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Treatment Outcomes among HCV Patients on Novel Direct Acting Antiviral Therapies in a Primary Care-Based Hepatitis C Clinic

By

Frances Y. Kim
Degree to be awarded: Master of Public Health

Global Epidemiology

_____ _____

Anne Spaulding, MD, MPH Date

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By

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B.S., Emory University, 2012

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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 for the degree of
Master of Public Health
in Global Epidemiology
2015

Abstract

Treatment Outcomes among HCV Patients on
Novel Direct Acting Antiviral Therapies in a
Primary Care-Based Hepatitis C Clinic

By
Frances Y. Kim

Background: The introduction of direct acting antiviral agents (DAA) represents a new era in Hepatitis C (HCV) treatment, leading to significant improvements in efficacy, as well as a shorter and more tolerable treatment process.

Purpose: Despite advances in HCV therapies, successful treatment outcomes have been difficult to observe in primary care-based HCV clinics. The aim of this study is to evaluate whether largely uninsured, underserved, and minority patients of the Grady Liver Clinic (GLC) have better treatment outcomes on newer, interferon (IFN)-free DAA regimens compared to earlier patients on IFN-containing regimens.

Methods: A retrospective chart review of patients started on HCV treatment in the first IFN-containing triple therapy era (2011-2013) and the newer IFN-free DAA era (2013-2015) was performed (n=112). Various demographic, HCV-specific, and co-morbidity factors were also analyzed to determine whether patients with certain characteristics were more likely to successfully complete treatment and achieve SVR after 12 weeks of treatment.

Results: Out of the patients with complete outcome data, there were 61 patients on IFN-containing DAAs, and 51 patients on IFN-free DAAs. A higher percentage of patients on newer DAA regimens achieved SVR (94%) compared to patients on older DAA regimens (79%) ($p=0.0659$). The average age of the study population was 58 years, 82% were black, and half had public health insurance. More than a quarter of patients (29%) had a prior history of IFN-containing HCV treatment, and patients on newer regimen had more comorbidities than patients on older regimens. Continuous age was found to be associated with successful treatment outcome at the $p<0.1$ level ($p=0.0889$), as well as HIV and diabetes comorbidities at the $p<0.2$ level. However, no significant predictors of achieving SVR were found in models with the exposure of DAA regimen type.

Conclusions: Despite the challenges of this population, patients on newer, IFN-free DAA regimens have better treatment outcomes and SVR rates compared to those on older, IFN-containing regimens. These findings indicate that as improved and more effective IFN-free treatments become available, the GLC is a successful model for treating underserved, racial minorities with HCV, while reducing significant barriers to treatment that patients typically face.

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INTRODUCTION

Chronic Hepatitis C (CHC) is an emerging public health concern, with an estimated 170 million people, or 3% of the world's population, infected with the Hepatitis C virus (HCV).[57] In the United States alone, an estimated 3 million or more are living with chronic HCV infection, and estimates of annual HCV-related deaths are as high as 80,000.[12, 55] Untreated, 75% of those ever infected will develop chronic liver disease, up to 30% will develop cirrhosis, and 5% per year will develop decompensated liver disease or hepatocellular carcinoma.[3] HCV is the most common blood borne pathogen in the U.S.,[63] and deaths from HCV infection have superseded deaths from HIV infection.[39] Twenty-five percent of liver-related deaths are attributed to hepatitis C globally, and it is expected that hepatitis C-related morbidity and mortality will reach its peak in the U.S. in the next 10 years.[39] Although effective treatments to clear HCV infection are widely available, most of these individuals do not know they are infected. An estimated 65-75% of those infected with HCV remain untested and unaware of their infection, and therefore are not evaluated for treatment.[31]

CHC Treatment

In the past decade, dual therapy consisting of pegylated-interferon (IFN) and ribavirin (RBV) has been a standard of care for the management of CHC. Depending on genotype, there is a 50-70% success rate in curing disease with this combination therapy.[22] However interferon is often poorly tolerated and a large number of patients with CHC remain untreated due to the large number of adverse side

effects.[3] Prior to the introduction of new regimens, treatment options for patients with CHC who fail interferon-based therapy were very limited. Health outcome analyses estimated that treatment patterns prior to new medications would prevent only 14.5% of liver-related deaths attributed to CHC between 2002 and 2030.[10] CHC treatment success is achieved with a Sustained Virological Response (SVR), which is defined as undetectable HCV RNA in the blood 12 or more weeks after completion of antiviral therapy.[57] The previously used combination of interferon and ribavirin achieved a global success rate of about 50% among HCV genotype 1 patients.[25] Other shortcomings of interferon and ribavirin therapy are that HCV eradication is hardly expected in patients with high baseline viral loads, older age, advanced fibrosis and high body mass index.[39]

New DAA regimens

The recent approval of new anti-HCV drugs, including interferon-free regimens, has drastically changed the landscape of CHC treatment in a span of a few years. The introduction of these direct acting antiviral (DAA) agents, or medications designed specifically to block replication of HCV, represents a new era in CHC treatment, as they have been shown to be cost-effective and drastically improve patients' health-related quality of life.[11, 27, 37, 46, 70, 71] These novel regimens have led to significant improvements in efficacy, as well as a shorter and more tolerable treatment process.[70, 71]

Telaprevir and boceprevir were the first DAAs introduced for treatment of genotype 1 HCV in May 2011. These protease inhibitors when used in combination

with pegylated-interferon and ribavirin, also known as “triple therapy”, improved efficacy in patients with CHC compared to the traditional dual therapy. However, this combination continued to be associated with adverse events that often led to an early termination of CHC therapy, which led to the approval of a second wave of DAAs.[25] In late 2013, the FDA approved sofosbuvir and simeprevir, which opened the door for interferon-free combination regimens. Sofosbuvir can achieve fairly high SVR rates in substantially shorter treatment times than previously existing regimens, resulting in a combination that is highly efficacious and well tolerated in patients with HCV genotype 1. Most recently, the fixed-dose oral combination of sofosbuvir and ledipasvir, along with paritaprevir/ritonavir, ombitasvir, and dasabuvir were approved, and were proven to be the most effective in targeting HCV viral proteins.[25] Studies have shown that these DAA regimens exhibit over 95% sustained response and efficacy, a clear improvement in CHC treatment rates.[25, 32] It is anticipated that these new DAA therapies will have a substantial impact on CHC management and treatment, particularly in terms of the potential for interferon-free treatment.

Although emerging therapeutics and drugs raise the possibility of reducing HCV-related mortality and morbidity, major barriers remain with regard to identifying infections and improving access to treatment. Numerous studies proved HCV antiviral treatment as cost-effective, even with the more expensive DAA medications.[11, 27, 37, 46, 51] However despite the data, a surprisingly small proportion of patients have successfully received antiviral treatment to date. Cumulative data from the VA (Veterans Affairs) HCV Registry indicates that the percentage of VA

patients with HCV who have ever received antiviral therapy rose from 10.9% in 2004, to 14.4% in 2007, and 23% in 2013.[61] In the general US population, an estimated 7-11% of HCV patients have had antiviral treatment.[30]

As more effective treatments are developed, an expansion in treatment rates needs to be of equal priority to reduce the burden of CHC on the individual and the community. Efforts to increase treatment rates by understanding barriers to CHC care and factors associated with increased treatment uptake for patients is essential in addressing this burden on liver-related morbidity and mortality. Characteristics associated with poor access to care will now be explored through a literature review of studies involving both interferon-containing and new DAA-containing drug regimens.

PART I:

LITERATURE REVIEW

Factors Associated with CHC Treatment Uptake

With the introduction and widespread availability of emerging drug regimens, treatment uptake is expected to increase due to a rise in physician confidence in treatment outcomes, as well as gradually declining concerns about treatment side effects. Furthermore, the simplification CHC treatment without interferon will allow for more extensive care by general practice physicians, reducing the need for specialist referral and care.[26, 58] However, there are many factors that influence access to treatment that need to be addressed in order to considerably improve treatment levels for CHC.

