ABSTRACT

Background. All-oral direct acting antivirals (DAAs) provide an unprecedented opportunity to eliminate hepatitis C virus (HCV) as a public health threat. But challenges across the care continuum persist. These challenges are particularly poignant for persons co-infected with HIV who are high-priority to cure but not well engaged in HCV care. Strategies to improve the HCV care continuum for this population are urgently needed.

Methods. The Care2Cure study was a single-blinded randomized controlled trial to test the effect of a multi-component HCV nurse case management intervention (nurse-initiated referral, strengths-based education, patient navigation, and care coordination) on linkage to HCV care and time to DAA initiation. Adults co-infected with HIV/HCV not engaged in HCV care were recruited from an urban, outpatient infectious disease practice.

Results. Between July 2016 and February 2018, 68 participants were randomized to receive nurse case management (n=35) or an HCV fact sheet (n=33) in addition to usual care. Participants were primarily Black/African-American (81%) and low income (98% on public health insurance). At day 60, 47% of nurse case management participants linked to HCV care, compared to 25% of usual care participants (p=0.036 by z test for difference in proportions; confidence bound 3.2%-40.9%). There was no significant difference in time to treatment initiation by Kaplan Meier estimates. In logistic regression, participants who drank alcohol were more likely to schedule an HCV appointment (adjusted odds ratio [aOR]=3.8), attend the appointment (aOR=3.8), and be prescribed DAAs (aOR=4.2). Knowing someone who cured HCV increased the
likelihood of being prescribed (aOR=5.2) and initiating (aOR=8.0) DAAs. A higher CD4 cell count was associated with greater odds of scheduling an HCV appointment (aOR=1.002). Participants taking medication-assisted treatment (MAT) were less likely to be prescribed DAAs (aOR=0.25).

Conclusions. These results support provision of nurse case management to link adults co-infected with HIV to HCV care. Interventions that continue from linking to care through cure are needed to achieve HCV elimination in this high-priority population. Capitalizing on social networks and treatment pathways for patients drinking alcohol may help improve the HCV care continuum. Integrated substance use and HCV care to engage patients taking MAT should be considered.

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PREFACE

Acknowledgements

The last five years would not have come to this end without the unwavering support of the community around me. Johns Hopkins University is a place of collective thought, where sharing is the norm and there is a sense that we’re all in it together. Thank you to my colleagues and lifelong friends in the PhD program; it feels like this dissertation work is as much yours as it is mine.

I am grateful for the guidance offered by the faculty and staff at the School of Nursing and across the East Baltimore Campus. Dr. Jason Farley, my advisor, dedicated his time and intellect to years of invaluable mentorship about all-things PhD, from designing and managing a research study, to perfecting a visual presentation, to career advice that I will take with me for years to come and hope to pass on to the next generation. Dr. Mark Sulkowski guided me through his world of viral hepatitis with renowned expertise that I am so fortunate to benefit from. Dr. Chakra Budhathoki provided encouragement and clarity to the methods of this study and others. Dr. Hae-Ra Han critiqued this work with her brilliant eye and improved this research considerably. Dr. Nancy Reynolds stepped in as an advocate for this dissertation project and giver of wisdom for the future of my work.

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pick me up, give me my own voice, and never let me get away with not being my true self. I love you all.

Finally, this dissertation work is dedicated to my grandmother, Claire Wade. In our final conversation shortly after my 18\textsuperscript{th} birthday, I promised Granny I would become a doctor so I could prevent others from suffering. While this may not be the type of doctor either of us imagined at the time, it is my hope that this dissertation represents the beginning of a trajectory of nursing research to realize this goal of mitigating human suffering.

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CHAPTER 1: Introduction

Chronic infection with hepatitis C virus (HCV) is a leading cause of liver cancer and the most common non-AIDS-related cause of death among persons living with HIV (PLWH) (Centers for Disease Control and Prevention, 2016; Ly et al., 2012). One in four people with HIV are co-infected with HCV, and approximately 80% of injection drug users who have HIV also have HCV (Centers for Disease Control and Prevention, 2016). Co-infection with HIV increases HCV-related progression to cirrhosis and end stage liver disease three-fold, indicating an urgent need to treat and cure HCV in this population (Deng, Gui, Zhang, Gao, & Yang, 2009; Graham et al., 2001; Lo Re et al., 2014).

The World Health Organization has called for HCV elimination by 2030 (World Health Organization, 2016). Prior to 2014, HCV treatment among PLWH was minimally effective and highly toxic with interferon injections, but contemporary all-oral direct acting antivirals (DAAs) are exceptionally effective, shorter in duration and much less toxic (Thomas, 2014). With these advancements, we have the opportunity to cure HCV in at least 94-97% of people, including PLWH (Naggie et al., 2015; Sulkowski et al., 2015; D. Wyles et al., 2017; D. L. Wyles et al., 2015). However, medication availability and the promise of HCV cure alone are not sufficient to engage all people in care. Challenges across the HCV continuum of care persist, especially in the HIV-co-infected population, who have a lower odds of receiving HCV treatment than HCV mono-infected individuals (Grebely et al., 2008; Mehta et al., 2008; Reed et al., 2008). Nonetheless, HCV treatment guidelines recommend prioritizing treatment for persons co-
infected with HIV (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018).

**The HCV care continuum among PLWH is unsatisfactory.** In 2014, it was reported that only 7% of persons with HIV/HCV co-infection had achieved an HCV cure (Cachay et al., 2014). A large, multi-site study of PLWH who had access to HCV care found that 50% had not been prescribed DAAs and only 44% initiated treatment, even after DAAs had been available for several years (Jayaweera et al., 2018). Understanding the barriers to curing HCV among PLWH is essential. Although we know that the low perceived threat of HCV, low knowledge among patients and providers, and difficulty accessing specialty providers and navigating the healthcare system were barriers to improving the HCV care continuum prior to the introduction of DAAs, few studies have examined predictors of receiving DAAs among PLWH (Alavi et al., 2013; Harris & Rhodes, 2013; Mehta et al., 2008; Yap et al., 2014; Zickmund, Campbell, Tirado, Zook, & Weinrieb, 2012).

In addition, the advent of DAAs has introduced a new barrier that has not yet been addressed among persons co-infected with HIV/HCV: **up to 88% of PLWH may have to switch their HIV treatment regimen to avoid contraindicated drug interactions** (Cope et al., 2015; Patel et al., 2015; Poizot-Martin et al., 2015). The Guidelines for the Use of Antiretroviral Agents in HIV-1-infected Adults and Adolescents emphasize the need to modify HIV regimens to treat HCV in many PLWH (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017). But modifying antiretroviral therapy (ART) can have severe negative consequences, including decreased quality of life, increased symptom burden, and loss of viral suppression (Cope et al., 2015; Sherr et al.,
New approaches to modifying ART are now crucial to smooth the transition into initiating HCV therapy for PLWH.

Prior interventions to promote the care continuum have included a variety of approaches with moderate success. For example, brief HCV education alone was shown to significantly increase knowledge and linkage to HCV care by 14-25% (Chen et al., 2013; Gupta, Romney, Briggs, & Benker, 2007; Surjadi, Torruellas, Ayala, Yee, & Khalili, 2011; Tyler et al., 2014). Similarly, nurse case management and care coordination have also been shown to improve linkage to HIV or HCV care by up to 30% (Craw et al., 2008; Gardner et al., 2005; Tyler et al., 2014). Reminder systems using text and phone messages have also been effective strategies in increasing linkage to HIV care and substance use services in combination with other interventions, but have not been tested in the context of HCV care (Farmer, Brook, McSorley, Murphy, & Mohamed, 2014; Finitis, Pellowski, & Johnson, 2014; van Velthoven, Brusamento, Majeed, & Car, 2013). Yet, a critical gap in the existing approaches is that few linkage to care studies target HCV; the majority of evidence comes from similar populations, including PLWH and substance use disorders. Those that are targeted towards HCV were conducted prior to the era of DAAs, often excluding high-priority populations including persons with mental illness, substance use, or uncontrolled HIV.

This study was designed to address these gaps by testing comprehensive, multi-component nurse case management to improve the HCV care continuum among high-priority adults co-infected with HIV and HCV. The intervention was guided by Andersen’s Behavioral Model of Health Services Use.
Conceptual Framework

Andersen’s Behavioral Model of Health Services Use explains the conditions that facilitate or impede utilization of health care (Andersen, 1995). Initially developed in the 1960s, the model posits that a person’s use of health services is a function of predisposing factors, perceived and actual need for care, and enabling or impeding resources (figure 1). Predisposing characteristics, such as age, sex, race/ethnicity, and substance use, are not easily modified. But perceived need, according to Andersen, can be changed through education; the greater the perceived and actual need, the more likely one is to use services. Andersen also suggests that enabling resources can be influenced by interventions at the system, provider, and patient level. The more enabling resources one has, the greater the likelihood of healthcare utilization.

Interventions that increase perceived need and maximize enabling resources have the potential to improve the HCV care continuum for PLWH. Nurse case management (NCM) components used in similar contexts can be combined to achieve this improvement. Andersen’s model has been applied previously to explain HCV and HIV health care utilization (Henry, Goetz, & Asch, 2012; Holtzman et al., 2015; Mehta et al., 2005; Rapp et al., 2008), and informed the intervention components of this study (nurse-initiated referral, strengths-based education, patient navigation, appointment reminders, and coordinated ART modification).

Purpose

The Care2Cure study was a randomized, single-blinded controlled trial to test whether a nurse case management intervention improves the HCV care continuum among
high-priority PLWH compared to usual HIV primary care. The specific aims of this study were to:

1. Test whether a nurse case management intervention increases linkage to the viral hepatitis practice among persons with HIV/HCV co-infection compared to usual care

   **Hypothesis 1:** A higher proportion of those who are randomized to the intervention arm will attend an appointment at the viral hepatitis practice within 60 days of randomization compared to those who receive usual care.

2. Determine if a nurse case management intervention decreases time to HCV treatment initiation among persons with HIV/HCV co-infection compared to usual care

   **Hypothesis 2:** Those who are randomized to the intervention arm will have a decreased time to HCV treatment initiation from the point of randomization compared to those who receive usual care.

3. Describe the characteristics associated with linkage to HCV care among PLWH, controlling for covariates.

   **Research question 3.1:** What patient-level characteristics are associated with increased linkage to HCV care?

   **Research question 3.2:** Compared to the known historical factors associated with engaging in HCV care, what factors continue to be related to linkage to HCV care in the new paradigm of HCV treatment for PLWH?

**Organization of the Dissertation**

There are six chapters in this dissertation. Chapters 2 through 5 are formatted as manuscripts in accordance with the requirements of the proposed journal for submission.
Chapter 1 introduces the dissertation and provides background information relevant to the study purpose, conceptual framework, and aims of the dissertation.

Chapter 2 offers a guide to nurses on drug-drug interactions between antiretroviral therapy for HIV and direct acting antivirals for HCV. This manuscript reviews the mechanism of action and major considerations of currently-approved DAAs for persons co-infected with HIV. It also suggests that nurse-led interventions may minimize the impact of modifying ART in this population.

Chapter 3 presents the protocol for the Care2Cure study. This manuscript details the significance, planned procedures, statistical methods, and strengths and limitations of the randomized controlled trial. This manuscript has been accepted for publication in *Research in Nursing & Health*.

Chapter 4 reports the results of the Care2Cure nurse case management intervention trial. Sixty-eight participants were enrolled in the study. Participants who received the nurse case management intervention linked to care at a greater proportion (47%) than participants who received usual care plus an HCV fact sheet (25%) (AIM 1). There were no differences in time to treatment initiation among the two study arms (AIM 2).

Chapter 5 describes the patient-level characteristics associated with engaging in HCV care across the continuum, from scheduling an appointment through achieving an undetectable HCV viral load (AIM 3). Among 68 participants, alcohol use, higher CD4 cell count, and knowing someone who had cured HCV were associated with greater odds of succeeding in the HCV care continuum. Medication assisted treatment for opiate use predicted a decreased likelihood of engaging in the HCV care continuum.
Chapter 6 synthesizes the findings of the dissertation. Lessons learned from the Care2Cure nurse case management intervention are discussed, along with implications of the results, situated within the study’s strengths and limitations, for eliminating HCV in HIV care settings.
References


Andersen’s Behavioral Model of Health Services Use applied to the HCV care continuum
CHAPTER 2: Management of the patient with HIV/hepatitis C drug interactions: A guide for nurses and nurse practitioners

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Abstract

Background: Up to 88% of people co-infected with HIV/HCV who are initiating HCV treatment will have to switch their HIV treatment regimen. But antiretroviral therapy (ART) switches can negatively impact quality of life, increase HIV symptom burden, and delay HCV therapy. New approaches to switching ART that minimize barriers to curing HCV are urgently needed and nurses should be prepared to manage patients with HIV/HCV drug-drug interactions.

Purpose: The purpose of this paper is to provide a guide for nurses who are caring for patients co-infected with HIV and HCV on HIV/HCV drug interactions and to delineate nursing strategies to manage ART switches when needed.

Methods: To complete this review, a search of English language publications was conducted in PubMed, CINAHL, and Embase databases (2011–2017). HIV and HCV treatment guidelines were also reviewed.

Conclusions: The potential for ART/DAA drug interactions poses a clinical challenge in the HIV co-infected population. No studies to date describe interventions to ease ART modifications in the setting of HCV treatment initiation. Nurses are in a position to lead the way in addressing this new and major need for ART switches among PLWH. This paper provides a framework for nurses to identify, coordinate and support ART switches to improve HIV and HCV outcomes in their patients.

