liver Clinic physicians to manage psychiatric comorbidities that would traditionally have excluded many individuals from interferon-based treatment. Similar models of integrated HCV and psychiatric care have been successful in other settings as well.[90,109]

Associations between race and treatment

Logistic regression models using NHANES data confirmed the findings of Younossi *et al.* that there is no association in the NHANES sample between race and CHC treatment, regardless of how race is categorized.

Among Grady subjects, associations between race and treatment uptake were mixed. First, Hispanic subjects were more likely to be treated compared to whites. This association is the opposite of those found in other studies, indicating greater access to treatment for Hispanic individuals at the Grady Liver Clinic than has been reported elsewhere.

Although black race was associated with non-treatment at Grady in univariate analyses, adjusted models revealed a more complicated relationship modified by the presence of hypertension. At Grady, black individuals with hypertension were less likely to be treated compared to whites, while those without hypertension

had equal likelihood of treatment. The opposite relationship was true among white individuals, among whom those with hypertension were more likely to be treated compared to non-whites and those without hypertension were equally likely to be treated as non-whites.

During the 2002-2007 time period when these data were collected, the Grady Liver Clinic identified uncontrolled hypertension as a contraindication to CHC treatment. Combined with the greater proportion of black patients with hypertension compared to whites (57% vs. 24%, respectively), this treatment protocol could explain why the presence of hypertension would reduce the likelihood of CHC treatment among black patients. However, it does not account for the opposite effect among white patients, indicating that there may be explanations for this interaction that cannot be ascertained from available data. One possibility is that hypertension among white patients was less severe or better controlled compared to black patients, preventing their hypertension diagnosis from acting as a contraindication to CHC treatment. This hypothesis is supported by literature finding that uncontrolled hypertension is more common among black individuals than among whites, for reasons including discrimination-related stress leading to poor medication adherence.[110,111] However, data were not collected in the Liver Clinic sample to measure the severity of hypertension or whether patients took medication to control it. Further study is needed to determine the reasons that black individuals with hypertension and white individuals without hypertension were less likely to be treated at Grady, and to target points in care where these disparities can be addressed.

Study limitations

Cross-sectional study design

Due to this study's cross-sectional nature, exposure and outcome variables were measured at the same point in time, and direct causality cannot be inferred.

Population differences

As discussed above and demonstrated in descriptive analyses (Table 2), the NHANES and Grady samples have different demographic characteristics and selection biases. In the NHANES sample, selection bias may arise if there are differences between the 203 HCV-positive participants who responded to the HCV follow-up survey and the 297 who did not. Although published research suggests that Grady's demographics and inclusion of incarcerated and homeless persons would result in a more representative sample of the US HCV-infected population compared to NHANES,[102] generalization should be undertaken cautiously.

Because the Grady dataset comes from a clinical population while the NHANES dataset reflects a household survey, the overall health of subjects and their engagement in medical services may differ for reasons unrelated to HCV, potentially affecting their likelihood of being treated. To be included in the Grady sample, individuals had to attend at least one medical visit at the Liver Clinic; the NHANES sample includes individuals who followed up with a doctor after their HCV diagnosis as well as those who did not. An NHANES sample that only includes subjects who followed up with a physician after HCV diagnosis would be more comparable to the Grady Legacy sample. However, the small sample size would preclude sub-analyses. The Grady Liver Clinic is currently compiling a second database that tracks individuals starting at the time of HCV diagnosis rather than at their Liver Clinic visit. Follow-up studies using this database could be more comparable to the NHANES sample.

Variable definitions

Treatment and co-morbidity data were determined by physicians' review of medical charts in the Grady sample, while NHANES data were self-reported by the subjects. This difference could result in varying levels of bias and data validity. In addition, some variables were defined differently in each sample according to the data available (Table 1).

Data limitations

The NHANES sample size is very small, and missing data are common due to skip patterns in the HCV follow-up questionnaire. Due to small cell sizes, some variables were dropped from NHANES models but were retained in Grady models where data were more consistently available. Similarly, some variables available in NHANES were incomplete or unavailable in the Grady database, resulting in variation in the composition of initial models.