Barriers to Treatment Access

Hepatitis C disease management, whether in a primary or specialist setting, can assist patients to manage symptoms and prevent acceleration of liver disease. Despite these benefits, patient nonattendance rates in clinics have a large range from 28% to 80%, and little is known in previous research as to exact reasons why.[6] Although adherence is critical for patients to attain SVR, up to 50% have difficulty in maintaining 80% adherence to treatment, which greatly compromises treatment outcomes.[26] Nonattendance and non-adherence result in not only wasted clinician time and health care resources, but also more importantly, a delay in presentation

and a lack in monitoring that could predispose the patient to preventable complications. [6]

Gaps in CHC care and disease management have been noted to result from both sides of the provider and the patient. However whether or not a patient starts treatment depends first on the provider's decision to recommend treatment. Decisions to offer treatment from the provider were usually found to be influenced by severity and stage of liver disease, stability of the patient's medical status in the presence of other medical comorbidities, perception of the patients' readiness to tolerate and adhere to treatment, and the provider's beliefs and attitudes related to the urgency and expected outcomes of treatment. [33, 64]

However other barriers imposed by care providers can include failure to even screen for HCV, failure to discuss the illness with the patient and deferral of treatment, a lack of knowledge or skill for diagnosis and treatment of HCV, poor communication skills and care provider stigma.[48] Other cracks occur when primary care providers refer patients with a history of nonattendance to a specialist, where many will then fail to attend the specialist appointment. Gaps in a lack of knowledge, lack of understanding or misinterpretation of information, and difficulty evaluating information, are other factors that contribute to large gaps between the HCV patient and the provider. [6] The absence of monitoring and missed opportunities for patient education in primary care are especially important in HCV care and treatment, as well as properly understanding HCV information from providers. All of these factors in HCV care and proper treatment, similar to other chronic diseases, involve

cooperation and clarity between the patient, the provider, and the health care system. [6]

When approaching barriers to CHC treatment from the patients' perspective rather than the physicians' perspective, many issues emerge. Some of the most commonly cited categories of barriers to care and reasons for nonattendance in primary care clinics were factors related to patients' preferences and behaviors, physicians' perceptions of their patients, medical eligibility for treatment, difficulties with the healthcare system, as well as issues of communication with the patient and stigmatization. The most frequently cited reasons for medical ineligibility for treatment were substance use, psychiatric disorders, and other medical comorbidities. [48] Psychosocial factors such as lack of social support, language barriers, unstable housing, social marginalization, discrimination and employment also negatively affect access and adherence to CHC treatment. [33, 57]

In an observational study consisting of focus groups of CHC patients in 2009, various differences between the perceptions of patients and providers regarding access to care were explored and discovered. [48] In this study, types of patient-identified barriers consist of perceived social stigma, unrealistic, inaccurate, or unmet patient expectations, and communication difficulties with physicians. Misunderstanding of the treatment process and adherence risk, fear of side effects, low confidence in treatment effectiveness, perception of liver disease as too mild and unimportant, not feeling symptoms, and other competing medical and psychosocial priorities were important factors that influenced patients' decisions for treatment. [44, 48] In Khokhar and Lewis' US study of CHC patients, they found that a

considerable proportion (41%) of their eligible, treatment-naïve patients declined dual therapy in 2006, also with no contraindications. Out of patients who declined therapy, the majority of them (44%) did so because they had been asymptomatic despite being infected for more than 20 or 30 years, and judged themselves as having relatively mild, non-progressive disease.[33] Additionally, Lowry *et al.* observed a large dropout of patients after initial outpatient visits in clinics in the US. They considered it likely that many patients wish only to discover their HCV status and prognosis, without necessarily intending to pursue treatment options in the near future.[38] These are only a few of the examples of why patients with CHC will decline or postpone treatment in clinical settings.

Since fewer studies have been able to assess therapies with the newer drug regimens, studies involving both interferon-containing and DAA-containing drug therapies will be considered in the following review. Various demographic, clinical, and psychosocial factors can combine to create barriers with regards to accessing proper CHC care and completing treatment, which will be addressed below.

I. Demographic variables

A. Race/Ethnicity

Race/ethnicity has been shown in previous studies of interferon-based regimens to play a significant role in CHC treatment response. Those of Black, Hispanic, and Asian racial groups, three of the most commonly discussed groups in current literature, will be analyzed below.

Black race

Historically, most studies have suggested that black race is associated with a poorer response to treatment for HCV, which may affect patients' and providers' decisions regarding treatment for HCV.[24, 27, 33, 41, 43, 52, 56] A significant obstacle to achieving SVR with dual therapy has been the presence of the IL-28B genotype in black patients. A higher prevalence of the IL-28B T/T genotype has been associated in black patients with lower SVR rates, which can partially explain the observed racial variation in treatment response comparing African Americans with Caucasian Americans.[54] On the other hand, presence of the IL-28B C/C genotype strongly correlates with natural clearance and spontaneous resolution of HCV infection, which investigators have been able to use as a marker to potentially determine responsiveness to interferon-based treatment among CHC patients.[43] Presence of this homozygous CC haplotype is found less frequently in blacks than in non-blacks, accounts for approximately half of the observed difference in SVR rates with dual therapy between blacks and whites.[24]

In some studies, black ethnicity seemed to be an independent predictor of failure to achieve SVR.[23, 28] Response rates for US patients completing dual therapy of interferon and ribavirin were found to be significantly lower among African American patients compared with Caucasian American patients (28% vs. 52%).[13] Conjeevaram *et al.* also found that the reduced response rate to dual therapy among African Americans compared with Caucasian Americans was not caused by clinical patient characteristics, disease severity, or amount of medication taken. However they still found a very strong and independent association after controlling for

important factors association with therapy response, such as HCV-RNA levels, sex, and liver fibrosis.[13] In a population of veterans in the US, Butt *et al.* also found that successfully treated patients were younger and more likely to be white. Out of those who received care for HCV infection, 40% were white, 22% were black, and 5% were Hispanic. This study also found that the negative effect of black race is increased if also infected with HIV, with odds of treatment recommendation for HIV/HCV co-infected black patients much lower compared to co-infected white patients.[5] Adherence to treatment can also be a confounding factor, with some studies of interferon-based regimens reporting higher SVR rates in white Americans than black Americans most likely in relation to the significantly higher rates of adherence in white Americans as well.[13]

Although the novel triple therapy combinations have been effective among most racial subgroups of CHC patients, the response of African American patients with CHC remains relatively low when compared to other racial groups.[43] Melia *et al.* also found that in addition to lower response, fewer African Americans may be eligible for therapy in the first place largely due to higher rates of neutropenia, anemia, diabetes, and renal dysfunction.[41] This higher prevalence of HCV infection, lower response to treatment, with lower proportion of eligible individuals places black CHC patients at a disadvantage in the current situation of high CHC disease burden and low treatment efficacy.[43]

Hispanic race

In regards to Hispanics with combination therapy with pegylated-interferon and ribavirin for CHC, Hispanics seemed to have higher rates of early treatment discontinuation than their non-Hispanic white counterparts, and fewer Hispanics completed therapy.[73] SVR in genotype 1 patients were similar between Hispanics and non-white Hispanics. However, a large disparity was noted in SVR of genotype 2 and 3 patients.[73] Yu *et al.* goes on to explain that this disparity in genotype 2 and 3 Hispanics seems to stem from a higher post-treatment relapse rate in Hispanic patients compared with the non-Hispanic whites in the study.[73] Cachay *et al.* also found in their study that there were a significantly higher proportion (85%) of non-Hispanics referred to their HIV primary care model, compared to Hispanic patients.[8]

Asian race

Of the many factors that predict response to treatment, Asian race/ethnicity seems to be a strong independent predictor of SVR, with specifically non-South Asians having a better response to treatment than Caucasians, African Americans or Latinos.[42, 73] In Missiha *et al.*'s study specifically, Asians were more likely to achieve an SVR to treatment with interferon and ribavirin than whites with CHC (65% versus 45%), which was consistent among the three genotypes.[37] Missiha *et al.* assumed that it was likely that a higher proportion of Asian subjects in their study were rapid virological responders with a constantly lower rate of relapse or breakthrough and a higher rate of SVR.[42] However, further research needs to be

directed towards explaining the underlying immunogenetic pathways that may be responsible for this racial variation in response. [42]