Key Words: antiretroviral therapy, hepatitis C, direct acting antivirals, drug interactions, HIV, nursing care
**Background**

We are at a defining moment for hepatitis C virus (HCV) care. Although one in four people living with HIV (PLWH) are co-infected with HCV (Centers for Disease Control and Prevention, 2016), all-oral direct acting antivirals (DAAs) can cure HCV in just 12 weeks for most patients, paving a path for HCV elimination (World Health Organization, 2016). While necessary, these new advances are not sufficient to get PLWH to the point of starting and succeeding in HCV treatment. Challenges in the HCV care continuum, including linking patients to care and medication adherence, persist (Cachay et al., 2014). In addition, the presence of drug interactions between antiretroviral therapy (ART) and DAAs complicate both HIV and HCV care decisions in this new era (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017; Patel et al., 2015). HCV treatment guidelines no longer separate patients with HIV/HCV co-infection from those with HCV mono-infection because cure rates (over 93%) are similar in both groups (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018). According to the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) HCV Guidance, the only difference in treatment of HCV among those co-infected with HIV is the need to manage interactions with ART (AASLD/IDSA 2018).

Multiple studies have demonstrated a high prevalence of drug-drug interactions in clinical cohorts of HIV/HCV co-infected patients. A cross-sectional examination of medication lists revealed that the prevalence of interactions was as high as 88.4% depending on the HIV and HCV regimens (Patel et al., 2015). In retrospective chart reviews, studies have similarly found that the majority of HIV/HCV co-infected patients
in their clinics were prescribed ART regimens that are contraindicated with common DAAs (Cope et al., 2015; Poizot-Martin et al., 2015). Prospectively, studies report that around one-third of HIV/HCV co-infected adults have changed their ART regimens to safely initiate DAAs, including 27 percent to start paritaprevir/ritonavir/ombitasvir with (3D) or without (2D) dasabuvir (Chromy et al., 2018), 31 percent for ledipasvir/sofosbuvir or simeprevir plus sofosbuvir (Falade-Nwulia et al., 2017), and 68 percent to take elbasvir/grazoprevir (Chromy et al., 2018).

A considerable number of PLWH who are initiating HCV treatment in the era of DAAs will likely have to switch their HIV treatment regimen to avoid a drug-drug interaction. Stopping ART to accommodate DAAs is not a viable option; interruptions in ART are associated with increased risk of mortality in HCV-co-infected PLWH (Tedaldi et al., 2008) and not recommended by the AASLD/IDSA guidelines (AASLD/IDSA, 2018). Thus, according to the Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents, “if the decision is to treat HCV, the ART regimen may need to be switched before HCV treatment is initiated to reduce the potential for drug-drug interactions and/or toxicities that may develop during the period of concurrent HIV and HCV treatment” (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017). But switching an HIV treatment regimen has many clinical and systemic implications for patients who may or may not be virologically suppressed. At the individual level, adverse drug reactions, decreased tolerability, and greater symptom burden can occur in the setting of switching ART (Cope et al., 2015; Sherr et al., 2007). Switching ART can also take several months, decrease quality of life, and deter PLWH from starting HCV treatment (Sherr et al., 2007). ART switches require additional follow
up visits, which can be a burden to the patient in terms of transportation, caregiving, and finances and well as result in greater than 10% higher mean annual health care costs and higher pharmacy costs compared to patients who do not switch ART (Rosenblatt et al., 2017).

Therefore, new approaches to switching ART that minimize barriers to HCV treatment initiation are urgently needed to smooth the transition for PLWH. The development of new all-oral DAAs has created a need to educate nurses to provide patient support and manage their interactions with other key medications. The purpose of this paper is to provide a guide for nurses who are caring for patients co-infected with HIV and HCV in the United States on HIV/HCV drug-drug interactions and to delineate nursing strategies to manage ART switches when needed. To inform this guide, a search of English language publications was conducted with a medical librarian in PubMed, Embase, CINAHL, and Scopus from 2011 to 2017 to account for the beginning of HCV protease inhibitor triple therapy using keywords and major terms including “hepatitis C,” “HIV,” “drug interactions,” and “continuity of care.”

**Direct Acting Antiviral Mechanisms of Action**

HCV is a positive, single-stranded, enveloped RNA virus with extremely high genetic variability (Simmonds, 1999). HCV is comprised of structural and non-structural proteins; structural proteins E1 and E2 play a major role in viral attachment, entry, and fusion and account for most of the variability of HCV, while nonstructural (NS) proteins are far less variable and, consequently, have been the targets of anti-HCV drug development (Simmonds, 1999). Four classes of DAAs targeting NS proteins are available: NS3/4A protease inhibitors, nucleoside and nucleotide NS5B polymerase
inhibitors, non-nucleoside NS5B polymerase inhibitors, and NS5A inhibitors (Table 1). Telaprevir and boceprevir were the first NS3 and NS4A protease inhibitors, respectively, for the treatment of HCV, and have since been replaced with more tolerable and effective DAA NS3 and NS4A protease inhibitors such as grazoprevir, simeprevir, paritaprevir, glecaprevir, and voxilaprevir (AASLD/IDSA, 2018). Recent advances have also introduced NS5B nucleotide polymerase inhibitors (sofosbuvir and dasabuvir) and NS5A protein inhibitors (daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir, and pibrentasvir) with a much greater ability to inhibit the HCV lifecycle. The NS5B protein is key in HCV RNA translation and replication, while NS5A is involved in HCV replication, assembly, and release (Kim & Chang, 2013).

The goal of HCV therapy is sustained virologic response (SVR). SVR is defined as maintaining an undetectable HCV RNA viral load twelve weeks after completing DAA treatment. SVR is considered a cure; 5-year relapse rates after achieving SVR are as low as 0.4% in HCV mono-infected patients and 0.0% in HIV/HCV co-infected patients (Simmons, Saleem, Hill, Riley, & Cooke, 2016). In clinical trials of the new DAAs with co-infected patients, SVR was achieved in 93-100% of study participants (Naggie et al., 2015; Sulkowski et al., 2015; D. Wyles et al., 2017; D. L. Wyles et al., 2015).

**HCV Treatment Guidelines**

The AASLD-IDSA’s continuously updated guidelines for the treatment of HCV are available at www.hcvguidelines.org. Table 2 outlines the approved and recommend first-line treatments for HCV as of October 2017. There is no difference in recommended use for HIV co-infected patients compared to HCV mono-infected patients.
Modifications are instead made to accommodate genotype, severity of liver disease, and presence of renal disease. In 2016, the first pan-genotypic drug, elbasvir/grazoprevir, was approved, although all regimens have been approved to treat genotype 1a, the most common strain in the United States. Additionally, all regimens may be used in naïve and PEGylated interferon/ribavirin treatment-experienced patients without cirrhosis (i.e. metavir score ≤3). Special considerations must be made for patients with compensated and, especially, decompensated cirrhosis; as described in Table 2, these patients may require adding ribavirin and/or extending treatment to 24 weeks (AASLD/IDSA, 2018).

**HIV/HCV Drug Interactions**

Co-prescribing DAAs and ART require diligence to avoid potentially toxic drug-drug interactions. Drug-drug interactions depend on the classes of DAAs and ART involved. Table 3 provides a summary of the ART-DAA interactions by prescribed DAA regimen. Simeprevir administration is the most problematic with ART, as 76-88% of PLWH may encounter a contraindicated drug-drug interaction. Similarly, elbasvir/grazoprevir is contraindicated with all ritonavir-boosted HIV protease inhibitors as well as efavirenz (AASLD/IDSA, 2018).

Sofosbuvir has the fewest interactions with ART of any DAA. The prevalence of drug-drug interactions among PLWH ranged from zero to 24 percent in different studies (Cope et al., 2015; Patel et al., 2015; Poizot-Martin et al., 2015), with tipranavir being the only contraindicated ART along with renal considerations when tenofovir disoproxil fumarate is present (AASLD/IDSA, 2018). For PLWH, the regimens with the fewest drug-drug interactions include sofosbuvir/ledipasvir and sofosbuvir/daclatasvir (Patel et
al., 2015; Cope et al., 2015; Poizot-Martin et al., 2015). Sofosbuvir/velpatasvir also provides a relatively low-risk option (AASLD/IDSA, 2018).

According to a retrospective chart review, 40% of PLWH on boosted PI regimens may be unable to switch to a non-PI regimen to accommodate starting DAAs (Cope et al., 2015). But when indicated, PLWH should switch to an integrase inhibitor-based regimen, as contraindicated drug interactions with DAAs are rare (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017).

The Role of Nurses in Preventing Drug-Drug Interactions and Coordinating ART Switches

Nurses are in a strong position to identify and prevent drug-drug interactions in patients who are concurrently treated for HIV and HCV. A literature review of nurse-led interventions to coordinate drug-drug interaction identification and prevention yielded a framework of nursing activities, many of which are already used by HIV nurses and can easily be adapted to a special focus on HCV. Two studies testing an intervention to improve care for the patient with drug-drug interactions (Adams et al., 2012; Stambough, Roman, Blair, Sidman, & Miller, 2016) and one nurse-specific intervention for HCV management were identified. These evidence-based nursing activities to coordinate drug-drug interactions among the patient with HIV/HCV are depicted in Figure 1.

Systems in place to guide the nurse in recognizing the potential for drug-drug interactions, pre-emptively acting to coordinate and ART switch, and nurse-driven pathways for HCV treatment initiation and adherence can support the role of nurses in this process. Nurses should be prepared to initiate pre-emptive ART switches in patients at least one month prior to a planned DAA start date (Stambough et al., 2016).
retrospective chart review, Stambough et al. (2016) found that, among patients who received a pre-emptive ART switch to a raltegravir-based regimen 4-8 weeks prior to the planned DAA start date, there was no loss of HIV virologic control during HCV therapy or 24 weeks after in their small sample (n=15). Nurse-led coordination of this pre-emptive switch should be aided by decision support tools, such as a drug-drug interaction algorithm (Adams et al., 2012). Adams et al. (2012) employed a non-physician care manager to manage treatment switches and medication switches in PLWH who were starting antidepressant treatment. Similarly, a nurse-driven pathway has been effective in the treatment of HCV prior to the advent of DAAs; Redulla et al. (2015) employed a nurse-driven model to manage initiation of HCV treatment with pegylated interferon/ribavirin and support medication adherence. This protocol included electronic reminder systems for the nurse to collect needed labs, obtain insurance approvals, and schedule patient appointments to avoid delays in treatment initiation and management.

**Discussion and Conclusions**

We have the opportunity to cure all patients infected with chronic HCV, but drug-drug interactions between DAAs and ART pose a clinical challenge in the HIV/HCV co-infected population. Although ART/DAA drug interactions are prevalent, it is important to note that ART switches should be avoided if possible. In 2018 there are multiple options for effective, direct-acting HCV treatment, with newer medications that have limited drug interactions with ART. In addition, the U.S. Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents Living with HIV (2017) have replaced protease inhibitors with integrase inhibitor-based regimens as the recommended initial therapy for HIV. The currently recommended DAAs do not have major interactions with
HIV integrase inhibitors; thus, as patients are newly initiating ART and some treatment-experienced patients choose to transition to INSTI-based regimens for reasons other than HCV treatment, the prevalence of ART/DAA drug interactions may naturally decrease. Similarly, the addition of tenofovir alafenamide (TAF) to replace TDF will render the renal considerations in patients prescribed tenofovir-containing regimens potentially obsolete. Clearly, there is strong clinical evidence for ART regimen modification and simplification in accordance with present guidelines among HCV treatment candidates, but the benefits of ART modification and simplification are just as important for patients who do not have HCV co-infection. Many patients remain on outdated HIV regimens that do need modification to prevent other toxicities. As the HIV treatment guidelines are favorable towards minimizing toxic drug interactions, HIV providers should continue to move toward INSTI-based HIV therapy in all patients, regardless of HCV infection (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017).

While ART/DAA drug interactions are well documented, there is a paucity of research examining interventions to minimize the impact of ART/DAA interactions on PLWH who are starting treatment for chronic HCV. Nurses are in a position to lead the way in addressing this new need for ART switches among PLWH where switching ART cannot be avoided. This article reviews successful interventions used to improve both HCV care in the pegylated interferon era and HIV to present evidence-based nurse-led interventions to decrease the impact of HIV-HCV drug interactions for this complex group. We provide a framework for nurses to identify, coordinate and support ART switches to improve HIV and HCV care continuum outcomes in their patients co-infected with HIV and HCV and reduce morbidity and mortality. Few studies describe
interventions to improve the HCV care continuum in this all-oral era of HCV therapy; most available research was conducted prior to DAAs, representing a very different HCV epidemic. Lessons can be learned from HIV nurse case management and care coordination models; however, more research is needed in this era of all-oral HCV therapy to determine the most effective strategies to proactively identify drug-drug interactions and support ART switches to accommodate DAAs in a safe and timely manner.