Data were not available to explore all barriers to HCV treatment identified in the literature review. Specifically, provider- and system-level barriers such as physicians' reluctance to treat IDUs, level of integration of healthcare services, and population-specific individual-level barriers like IDU-related stigma were not addressed. The role of HIV co-infection as a potential barrier to HCV treatment uptake was not addressed due to lack of data from co-infected individuals.

Conclusions

The comparability of treatment prevalence in the Grady Liver Clinic to that reported in NHANES, despite the differences in their racial and socioeconomic composition, illustrates the value of the Grady model. Grady's ability to treat uninsured individuals and those with depression further highlights its strengths

and capacity to reach those who have historically been ineligible for or unable to access CHC care.

Because Grady's population includes a high proportion of uninsured minority individuals, any relationship between race and treatment could be expected to favor non-minority groups. However, the results from this analysis indicate that when race/ethnicity does affect treatment uptake at Grady, the association is either mediated by a third variable (hypertension) or reflects improved chances of treatment for minority groups (*e.g.* Hispanics). These findings indicate that Grady is a successful model for engaging and retaining members of underserved racial minorities in CHC care.

In recent years, a variety of clinical models have been developed to increase access to CHC treatment for underserved populations. For example, Project ECHO, which began in New Mexico and has been replicated in several other areas in the US, has pioneered a case-based learning platform through which primary care physicians in rural areas can regularly access specialists via video conferencing to enhance their own capacity to treat individuals with HCV infection.[112] In another model, New York State's Hepatitis C Continuity Program links HCV-infected incarcerated individuals with care upon release and maintains relationships with local providers to accept their referrals.[113]

The Grady Liver Clinic's success in engaging and treating difficult to reach individuals is an early indication of the impact that similar programs could have to reduce CHC-related morbidity and mortality in the US. Combined with enhanced screening strategies and increased access to interferon-free drug regimens that will simplify treatment, innovative models like Grady's targeting high-risk, high-prevalence populations can make significant contributions toward HCV eradication.

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Table 1. Variable definitions, NHANES and Grady Liver Clinic datasets		
	NHANES	**Grady**
Demographics		
Age	Age at time of NHANES survey	The oldest of age at first visit, age at liver biopsy, age at treatment
Comorbidities		
Chronic pain	Yes to: "Have you ever had a problem with pain that lasted > 24 hours?" AND "Lasted for 3 months or more"	Chart abstraction
Depression	Positive diagnosis after completing Composite International Scientific Interview, depression component OR score ≥ 10 on Patient Health Questionnaire (PHQ-9)	Chart abstraction
Diabetes	Yes to: "Have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?"	Chart abstraction
Heart disease	Yes to: "Have you ever been told by a doctor or health professional that you have had coronary artery disease/congestive heart failure/angina/a stroke/a heart attack?"	Chart abstraction, includes coronary artery disease, congestive heart failure, atrial fibrillation, and valvular heart disease
Hypertension	Yes to: "Have you ever been told by a doctor or health professional that you have high blood pressure?"	Chart abstraction
Lung disease	Yes to: "Have you ever been told by a doctor or health professional that you have asthma/emphysema/ chronic bronchitis?"	Chart abstraction, includes asthma, sarcoidosis, and pulmonary hypertension
Mean number comorbidities	Sum of comorbidities above (excluding depression)	Sum of comorbidities above (excluding depression)

Drugs/alcohol		
History of IDU	Yes to "Have you ever used a needle to take street drugs?" OR yes to "Have you ever used a needle to inject a drug not prescribed by a doctor?"	Chart abstraction
Current IDU	Injected within the last year	Chart abstraction, as of first clinic visit
Currently use drugs (unspecified type)	NA	Chart abstraction, as of first clinic visit
Currently drink alcohol	Drank alcohol within the last year	Chart abstraction, as of first clinic visit

Table 2. Demographics of HCV mono-infected subjects from NHANES (2001-2010) and the Grady Liver Clinic (2002-2007)