Many individual and structural barriers to care exist for Asian Americans and any immigrants in general, and have been analyzed in prior literature. Russ *et al.* describes several barriers in his study with HIV/HCV co-infected Asian Americans.[53] A lack of English proficiency is a major barrier to seeking services. It has been found that for many Asian immigrants, navigating the health care system remains difficult due to language barriers as well as a lack of knowledge about the US health care system. Undocumented immigrants also tend to "stay away from the medical system… for fear of being reported or deported back to their country", [53] in which they then wait to seek services until they are seriously ill. Immigrants are also afraid of deportation because their home countries may lack the appropriate health services to manage their HIV and HCV. Asian immigrants were also found to display an attitude of submissiveness towards their doctors, and sometimes did not feel comfortable asking questions. Individual barriers are also exacerbated by the highly fragmented system in America, as patients must navigate multiple clinics and service centers to receive care for their HIV/HCV co-infection. [53]

B. Age

Younger age has been found to slightly correlate with SVR in clinical trials of both boceprevir and telaprevir therapies. In a review of predictors of response for HCV care, Berry and Irving found that an age under 40 was associated with SVR with an OR of 1.5 ($p=0.03$). [3] In a telaprevir and interferon with ribavirin trial, 83% of

patients under 45 years of age achieved SVR compared to 70% of those older than 45 years.[3] Similarly, in previous interferon-containing combination therapies, it has been found that those younger than 40 years have a better response to treatment compared to those older than 40 years.[47]

However, findings on the association between age and CHC treatment seem to be mixed. Based on recent literature, it seems that patients infected with HCV who are older than 40 years of age are referred for treatment more often.[59] Price *et al*. found that the median age of HCV patients who were treated with boceprevir and telaprevir in their study were of an older age group, with a median age of 56.[51] In an HIV primary care model, Cachay *et al.* also found that HCV patients who were referred had a median age of 45 years, with a wide distribution ranging from 26 to 73 years of age.[13] In a population of HCV patients in Scotland, McAllister *et al.* found that attendance at specialist hepatitis clinics within 12 months of HCV screening date was significantly reduced among individuals aged less than 35 years of age.[40]

Butt *et al.* found that treated patients for CHC tended to be younger, under the age of 50, most likely due to a greater proportion of patients under 40 years being able to achieve an SVR compared to those older than 40 years of age.[5] Additionally Toresen *et al.* found that patients less than 40 years of age don't seem to attend clinics after diagnosis as often, and therefore have less of a chance of completing treatment compared to those over 40 years of age.[59]

C. Gender

In a cohort of NHANES participants, Younossi *et al.* found that male gender was associated with a lack of knowledge about being infected with HCV, which would keep patients from seeking CHC treatment. Female patients were more likely to have known and been aware of their HCV infection prior to finding out from the NHANES disease screening. [69] This finding highlights the importance of HCV screening among those at high risk of progressive liver disease and liver-related mortality.

Males have also been shown to have a slightly higher prevalence of HCV infection compared to females, [52] and male gender has also been associated with more severe liver disease and a more rapid disease progression among those with alcoholic liver disease and HCV infection. [56] In a US study of HIV/HCV co-infected patients, co-infected women were found to be more likely to interrupt or change CHC treatment before men, differ in reasons for therapy interruption, and have an overall lower cumulative survival. [19] Male gender was also identified as a key risk factor for patient nonattendance among CHC treatment centers in Lowry *et al.*'s study. [38] However, treatment adherence in their female patients was not a significant factor leading to treatment interruption or change, but rather comorbidities such as various neuropsychiatric issues. [19]

In studies with interferon-containing regimens, the effect of gender on SVR has been controversial, with higher overall SVR rates in females confounded by ostrogen levels and menopausal status. [63] Cachay *et al.* found that 84% of HCV patients referred to their HIV primary care model were male. [8] Price *et al.* also found

that the majority of patients (61%) treated for HCV with telaprevir and boceprevir were male. [51] Additionally, in a general population in Scotland, McAllister *et al.* discovered that out of the individuals who tested positive for HCV, there were a higher percentage of males who started treatment within 18 months (19.4%), compared to females (14.9%). [40]

However a few other studies showed a little to no association between gender and probability of starting treatment. [9, 45, 60]

II. Clinical stage variables

A. Fibrosis stage and cirrhosis

Patients with cirrhosis have always proven to be a major challenge due to the fact that they urgently require therapy to prevent further complications. Additionally, they respond least well to treatment and suffer the greatest number of adverse events. Many studies of interferon-free DAA combinations excluded cirrhotics due to these factors. However, although DAA combinations may be less effective in patients with cirrhosis, it is not clear that adding interferon will be any more effective and have an impact on safety. [21]

Based on Berry and Irving's review, absence of bridging fibrosis and cirrhosis were found to be predictive of SVR with interferon and ribavirin therapies. Higher rates of SVR in patients without severe fibrosis were found than in those with severe fibrosis. [3] Many of the trials with the new DAAs seem to exclude cirrhotic patients, making it difficult to assess the efficacy of the drugs in this patient group. However, cirrhosis had a strong impact on treatment response among genotype 3

patients in Berry and Irving's study. In patients given 24 weeks of sofosbuvir and ribavirin, SVR rates after treatment completion were 60% for cirrhotics, and 87% for non-cirrhotics. [3]

Several studies show the effect of fibrosis stage on the probability of starting treatment [16, 59] In their cohort of genotype 1 HCV patients in Spain, Crespo *et al.* found that those with advanced liver disease (fibrosis ≥ F2) were much more likely to receive triple therapy. [16] However in patients with advanced fibrosis (F3-F4), 19% did not initiate treatment due to patient refusal, hope of newer treatment, and healthcare provider restrictions, despite having no other contraindications or comorbidities. [16] On the other hand, Toresen *et al.* found in their study population of HIV/HCV co-infected patients, that most patients who started treatment had a low prevalence of significant liver fibrosis. They explained it from the hepatologist's point of view, saying that these patients often represent easy-to-treat patients with a predicted high rate of SVR. [59]

III. Comorbidity conditions

A. HIV/HCV co-infection

HCV infection is one of the most frequent causes of comorbidity and mortality in the HIV population, and liver-related mortality is the second highest cause of death in HIV-position patients. [15] Patients with HIV are at a high risk of co-infection because both infections can be transmitted by injection drug use. [68] However many HIV-infected patients with CHC infection do not receive treatment for HCV infection, often due to contraindications, patient refusal, or poor adherence

to anti-HIV therapy.[2, 7, 8, 15, 26, 66] Adherence to treatment for HIV infection, as judged by the physician, has been found to be a major influence on the decision to begin CHC treatment in co-infected patients. In the first published trials of antiviral therapy, the peginterferon with ribavirin combination was less effective in HIV co-infected patients. SVR ranged from 14% to 38% among patients with HIV and HCV genotype 1 and from 44% to 73% among those with genotype 2 or 3 infections.[66] Although SVR rates have been markedly high among co-infected patients, reaching more than 50%, in the last few years, under-treatment of CHC in HIV-infected patients still remains frequent. In Winnock *et al.*'s study of HIV-HCV co-infected patients, they found that the only factor associated with HCV treatment initiation was good perceived adherence to HIV treatment from their physician.[66]

Social determinants have also been found to play an impact in the decision to start HCV treatment for HIV/HCV co-infected patients. In Winnock *et al.*'s study, parenthood was a strong factor associated with a lower rate of HCV therapy, with the long duration of HCV therapy and side effects such as asthenia and depressive symptoms most likely being the barrier in mothers. Although housing status was not directly associated with HCV treatment initiation in their study, co-infected patients who did not own or rent their home were more likely to be considered as having poor adherence to therapy by physicians.[66] Other disincentives for co-infected patients include low efficacy and severe side effects with interferon and ribavirin therapies, long waiting time prior to HCV intake appointments in sub-specialty clinics, and commuting to a different location rom where patients usually receive HIV care.[7]

Other severe psychiatric disorders and ongoing alcohol use were mentioned frequently as barriers to HCV treatment for HIV/HCV co-infected patients.[66] Cardiovascular disease and respiratory distress were also barriers to treatment initiation, and patients with a history of multiple treatments for depression were less likely to be treated.[66]

However, Cooper *et al.* found in the context of a socialized, multidisciplinary clinic, that HIV/HCV co-infected patients received similar access to HCV care and treatment as HCV mono-infected patients.[14] The slight diminishment of SVR in HIV/HCV co-infected patients was found associated only with genotype and biological factors, and not due to concurrent barriers to therapeutic success. They found that barriers to healthcare provision, which included poverty, language barriers, socioeconomic status, substance abuse, and mental health disease, did not further diminish overall SVR in HIV/HCV co-infected patients.[14] Kieran *et al.* also found little association between co-infection with HIV and CHC treatment uptake in their study of HCV treatment outcomes in a dedicated co-infection clinic.[34]