**Resources for the Management of the Patient with HIV/HCV Co-infection**

**AASLD-IDSA HCV Guidance**

- hcvguidelines.org

**University of Liverpool HEP Drug Interaction Checker**

- hep-druginteractions.org

**Adult and Adolescent ART Guidelines (Table 12)**

- aidsinfo.nih.gov/guidelines

**List of current FDA-approved and discontinued HCV treatments with prescribing information and links to relevant clinical trials**

- http://www.hepatitisc.uw.edu/page/treatment/drugs
References


Accommodate Direct Acting Antivirals. *AIDS Patient Care and STDs, 29*(7), 379–383. https://doi.org/10.1089/apc.2015.0004


## Tables and Figures

### Table 1: Four Classes of Direct Acting Antivirals

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<thead>
<tr>
<th>DAA Class</th>
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</thead>
<tbody>
<tr>
<td>NS3/4A protease inhibitors</td>
<td>-previr-</td>
<td>grazoprevir paritaprevir simeprevir glecaprevir voxilaprevir</td>
</tr>
<tr>
<td>NS5B polymerase inhibitors</td>
<td>-buvir-</td>
<td>sofosbuvir dasabuvir</td>
</tr>
<tr>
<td>Nucleoside and nucleotide</td>
<td>-buvir-</td>
<td>sofosbuvir dasabuvir</td>
</tr>
<tr>
<td>Non-nucleoside and nucleotide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS5A inhibitors</td>
<td>-asvir-</td>
<td>daclatasvir elbasvir ledipasvir ombitasvir velpatasvir pibrentasvir</td>
</tr>
</tbody>
</table>

**Table 1.** Four Classes of Direct Acting Antivirals
# Table 2: Available Direct Acting Antiviral Regimens

<table>
<thead>
<tr>
<th>DAA</th>
<th>Dose/Duration</th>
<th>Recommended Use</th>
</tr>
</thead>
</table>
| Ledipasvir/sofosbuvir (Harvoni) | 90mg/400mg PO daily 12 to 24 weeks | - GT 1, 4, 5, 6  
- No cirrhosis  
- Compensated cirrhosis (GT 4)  
- Decompensated cirrhosis (+RBV; GT 1, 4) |
| Elbasvir/grazoprevir (Zepatier)  | 50mg/100mg PO daily 12 to 16 weeks | - GT 1, 4  
- No cirrhosis  
- Compensated cirrhosis  
- ESRD (GT 1, 4) |
| Sofosbuvir/velpatasvir (Epclusa)  | 400mg/100mg PO daily 12 weeks | - GT 1, 2, 3, 4, 5, 6  
- No cirrhosis  
- Compensated cirrhosis  
- Decompensated cirrhosis (+RBV or 24wks; GT 1, 2, 3, 4) |
| gleecapevri/pibrentasvir (Mavynret)  | 300mg/120mh PO daily 8 to 16 weeks | - GT 1, 2, 3, 4, 5, 6  
- No cirrhosis  
- Compensated cirrhosis  
- ESRD |
| Sofosbuvir/velpatasvir/voxilaprevir (Vosevi)  | 400mg/100mg/100mg PO daily 12 weeks | - GT 1, 3, 4, 5, 6  
- No cirrhosis  
- Compensated cirrhosis  
- NS5A and non-NS5A-experienced (GT 1)  
- P/R-experienced (GT 3)  
- DAA-experienced (GT 4, 5, 6) |

Note: simeprevir plus sofosbuvir, paritaprevir/ritonavir/ombitasvir plus dasabuvir, and daclatasvir plus sofosbuvir are longer recommended as first-line HCV treatments by the AASLD/IDSA and therefore excluded from this table.

GT=Genotype; ESRD=end stage renal disease; PI=protease inhibitor; +RBV= add ribavirin; P/R=peginterferon/ribavirin

Source: AASLD/IDSA, 2017
### Table 3: Drug Interactions between HCV direct acting antivirals and HIV antiretroviral therapy

<table>
<thead>
<tr>
<th>DAA</th>
<th>Contraindicated ART</th>
<th>Mechanism of Interaction</th>
<th>Additional Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High ART interaction risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elbasvir/ grazoprevir (Zepatier)</td>
<td>all protease inhibitors</td>
<td>increases grazoprevir concentration 5-11-fold via OATP1B inhibition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cobicistat</td>
<td>may increase grazoprevir exposure due to OATP1B inhibition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>efavirenz</td>
<td>decreases elbasvir and grazoprevir concentrations via CYP3A/P-gp induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>etravirine</td>
<td>may decrease elbasvir and grazoprevir concentrations via CYP3A induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nevirapine</td>
<td>may decrease elbasvir and grazoprevir concentrations via CYP3A induction</td>
<td></td>
</tr>
<tr>
<td>glecaprevir/ pibrentasvir (Mavyret)</td>
<td>ritonavir-containing regimens</td>
<td>increases glecaprevir/pibrentasvir concentrations via OATP1B inhibition</td>
<td>Additional monitoring for hepatic toxicity with elvitegravir/cobicistat</td>
</tr>
<tr>
<td></td>
<td>atazanavir</td>
<td>increases risk for ALT elevation and increases glecaprevir concentration due to OATP1B inhibition</td>
<td></td>
</tr>
<tr>
<td></td>
<td>efavirenz</td>
<td>decreases glecaprevir/pibrentasvir concentrations via CYP3A4 induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>etravirine</td>
<td>may decrease glecaprevir/pibrentasvir concentration via CYP3A4 induction</td>
<td></td>
</tr>
<tr>
<td>sofosbuvir/ velpatasvir/ voxilaprevir (Vosevi)</td>
<td>ritonavir-boosted atazanavir</td>
<td>increases voxilaprevir 4-fold via OATP1B1 and P-gp inhibition</td>
<td>Additional monitoring for hepatic toxicity with elvitegravir/cobicistat</td>
</tr>
<tr>
<td></td>
<td>efavirenz</td>
<td>decreases concentrations of velpatasvir</td>
<td></td>
</tr>
<tr>
<td></td>
<td>etravirine</td>
<td>decreases sofosbuvir/ velpatasvir/voxilaprevir concentration due to CYP3A4 induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nevirapine</td>
<td>may decrease sof/vel/vox concentration due to CYP3A4 and CYP2C8 induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tipranavir</td>
<td>may decrease sofosbuvir/velpatasvir/ioxilaprevir concentration</td>
<td></td>
</tr>
<tr>
<td><strong>Low ART interaction risk</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ledipasvir/ sofosbuvir (Harvoni)</td>
<td>tipranavir</td>
<td>may decrease concentration of ledipasvir/sofosbuvir</td>
<td>Avoid TDF if CrCl&lt;60mL/min</td>
</tr>
<tr>
<td>daclatasvir (Daklinza)/ sofosbuvir (Sovaldi)</td>
<td>tipranavir</td>
<td>reduces therapeutic effect of sofosbuvir via induction of P-gp</td>
<td>Decrease daclatasvir dose to 30mg once daily with atazanavir/r Increase daclatasvir dose to 90mg once daily with efavirenz</td>
</tr>
<tr>
<td>sofosbuvir/ velpatasvir (Epclusa)</td>
<td>efavirenz</td>
<td>decreases velpatasvir concentration</td>
<td>Avoid TDF if CrCl&lt;60mL/min</td>
</tr>
<tr>
<td></td>
<td>etravirine</td>
<td>decreases sofosbuvir/velpatasvir concentration due to CYP3A4 induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nevirapine</td>
<td>decreases sofosbuvir/velpatasvir concentration due to CYP3A4 and CYP2B6 induction</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tipranavir</td>
<td>may reduce sofosbuvir/velpatasvir concentration</td>
<td></td>
</tr>
</tbody>
</table>

**DAA** = direct acting antiviral; **ART** = antiretroviral therapy; **TDF** = tenofovir disoproxil fumarate; **CrCl** = creatinine clearance; **Source:** AASLD/IDSA, 2017; University of Liverpool, 2018
Figure 1: Framework for Nursing Activities to Coordinate Drug-Drug Interactions

- Calendar reminder to check HCV clinic notes and treatment decision (Redulla et al., 2015)
- Proactively identify potential drug-drug interactions (Stambough et al., 2016)
- Contact HIV provider and forward drug-drug interaction information
  - Suggest appropriate ARVs (Adams et al., 2012)
- Personalized meeting with patient to discuss ART switch barriers & preferences
- Follow up with patient to ensure adherence and side effect management (Redulla et al., 2015; Adams et al., 2012)
- Follow up with HCV provider when switch is complete to initiate DAAs
CHAPTER 3: Care2Cure: A randomized controlled trial protocol for evaluating nurse case management to improve the hepatitis C care continuum within HIV primary care

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Abstract

Co-infection with HIV and hepatitis C virus (HCV) results in a three-fold increase in progression to end stage liver disease and cirrhosis compared to HCV alone. Although curative treatments exist, less than one quarter of people with HCV are linked to care and even fewer have received treatment. The Care2Cure study is a single-blinded, randomized controlled trial to improve the HCV care continuum among people co-infected with HIV. This ongoing study tests whether a nurse case management intervention can 1) improve linkage to HCV care and 2) decrease time to HCV treatment initiation among 70 adults co-infected with HIV who are not engaged in HCV care. The intervention is informed by the Andersen Behavioral Model of Health Services Use and consists of nurse-initiated referral, strengths-based education, patient navigation, appointment reminders, and care coordination for drug-drug interactions in the setting of HIV primary care. Validated instruments measure participant characteristics including HCV knowledge, substance use, and depression. The primary outcome is linkage to HCV care (yes/no) within 60 days. This protocol paper describes the first clinical trial to examine the effects of a nurse case management intervention to improve the HCV care continuum among people co-infected with HIV/HCV in the era of all-oral HCV treatment. We describe our work in progress, challenges encountered, and strategies to engage this hard-to-reach population.

Keywords: AIDS, health care delivery, nursing care/interventions, randomized controlled trials, social and economic aspects of illness
Background

Chronic infection with hepatitis C virus (HCV) is a leading cause of liver cancer and the most common non-AIDS-related cause of death among persons living with HIV (PLWH) (Centers for Disease Control and Prevention, 2016; Ly et al., 2012). One in four people with HIV are co-infected with HCV, and 80% of injection drug users who have HIV also have HCV (Centers for Disease Control and Prevention, 2016). HIV increases relative risk of HCV-related progression to cirrhosis and end stage liver disease three-fold (Deng, Gui, Zhang, Gao, & Yang, 2009; Graham et al., 2001; Lo Re et al., 2014).

Prior to 2014, HCV treatment for PLWH was less effective and highly toxic with interferon injections, but contemporary all-oral direct acting antivirals (DAAs) are exceptionally effective, shorter in duration and much less toxic in this population (Thomas, 2014). With new advances in treatment, we have the opportunity to cure HCV in at least 94-97% of people, including PLWH (Naggie et al., 2015; Sulkowski et al., 2015; D. Wyles et al., 2017; D. L. Wyles et al., 2015). However, medication availability and the promise of HCV cure alone are not sufficient to engage all people in care. Challenges across the HCV continuum of care persist, especially in the HIV-co-infected population, indicating a need for interventions to minimize barriers to linking HIV/HCV co-infected patients into HCV care and providing support for this population to succeed in treatment (Cachay et al., 2014).

The greatest gap in the HCV care cascade in the United States falls between diagnosis and treatment initiation (Cachay et al., 2014; Linas et al., 2014; Yehia, Schranz, Umscheid, & Lo Re, 2014). As few as half of those with an HCV diagnosis are linked to HCV care (Yehia et al., 2014), while in a multi-site study of 1,303 HIV/HCV co-infected
patients linked to care, researchers found that only half were prescribed DAAs and 43% started a DAA between 2014 and 2017 (Jayaweera et al., 2018). Some of this gap in linkage to care and treatment initiation may be attributed to the low perceived threat of HCV and, as such, a low perceived need for HCV treatment and limited motivation (M. Harris & Rhodes, 2013; Yap et al., 2014). Likewise, U.S. adults with HCV have reported difficulty in accessing HCV-treating providers and navigating the healthcare system (Zickmund, Campbell, Tirado, Zook, & Weinrieb, 2012). In particular, with few overt symptoms, HCV is a “silent epidemic,” often taking a lower priority among PLWH and their providers compared to other comorbidities (Alavi et al., 2013; Reiberger et al., 2011; C. Treloar, Newland, Rance, & Hopwood, 2010), whereas HIV poses a greater perceived threat and a more imminent one (Munoz-Plaza et al., 2008; Wagner et al., 2009).

The low perceived threat of HCV is exacerbated by a lack of knowledge about HCV and available therapies (Coupland, Day, Levy, & Maher, 2009; Carla Treloar, Hull, Dore, & Grebely, 2012; Zickmund et al., 2012). While HCV treatment initiation is associated with greater HCV knowledge (Grebely et al., 2011), lack of knowledge is a self-reported barrier to starting HCV treatment in up to 78 percent of patients (Alavi et al., 2013; Mehta et al., 2008). It is important to note that peer networks facilitate an exchange of 42% of HCV-related information (Watson et al., 2007), yet this peer pipeline can also focus on the negative effects of treatment, many of which have been eliminated with newer DAA-based regimens (North, Devereaux, Pollio, Hong, & Jain, 2014; Carla Treloar et al., 2012; Zickmund et al., 2012). Clearly, interventions to increase HCV knowledge, motivation, and access are needed to improve linkage to HCV care.
Prior interventions to promote the care continuum have included a variety of approaches with some success. For example, brief HCV education alone was shown to significantly increase knowledge and linkage to HCV care by 14-25% (Chen et al., 2013; Gupta, Romney, Briggs, & Benker, 2007; Surjadi, Torruellas, Ayala, Yee, & Khalili, 2011; Tyler et al., 2014). Similarly, nurse case management and care coordination have also been shown to improve linkage to HIV or HCV care by up to 30% (Craw et al., 2008; Gardner et al., 2005; Tyler et al., 2014). Reminder systems using text and phone messages have also been effective strategies in increasing linkage to HIV care and substance use services in combination with other interventions, but have not been tested in the context of HCV care (Farmer, Brook, McSorley, Murphy, & Mohamed, 2014; Finitsis, Pellowski, & Johnson, 2014; van Velthoven, Brusamento, Majeed, & Car, 2013).

Yet, a critical gap in the existing approaches is that few linkage to care studies target HCV; the majority of evidence comes from similar populations, including PLWH and substance use disorders. Those that are targeted towards HCV were conducted prior to the era of DAAs, often excluding persons with mental illness, substance use, or HIV co-infection.