	NHANES	Grady
n	**200**	**810**
Demographics		
Age (years)	50 ± 0.89	50.4 ± 0.33
18-59	160 (80.0)	547 (88.9)
60+	40 (20.0)	68 (11.1)
Gender		
Male	128 (64.0)	425 (52.5)
Race		
White	95 (47.5)	169 (20.9)
Black	56 (28.0)	617 (76.4)
Hispanic	42 (21.0)	17 (2.1)
Other	7 (3.5)	5 (0.6)
Education		
Completed high school	134 (68.7)	Unavailable
Income:Poverty ratio	1.96 ± 0.11	Unavailable
Health Insurance		
Private insurance	77 (39.7)	20 (2.5)
Public insurance	64 (33.0)	312 (39)
No insurance	53 (27.0)	468 (58.5)
HCV-specific characteristics		
Prior awareness of infection	98 (45.0)	Unavailable
Had liver biopsy	44 (43.6)	348 (43.0)
Genotype 1	33 (64.7)	519 (89.6)
Fibrosis stages (from biopsy)		
F0	Unavailable	55 (15.3)
F1	Unavailable	112 (31.2)
F2	Unavailable	91 (25.3)
F3	Unavailable	53 (14.8)
F4	Unavailable	48 (13.4)
Cirrhosis (determined by chart review)	Unavailable	102 (12.9)
Cirrhosis (determined by APRI > 1.5)	18 (9.23)	166 (47.7)
Mean APRI score	0.69 ± 0.07	1.27 ± 0.04
Comorbidities		
Chronic pain	27 (28.1)	137 (17.0)
Depression	18 (18.4)	176 (28)
Diabetes	26 (13.0)	157 (19.4)
Heart disease	33 (16.5)	81 (10.0)
Hypertension	77 (39.09)	402 (49.8)
Lung disease	46 (23.0)	96 (11.9)
Mean weight (kg)	79.0 ± 1.3	83.9 ± 0.68
Obese (BMI > 30)	45 (22.5)	Unavailable

Mean number comorbidities	1.05 ± 0.07	1.1 ± 0.03
Drugs/alcohol		
History of IDU	79 (57.3)	422 (52.6)
Current IDU	9 (6.6)	Unavailable
Currently use drugs (unspecified type)	Unavailable	32 (4)
Currently drink alcohol	106 (59.9)	160 (20)
Currently drink > 5 alcoholic drinks per day	95 (53.7)	Unavailable

Table 3a. Comparison of those treated vs. not treated for CHC, NHANES (2001-2010)					
	NHANES (n=200)				
	Untreated		Treated		*p*
n (%)	**166 (83)**		**34 (17)**		
	with characteristic	with response	with characteristic	with response	
Demographics					
Age (years)					
18-59	132 (79.5)	166	28 (82.4)	34	0.7066
60+	34 (20.5)		6 (17.6)		
Gender					
Male	108 (65.1)	166	20 (58.8)	34	0.4901
Race					0.8993
White	77 (46.4)	166	18 (52.9)	34	0.4856
Black	48 (28.9)		8 (23.5)		0.524
Hispanic	35 (21.1)		7 (20.6)		0.9484
Other	6 (3.6)		1 (2.9)		1
Socioeconomic characteristics					
Education					
Completed high school/GED	107 (66.5)	161	27 (79.4)	34	0.1388
Income:Poverty ratio	1.9	156	2.3	34	0.1358
Health Insurance					0.1677
Private insurance	60 (37.5)	160	17 (50.0)	34	0.1761
Public insurance	52 (32.5)		12 (35.3)		0.753
No insurance	48 (30.0)		5 (14.7)		0.0895
HCV-specific characteristics					
Prior awareness of infection	70 (43.5)	161	28 (84.9)	33	<0.0001
Had liver biopsy	16 (22.9)	70	28 (82.4)	34	<0.0001
Genotype 1	15 (35.7)	42	3 (33.3)	9	1
Fibrosis stages (from biopsy)					
F0	Unavailable				
F1	Unavailable				
F2	Unavailable				
F3	Unavailable				
F4	Unavailable				
Cirrhosis (determined by chart review)	Unavailable				
Cirrhosis (determined by APRI > 1.5)	14 (8.6)	162	4 (12.1)	33	0.5145