B. Psychiatric comorbidities

Despite drug improvements, many HCV patients may be considered poor treatment candidates because of psychiatric co-morbidity and substance use disorders. Various studies have found strong associations of psychiatric disorders acting as a barrier between CHC patients and appropriate antiviral treatment.[7, 9, 29, 30, 48, 49, 66] In a population of US veterans, a history of prior psychiatric disorder and active drug use was significantly associated with less likelihood of achieving SVR.[29]

These co-morbidities are common among HCV patients and have been the most frequently cited reasons for withholding antiviral therapy in the past. [29, 30, 48]

In a review of barriers to HCV antiviral treatment, Oramasionwu *et al.* classified psychiatric illness and depression as a strong barrier, as depression was the most common contraindication to treatment that was present in two-thirds of patients. [49] Health providers did not evaluate patients for therapy if a diagnosis with a psychiatric illness or depressive condition was present. Because interferon can cause depressive-like symptoms in patients taking dual therapy, it is of major concern as underlying mood instability and other neuropsychiatric symptoms can worsen during the treatment process. Distinction between severe, active psychiatric illnesses and non-active illnesses is extremely important, given that HCV treatment seemed to be considered for patients who have undergone successful psychiatric care for depression. [49]

C. Substance and drug use

Substance abuse, which included either abuse of injection drugs or alcohol use, was another common barrier to treatment access, and a significant predictor for lack of HCV therapy. Many studies also explicitly cited alcohol, injection drug use (IDU), or substance abuse as a reason for excluding patients from receiving HCV therapy altogether. [9, 29, 49, 54, 69, 72] Yehia *et al.* found in their study of HIV/HCV co-infected veterans that patients who were injection drug users were at an increased risk of HCV and disproportionately account for 80% of new infections and 60% of existing cases in developing countries. [67] Despite this risk, IDU patients in their

cohort were less likely to be screened for HCV then men who have sex with men (MSM). This may be due to multiple comorbidities and psychosocial barriers that IDU patients often face. Deferral of preventative care services, which typically occur during complicated visits, and the need to review lengthy medical records to verify test results may lead to lower HCV screening, and a lower probability of initiating CHC treatment. [67] In a cohort of CHC patients, Lowry *et al.* found that the key risk factors for patient nonattendance in CHC clinics and hospitals were identified as male sex and IDU background. [38]

Heavy alcohol intake and HCV infection together significantly promotes the development of chronic liver disease. As a result, heavy drinkers are excluded from treatment most often, even though they are also at most risk of disease progression. However there have been recent studies in Switzerland and France that have demonstrated reasonable rates of SVR in alcohol-dependent patients. [4, 35] Poorer responses to CHC treatment in the US VA system were hypothesized to be related to poor treatment adherence rather than a direct effect of alcohol intake. [1] It is theorized that maintaining adherence to treatment may be as important or more important than enforcing abstinence.

D. Other medical comorbidities

Patients with other medical comorbidities such as anemia, hepatitis B co-infection, coronary artery disease, stroke, diabetes, and pulmonary disease were found less likely to have been prescribed HCV treatment, and therefore less likely to have completed any type of therapy. [5] Providers were found to be hesitant to

prescribe treatment that may exacerbate medical conditions or precipitate complications since ribavirin is associated with a dose-dependent haemolytic anemia.[5] Schizophrenia was not considered an absolute contraindication to CHC treatment,[5] and an analysis of US NHANES data found no association between diabetes and CHC non-treatment.[69]

IV. Socioeconomic status

Socioeconomic status has been found to impact overall health outcomes due to the strong influence of education, income, and social class on an individual's exposure to stressors, health practices, behaviors, and access to medical care.[57]

A. Income

Poverty or limited financial resources were found to be significant barriers to HCV services and treatment. Increasing costs of patient management due to the high market price of DAAs has ignited a fairly large debate on affordability and prioritization issues versus the ethical obligation to treat. Treatment costs are expected to further increase with association of different DAA classes, and as a result, there are concerns that new drugs will be limited only to the sickest patients with end-stage hepatitis.[20] For example, the European Association for the Study of the Liver guidelines reflects this approach. It acknowledges that all patients willing to be treated should be considered for the new therapies, but it also states that therapy can be delayed until moderate liver disease is present.[20, 32]

In Butt *et al.*'s qualitative study of factors contributing to nonattendance for HCV care, patients provided detailed examples of delayed care and treatment due to limited financial resources for things such as the drugs, transportation, phone calls, and childcare. The study found that travel from rural or remote areas was especially difficult for the patient if the patient had to pay for a caregiver to accompany, or for a hotel stay if the specialist was particularly far. [6]

Additionally, North *et al.* also found that financial and logistical barriers were substantial impediments to HCV medical care and treatment. Patients interviewed described feeling overwhelmed by complicated systems of insurance and reimbursements, and some could not figure out the cost of treatment. Even though participants described a lack of understanding of the treatment process, patients strongly desired treatment and expressed frustration regarding financial barriers to treatment that they had encountered. [48]

Younossi *et al.* found that a higher income and a higher income-to-poverty ratio was associated with awareness of HCV infection and therefore associated with receiving appropriate care. [69] Toresen *et al.* found that being unemployed and infection with genotype 1 or 4 were strongest predictors for not initiating treatment. [59]

B. Education

In a study among patients with HCV genotype 1 in Spain, Crespo *et al.* found a clear relationship between initiating CHC treatment with education level of patient. Among patients with primary school, secondary school, and university levels of

education, patients with a higher level of education were more open to and more likely to receive treatment. [16] The authors hypothesized that refusal by the patient to initiate treatment was directly related to a low level of education, not only in patients with mild disease but also in those with advanced CHC. Younossi *et al.* also found among US NHANES data that having a college degree is associated with treatment uptake independently. [69]

C. Health insurance status

Lack of insurance, or insufficient insurance coverage, is common among HCV-infected patients. [54] In terms of seeking HCV care, Ditah *et al.* found in their analysis of NHANES HCV follow-up data that the main barrier to seeking downstream HCV care was a lack of health insurance. [18] While clinical contraindications and side effects are becoming less of a problem with the new DAA drugs, cost remains a major concern. In their national sample, they found that having health insurance or not was the only factor that determined whether an individual pursued downstream care or not following a positive result. [18] Khokhar and Lewis also found that a lack of support or health insurance played a role in whether or not CHC patients followed through with treatment or not. [33]

Poor coordination between caregivers and hospitals and between caregivers and third party payers may lead to unanticipated treatment interruptions. [54] Yehia *et al.* also found in their cohort of HIV/HCV co-infected patients that patients with Medicaid were more likely to be screened than those with private insurance. [67]

V. Stigmatization

For those living with CHC, stigma and discrimination are defining features given the association of HCV with the practice of injection drug use. Of HCV participants in Moore *et al.*'s US cohort, about 85% of participants experienced HCV-related stigma. [44] Levels of stigma perceived by those who inject drugs can persist even when drug use is reduced or ceased, and can have an adverse impact on the prevention of HCV transmission, on HCV treatment-seeking, uptake, and adherence, and on quality of life, which was identified in several studies. [6, 47, 48, 60] Researchers have found that stigma arises not only from the association between HCV and IDU, but also from misconceptions concerning the causes and modes of transmission of HCV, as well as the general perception of HCV as being a highly contagious, fatal disease. [44] Qualitative literature analyzed by Treloar *et al.* found that participants reported concerns of stigmatization by family members or intimate partners, the general public, and most particularly, via healthcare settings. The healthcare setting is the most commonly reported site for those with HCV to experience stigma. [60]

In Russ *et al.*'s study of HIV-positive Asian Americans with HCV co-infection, they found stigma to be a severe barrier to access to CHC care. [55] The authors found that stigma is a particularly important barrier to coordinating treatment and care when it comes to HIV/HCV co-infection, and is recognized as a barrier to care by both patients and providers. Stigma as a barrier may impede appropriate use of medical and social services, such as HIV or HCV provider visits, mental health and substance abuse services, as well as other social services. For example, they found that patients would not follow through on referrals, particularly when the referral is

for a primarily Asian American provider or social service agency, due to fear of having their HIV status disclosed.[55] Although numerous providers express interest in closely coordinating ethnically and linguistically appropriate care, providers also report that patients' fear of stigma was a powerful barrier to patients pursuing follow-up care, and ultimately treatment.[55]