In addition, HIV-HCV drug interactions will exist for up to 88% of PLWH (Patel et al., 2015). Because cure rates are now similar between HCV mono- and HIV/HCV co-infected individuals, the only difference in management of HCV in PLWH is the need to address drug interactions (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018). A large proportion of PLWH who are initiating HCV treatment will have to modify their HIV treatment regimen to accommodate these drug-drug interactions, but modifying HIV treatment regimens add a
further delay and deter PLWH from starting HCV treatment, as well as negatively impact quality of life and increase HIV symptom burden (Sherr et al., 2007). Moreover, HCV cure rates may be lower in persons who switch antiretroviral therapy (ART) to accommodate DAAs (Falade-Nwulia et al., 2017). The addition of care coordination for ART modification may address this important new barrier for PLWH. To our knowledge, no published interventions to date have sought to support ART modifications to accommodate HIV/HCV drug interactions.

The Care2Cure intervention was designed to address these gaps by testing comprehensive, multi-component nurse case management to improve the HCV care continuum among vulnerable HIV co-infected adults with HCV. The aims of the Care2Cure Study are to: 1) test whether a nurse case management intervention will increase linkage to HCV care among persons with HIV/HCV co-infection compared to usual care; and 2) determine if a nurse case management intervention will decrease time to HCV treatment initiation among persons with HIV/HCV co-infection compared to enhanced usual care. This paper describes the protocol of the randomized, single blinded, controlled trial. The SPIRIT Statement checklist was adhered to in reporting this intervention protocol.

Methods

Study Aim and Design

The Care2Cure study is designed to evaluate the preliminary efficacy of a standardized nurse case management intervention to improve the HCV care continuum among PLWH in a randomized controlled trial. PLWH who are co-infected with chronic
HCV and not engaged in HCV care are randomized to enhanced usual care or usual care plus HCV nurse case management (NCM) and followed for six months. After baseline assessment, participants are randomly assigned to the intervention arm in a 1:1 allocation using a block randomization scheme. Participants are evaluated at 60 days for linkage to care and 6 months for time to treatment initiation. We hypothesize that a) a higher proportion of participants in the intervention arm will attend an appointment for HCV care within 60 days, and b) participants in the intervention arm will have a decreased time to HCV treatment initiation compared to participants in the usual care arm. This study protocol has been approved by the IRB of Johns Hopkins Medicine and is registered on ClinicalTrials.gov (NCT02707991). An integrated study flow and conceptual framework is detailed in Figure 1.

The NCM intervention development was guided by Andersen’s Behavioral Model of Health Services Use. Initially developed in the 1960s, this model explains the conditions that facilitate or impede utilization of health care (Andersen, 1995). The model posits that a person’s use of health services is a function of predisposing factors, perceived and actual need for care, and enabling or impeding resources. Predisposing characteristics, such as age, sex, race, ethnicity, substance use, and comorbidities are not easily modified. But perceived need, according to Andersen, can be changed through education; the greater the perceived and actual threat, the more likely one is to use services. Andersen also suggests that enabling resources can be influenced by interventions at the system, provider, and patient level. The more enabling resources one has, the greater the likelihood of healthcare utilization. We hypothesize that enabling resources for the uptake of HCV care among PLWH may include patient navigation,
appointment reminders, and ART modification support, all addressed by nurse case management in the Care2Cure intervention.

Andersen’s model has been applied previously to explain HCV and HIV health care utilization patterns, and informs the intervention components of the Care2Cure study (Henry, Goetz, & Asch, 2012; Holtzman et al., 2015; Mehta et al., 2005; Rapp et al., 2008). Interventions that increase perceived need, minimize barriers, and maximize resources have the potential to improve the HCV care cascade for PLWH.

**Study Setting**

The Care2Cure Study is being conducted at the Johns Hopkins Hospital HIV clinic which is part of the Bartlett Specialty Practice in Baltimore, Maryland. This is a hospital-based outpatient infectious disease clinic that provides both HIV primary care and HCV specialty care. The HIV practice cares for approximately 3,500 patients per year. The clinic serves a primarily adult, urban population, with approximately 75% of patients being African American. The average age of clinic patients is 48 years (Lesko, Lau, Chander, & Moore, 2018; Moore, 1998). Approximately 50% of patients with HIV are co-infected with HCV. The Bartlett Viral Hepatitis Practice, staffed with hepatologists and viral hepatitis-focused infectious disease physicians and nurse practitioners, is also part of the broader Bartlett Specialty Practice.

**Sample Size and Eligibility Criteria**

Seventy participants will be enrolled, with 35 in each treatment arm. In prior studies testing the intervention components in similar populations, including PLWH and/or substance use disorders, researchers found an improvement in linkage to care of
18-30% (Craw et al., 2008; Gardner et al., 2005; Masson et al., 2013; Rapp et al., 2008). At the time of study initiation, 40% of new HCV Practice appointments were attended by patients (i.e., 60% no-show rate). We assume that we will find an improvement in linkage to care of at least 30% in the context of HCV (i.e., 70% attendance [0.70] in the NCM group compared to 40% attendance [0.40] in the enhanced usual care group). Using these figures and an alpha of 0.05, an estimate of the total sample size required to achieve 80% power is 33 per group, or a total of 66 participants (G*Power 3.1.9.2). Therefore, a sample size of 35 participants in each group should be adequate to detect the difference of interest in proportion of linkage to care for the primary aim.

Participants are included in this study if they 1) are HIV positive; 2) are current patients of the Bartlett HIV Practice, defined as having a visit with an HIV provider in the past 12 months; 3) have chronic HCV infection with a detectable plasma HCV RNA; 4) are 18 years of age or older; 5) speak English; and 6) did not attend an appointment for HCV care in the past 12 months. Participants are excluded from participation in this study if they are pregnant or unable to independently provide informed consent.

**Recruitment and Enrollment**

Patients either 1) self-refer by contacting the research team after seeing flyers and brochures posted in the clinic; 2) are referred by their HIV provider in clinic; 3) self-refer after receiving a targeted recruitment letter in the mail; or 4) self-refer after finding the study on clinicaltrials.gov, Trials@Hopkins (an institutional database of research studies), or referral from the Johns Hopkins Center for AIDS Research Study-Finder Hotline. The clinic schedule is screened weekly by the study team to identify eligible patients. Letters are mailed to eligible patients indicating that they may qualify to
participate in a research study while at their next clinic appointment with information about how to contact the study team. HIV providers are also notified by the study team if they have eligible patients scheduled each day and are asked to refer those patients to the study at the end of the visit. After the patient has contacted our study team, a member of the study team provides information regarding the study, answers questions, and obtains informed consent. The consent form was developed at a 5th grade reading level. Participants in both arms are compensated $20 for their time at the end of the baseline visit.

**Study Interventions**

*Control group – enhanced usual care.* After randomization into the enhanced usual care arm, or the “fact sheet group,” the study team member provides participants with a CDC HCV Fact Sheet which contains basic educational information about HCV transmission, signs and symptoms, treatment, and prevention (Centers for Disease Control and Prevention, 2015). Participants are then referred to the usual clinic appointment check-out process. It is important to note that the clinic relocated during the course of this study, slightly changing the check-out process. For the first 9 months of enrollment, patients in the clinic returned to the front desk or check out area with a billing page and printed appointment referrals if applicable. The administrative staff closed the appointment encounter and gave the patient a phone number for the Johns Hopkins Hospital central scheduling to schedule referral-based appointments. Patients were responsible for calling central scheduling to set up the specialty appointment. In the new clinic, all encounters are handled electronically; the patient still goes to a check out area to end an appointment and the clinic staff reviews referrals and closes the appointment.
The clinic procedure is to assist the patient to schedule any follow-up appointments indicated in the electronic record, although specialty referral-based appointments are often left unscheduled and therefore the patient is responsible for calling central scheduling to set up a specialty appointment. When an appointment is scheduled at this health system, all patients receive an automated appointment reminder call 2 days before the scheduled appointment.

Patients at the Bartlett Specialty Practice have access to HIV nurse case managers and Ryan White-funded social workers, similar to many HIV care settings. Participants in the enhanced usual care arm will continue to have usual access to these services. Per the Bartlett Specialty Practice standard care protocol, once a prescription is written for HCV treatment, the assigned HIV nurse case manager will work with the patient to coordinate HCV care; however, HIV nurse case managers are not directly involved in HCV care until after prescription for HCV treatment is written, which is the gap our NCM intervention seeks to fill.

**Experimental group – usual care plus HCV NCM.** The NCM intervention components per intervention phase (Phase 1: Linkage to care and Phase 2: Treatment initiation) are outlined in Table 1.

**Phase 1: Linkage to care.** This phase of the intervention is hypothesized to increase the proportion of participants who link to HCV care through NCM consisting of nurse-initiated referral, strengths-based HCV education, patient navigation, and HCV appointment reminders.

**Nurse-initiated referral.** The nurse case manager initiates an HCV referral for participants randomized to the intervention group via the electronic health record or in-
person conversation with the provider. This cues the HIV provider to submit the referral to HCV specialty care and minimizes the barrier of non-referral by the provider.

Strengths-based education. Participants receive brief strengths-based HCV education (Gottlieb, 2014). Strengths-based education can improve knowledge and motivation to achieve health-related goals among PLWH (Craw et al., 2008; Gardner et al., 2005; Gottlieb, 2014). The nurse case manager helps participants identify their strengths within the context of engaging in HCV care, including social support and engagement in HIV primary care (Fusfeld et al., 2013; Grebely et al., 2011). HCV education topics include transmission, symptoms, treatment, and risk reduction, with a focus on the fact that there is a cure. Education is standardized and guided by a study-developed “Hepatitis C Basics” patient education handout.

Study participants also identify barriers to linkage to care and form a plan with the nurse case manager to minimize these barriers; this may include referrals to benefits counseling, substance use or mental health services, and/or an HCV support group called the “Cure Club” (Masson et al., 2013).

Patient navigation and clinical coordination. Because appointment scheduling is a known barrier to linkage to care, and specialty appointments are often left for patients to schedule themselves, patient navigation includes scheduling an appointment for the HCV Practice with the participant (Coupland et al., 2009; Carla Treloar et al., 2012; Zickmund et al., 2012). After receiving permission from the patient as well as preferred dates and appointment times, the nurse case manager calls the central scheduling office during the baseline research visit to navigate participants through the HCV Practice scheduling process. The nurse case manager also assists participants in the NCM arm
with rescheduling HCV Practice appointments and coordinating access to hepatitis C-treating research studies currently recruiting at the clinic.

**Appointment reminders.** Participants in the NCM arm receive personalized HCV appointment reminders in addition to the automated phone reminder that all patients receive through the Johns Hopkins Hospital usual care system. A plan for contacting participants for personalized appointment reminders is made, including the best mode of contact (phone, text, or email) and time of day. Participants are contacted by the nurse case manager both one week and one day before their scheduled HCV Practice appointment for an appointment reminder (Gardner et al., 2014). During this reminder, participants are also given the opportunity to ask the nurse case manager questions about HCV or their care and the nurse case manager again emphasizes that HCV can be cured.

**Phase 2: Time to treatment initiation.** This phase of the intervention is hypothesized to decrease time to HCV treatment initiation by using a nurse case manager to coordinate communication about ART modifications between the patient and HIV provider, based on need identified in the HCV provider’s documentation. Participants who are enrolled in another clinical trial are not included in this phase because participants in HCV-treating clinical trials receive an intervention to initiate HCV treatment within those trials. These participants are expected to follow a different timeline than clinical patients and face different challenges. Therefore, this phase includes a subgroup of consented Care2Cure study participants who link to an appointment at the HCV Practice through a clinical process. An algorithm is used to guide eligibility determination for Phase 2 (Figure 2).
After the participant attends an HCV Practice appointment, the research nurse case manager reviews the HCV provider’s note in the electronic medical record to determine what decision was made about initiating HCV treatment (defer or start). This phase is single-blinded; no direct communication occurs between the research team and the HCV provider to avoid influencing the HCV management of the patient. Instead, the intervention supports the HIV provider and patient without influencing the HCV provider’s decisions. Using the Phase 2 Algorithm, the research nurse case manager identifies participants who have a decision to start treatment indicated in the HCV visit note. The anticipated HCV therapy regimen in the clinic note is assessed for potential drug-drug interactions with the participants’ current ART regimen. If a modification in ART is indicated because a contraindicated drug-drug interaction exists, the research nurse case manager contacts the participant via his/her preferred contact method to schedule a follow-up NCM visit. At this visit, the participant is given an investigator-developed one-page drug interaction sheet tailored to his/her ART regimen. The research nurse case manager also sends a secure email to the participant’s HIV provider notifying him/her of the potential need for ART modification. This email includes the latest DHHS “Concomitant Use of Selected HIV Drugs and FDA-Approved HCV Drugs for Treatment of HCV in HIV-Infected Adults” Table 12 (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017). The table serves as a decision-making aid for the HIV provider to modify the ART regimen if needed. The research nurse case manager coordinates an ART modification appointment with the participant’s primary HIV provider as needed so the patient does not wait the usual 3 to 6 months until his or her next regularly scheduled HIV primary care visit.
**Fidelity.** Several mechanisms are in place to ensure the intervention is delivered as planned. A detailed protocol and standard operating procedure manual that clearly specify the intervention components are available to the interventionist. Checklists have been developed for each interaction with a study participant to ensure consistency and handouts are used to guide the intervention components. All study team members were trained and observed for adherence to the protocol. To minimize potential bias with the interventionist’s involvement in every step of the research, a study team member who is blinded to randomization collects medical record data for the outcome variables at 60 days and 6 months.

**Measures**

Three types of study assessments are collected: 1) baseline data (including a self-report questionnaire and medical record review); 2) monthly healthcare utilization logs (via the medical record); and 3) outcome data (at 60 days and 6 months via the medical record). All study assessments are conducted by trained study staff. The baseline assessment is collected in the clinic after consent and before the participant is randomized to a study arm. Sixty-day and 6-month assessments are collected from the participants’ electronic medical record by study staff who are blind to treatment allocation.