Mean APRI score	0.64	162	0.93	33	0.3515
Comorbidities					
Chronic pain	24 (27.3)	88	3 (37.5)	8	0.6827
Depression	16 (21.9)	73	2 (8.0)	25	0.1459
Diabetes	20 (12.1)	166	6 (17.7)	34	0.3765
Heart disease	31 (18.7)	166	2 (5.9)	34	0.0777
Hypertension	59 (36.2)	163	18 (52.9)	34	0.0687
Lung disease	37 (22.3)	166	9 (26.5)	34	0.5976
Mean weight (kg)	77.6	158	85.7	34	0.0452
Obese (BMI > 30)	33 (21.2)	156	12 (35.3)	34	0.0499
Mean number comorbidities	1.03	166	1.12	34	0.3884
Drugs/alcohol					
History of IDU	63 (57.3)	110	16 (57.1)	28	0.9901
Current IDU	8 (7.3)	109	1 (3.6)	28	0.6836
Currently use drugs (unspecified type)	Unavailable				
Currently drink alcohol	92 (63.3)	150	14 (42.4)	33	0.0396
Currently drink > 5 alcoholic drinks per day	75 (51.7)	145	20 (62.5)	32	0.2685

Table 3b. Comparison of those treated vs. not treated for CHC, the Grady Liver Clinic (2002-2007)					
	Grady (n=810)				
	Untreated		Treated		*p*
n (%)	**672 (83)**		**138 (17)**		
	with characteristic	with response	with characteristic	with response	
Demographics					
Age (years)					
18-59	417 (87.2)	478	131 (94.9)	138	0.0111
60+	61 (12.8)		7 (5.1)		
Gender					
Male	352 (52.5)	671	73 (52.9)	138	0.925
Race					0.0679
White	133 (19.9)	670	36 (26.1)	138	0.101
Black	523 (78.1)		94 (68.1)		0.0123
Hispanic	12 (1.8)		5 (3.6)		0.1887
Other	2 (0.3)		3 (2.2)		0.0374
Socioeconomic characteristics					
Education					
Completed high school/GED	Unavailable				
Income:Poverty ratio	Unavailable				
Health Insurance					
Private insurance	17 (2.6)	664	3 (2.2)	136	1
Public insurance	268 (40.4)		44 (32.4)		0.0811
No insurance	379 (57.1)		89 (65.4)		0.0713
HCV-specific characteristics					
Prior awareness of infection	Unavailable				
Had liver biopsy	236 (35.2)	671	112 (81.2)	138	<0.0001
Genotype 1	404 (91.0)	444	115 (85.2)	135	0.0526
Fibrosis stages (from biopsy)					<0.0001
F0	48 (19.7)	244	7 (6.1)	115	0.0009
F1	87 (35.7)		25 (21.7)		0.0079
F2	50 (20.5)		41 (35.7)		0.0021
F3	29 (11.9)		24 (20.9)		0.0251
F4	30 (12.3)		18 (15.7)		0.3832
Cirrhosis (determined by chart review)	76 (11.6)	653	26 (19.1)	136	0.018
Cirrhosis (determined by APRI > 1.5)	91 (38.6)	236	75 (67.0)	112	<0.0001

Mean APRI score	1.13	236	1.56	112	<0.0001
Comorbidities					
Chronic pain	108 (16.1)	671	29 (21.2)	137	0.1493
Depression	136 (26.6)	512	40 (34.2)	117	0.0974
Diabetes	127 (19.0)	672	30 (21.9)	137	0.4185
Heart disease	72 (10.8)	670	9 (6.6)	137	0.1382
Hypertension	334 (49.8)	671	68 (49.6)	137	0.9759
Lung disease	82 (12.2)	672	14 (10.2)	137	0.5129
Mean weight (kg)	83.6	647	85.1	137	0.331
Obese (BMI > 30)	Unavailable				
Mean number comorbidities	1.08	672	1.11	137	0.6365
Drugs/alcohol					
History of IDU	348 (52.1)	668	74 (54.8)	135	0.5639
Current IDU	Unavailable				
Currently use drugs (unspecified type)	31 (4.7)	659	1 (0.8)	134	0.0295
Currently drink alcohol	153 (23.0)	664	7 (5.2)	134	<0.0001
Currently drink > 5 alcoholic drinks per day	Unavailable				