However in Sublette *et al.*'s study of CHC patients, they found that fear and shame were motivators for both uptake and completion of treatment. Patients reported that completing treatment would eradicate the virus, and the shame and embarrassment they experienced from having the condition. The authors hypothesize that patients' appraisal of the severity of the threat of CHC and their confidence that they can successfully overcome the disease may be the reasons for shame and stigma being motivators for treatment uptake. However, among their Australian cohort, stigma was also found to be a barrier to treatment adherence and completion.[58]

PART II

INTRODUCTION

CHC Treatment at the Grady Liver Clinic (GLC)

The Grady Liver Clinic (GLC) was founded by general internists in 2002 as a clinical model developed to increase access to CHC treatment for underserved populations. Staffed by members of the Division of General Medicine at Emory University, the GLC is housed at Grady Memorial Hospital in Atlanta, GA, which serves an inner-city population of predominantly low-income, uninsured African Americans. The purpose of the Liver Clinic is to provide comprehensive care, including treatment, to patients in the Grady Health System with HCV infection. The GLC is the primary site in the Grady Health System that provides medical treatment for those with hepatitis C infection.

The introduction of direct acting antiviral agents (DAAs) has initiated a new era in HCV treatment. In May 2011 the first DAA medications, NS3/4A protease inhibitors boceprevir and telaprevir, were FDA approved and available for HCV patients. Starting in July 2011, patients were treated with pegylated-interferon and ribavirin in combination with either boceprevir or telaprevir, which was also known as "triple therapy" (telaprevir/boceprevir, pegylated-interferon, and ribavirin). In October 2013 newer DAAs such as sofosbuvir, had been approved and released. All interferon-containing drug regimens were replaced with this second generation of CHC therapies starting in 2014, which were all oral interferon-free regimens. From 2013-2015, patients were either started on a combination of sofosbuvir, interferon

and ribavirin (SOF/P/R), or on regimens without interferon: sofosbuvir and ribavirin (SOF/R), sofosbuvir and ledispasvir (SOF/LDV), or simeprevir and sofosbuvir (SIM/SOF).

The following analysis will examine whether these successful trials of interferon-free treatment can be replicated in practice with similar results at an urban liver clinic managed by general internists. Factors found to be barriers to CHC treatment in the literature will also be analyzed in the Grady Liver Clinic, a primary care model of CHC management specifically designed to reach underserved individuals of low socioeconomic status, and who are mostly African Americans. This study will focus on whether GLC patients on newer, interferon-free DAA regimens had a higher probability of completing treatment, and whether they had better treatment outcomes compared to earlier patients on interferon-containing regimens. The demographics of patients who have started and completed treatment regimens containing older DAAs (interferon-containing triple therapy with telaprevir, boceprevir, or sofosbuvir) will be analyzed and compared to the demographics of patients started on treatment regimens with newer DAAs without interferon.

METHODS

Data sources

This analysis models success rates of CHC treatment in patients of HCV-positive individuals at the Grady Liver Clinic in Atlanta, GA since DAAs for hepatitis C treatments became available.

Grady Liver Clinic physicians performed a retrospective chart review of all HCV-positive patients having started treatment since new DAA treatments became available, which was between May 1, 2011 and May 1, 2015. The dataset was provided for this analysis in de-identified form by the Director of the Liver Clinic.

This study was approved by the Emory University Institutional Review Board (IRB) and the Grady Research Oversight Committee (GROC) as an amendment to the original study, "Grady Liver Clinic: Description of a patient population and analysis of success rates of hepatitis C treatment". The IRB and GROC determination letters are available in the Appendix.

Variables used in analysis

The primary predictor variable was the type of treatment regimen GLC patients were started on. In this study, the various types of treatment were categorized by whether they contained pegylated-interferon. Treatments that contained interferon were referred to as "older" DAA regimens, while treatments without interferon were referred to as "newer" DAA regimens.

Old (Interferon-containing) DAA Regimens	**New (Interferon-free) DAA Regimens**
Telaprevir/Pegylated-interferon/Ribavirin (T/P/R)	Sofosbuvir/Ribavirin (SOF/R)
Boceprevir/Pegylated-interferon/Ribavirin (B/P/R)	Sofosbuvir/Ledispasvir (SOF/LDV)
Sofosbuvir/Pegylated-interferon/Ribavirin (SOF/P/R)	Simeprevir/Sofosbuvir (SIM/SOF)

Other measures of interest included patients' demographic data, such as race/ethnicity, age, gender, and health insurance status. Medical and psychiatric comorbidities were also analyzed, and included HIV co-infection, depression, diabetes, and hyperlipidemia. Hepatitis C-related characteristics, such as liver fibrosis stage, genotype, mean APRI score (composite score indicating level of liver fibrosis), FIB4 score, and previous HCV treatment history were also included in the analysis. Race/ethnicity was defined categorically (White, Black, Hispanic). Age at the start of CHC treatment, was dichotomized by 18 to 59 years of age, and 60 years and older.

The primary outcome of interest was treatment success, measured by successfully completing treatment and achieving a sustained virologic response (SVR) 12 weeks after completion of CHC therapy. Attaining this outcome was determined from follow-up chart reviews. Any patients missing treatment completion or SVR data from these reviews were assumed to be lost to follow-up and therefore not achieving a successful treatment outcome. Other dependent variables included obtaining a successful end of treatment response (ETR), where HCV RNA is not detected in the blood at the end of treatment. Patients' wait time was also calculated in weeks between the first appointment date and the date the patient started HCV treatment.

Statistical Analysis

Baseline characteristics were examined for patients with complete data (those with a non-pending treatment status) based on all variables of interest.

Univariate associations were also calculated between the outcome variable and all predictor variables for patients with complete treatment data. Chi-squared tests were used for categorical variables and the Wilcoxon two-sample test was used for continuous variables. Fisher's exact test was used for variables with cell counts less than 5, and all tests were performed at a significance level of 5%. Odds ratios for achieving SVR after 12 weeks of treatment were calculated for all predictor variables, for patients with complete data.

Variables that returned p-values ≤ 0.25 were included in a multivariate logistic regression model as potential confounders. Variables that were missing more than 10% of observations, which were hyperlipidemia and wait time in weeks, were excluded.

To address effect modification in this study, all two- and three-way interaction terms between treatment regimen type and potential confounders were included in initial models. Interaction terms were dropped when they were not significant at $p<0.05$. An all-possible-subsets approach was used to assess confounding and compare odds ratios for each subset of variables. Precision estimates were made based on the ratio of the 95% confidence intervals of the odds ratio. The model that retained all covariates, and therefore controls for all potential confounders, was considered the gold standard (GS) model. However, if a subset model had an odds ratio that did not differ by a magnitude of 10% of the GS model, and also had a gain in precision, then this was the recommended model. Models were assessed for collinearity and goodness of fit using the Hosmer-Lemeshow

statistic. All statistical analyses were conducted using SAS 9.4 (SAS Institute, Inc., Cary, North Carolina, USA).

RESULTS

Descriptive statistics

The major findings of descriptive analyses of the 112 HCV-positive patients started on IFN-containing or IFN-free DAA treatment at the GLC are summarized in Table 1. Breakdowns of treatment regimen type are outlined at the top of the table for reference.

There was a higher distribution of male patients on interferon-free treatment regimens compared to those on interferon-containing treatment (63% vs. 48%). The mean age of both groups were fairly similar (57 years vs. 58 years), however there was a higher percentage of younger patients in the group on older DAAs. Majority of patients on older DAAs were black (90%, n=55), and only 8% were white (n=5). Among patients on newer DAAs, a fourth of patients were white (n=13), and 75% of patients were black (n=38). There was only one patient of Hispanic ethnicity in the whole study, who was also treated with an interferon-containing treatment regimen. There was a higher distribution of patients with public health insurance among the newer DAA group (61% vs. 49%), and a similar distribution of patients with private health insurance (about 12% for both regimen types). However, there were more patients without health insurance on older DAAs (40%, n=24) compared to patients on newer DAAs (27%, n=14).