**Baseline characteristics.** The baseline characteristics questionnaire used in the Care2Cure study includes demographics (age, race, ethnicity, gender), education and employment status, income and financial strain, self-reported health history, and substance use in the past 6 and 12 months. The current study team has used this questionnaire for a prior study in the same setting (Farley et al., 2017). Questions have been added or removed as applicable to this study and patient population. In addition to
these baseline characteristics, validated instruments to assess HCV knowledge, depression, and alcohol use are also administered at baseline.

**Hepatitis C knowledge.** The 19-item Brief Hepatitis C Knowledge Scale (Cronbach’s $\alpha=0.87$) is administered to measure HCV knowledge (Balfour et al., 2009). The Brief HCV Knowledge Scale is a unidimensional measure comprising a comprehensive list of items that address the main aspects of HCV knowledge: prevention, risk reduction, transmission, and treatment. It was designed and tested on a diverse sample of patients, health care workers, and students with varying socioeconomic and demographic backgrounds. It uses a simple true/false scoring system with a total score range of 0-19.

**Depression.** The Patient Health Questionnaire (PHQ-9) is used to measure depression, which can be associated with engagement in care (Cronbach’s $\alpha=0.89$) (Kroenke, Spitzer, & Williams, 2001). The PHQ-9 is scored immediately. Participants scoring 10-19, indicating moderate depression, are referred to their primary care provider for further follow up after the baseline study visit is complete per a standard protocol. Those with scores of 20 or greater (severe depression) are immediately referred to their primary provider, or, if the primary provider is not available, the covering urgent provider of the day, for further evaluation before the study visit is completed.

**Alcohol use.** The Alcohol Use Disorders Identification Test (AUDIT) is administered to any participant who reports any alcohol use in the past 6 months on the baseline characteristics questionnaire (Babor, Higgins-Biddle, Saunders, Monteiro, & Dependence, 2001). The AUDIT consists of 10 items about recent alcohol use, alcohol dependence, symptoms, and alcohol-related problems. It was first developed in 1989 and
has been validated in diverse international samples. The internal consistency reliability has been reported at 0.83 (Hays, Merz, & Nicholas, 1995) to the mid-0.90s (Babor et al., 2001). In a primary care setting, the AUDIT is intended to be administered by a nurse or social worker (Babor et al., 2001). It is administered by a registered nurse in the Care2Cure study. The research nurse case manager counsels participants about alcohol use according to the recommended actions of the World Health Organization based on the individual AUDIT score. Participants scoring in Zone IV, suggesting alcohol dependence, are referred to their Bartlett Specialty Practice social worker to discuss further counseling and treatment options.

**Medical record review.** At the end of each baseline visit the research team reviews the patient’s medical record to verify specific pieces of the medical history. These variables of interest include CD4+ T cell count, CD4 nadir (i.e. lowest historical CD4 count), HIV viral load, prescribed ART, year of HCV diagnosis, HCV treatment history, HCV viral load, liver fibrosis level, HCV genotype, HCV appointment history, comorbidities, urine toxicology screening results if available, and health insurance status.

**Health care utilization.** In addition to baseline and outcome data collection, monthly activity logs are completed for each study participant, independent of allocated study arm. These data are collected from the study participant’s electronic medical record and the research nurse case manager’s notes. The type, quantity, and content of all encounters with a study participant in the Johns Hopkins system are recorded each month, including nurse visits. This will define usual care for Bartlett Specialty Practice patients. The type, quantity, and content of all Care2Cure study visits are also recorded to define the dose of the intervention.
**Outcomes.** Study outcomes (linkage to care and time to treatment initiation) are assessed using objective data extracted from the participants’ medical records.

**Linkage to care.** For the primary outcome of linkage to care, the medical record is reviewed 60 days after the baseline visit to verify whether the participant attended one or more HCV Practice appointment since randomization (yes/no). All provider visits at the HCV Practice are registered in the electronic medical record, so absence of a registered appointment during the study period is considered non-attendance for the primary outcome variable.

**Time to treatment initiation.** To measure our secondary outcome of time to treatment initiation, the electronic medical record is reviewed 6 months after the baseline visit. The study team collects multiple variables related to treatment initiation from the medical record, including whether a change in ART was made during the study period (yes/no), if a prescription for HCV therapy was written during the study period (yes/no and the drug(s) prescribed), if and when the participant started taking the prescribed DAA, and the number of days between the baseline visit and the date HCV therapy was started. The pharmacy at the Specialty Practice documents in the electronic medical record when DAAs are dispensed and the first dose of DAAs, which, per clinic protocol, is directly observed by a clinic nurse or provider. The 6-month period for final data collection should be adequate to account for the various steps in HCV treatment preparation among PLWH: 1) linkage to care; 2) ART modification as needed; 3) rechecking the HIV viral load 4 to 8 weeks after modification to ensure viral suppression on new regimen (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017);
4) HCV-related blood tests and imaging, and 5) uncontrollable factors such as appointment cancellations, rescheduling, and payer reimbursement.

Participant characteristics obtained in the baseline medical record abstraction are recollected at 6 months as well. This includes HCV RNA, which will indicate whether a participant achieved sustained virologic response (SVR) during the study period. Additional items to record specific barriers to HCV treatment referral, appointment scheduling, appointment attendance, and treatment initiation are also added to the 6-month medical record review.

**Data Storage and Monitoring**

All data are collected and managed using REDCap electronic data capture tools hosted at Johns Hopkins University (Harris et al., 2009). REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Randomization occurs directly in REDCap to ensure that the study team has no a priori knowledge of group assignment when enrolling and randomizing study participants.

**Statistical Analysis**

Exploratory and descriptive analyses will be completed for all study variables. Variables will be inspected for normality and examined with means and standard deviations or medians and interquartile ranges accordingly. Baseline characteristics of the
two groups (enhanced usual care vs. NCM intervention) will be assessed. Any differences between the groups will be adjusted for in further analysis. The significance level will be set at 0.05. The primary (outcome) analysis will follow the principle of intention-to-treat. The primary outcome is linkage to care, measured by attendance at the HCV Practice within 60 days of randomization (yes/no). The group difference in the primary outcome will be tested using a two-sample z-test for the difference in proportions comparing the NCM intervention group to the enhanced usual care group. Binary logistic regression will be used to determine an effect on linkage to care controlling for differences in age, sex, race, HCV knowledge, substance use, liver fibrosis level, CD4+ T cell count, HIV viral load, and health insurance type.

The secondary outcome is time to HCV treatment initiation, measured by the number of days from randomization to the date the participant starts taking DAAs in the medical record. Kaplan Meier estimates will be conducted to compare time to HCV treatment initiation between participants in the NCM intervention group and the enhanced usual care group, and a log-rank test will be used to examine the difference. Potential covariates (age, sex, race, HCV knowledge, substance use, liver fibrosis level, CD4+ T cell count, HIV viral load, and health insurance type) will be included in the Cox regression model. To account for a time to treatment initiation greater than the observed time period of 6 months, right censoring will be implemented for participants who have not initiated HCV treatment at the end of the 6-month period (Hosmer, Lemeshow, & May, 1999).
Discussion

To our knowledge, this is the first clinical trial to examine the effects of a nurse case management intervention protocol to improve the HCV care continuum among people co-infected with HIV/HCV in the era of all-oral DAAs. Given the acceleration of liver disease among people co-infected with HIV/HCV, timely treatment is essential, and DAAs make this possible (Bhattacharya et al., 2017; Lo Re et al., 2014). The Care2Cure study attempts to increase the proportion of HIV/HCV co-infected adults who link to HCV care and decrease time to DAA initiation. The findings from this study will inform efforts to ensure that the most effective linkage to care and treatment approach is integrated into care of this population.

The Care2Cure study attends to the needs of hard-to-reach patient populations. At the time this study was rolled out, the clinic had already linked the majority of its HIV/HCV co-infected patients to HCV care and achieved a cure in 43%, indicating that many patients who were immediately ready for HCV therapy and the ideal treatment candidates had already received HCV treatment in the first few years of DAA availability. The remaining population may be less engaged in their healthcare and/or more complex to treat, including those who inject drugs, drink alcohol, have mental health diagnoses, and may not be well engaged in HIV care, including patients not virally suppressed on ART. Our HCV NCM intervention is designed to improve care for these populations and the sample enrolled is expected to reflect the real-world challenges of improving the HCV care continuum. This study will also help us to identify characteristics associated with, and barriers to, engaging in the HCV care continuum
among a complex HIV co-infected population impacted by multiple barriers influenced by their social determinants of health.

**Challenges**

The target population for the Care2Cure study introduces many challenges. Recruitment of patients who are not well engaged in health care into research is difficult, and many strategies have been employed in response to this challenge. We obtained IRB approval to mail letters to potentially eligible clinic patients who were scheduled for an HIV appointment each week to encourage them to attend their HIV appointment and meet with research staff on the same day. We engaged providers in the clinic, who have trusting relationships with their patients, to refer eligible participants to our study. To attract more participants, we also increased compensation for the baseline study visit from $10 to $20. With these adjustments, we have enrolled 68 study participants and are continuing to collect data and implement the intervention.

Barriers to successful implementation of the intervention occur at the provider and payer levels. At the HIV provider level, hesitation to provide an HCV care referral for participants who have a detectable HIV viral load, are currently injecting drugs, or frequently miss HIV primary care appointments has led our research team to collaborate with the HCV Practice on a campaign to stress the ability to cure every patient, regardless of these stigmatizing factors. Insurance approval for DAAs has slowed time to treatment initiation and overall treatment initiation abilities, but our study team has worked with the pharmacy prior authorization team to minimize this barrier and refers participants to HCV-treating research studies to work around insurance approval.
Strengths and Limitations

Despite overcoming these challenges, the Care2Cure study has a few limitations worth noting. Self-reported assessments in the baseline questionnaire may be subject to desirability bias. However, the items and instruments chosen, including the AUDIT, for example, are widely used and regarded as valid and reliable measures of the concepts of interest. We also verify important health-related measures, including medications and lab values, in the medical record. We are unable to control for external factors that may affect study results, such as change in clinic processes, change in state Medicaid reimbursement policies, FDA approval of new DAAs, and changes in HIV and HCV treatment guidelines. The HIV clinic moved nine months into study recruitment and became co-located with the HCV Practice, which was expected to improve linkage to HCV care naturally within usual care. In addition to randomization, which ensures external factors are applied to both groups equally, we are documenting these contextual factors to help with interpretation of findings. Finally, given the fortunate and fairly unique situation of having a co-located HIV and HCV clinic, HIV patients in this setting may generally do better in engaging in HCV care than settings that do not have HCV resources, limiting the generalizability of the Care2Cure study. However, the NCM protocol is not specific to a co-located setting and can be translated to other settings for future studies.

This study does have several strengths as well. The intervention is theory-driven and its components are based on prior effective interventions with similar populations (Andersen, 1995; Craw et al., 2008; Gardner et al., 2005). The RCT design minimizes bias and baseline differences between groups, while also allowing causal relationships to
be tested. Standard operating procedure manuals have been developed to maintain intervention fidelity and protect human subjects, including procedures for participants reporting depressive symptoms and alcohol dependence. Our outcome variables are objective measures and collected from the medical record by a study team member blinded to study arm assignment. Our primary outcome of linkage to care will have minimal to no missing data because HCV Practice visits are required to be entered in the electronic medical record. The study does not require extensive follow up with participants, which will enhance retention and feasibility. The NCM intervention is fairly low-intensity and is intended to be easily integrated into HIV primary care settings that already have nurse case managers.

**Conclusions**

This study of HCV nurse case management will provide much-needed evidence for the feasibility and usefulness of this novel intervention. Results of this trial will be important in informing clinical care and future research to improve the care continuum for people living with HIV and HCV, particularly as we reach to achieve the World Health Organization’s goal of HCV elimination by 2030 (World Health Organization, 2016).
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This figure illustrates the Care2Cure study design in the context of the Andersen Behavioral Model of Health Services Use. HCV = chronic hepatitis C virus; NCM = nurse case management.
Table 1: Hepatitis C Nurse Case Management Intervention

<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
<th>Process Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nurse-Initiated Referral</td>
<td>Verify insurance and need for referral</td>
<td>Baseline presence of referral (y/n)</td>
</tr>
<tr>
<td></td>
<td>Request referral from PCP</td>
<td>Referral requested (y/n)</td>
</tr>
<tr>
<td></td>
<td>Confirm referral entrance in Epic</td>
<td>Referral obtained (y/n)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time spent obtaining referral</td>
</tr>
<tr>
<td>Strengths-Based Education</td>
<td>Handout-guided education on HCV symptoms, transmission, treatment, liver health</td>
<td>Baseline HCV knowledge scale</td>
</tr>
<tr>
<td></td>
<td>Assessment of strengths and barriers related to HCV care</td>
<td>Time spent on education &amp; content</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Referrals made to other services (i.e. social work, support group, psych)</td>
</tr>
<tr>
<td></td>
<td>Set goals for engagement in liver health/HCV care</td>
<td></td>
</tr>
<tr>
<td>Patient Navigation</td>
<td>Make appointment with HCV provider per patient’s request and needs</td>
<td>Appointment scheduled (y/n)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of days to first appt.</td>
</tr>
<tr>
<td></td>
<td>Reschedule as needed</td>
<td>Number of appointments. scheduled &amp; attended in 6 months</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time spent on navigation</td>
</tr>
<tr>
<td>Appointment reminders</td>
<td>1-week and 1-day appointment reminders</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phone, text, or email</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td>PCP= primary care provider; y/n= yes or no; HCV= hepatitis C virus</td>
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</table>
This figure illustrates the decision algorithm for determining participant eligibility for Phase 2 of the nurse case management intervention (time to treatment initiation).
CHAPTER 4: Nurse case management to improve the hepatitis C care continuum:

Results of a randomized controlled trial

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Abstract

**Background.** The opportunity to eliminate hepatitis C is at hand, but challenges remain which negatively influence progress through the care continuum, particularly for persons co-infected with HIV or those not well engaged in care.