Table 4a. Race as predictor of CHC treatment, results of logistic regression models, NHANES (2001-2010)

	NHANES				
	OR	**95% CI**	**p**	**GOF p**	**Control Variables**
Race (Non-Hispanic white=reference)					Prior knowledge of HCV infection
Hispanic	0.843	0.304-2.336	0.7431	0.6021	
Non-Hispanic black (unstratified)	0.842	0.321-2.208	0.7261		
Non-Hispanic white vs. all others					Prior knowledge of HCV infection, hypertension, heart disease
Non-Hispanic white (unstratified)	1.343	0.591-3.054	0.4811	0.8028	
Non-Hispanic black vs. all others					Prior knowledge of HCV infection, hypertension
Non-Hispanic black (unstratified)	0.812	0.319-2.065	0.6624	0.9692	
Hispanic vs. all others					
Hispanic	0.971	0.39-2.414	0.9487	NA	None

GOF = Hosmer-Lemeshow p-value testing for model fit

Table 4b. Race as predictor of CHC treatment, results of logistic regression models, the Grady Liver Clinic (2002-2007)					
	Grady				
	OR	95% CI	p	GOF p	Control Variables
Race (Non-Hispanic white=reference)					
Hispanic	3.506	0.033-11.897	**0.0442**	0.9882	
Non-Hispanic black with hypertension	0.321	0.157-0.657	**0.0088**		cirrhosis
Non-Hispanic black without hypertension	1.097	0.609-1.974			
Non-Hispanic white vs. all others					
Non-Hispanic white with hypertension	3.356	1.667-6.757	**0.0033**	1	
Non-Hispanic white without hypertension	0.87	0.493-1.536			
Non-Hispanic black vs. all others					
Non-Hispanic black with hypertension	0.318	0.165-0.614	**0.021**	1	None
Non-Hispanic black without hypertension	0.864	0.506-1.479			
Hispanic vs. all others					
Hispanic	2.061	0.714-5.949	0.1809	NA	None
GOF = Hosmer-Lemeshow p-value testing for model fit					

EMORY UNIVERSITY
Institutional Review Board

1/23/2014

Liesl Hagan
Department of Global Health
Rollins School of Public Health
Emory University

RE: Determination: No IRB Review Required
eIRB#: IRB00070090
Title: *Predictors of Treatment Uptake for Chronic Hepatitis C: NHANES and Grady Memorial Hospital, 2001-2010*
PI: Liesl Hagan

Dear Ms. Hagan:

Thank you for requesting a determination from our office about the above-referenced project. Based on our review of the materials you provided, we have determined that it does not require IRB review because it does not meet the definitions of research with "human subjects" or "clinical investigation" as set forth in Emory policies and procedures and federal rules, if applicable. Specifically, in this project, you will examine the cost-effectiveness of novel treatments for chronic hepatitis C infection and to identify factors associated with treatment uptake in two different populations (National Health and Nutrition Examination Survey and Grady Hospital). You will not have access to the code linking subjects with their identifiers for any of the three datasets you plan to analyze (Grady Legacy database, TILT-C database, and NHANES). Without access to these identifiers, you will access 808 study research subjects' data in the Grady Legacy dataset, 500 in the NHANES subset that will be analyzed, and 150 in the TILT-C dataset.

Please note that this determination does not mean that you cannot publish the results. If you have questions about this issue, please contact me.

This determination could be affected by substantive changes in the study design, subject populations, or identifiability of data. If the project changes in any substantive way, please contact our office for clarification.

Thank you for consulting the IRB.

Sincerely,

Michael Arenson, MA
Analyst Assistant