Although onset of fibrosis ranged greatly in the study population, there seemed to be greater liver damage among patients on older DAA regimens. Almost a third of patients on newer DAAs had no liver fibrosis (31%, n=16), vs. four patients on older DAAs having no liver fibrosis (7%). A higher distribution of patients on older DAAs were among F1, F2, and F3 liver fibrosis stages compared to patients on newer DAAs. However, there were eight patients with liver cirrhosis on newer DAAs (16%) compared to four patients with cirrhosis on older DAAs (7%). Three patients on older DAA regimens had missing data on fibrosis stage.

Having a genotype 1 HCV infection was an inclusion criteria among patients on triple therapy (interferon-containing regimens with either boceprevir or telaprevir). As a result, most of the patients on older DAA regimens had a genotype 1 infection (97%, n=59). Two patients on the interferon-containing regimen (3%), SOF/P/R, had a genotype 4 infection. Three quarters of patients on new DAA regimens had a genotype 1 infection, 20% had a genotype 2 infection, and one patient (2%) had a genotype 3 infection. No patients on newer DAA regimens had a genotype 4 infection.

Both APRI and FIB4 score averages were higher among patients on newer, interferon-free regimens. Three quarters of patients on older DAAs had not had prior CHC treatment (77%, n=47), while a greater number of patients on newer DAAs had a treatment history of interferon and ribavirin for CHC (35% vs. 23%).

Medical and psychiatric comorbidities seemed to be slightly more prevalent among patients on newer DAA regimens. However, this was not the case with hypertension, as 73% of patients on older DAAs had hypertension compared to 63%

of patients on newer DAAs. Patients on triple therapy were excluded if they had an HIV/HCV co-infection, which resulted in more patients with HIV and HCV in the newer DAA group. The distribution of depression, diabetes, and obesity were similar among the two groups of patients. Patients on triple therapy did not have data on hyperlipidemia.

Treatment outcomes

Only three out of 51 patients on newer DAA regimens did not complete treatment (6%) due to non-compliance or incarceration during treatment. However, 13 patients out of 61 on older DAAs (21%) did not complete treatment, and 48 patients (79%) completed treatment. Reasons for not completing treatment among patients on older DAAs were lost to follow-up or discontinuing treatment due to side effects. The average wait time for patients on newer DAAs was 80.5 weeks. The wait time for patients on older DAA regimens was 60.5 weeks, however patients on triple therapy had missing data on wait time.

A higher percentage of patients on interferon-free treatments were able to achieve SVR after 12 weeks of treatment (73%) compared to patients on interferon-containing regimens (56%). Out of the 61 patients on older DAAs, 24 of them did not clear SVR (39%), compared to 8 out of 51 patients on newer DAAs who did not clear SVR (16%). Most patients on newer DAAs had a successful end-of-treatment response (ETR) (90%, n=46), compared to 74% of patients on older DAAs (n=45).

Univariate analyses

Table 2 examines the univariate associations between the outcome of achieving SVR after 12 weeks of treatment completion and various exposure variables of interest for study patients with data on treatment status (n=112).

Treatment regimen

When comparing interferon-containing regimens with interferon-free treatment regimens, there was an overall association between regimen and SVR, significant at the $p<0.1$ level. Patients who cleared SVR after 12 weeks of treatment were more likely than those who did not clear SVR to be on newer, interferon-free treatment. There was also an overall association between the individual types of CHC treatment and successful treatment outcome. There were significant associations between treatment outcome and the TVR, BCV, and SOF/LDV regimens. Being treated with either of the triple therapy regimens (telaprevir or boceprevir with interferon and ribavirin) or the SOF/LDV regimen (sofosbuvir with ledispasvir) was significantly associated with *not* achieving SVR after 12 weeks of treatment.

Other variables

No demographic, HCV-specific, or comorbidity variables were found to be associated with successful treatment outcome at the $p<0.1$ level, except continuous age ($p=0.0889$). Race/ethnicity was not found to be associated with successful treatment outcome, as well as most of the other demographic or HCV-specific

variables of interest. However certain comorbidities were found to be associated with achieving SVR at the $p<0.2$ level, such as an HCV co-infection with HIV and diabetes.

Multivariate analyses

Based on the results of univariate analyses, an appropriate model was chosen and analyzed for multiple logistic regression. The adjusted odds ratios, corresponding 95% confidence intervals, and p-values for the potential models are summarized in Table 3. Interaction assessment was performed between all possible covariates. All two- and three-way interaction terms returned p-values greater than 0.05 when comparing full and reduced models, and were subsequently removed. The reduced model without interaction was then used as the GS model when assessing the presence of confounding.

The logistic regression model included the main predictor, treatment regimen type, as a dichotomous variable, and exposures of age, HIV/HCV co-infection, and diabetes co-infection. Using an all-possible subsets approach, the associations between all combinations of predictors and successful treatment outcome, achieving SVR after 12 weeks of CHC treatment, were examined. Odds ratios were compared to that of the gold standard (GS) model, and precision was examined by the ratio of 95% confidence intervals.

There were several models that were within 10% of the GS estimate (OR = 1.951 [0.818, 4.658]), including models 2, 4, 5, 6, and 8 (Table 3). Only two models were outside of the 10% range, which were the models containing age and diabetes,

and only diabetes, in combination with exposure of DAA regimen type. Out of the five acceptable models, the model with the tightest confidence intervals was the model with no covariates except treatment regimen type (model 8: OR = 2.10 [0.947, 4.651]). The next model with the highest precision contained DAA regimen type and age (model 5: OR = 2.09 [0.942, 4.647]). Since there was no interaction, these two models are the only models with an OR estimate within 10% of the GS model, and they also both have more precision than the GS model. Although model 8 is slightly more precise, these two models were very similar in point estimates and confidence interval ratios.

All Hosmer-Lemeshow p-values were >0.05, indicating good model fit. There was no evidence of collinearity in any of the models analyzed.

DISCUSSION

General findings

Baseline characteristics showed that there were more patients without health insurance, of black race, and younger age who were started on older DAA regimens with interferon (Table 1). There seemed to be more patients with a higher fibrosis stage on older DAA regimens, but more patients with cirrhosis on newer DAA regimens. Patients on newer DAAs also had higher mean APRI scores and FIB4 scores. Additionally, patients on the newer DAA treatments tended to have more medical and psychiatric comorbidities (except hypertension), which may indicate the greater ability of newer DAA therapies to treat CHC.

Although age, HIV/HCV co-infection, and the presence of diabetes seemed to significantly affect successful CHC treatment, these associations did not hold true when controlled for in multivariate logistic regression.

Associations between race and treatment outcome

The Grady Liver Clinic is a unique model in which general internists provide CHC treatment and management of a predominantly low-income, underserved, minority population. This was apparent in the racial distribution of patients in our study, as more than 80% of the original study population was black. There were also distinct associations between race and successful treatment outcome, although not evident statistically. For example, there were only five white patients who were started out on older DAA regimens (one on SOF/P/R, and four on triple therapy with telaprevir), and only three of these five completed treatment. Out of the three white patients who completed treatment, the one patient on SOF/P/R was the only patient who achieved SVR out of all the white patients in the study. Majority of patients who cleared SVR on older DAA regimens (n=32, 94%) were black.

The racial distribution of patients on newer DAAs was slightly more even, as 73% (n=27) of those achieving SVR were black, and 27% (n=10) were white. White patients on the newer DAA regimens did not have the same race-treatment association as white patients on older DAAs, as 10 out of the 13 white patients (77%) were able to complete treatment and achieve SVR.

Associations between DAA regimen type and treatment outcome

This study shows that patients on interferon-free treatment regimens had a higher chance of being able to complete treatment and achieve SVR compared to patients on interferon-containing treatment regimens. There were significant associations between newer DAA treatment regimens and overall successful treatment outcomes in initial, univariate comparisons. Patients on newer DAA regimens were more likely to achieve SVR after 12 weeks of treatment at the $p<0.1$ level ($p=0.0659$). GLC patients were also found to more likely complete treatment when on newer, interferon-free DAA regimens at the $p<0.5$ level ($p=0.0201$).