**Methods.** The Care2Cure study was a single-blinded randomized controlled trial to test the effect of a multi-component hepatitis C nurse case management intervention on linkage to hepatitis C care, defined as attendance at a hepatitis C practice appointment within 60 days, and time to direct acting antiviral initiation. Adults co-infected with HIV/hepatitis C who have not seen a hepatitis C-treating provider in the past year were recruited in an urban, outpatient infectious disease practice.

**Findings.** Between July 2016 and February 2018, 68 eligible participants were enrolled and randomized to receive either nurse case management (n=35) or a hepatitis C fact sheet (n=33) in addition to usual care. Our sample was 81% Black/African American, 85% received Medicaid, 46% reported illicit drug use, and 43% had an undetectable HIV viral load. At day 60, 47% of nurse case management participants linked to HCV care, compared to 25% of enhanced usual care participants (p=0.036; 95% confidence bound for difference 3.2-40.9%). There was no significant difference in time to treatment initiation.

**Interpretation.** Our results support provision of nurse case management as a successful strategy to link persons co-infected with HIV to HCV care. Interventions that address the intersection of hepatitis C and HIV that continue from linking to care through cure are needed to achieve hepatitis C elimination in this vulnerable population.
**Funding.** This study received funding from the NINR at NIH under award number F31NR016200, a CANS/SNRS Dissertation Grant, and a STTI/ANAC Research Grant. This study is registered with ClinicalTrials.gov, number NCT02707991.
Introduction

Hepatitis C virus (HCV) has emerged as a major public health concern, killing more people than 60 other nationally notifiable infectious conditions in the United States (U.S.) combined, including HIV, Staphylococcus aureus, and influenza (Ly, Hughes, Jiles, & Holmberg, 2016). Risk for HCV-related hepatic decompensation is increased in the setting of HIV co-infection, and at least one in four persons living with HIV (PLWH) in the U.S. are co-infected with HCV (Centers for Disease Control and Prevention, 2018; Lo Re et al., 2014). With the advent of effective and tolerable all-oral direct acting antivirals (DAAs), we can cure HCV in essentially anyone; in fact, the World Health Organization has declared the target of eliminating HCV as a public health threat by 2030 (World Health Organization, 2016).

While necessary, DAAs alone are not sufficient to ensure HCV elimination without improving linkage to HCV care (Linas et al., 2014). This is particularly true among PLWH who have historically lower odds of receiving HCV treatment compared to HCV mono-infected individuals (Grebely et al., 2008; Mehta et al., 2006; Reed et al., 2008). Other barriers to engaging in care for persons with HCV include comorbidities and competing priorities such as substance abuse, poor access to specialty care, navigating the healthcare system, low knowledge and perceived threat of HCV, lack of provider expertise, and non-referral to specialty care by primary care providers (Clark, Garcia-Tsao, & Fraenkel, 2012; Harris & Rhodes, 2013; McGowan et al., 2013; Zickmund, Campbell, Tirado, Zook, & Weinrieb, 2012). Drug interactions between antiretroviral therapy (ART) and DAAs have introduced an additional barrier to initiating HCV treatment among PLWH (Cope et al., 2015; Patel et al., 2015). Up to 88% of
PLWH will need to switch ART to accommodate starting DAAs due to drug-drug interactions (Patel et al., 2015).

Whether an individual is well engaged in HIV care is a major consideration in success across the HCV continuum. Persons with uncontrolled HIV, including high HIV viral load and low CD4 cell count, are less likely to be prescribed DAAs (Jayaweera et al., 2018). Not only is HIV care frequently prioritized, but HIV providers are often hesitant to address HCV if a patient’s HIV is not controlled (Reiberger et al., 2011; Treloar, Newland, Rance, & Hopwood, 2010). But it is a misconception that HCV cannot be treated until HIV is controlled. DAA cure rates are not associated with HIV viral load or CD4 count, confirming that curing HCV should be addressed in PLWH regardless of success in HIV care (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018; Falade-Nwulia et al., 2017; Reiberger et al., 2011). On the contrary, HCV treatment guidelines recommend prioritizing treatment for PLWH (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018).

With DAAs that are 93-97% effective in curing HCV among PLWH, getting patients to the point of starting treatment is a critical step; once treatment is started, PLWH are very likely to be cured (Falade-Nwulia et al., 2017; Naggie et al., 2015; Sulkowski et al., 2015; D. Wyles et al., 2017; D. L. Wyles et al., 2015). Strategies to link patients to care and minimize barriers to initiating treatment, regardless of HIV viral load and CD4 cell count, are needed to eliminate HCV. Prior studies have shown that HCV education can have a small effect on improving linkage to HCV care (Chen et al., 2013; Tyler et al., 2014). Among PLWH, care coordination strategies such as case management
and reminder systems have been effective for engaging patients in HIV care (Craw et al., 2008; Farmer, Brook, McSorley, Murphy, & Mohamed, 2014; Gardner et al., 2005). However, few interventions to date promote linkage to HCV care. Those conducted prior to the availability of DAAs are no longer relevant because of the more effective, less toxic, and shorter treatment course of DAAs, which may change patient and provider motivations regarding treatment decisions (Afdhal et al., 2013). Furthermore, interventions that include persons with uncontrolled HIV, mental illness, or substance abuse are needed to maximize the impact of DAAs. In the Care2Cure Study, we aimed to investigate whether nurse case management improves the HCV care continuum compared to usual care among high-priority PLWH, regardless of comorbidities or HIV viral load, in an HIV primary care practice. Because a cure is promising among individuals who start treatment, linkage to care and treatment initiation were selected as the outcomes of interest. We hypothesized that a higher proportion of those randomized to receive nurse case management would attend an HCV specialty appointment within 60 days and initiate DAAs in fewer days compared to those who received usual care plus HCV education.

**Methods**

**Study Design and Population**

The Care2Cure Study was a single-blinded randomized trial comparing the effect of HCV nurse case management (NCM) to enhanced usual care on the proportion of participants who link to HCV care and the time to HCV treatment initiation. The Johns Hopkins Medicine Institutional Review Board approved this trial. This study is registered
on ClinicalTrials.gov, number NCT02707991. The trial protocol has previously been reported (Starbird et al., in press).

We included individuals age 18 years or older with HIV and chronic HCV (most recent HCV plasma RNA >15). Eligible participants were engaged in HIV care with at least one visit to the HIV clinic in the past 12 months, but not engaged in HCV care (i.e., no visit to the viral hepatitis practice in the past 12 months). We excluded pregnant women and persons with cognitive disabilities that affect their ability to provide independent informed consent.

**Procedures.** We enrolled participants from a large, urban infectious disease outpatient practice providing HIV primary care and HCV specialty care in Baltimore, Maryland. Participants self-referred from study flyers and clinic advertisements or were referred to the study by their clinical care team during HIV primary care visits.

Eligible individuals provided written informed consent and responded to a sociodemographic survey that included validated measures of alcohol use (Babor, Higgins-Biddle, Saunders, Monteiro, & Dependence, 2001), depressive symptoms (Kroenke, Spitzer, & Williams, 2001), and HCV knowledge (Balfour et al., 2009) at the enrollment visit. Additionally, we collected objective data from the electronic medical record, including CD4 cell count, HIV viral load, prescribed ART, HCV viral load and genotype, liver fibrosis level, receipt of prior HCV treatment, date of last visit with an HCV-treating provider, comorbidities, urine toxicology for substance use, and health insurance provider at the enrollment visit. Randomization to either HCV nurse case management or enhanced usual care occurred during the enrollment visit immediately following completion of the baseline questionnaire. Participants were compensated $20
for their time completing the enrollment study visit. We followed participants for 6 months via the electronic medical record, collecting monthly logs of healthcare utilization at the Johns Hopkins Medical System and study outcomes at 60 and 180 days. The 180-day study period is consistent with Linas et al.’s 6-month simulated integrated case management intervention to improve linkage to HCV care and treatment initiation that predicted substantial improvements in cure rates and cost savings (Linas et al., 2014).

Enhanced usual care consisted of normal outpatient clinical processes with the addition of receipt of the Centers for Disease Control and Prevention (CDC) HCV Fact Sheet (Centers for Disease Control and Prevention, 2015). After randomization, participants in the enhanced usual care group were given the HCV fact sheet and referred back to usual clinic care. The infectious disease practice has HIV nurse case managers and Ryan White-funded social workers, which continued to be available to both groups in the study at the patients’ request. In addition, all patients in the health system receive automatic telephone appointment reminders two days before any scheduled appointment.

At the time of the study, Maryland Medicaid mandated that HCV therapy be managed by hepatology, gastroenterology, and infectious disease specialists, therefore requiring the primary care provider to refer patients to specialty care unless trained through a State of Maryland/Johns Hopkins Medicine/CDC initiative (Maryland Department of Health and Mental Hygiene, 2015). This was changed after our study completed enrollment in February 2018 to allow a broader set of clinicians to treat HCV under Medicaid reimbursement (Maryland Department of Health, 2018).

The NCM intervention consisted of two phases to address the following study outcomes – 1) Linkage to Care and 2) Time to Treatment Initiation. Phase 1 included a
nurse-initiated HCV referral, strengths-based HCV education, patient navigation and clinical coordination, and appointment reminders. The study nurse case manager initiated the referral to HCV care and assisted participants to schedule an appointment in the HCV practice. Strategies to minimize barriers to attending the appointment were discussed. Personalized appointment reminders by phone, email, or text message were offered to participants both 1-week and 1-day before their scheduled HCV practice appointments. Strengths-based HCV education (Gottlieb, 2014) was directed by a study-developed HCV Basics patient guide, and focused on goal-setting and coaching participants to identify their strengths (e.g., social support, adherence to HIV treatment, resilience) and apply them to improving their liver health.

Phase 2 involved nurse reconciliation with the goal of minimizing potential ART/DAA drug interactions in order to reduce time to HCV treatment initiation. After a participant attended an appointment at the HCV practice, the nurse case manager examined the medical record for a potential drug interaction between ART and DAAs. If a contraindicated drug interaction was present, the study protocol directed the nurse case manager to coordinate an ART modification with the participant and his/her primary HIV provider.

Randomization and masking. Participants were randomized in a 1:1 fashion using a block randomization scheme after completion of the baseline questionnaire at enrollment. The randomization scheme was developed by the study team statistician, who did not enroll participants into the study, but contributed to data analysis and interpretation. A study team member who was masked to randomization collected all
outcome data. In addition, the viral hepatitis providers were blinded to the treatment allocation as to not influence their treatment decisions for the patient.

**Outcomes.** The primary outcome was linkage to care, defined as attendance at an appointment in the Viral Hepatitis Practice within 60 days of study enrollment (yes/no). All attended appointments are registered in the electronic medical record, and so absence of a documented appointment or documentation of a no-show in the electronic medical record was considered non-attendance. The secondary outcome was time to HCV treatment initiation, defined as the number of days between study enrollment and the start date of DAAs, according to the electronic medical record. The patient care team at the practice uses standardized documentation to record DAA start dates for every patient, so these data are readily available in the medical record as well. Exploratory outcomes included whether a participant was scheduled for an HCV clinic appointment, was prescribed DAAs, started taking DAAs, and achieved an undetectable HCV RNA within the 6-month follow-up period.

**Statistical Analysis**

We summarized continuous variables with mean and standard deviation or median and interquartile range (IQR), and categorical variables with frequencies and percentages. We used a one-tailed intention-to-treat z test for difference in proportions to estimate the effect of the intervention on linkage to care. A one-tailed test was justified given that the NCM intervention was additive to usual care and there was no reasonable reason for participants in the NCM group to do worse than those in the usual care group. A sample size of 66 was determined a priori to be sufficient to detect a 30% difference in linkage to care, the primary outcome, between the nurse case management and enhanced
usual care arms (G*Power 3.1) (Craw et al., 2008; Gardner et al., 2005). We calculated a phi coefficient to determine the effect size of the intervention on our primary outcome (Cohen, 1988). We also examined the exploratory outcomes to determine the effect of the intervention on the full continuum of care using a z test for difference in proportions.

We conducted Kaplan Meier estimates to compare time to linkage to HCV care and time to HCV treatment initiation between participants in the NCM intervention group and the enhanced usual care group. For each outcome of time to linkage to care and time to treatment initiation separately, we examined differences by randomization arm and participant characteristics of interest using log rank tests for categorical variables and Cox regressions for continuous variables. We chose participant characteristics based on prior literature and clinical knowledge, including age, gender, race, HCV knowledge total score, PHQ-9 total score, any illicit drug use, intravenous drug use, alcohol use, CD4 cell count, HIV viral load, liver fibrosis level, HCV genotype, and insurance provider. A multivariable Cox regression model for time to linkage to care was built with independent variables predicting the outcome with a p value of less than 0.20 in bivariate analyses (Tabachnick & Fidell, 2012). We employed a stepwise forward method, starting with covariates with the smallest p value in bivariate analyses, and adding covariates in order from smallest to largest p value, employing a likelihood ratio test to evaluate if the added variable contributed to the model significantly.

For time to HCV treatment initiation, we right censored participants who did not start HCV treatment at 180 days. We also stratified participants by covariates of interest, including age, sex, race, HCV knowledge, depressive symptoms, substance use, liver
fibrosis level, CD4 cell count, HIV viral load, and health insurance type, but were not powered for multivariate Cox regression analyses.

P values <0.05 were considered to be significant. Ninety-five percent confidence bounds (CB) were calculated for one-sided tests and 95% confidence intervals (CI) for two-sided tests. We did all analyses with Stata IC version 15.0 (StataCorp, 2017).

Results

Between July 2016 and February 2018, 463 appointments were scheduled at the HIV practice for patients who were eligible for inclusion in the trial, including unique individuals and individuals who had multiple missed HIV appointments during the study period. Sixty-eight participants were enrolled and randomized to receive HCV NCM (n=35) or enhanced usual care (n=33) (figure 1). The most common reason for not enrolling a patient was that they did not show up to a scheduled HIV practice appointment. Two participants were excluded after randomization (one in each arm) because, although their most recent HCV plasma RNA was detectable, an undetectable HCV RNA result became available in the medical record shortly after enrollment, indicating they had cleared the virus on their own and no longer needed to be linked to HCV treatment.

Participant Characteristics

There were no differences in baseline characteristics between participants in the HCV NCM group and the enhanced usual care group (table 1). The overall mean age was 55 years (SD 7.65) and 38% were female. The majority of participants identified as Black/African American (81%) and received less than $25,000 per year in government
benefits (social security, disability, or supplemental security income) as their primary income source. Most also had government-sponsored health insurance, including Medicaid (85%) and/or Medicare (25%) (9 participants [13%] had both Medicaid and Medicare).

Participants had been diagnosed with HIV for a median of 22 years (IQR 16-28) and all but two were prescribed ART (97%). Only 43% had an undetectable HIV viral load. The median CD4 cell count was 366 (IQR 198-653). Thirty-eight (56%) had liver biopsy, FibroSure, or liver elastography (FibroScan) results in their medical record at baseline, and, of those, 37% had Metavir stage F0-F1, while 63% had F2-F4. Most had HCV genotype 1 (88%), and 22% received prior HCV treatment with either interferon or DAAs.

Nearly half (46%) of participants self-reported any illicit drug use in the past 12 months, with 24% indicating they used intravenous heroin or cocaine. Forty-one percent reported alcohol use in the past 6 months; AUDIT total scores ranged from 1-36 with a median score of 3 (IQR 2-9). Scores greater than 8 indicate harmful and hazardous drinking (Babor et al., 2001).

Participants in the HCV NCM arm had a mean of 2.9 encounters with the research nurse case manager per month in the first 60 days, for a median of 60 minutes spent with the study nurse case manager per month. These encounters included linkage to HCV care activities (obtaining HCV referrals, scheduling HCV appointments), HCV education, and healthcare navigation assistance (appointment reminders, referrals to transportation and other benefit services). No participants randomized to the intervention arm were eligible
for Phase 2 of the study as no drug-drug interactions were identified in the medical record among participants in the intervention arm.

**Linkage to care**

A higher proportion of participants who received the HCV NCM intervention (47%) attended an HCV practice appointment within 60 days of enrollment compared to those who received enhanced usual care (25%) (p=0.036; 95% CB for difference 3.2%-40.9%) (Table 2). This translates to a medium effect size of 0.23 according to Cramer’s phi (Cohen, 1988). The median number of days to link to care was 24 (IQR 9-37.5). Among those who did link to care, there were no differences in time to linkage to care between the NCM and usual care arms (27.2 days versus 26.7 days, respectively; p=0.936). In bivariate analyses, self-reported use of illicit drugs in the past 12 months was associated with greater odds of linking to care at 60 days (hazard ratio [HR] = 3.61; p=0.017; 95% CI 1.26 – 10.33). This relationship held up in a multivariable Cox regression controlling for randomization arm (HR=3.66; p=0.018; 95% CI 1.25 – 10.67).

**Treatment initiation**

Twelve participants initiated treatment with DAAs within the study period, eight in the enhanced usual care arm (25%) and four receiving NCM (12%). Barriers to initiating HCV treatment within 180 days noted in the medical record included insurance denial for detectable HIV viral load (11%), insurance denial for fibrosis level <F2 (33%), prior authorization for DAAs still in progress (33%), lost to follow up (11%), and waiting to receive an HCV-positive kidney transplant (11%).
Among participants who initiated HCV treatment, the median time to initiation was 100 days (IQR 69.5-118.5 days), with a median of 72 days for participants in the HCV NCM group and 98 days for those in the enhanced usual care group. Fifty-four participants were censored at 180 days. We did not find a difference in time to treatment initiation between participants in the HCV NCM and enhanced usual care groups (p=0.192). Figure 2 depicts Kaplan Meier survival estimates. Hispanic ethnicity (p<0.001), Medicaid coverage (p<0.001), and knowing someone who had cured HCV (p=0.008) were significantly associated with HCV treatment initiation at 180 days in bivariate analyses; our sample size of those initiating treatment was not sufficient to conduct multivariable cox regression analyses.

**Exploratory Outcomes**

A higher proportion of participants in the HCV NCM group had an appointment scheduled with the viral hepatitis practice within 60 days compared to the enhanced usual care group (65% vs. 34%, respectively; p=0.007; 95% CI for difference 7%-53%). There were no differences in proportion referred to the viral hepatitis practice by their primary care provider within 60 days between the two groups (p=0.335). Reasons given by the HIV primary care provider for not referring patients to HCV care included too many missed visits (31%), competing comorbidities such as cancer treatment (25%), and the need to stabilize HIV first (25%) or decrease substance use (13%). We did not find a difference between the proportion of participants who were prescribed DAAs (p=0.670), initiated DAAs (p=0.164), or achieved an undetectable HCV RNA (p=0.651) within 180 days between the study arms.
Discussion

Our results showed a higher proportion of participants who received HCV nurse case management linked to HCV care compared to usual care in a real-world HIV practice setting. This supports the benefits of additional education, navigation, and care coordination for this population early in the continuum. Although we found an effect size similar to those reported by comparable interventions for linking persons to HIV care (Craw et al., 2008; Gardner et al., 2005), still less than half of our participants who received nurse case management attended an HCV practice appointment. This may be due to the characteristics of the sample enrolled, including high rates of competing demands and uncontrolled HIV. The fact that only one-quarter of enhanced usual care participants attended an HCV appointment, despite 70% having a referral from their primary care provider to HCV specialty care, is notable. We know from prior studies that patient self-scheduling specialty appointments is a major barrier to engaging in care (Coupland, Day, Levy, & Maher, 2009; McGowan et al., 2013; Zickmund et al., 2012). While we also found this to be true, our NCM intervention mitigated the barrier of scheduling the specialty appointment. Nevertheless, a large proportion of patients who had an HCV appointment scheduled did not attend, despite having co-located HIV and HCV providers. These findings reinforce the need to expand HCV treatment to non-specialist or community-based providers who may already have trusting relationships with patients to improve the HCV care continuum. Kattakuzhy and colleagues (2017) found that, among a sample of 600 persons with chronic HCV, patients treated with ledipasvir/sofosbuvir by primary care nurse practitioners and physicians had no difference in sustained virologic response compared to those treated by an HCV specialist.
Training for community-based primary care providers to treat HCV is needed to expand HCV treatment access (Jayasekera, Arora, & Ahmed, 2016; Johns Hopkins Medicine, Division of Infectious Diseases, n.d.).

We did not find any differences in the secondary outcome of time to treatment initiation or exploratory outcomes at 180 days. This may be attributed to our small sample size, as we were powered for the primary outcome of linkage to care only. Despite linking nearly half of participants in the NCM group to care, very few initiated treatment; this gap was due largely to insurance approval barriers. Clearly, Medicaid policies should be evidence-based and not exclude persons with minimal fibrosis and uncontrolled HIV from receiving HCV treatment (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018). Case management intervention may also help to mitigate these barriers through assistance with ensuring documentation is met, including fibrosis staging, insurance appeals and reapplications, as well as continued engagement with the patient while waiting for prolonged insurance approval.

The lack of treatment initiation is not surprising given that our intervention protocol a) primarily targeted linkage to care at 60 days and b) focused on ART/DAA drug interactions to decrease time to treatment initiation, although our sample did not experience ART/DAA drug interactions. It is likely that NCM interventions should continue until a patient has achieved a cure; linking to care alone is not sufficient to treat and cure HCV. Future research should examine NCM interventions that target multiple steps in the care continuum (Linas et al., 2014). Subsequent studies should also enroll a
sample size large enough to detect differences in outcomes across the care continuum, rather than linkage to care alone.

Control of HIV in this population is a critical issue. Despite being engaged in HIV primary care with 97% prescribed ART, 57% of our sample was not virally suppressed. Even though there is no evidence to support needing an undetectable HIV viral load prior to treating HCV, insurance payers often require this (Maryland Department of Health, 2018). We also found that HIV providers noted the need to stabilize HIV or decrease substance use as a reason for not referring their participants to HCV care. These misconceptions must be corrected; given the high burden of co-infection, HCV and HIV care cannot happen in silos. If a patient has both uncontrolled HIV and uncured HCV, efforts to improve HIV control, particularly among Ryan White funded case managers, should also focus on HCV. Case management can play an important role for patients who are struggling with adherence and have the opportunity to eliminate one of these chronic infections.

Case management services are relatively accessible for PLWH, especially in settings with Ryan White funding (Weiser et al., 2015). Because our intervention did not have any participants eligible for Phase 2, which would have required a case manager with clinical credentials to manage drug interactions, a non-nurse could likely implement the Care2Cure intervention components for linkage to care, saving nursing interventions for ART optimization and complex care coordination. Case management and reminder systems are effective for improving engagement in care for PLWH and persons who inject drugs, so integrating HCV care into these services in priority populations with high
burden of co-infection is sensible (Craw et al., 2008; Farmer et al., 2014; Finitis, Pellowski, & Johnson, 2014; Gardner et al., 2005).

A limitation of our study is that it was conducted at a single clinical site with integrated HIV and HCV practices, which may not be generalizable to other locations. Nevertheless, the low proportion of participants who linked to care and initiated HCV treatment even in this high-capacity site reveals an even greater need for HCV case management interventions in other settings, and emphasizes the challenge of engaging patients in care with a new provider. In addition, we were unable to conduct robust multivariable analyses on 180-day outcomes due to a small sample; however, our primary outcome showed a medium effect size and significant improvement in linkage to care. We could not control for external factors, such as clinical process and Medicaid reimbursement changes, as well as new approval of DAAs, but our randomized controlled trial design ensured no differences between our two groups. In addition, the primary outcome of this study was linkage to care. We did not look at sustained virologic response, which should be considered in future studies.

The strengths of this study include an intervention that was theory-driven and tested with a randomized controlled trial design (Andersen, 1995; Craw et al., 2008; Gardner et al., 2005). Intervention fidelity and human subjects protection were ensured with standard operating procedures, and the primary outcome was an objective measure. Additionally, the NCM intervention is fairly low-intensity and low-burden with a median of only 60 minutes of time from the case manager per month until linkage to care per participant. It could be integrated into HIV primary care settings that already employ case managers.
Conclusions

Nurse case management can improve linkage to HCV care among vulnerable persons co-infected with HIV by coordinating specialty referrals, navigating appointment scheduling, providing strengths-based education, and tailoring personalized appointment reminders. Future research should consider the intersection of HIV, HCV, and drug and alcohol use. Systems of care that eliminate barriers across the continuum, particularly related to scheduling and attending specialty appointments, are needed. In order to achieve HCV elimination, we need to be prepared to engage all patients in care, including those who are still working to control their HIV or substance abuse.
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https://doi.org/10.1093/cid/cix260


https://doi.org/10.1097/ADM.0b013e31825f491b
### Tables and Figures

**Figure 1. CONSORT Study Flow Diagram**

**Enrollment**

- Patient charts screened for eligibility (n=3000)
- Eligible pre-screened patients (n=443)
- Provided informed consent (n=68)
- Randomized (n=68)

**Allocation**

- **Enhanced usual care** (n=33)
  - Received allocated intervention (n=32)
  - Did not receive allocated intervention
    - Became ineligible (n=1)

- **Nurse case management** (n=35)
  - Received allocated intervention (n=34)
  - Did not receive allocated intervention
    - Became ineligible (n=1)

**Follow-Up**

- Linked to care at 60 days (n=32)
  - Yes (n=8)
  - No (n=24)
  - Initiated treatment within 180 days
    - Yes (n=8)
    - No (n=0)
    - Mean time to treatment initiation 98 days

- Linked to care at 60 days (n=34)
  - Yes (n=16)
  - No (n=18)
  - Initiated treatment within 180 days
    - Yes (n=4)
    - No (n=12)
    - Mean time to treatment initiation 72 days
Table 1: Participant Baseline Characteristics