Patients on boceprevir- or telaprevir- containing triple therapy seemed to have particularly low treatment completion and SVR rates. There were only three patients on triple therapy with boceprevir, and all three of them did not achieve SVR (two did not complete treatment, and the remaining one completed treatment but did not achieve SVR). There were 38 patients on triple therapy with telaprevir, however 11 of them did not complete treatment, and 6 more completed treatment, but did not achieve SVR. Three more patients had missing SVR data. The small sample size of both patient groups most likely further exacerbated the relationships found in this study.

Logistic regression confirmed the results of initial analyses between the exposure of DAA regimen type and successful treatment outcome. The odds of successfully completing CHC treatment and achieving SVR for those on newer, interferon-free DAA treatment is 2.10 compared to the odds of completing treatment and achieving SVR on older, interferon-containing DAA treatment. This

point estimate was found to be the strongest and most precise among all possible models controlling for certain variables. A model controlling for continuous age was also found to be quite strong, but less precise than the previously described model. There were fewer barriers to treatment completion found for patients on the newer generation of DAAs compared to patients on the older generation of DAAs.

Study limitations

Study design

Due to this study's cross-sectional design, patients and subsequent data were not followed over time, but only observed at one moment in time. Also, our patient group was first selected and then data was collected, rather than being able to select a population who are at risk of disease, like in a cohort study. The design of this study limits the conclusions that can be drawn about the direct causal effect of predictors on CHC treatment success.

Data limitations

The initial sample size of GLC patients on CHC treatment was relatively small, and missing data was common. Additionally, due to the recent treatment start date of many patients on the second generation of DAA regimens, many patients had a pending treatment completion status or pending SVR status. These patients had to be excluded from the bulk of analysis due to unusable outcome data, which greatly reduced the number of patients counted as successfully completing treatment on the newer DAAs. This was especially true for most of the patients on the

sofosbuvir/ledispasvir (SOF/LDV) regimen, one of the newer DAA therapies. Although there were 54 total patients on this interferon-free regimen, 46 of them (85%) had pending SVR statuses, which was half (49.54%) of the total number of patients on the second generation of DAAs. This factor could result in a loss of power in the statistical tests performed, which could explain the noticeable but not statistically significant univariate and multivariate associations among the predictors with treatment success.

Additionally, some variables available in the dataset of the triple therapy era (2011-2013) were incomplete or unavailable in the dataset of newer DAAs (collected 2013-2015), and vice versa. Patients from the triple therapy era did not have data on the date of their first appointment (for the calculation of the patient's wait time for treatment initiation), or presence of hyperlipidemia. These variables could not be addressed in analyses due to the lack of data.

GLC patients in the triple therapy era (2011-2013) were excluded if they had an HIV/HCV co-infection, but patients on newer DAA regimens were not. Therefore, selection bias is possible since patients infected with HCV and HIV were excluded in part of the dataset, and this exclusion was not applied for all patients in the study population. The same applies for analysis of HCV genotype, since only patients with a genotype 1 HCV infection were treated with triple therapy treatments. HIV co-infection was included in multivariate logistic regression due to its significance at a $p<0.2$ level, but was not a factor in the final selected model. The results in terms of HIV co-infection or HCV genotype in this study may not be representative of barriers to successful treatment among general CHC patient populations.

Outcome variable definitions

Patients who were lost to follow-up (whether they completed treatment or not) were categorized as not achieving SVR. This difference could result in varying interpretations of SVR results and data validity. For example, most of the patients on newer, interferon-free regimens who were categorized as not achieving SVR were actually lost to follow-up due to non-response, noncompliance, or incarceration. Many patients were able to complete CHC treatment, but had missing SVR statuses in the database.

CONCLUSION

Despite advances in treatment and novel regimens, successful treatment outcomes have been difficult to observe in primary care-based Hepatitis C clinics. This is especially true among low-income, uninsured, minority patient populations, who represent a significant gap in CHC care. The aim of this study was to evaluate whether CHC patients of a largely urban, and underserved population had better treatment outcomes on newer DAAs therapies compared to earlier patients on interferon-containing therapies.

Despite the various limitations, this study provides evidence that patients on older, interferon-containing treatment regimens may have more difficulty in successfully completing CHC treatment and achieving SVR. This was also supported in the literature and in clinical trials. Although SVR rates of GLC patients during the triple therapy era (2011-2013) were quite low, these were also the first generation of DAA regimens implemented in this primary care-based clinic. Once patients on

newer DAA regimens such as sofosbuvir/ledispasvir (SOF/LDV) complete treatment and have data on SVR rates, the results of these analyses have the potential to be much stronger and statistically significant. Even without full outcome data, GLC patients seemed to have greatly improved completion and SVR rates with the second installment of regimens, especially among the oral, interferon-free therapies. This improvement in treatment outcomes can only grow as interferon-containing regimens become less common, and oral, interferon-free therapies become standard treatment for CHC.

Additionally, there were no factors or predictors found to significantly affect achieving SVR after treatment other than the type of DAA regimen taken. These findings indicate that the Grady Liver Clinic is a successful model for retaining patients of underserved, racial minorities in CHC treatment, while reducing significant barriers to treatment that patients typically face in clinical models in these settings. As more improved and effective interferon-free treatments become approved and available, the GLC and other primary care clinics can expand treatment capacity in settings with clinically challenging patients, eliminating barriers that were prevalent in the past.

Next steps

More data are needed to better describe statistically the advantage of using these regimens without interferon, to treat CHC in clinical settings. Even analyzing the same cohort again in a few months would drastically improve the information and results available in this study. Once the 46 patients on the interferon-free regimen, sofosbuvir/ledispasvir, complete treatment and have SVR data, this analysis can be repeated again with the chance of stronger and more statistically significant results. This could further support the improvement and encouraged usage of treatment regimens without interferon. It would also be interesting to look at other demographic variables not covered in this study, such as household annual income or education level, in order to better understand the demographic barriers to completing CHC treatment and successfully achieving SVR.

TABLES

Table 1. Baseline characteristics of patients started on CHC treatment with complete data, GLC (2011-2015) (n=112)

	Patients on older DAAs (IFN-containing) (n=61)	Patients on newer DAAs (IFN-free) (n=51)
VARIABLES	**n (%)**	**n (%)**
Regimen	**TVR: 38 (62.30)**	**SIM/SOF: 32 (62.75)**
	BCV: 3 (4.92)	**SOF/R: 11 (21.57)**
	SOF/P/R: 20 (32.79)	**SOF/LDV: 8 (15.69)**
Demographics		
Gender		
Male	29 (47.54)	32 (62.75)
Age (years)	56.95 ± 5.52	57.96 ± 7.32
18-59	40 (65.57)	24 (47.06)
60+	21 (34.43)	27 (52.94)
Race/ethnicity		
White	5 (8.20)	13 (25.49)
Black	55 (90.16)	38 (74.51)
Hispanic	1 (1.64)	0
Health Insurance		
Public	30 (49.18)	31 (60.78)
Private	7 (11.48)	6 (11.76)
None	24 (39.34)	14 (27.45)
Biological characteristics		
Fibrosis stage		
F0	4 (6.56)	16 (31.37)
F1	9 (14.75)	5 (9.80)
F2	19 (31.15)	5 (9.80)
F3	16 (26.23)	10 (19.61)
F4	6 (9.84)	7 (13.73)
Cirrhosis	4 (6.56)	8 (15.69)
(missing)	3 (4.92)	0
Genotype		
1	59 (96.72)	40 (78.43)
2	0	10 (19.61)
3	0	1 (1.96)
4	2 (3.28)	0
FIB4	2.16 ± 1.16	3.88 ± 3.87
Mean APRI score	0.76 ± 0.64	1.47 ± 2.02
Treatment History		
Peg-IFN/RBV	14 (22.95)	18 (35.29)
naïve	47 (77.05)	33 (64.71)
Comorbidities		
HIV	4 (6.56)	18 (35.29)
Depression	21 (34.43)	21 (41.18)
Diabetes	15 (24.59)	16 (31.37)
Hyperlipidemia	5 (8.20)	3 (5.88)
(missing)	41 (67.21)	0

Obesity	28 (45.90)	16 (31.37)
Hypertension	44 (72.13)	32 (62.75)
Treatment Outcome		
Completed treatment?		
Yes	48 (78.69)	48 (94.12)
No	13 (21.31)	3 (5.88)
Pending	0	0
Wait Time in Weeks	60.51 ± 52.20	80.56 ± 51.57
(missing)	41 (67.21)	0
Cleared SVR in 12 weeks		
Yes	34 (55.74)	37 (72.55)
No	24 (39.34)	8 (15.69)
(missing)	3 (4.92)	6 (11.76)
ETR		
Yes	45 (73.77)	46 (90.20)
No	16 (26.23)	3 (5.88)
Pending	0	1 (1.96)
(missing)	0	1 (1.96)

Table 2. Univariate analysis of factors associated with achieving SVR among patients with complete data, GLC (2011-2015) (n=112)

VARIABLES	Unadjusted OR	95% CI	p-value
Demographics			
Gender			
Male	1.2289	(0.5682, 2.6576)	0.6005
Age (years)	1.066	(0.5470, 2.077)	**0.0899**
18-59	Referent		
60+	0.935	(0.4303, 2.0314)	0.8650
Race/ethnicity			0.7342
White	Referent		
Black	1.0123	(0.3638, 2.8163)	0.9814
Hispanic	1.766	(0.0703, 44.3535)	0.9494
Health Insurance			
Public	1.0526	(0.4866, 2.2769)	0.8964
Private	Referent		
None	1.1706	(0.5164, 2.6537)	0.7061
Biological characteristics			
Fibrosis stage			
F0	1.1481	(0.4167, 3.1630)	0.7895
F1	0.5574	(0.1803, 1.7229)	0.3100
F2	1.2692	(0.4888, 3.2958)	0.6244
F3	Referent		
F4	0.96	(0.2917, 3.1597)	0.9462
Cirrhosis	0.8262	(0.2441, 2.7967)	0.7590
Genotype			
1	1.0938	(0.3327, 3.5953)	0.8827
2	Referent		
3	1.766	(0.0703, 44.3535)	0.4453
4	0.5714	(0.0348, 9.3866)	0.6951
FIB4	0.712	(0.3650, 1.389)	0.3915
Mean APRI score	0.690	(0.3540, 1.3471)	0.5317
Treatment History			
Peg-IFN/RBV	0.9477	(0.4057, 2.2140)	0.9010
naïve	Referent		
Comorbidities			
HIV	2.2667	(0.7677, 6.6922)	**0.1385**
Depression	0.9028	(0.4090, 1.9927)	0.8001
Diabetes	0.5042	(0.2166, 1.1737)	**0.1121**
Obesity	0.7383	(0.03373, 1.6158)	0.4477
Hypertension	1.1549	(0.5095, 2.6178)	0.7302
Treatment regimen			
IFN-containing regimens (Old DAAs)	Referent		
IFN-free regimens (New DAAs)	2.0987	(0.0469, 4.6518)	**0.0659**
Regimen type			**0.0002**
TVR	0.4231	(0.1886, 0.9491)*	**0.0350**
BCV	0.0769	(0.0039, 1.5281)	**0.0468**
SOF/P/R	1.9286	(0.6450, 5.7666)	**0.2345**
SIM/SOF	Referent		
SOF/LDV	0.1691	(0.0324, 0.8814)*	**0.0494**
SOF/R	1.0117	(0.2775, 3.6880)	0.9859
Treatment Outcome			
Completed treatment?			
Yes	3.8400	(2.7411, 5.3794)	**<0.0001**
ETR			
Yes	4.5500	(3.0895, 6.7009)	**<0.0001**

*Denotes statistically significant confidence intervals

**P-values < 0.25 are bolded

Table 3. Multivariate logistic analysis of factors associated with achieving SVR among GLC patients with complete data (2011-2015) (n=112)

Model #	Variables in Model	OR	within 10% of GS?	95% CI	CI width	CI ratio	p	GOF p
1	Age, Diabetes, HIV co-infection, DAA type*	1.95	--	(0.818, 4.658)	3.840	5.690	0.1320	0.4980
2	Age, HIV co-infection, DAA type	1.79	**Yes**	(0.765, 4.191)	3.426	5.480	0.1794	0.7019
3	Age, Diabetes, DAA type	2.25	No	(0.992, 5.090)	4.098	5.130	0.0523	0.5715
4	Diabetes, HIV co-infection, DAA type	2.00	**Yes**	(0.841, 4.749)	3.908	5.650	0.1170	0.1000
5	Age, DAA type	2.09	**Yes**	(0.942, 4.647)	3.705	4.930	0.0699	0.5225
6	HIV co-infection, DAA type	1.82	**Yes**	(0.780, 4.225)	3.445	5.420	0.1661	0.2468
7	Diabetes, DAA type	2.27	No	(1.004, 5.134)	4.130	5.110	0.0489	0.5762
8	**DAA type alone**	**2.10**	**Yes**	**(0.947, 4.651)**	**3.704**	**4.910**	**0.0680**	**NA**

*Denotes GS model

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APPENDIX

EMORY UNIVERSITY | Institutional Review Board

TO: Lesley Miller, MD
Principal Investigator
GenMed

DATE: March 26, 2015

RE: **Notification of Amendment Approval**
AM13_IRB00008840
IRB00008840
The Grady Liver Clinic: Description of a patient population and analysis of success rates of hepatitis C treatment

Thank you for submitting an amendment request. The Emory IRB reviewed and approved this amendment under the expedited review process on **3/25/2015**. This amendment includes the following:

Changes to Protocol Document(s):

- Revised protocol to reflect the addition of a new cohort of subjects

Changes to Study Team members:

- Adding Anne Spaulding to the study team as a Co-Investigator

- Adding Fances Kim to the study team as a Co-Investigator

Changes to study enrollment:

- Adding a new cohort of subjects for a retrospective chart review

The following documents were reviewed with this submission:

- Liver Clinic Protocol AM13 (Version date, 3/18/2015) clean and tracked changes versions

- DAA Log (Version date, 3/17/2015)

Important note: If this study is NIH-supported, you may need to obtain NIH prior approval for the change(s) contained in this amendment before implementation. Please review the NIH policy directives found at the following links and contact your NIH Program Officer, NIH Grants Management Officer, or the Emory Office of Sponsored Programs if you have questions.

Policy on changes in active awards: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-129.html

Policy on delayed onset awards: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-12-130.html

In future correspondence with the IRB about this study, please include the IRB file ID, the name of the Principal Investigator and the study title. Thank you.

Sincerely,

Jennifer Truell, MA
IRB Analyst Assistant
This letter has been digitally signed

CC:	Fluker	Shelly-Ann	GenMed
	Kim	Frances	Public Health
	Spaulding	Anne	Epidemiology

Emory University IRB
1599 Clifton Road, 5th Floor - Atlanta, Georgia 30322
Tel: 404.712.0720 - Fax: 404.727.1358 - Email: irb@emory.edu - Web: http://www.irb.emory.edu/

Grady

Research Oversight Committee (ROC)
Division of Medical Affairs
80 Jesse Hill Jr. Drive SE
P. O. Box 26118, Atlanta, GA 30303

Research Administration
Office: 404-616-7757
Fax: 404-616-0747

PI Name: MILLER, LESLEY
C/O: MILLER, LESLEY
Organization: EMORY (SOM)
Department: Medicine
Office: (404) 778-1635
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Date: 4/14/2015

IRB#: 000-8840
IRB Expires: 1/24/2016
ROC Expires: 2/24/2016
CT Plan Code: N/A

Protocol Title: The Grady Liver Clinic- Description of a patient population and analysis of success rates of hepatitis C treatment

Re: **Research Protocol: MODIFICATION**

The Grady Research Oversight Committee (ROC) has reviewed and **APPROVED** the documents submitted for your research protocol.

Please note the ROC Expiration date listed above. Thereafter, continued approval is contingent upon the submission of a renewal form that must be reviewed and approved by the ROC prior to the expiration date of this study.

Please note the clinical trial insurance plan code assigned to your study, IF APPLICABLE. You will need to use this code when registering patients for Grady services related to this research protocol.

Also, please notify the ROC when this proposal has been terminated or completed. All inquiries and correspondence concerning this protocol must include the IRB # and the name of the Principal Investigator. Any further reviews by the IRB pertaining to this proposal should be submitted to the ROC. This includes: Approved IRB Renewals, Modifications (Protocol, Informed Consent, Personnel, etc.) and any Adverse Events.

The committee would be interested in receiving the report of your research results and copies of any publications or presentations resulting from this research.

Sincerely,

Curtis A. Lewis, MD
Sr. Vice President and Chief of Staff
Chairman, Research Oversight Committee