<table>
<thead>
<tr>
<th>Demographic Characteristics</th>
<th>Total Study Sample n=68</th>
<th>Enhanced Usual Care n=33</th>
<th>Nurse Case Management n=35</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>55.03 (7.65)</td>
<td>55.32 (7.73)</td>
<td>54.76 (7.68)</td>
<td>0.762a</td>
</tr>
<tr>
<td>Female</td>
<td>26 (38.24)</td>
<td>13 (39.39)</td>
<td>13 (37.14)</td>
<td>0.617b</td>
</tr>
<tr>
<td>Race/Ethnicity</td>
<td></td>
<td></td>
<td></td>
<td>0.366c</td>
</tr>
<tr>
<td>Black/African American</td>
<td>55 (80.88)</td>
<td>26 (78.79)</td>
<td>29 (82.86)</td>
<td></td>
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<td>White/Caucasian</td>
<td>10 (14.71)</td>
<td>4 (12.12)</td>
<td>6 (17.14)</td>
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</tr>
<tr>
<td>Native American/American</td>
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<td>1 (3.03)</td>
<td>0 (0.00)</td>
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</tr>
<tr>
<td>Indian</td>
<td>2 (2.94)</td>
<td>2 (6.06)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education and Employment</td>
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<td>0.393b</td>
</tr>
<tr>
<td>Education</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No high school diploma/No GED</td>
<td>28 (41.18)</td>
<td>11 (33.33)</td>
<td>17 (48.57)</td>
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</tr>
<tr>
<td>High school graduate/GED</td>
<td>25 (36.76)</td>
<td>13 (39.39)</td>
<td>12 (34.29)</td>
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</tr>
<tr>
<td>Some college or higher</td>
<td>15 (22.06)</td>
<td>9 (27.27)</td>
<td>6 (17.14)</td>
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<tr>
<td>Income source</td>
<td></td>
<td></td>
<td></td>
<td>0.130c</td>
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<tr>
<td>Government benefits</td>
<td>56 (82.35)</td>
<td>25 (75.76)</td>
<td>31 (88.57)</td>
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</tr>
<tr>
<td>Work full- or part-time</td>
<td>3 (4.41)</td>
<td>1 (3.03)</td>
<td>2 (5.71)</td>
<td></td>
</tr>
<tr>
<td>No income</td>
<td>9 (13.24)</td>
<td>7 (21.21)</td>
<td>2 (5.71)</td>
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<tr>
<td>Annual income &lt;$25,000</td>
<td>65 (95.59)</td>
<td>32 (96.97)</td>
<td>33 (94.29)</td>
<td>1.000c</td>
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<tr>
<td>Health insurance</td>
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</tr>
<tr>
<td>Medicaid</td>
<td>58 (85.29)</td>
<td>26 (78.79)</td>
<td>32 (91.43)</td>
<td>0.14b</td>
</tr>
<tr>
<td>Medicare</td>
<td>17 (25.00)</td>
<td>8 (24.24)</td>
<td>9 (25.71)</td>
<td>0.889b</td>
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<tr>
<td>Private</td>
<td>1 (1.47)</td>
<td>0 (0.00)</td>
<td>1 (2.86)</td>
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<tr>
<td>Health Status</td>
<td></td>
<td></td>
<td></td>
<td>0.291a</td>
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<tr>
<td>CD4+ T-cell count</td>
<td>452 (331)</td>
<td>491 (329)</td>
<td>417 (335)</td>
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</tr>
<tr>
<td>HIV viral load &lt;20</td>
<td>29 (42.65)</td>
<td>15 (45.45)</td>
<td>14 (40.00)</td>
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</tr>
<tr>
<td>Currently prescribed ART</td>
<td>66 (97.06)</td>
<td>33 (100)</td>
<td>33 (94.29)</td>
<td>0.493c</td>
</tr>
<tr>
<td>Fibrosis level</td>
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<td></td>
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<td>0.726b</td>
</tr>
<tr>
<td>Metavir &lt; F2</td>
<td>14 (20.59)</td>
<td>7 (21.21)</td>
<td>7 (20.00)</td>
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<tr>
<td>Metavir ≥ F2</td>
<td>24 (35.29)</td>
<td>13 (39.39)</td>
<td>11 (31.43)</td>
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<td>Unknown</td>
<td>30 (44.12)</td>
<td>13 (39.39)</td>
<td>17 (48.57)</td>
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<tr>
<td>HCV genotype</td>
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<td>0.249c</td>
</tr>
<tr>
<td>1a</td>
<td>44 (66.67)</td>
<td>21 (65.63)</td>
<td>23 (67.65)</td>
<td></td>
</tr>
<tr>
<td>1b</td>
<td>14 (21.21)</td>
<td>9 (28.13)</td>
<td>5 (14.71)</td>
<td></td>
</tr>
<tr>
<td>2b</td>
<td>1 (1.52)</td>
<td>1 (3.13)</td>
<td>0 (0.00)</td>
<td></td>
</tr>
<tr>
<td>3a</td>
<td>1 (1.52)</td>
<td>0 (0.00)</td>
<td>1 (2.94)</td>
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</tr>
<tr>
<td>4</td>
<td>1 (1.52)</td>
<td>0 (0.00)</td>
<td>1 (2.94)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (7.58)</td>
<td>1 (3.13)</td>
<td>4 (11.76)</td>
<td></td>
</tr>
<tr>
<td>Previously treated for HCV</td>
<td>15 (22.06)</td>
<td>8 (24.24)</td>
<td>7 (20.00)</td>
<td>0.810b</td>
</tr>
<tr>
<td>Knows someone who has cured</td>
<td>28 (41.18)</td>
<td>17 (51.52)</td>
<td>11 (31.43)</td>
<td>0.093b</td>
</tr>
<tr>
<td>HCV</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PhQ-9 total score</td>
<td>6.71 (5.27)</td>
<td>7.39 (6.03)</td>
<td>6.06 (4.53)</td>
<td>0.471d</td>
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<tr>
<td>HCV knowledge total score</td>
<td>15.10 (2.07)</td>
<td>15.39 (2.01)</td>
<td>14.83 (2.12)</td>
<td>0.264a</td>
</tr>
<tr>
<td>Substance Use</td>
<td></td>
<td></td>
<td></td>
<td>0.126b</td>
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</tbody>
</table>

106
<table>
<thead>
<tr>
<th></th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>Count (Percentage)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intravenous drug use, past 12 months</strong></td>
<td>16 (23.53)</td>
<td>9 (27.27)</td>
<td>7 (20.00)</td>
<td>0.480</td>
</tr>
<tr>
<td><strong>Medication assisted treatment, currently taking (i.e., methadone or buprenorphine)</strong></td>
<td>35 (51.47)</td>
<td>17 (51.52)</td>
<td>18 (51.43)</td>
<td>0.994</td>
</tr>
<tr>
<td><strong>Alcohol use, past 6 months</strong></td>
<td>28 (41.18)</td>
<td>10 (30.30)</td>
<td>18 (51.43)</td>
<td>0.077</td>
</tr>
<tr>
<td><strong>AUDIT total score, n=28</strong></td>
<td>6.82 (7.88)</td>
<td>6.60 (5.10)</td>
<td>6.94 (9.20)</td>
<td>0.650</td>
</tr>
</tbody>
</table>

a t-test; b Chi-square test; c Fisher’s exact test; d Mann-Whitney U test
Table 2: HCV Care Continuum Outcomes at 60 Days

<table>
<thead>
<tr>
<th></th>
<th>Enhanced Usual Care</th>
<th>Nurse Case Management</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=32</td>
<td>n=34</td>
<td></td>
</tr>
<tr>
<td>Referred to care by primary care provider</td>
<td>0.72 (0.59 – 0.85)</td>
<td>0.76 (0.65 – 0.88)</td>
<td>0.335</td>
</tr>
<tr>
<td>Scheduled HCV appointment</td>
<td>0.34 (0.21 – 0.48)</td>
<td>0.65 (0.51 – 0.78)</td>
<td>0.007</td>
</tr>
<tr>
<td>Linked to HCV care</td>
<td>0.25 (0.12 – 0.38)</td>
<td>0.47 (0.33 – 0.61)</td>
<td>0.031</td>
</tr>
</tbody>
</table>

*p-values are based on a 1-sided z test for difference in proportions; **bold** indicates primary outcome
Figure 2: Kaplan-Meier Estimates for Treatment Initiation

Kaplan-Meier survival estimates for treatment initiation

- - - - Enhanced usual care
- - - - Nurse case management

Number of days

0 50 100 150 200

0.00 0.25 0.50 0.75 1.00
CHAPTER 5: Predictors of engaging in hepatitis C treatment across the continuum among high-priority HIV co-infected patients

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Nancy R. Reynolds
Jason E. Farley

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Abstract

Background: Direct acting antivirals (DAAs) for hepatitis C virus (HCV) have allowed many well-engaged patients to be cured. But patient-level characteristics such as socioeconomic factors, substance use, and HIV co-infection may continue to hinder success in HCV care with DAAs. Understanding the barriers to and facilitators of engaging in HCV care among high-priority patients who remain untreated will inform interventions to improve the HCV care continuum.

Purpose: Describe characteristics that are associated with HCV outcomes across the HCV care continuum among high-priority adults co-infected with HIV.

Methods: Baseline and 6 month follow-up data from 68 adults with HIV/HCV co-infection in a randomized controlled trial designed to promote linkage to HCV care were used. Using logistic regression, we explored the factors associated with the following HCV outcomes across the care continuum, after controlling for intervention group assignment: scheduling and attending an HCV appointment, being prescribed DAAs, and initiating DAAs.

Results: Participants were primarily Black/African-American (81%), low income (98% on public health insurance), and 43% had an undetectable HIV viral load. Forty-one percent drank alcohol, 46% reported illicit drug use, and 51% took medication assisted treatment for opiate use (MAT). In multivariable analyses, participants who drank alcohol were more likely to schedule an HCV appointment (adjusted odds ratio [aOR]=3.8), attend the appointment (aOR=3.8), and be prescribed DAAs (aOR=4.2). Knowing someone who had cured HCV increased the likelihood of being prescribed DAAs (aOR=5.2) and initiating (aOR=8.0) DAAs. A higher CD4 cell count was associated with...
greater odds of scheduling an HCV appointment (aOR=1.002). Participants taking MAT were less likely to be prescribed DAAs (aOR=0.25).

**Conclusions:** Treatment pathways for patients drinking alcohol, who were more likely to engage in HCV care, are needed. Capitalizing on social networks may help to improve the HCV care continuum. Interventions to engage patients taking MAT, such as integrated substance use and HCV care, should be considered.
Introduction

Chronic hepatitis C virus (HCV) infection is a significant cause of morbidity and mortality, with approximately 2.5-4.7 million people infected in the United States (Edlin, Eckhardt, Shu, Holmberg, & Swan, 2015). Untreated HCV can lead to liver cirrhosis and hepatocellular carcinoma and is among the leading reasons for liver transplant in the US (“Definition & Facts of Liver Transplant | NIDDK,” n.d.). Prevalence of HCV is particularly high among people who inject drugs (53%) and persons living with HIV (PLWH) (25%). Progression to HCV-related liver disease is increased in the setting of HIV infection (Kirk et al., 2013; Sulkowski et al., 2007) and alcohol use (Bhattacharya & Shuhart, 2003; Jamal, Saadi, & Morgan, 2005; Khan & Yatsuhashi, 2000). However, with the advent of effective and tolerable direct acting antivirals (DAAs) to cure HCV, the World Health Organization has declared a goal of HCV elimination by 2030 (World Health Organization, 2016).

Although HCV treatment guidelines recommend prioritizing treatment for persons co-infected with HIV, the HCV care continuum among PLWH is lacking (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018). In 2014, it was reported that only 7% of persons with HIV/HCV co-infection had achieved an HCV cure (Cachay et al., 2014). A large, multi-site study in 2018 of PLWH who had access to HCV care found that 50% had not been prescribed DAAs and only 44% initiated treatment, even with the availability of DAAs for several years (Jayaweera et al., 2018). These statistics underscore the importance of understanding the barriers to curing HCV among PLWH. But few studies have examined predictors of engaging in HCV care among PLWH, even though HIV infection itself is a known predictor of poor
engagement in HCV care (Grebely et al., 2008; Mehta et al., 2008; Reed et al., 2008). In addition, most studies describing barriers to engaging in HCV care were conducted prior to all-oral DAAs which became available in 2014 (Grebely et al., 2008; McLaren, Garber, & Cooper, 2008; Swan et al., 2010; Treloar, Hull, Dore, & Grebely, 2012; Zickmund, Campbell, Tirado, Zook, & Weinrieb, 2012). This is important because the change to vastly more appealing treatment shifted the paradigm around treating HCV from toxic and ineffective to simply curable. Therefore, there is a need to understand which patients are at risk of succeeding in or dropping off of the HCV care continuum, particularly among PLWH, in this era of DAAs to inform strategies to engage high-priority populations in HCV eradication.

The purpose of our study was to describe the characteristics associated with engaging in HCV care across the continuum among a group of high-priority PLWH with high prevalence of uncontrolled HIV, drug and alcohol use, and psychiatric illness. The design of this study and organization of this paper were informed by Andersen’s Behavioral Model of Health Services Use, depicted in Figure 1. Andersen’s model posits that a person’s use of health services is a factor of predisposing characteristics, enabling resources, and perceived and actual need (Andersen, 1995).

Methods

Participants and Procedures

The data for this study were collected as part of the Care2Cure study, a randomized controlled trial to test a multi-component nurse case management intervention to improve the hepatitis C care continuum among PLWH coinfected with
HCV (Starbird et al., in press). This current paper examines the entire cohort of enrolled participants from the Care2Cure study and includes participant characteristics collected at enrollment and 6 months and outcomes at 6 months. Participants were recruited from a large, urban outpatient infectious disease practice in Baltimore, Maryland. The practice provides HIV primary care to over 3,000 men and women over the age of 18 per year. The practice also includes a viral hepatitis specialty practice, which delivers HCV specialty care to persons with and without HIV co-infection. Study team members screened the HIV practice schedule for potentially eligible patients and asked the HIV provider to refer their patients to the study if appropriate. Participants also self-referred to the study from recruitment brochures in the clinic, ClinicalTrials.gov (NCT02707991), or the Johns Hopkins Center for AIDS Research Study-Finder Hotline.

PLWH were included in this study if they had chronic HCV infection, were 18 years of age or older, had visited an HIV primary care provider in the past year, and did not attend an appointment at the viral hepatitis practice in the past year. We excluded pregnant women and persons unable to provide independent informed consent.

After providing informed consent, participants completed a sociodemographic questionnaire which has previously been used by these investigators in other studies (Farley et al., 2017). Additional measures were obtained from the electronic medical record at baseline and at 6 months. Ethical approval was granted by the Johns Hopkins Medicine Institutional Review Board.

**Measures**

*Predisposing characteristics.* We collected self-reported date of birth, gender, race and ethnicity, educational level, estimated annual income, and primary source of
income at baseline. Because annual income was similar across our first 18 participants, measures on financial strain were added for the remaining 50. The first measure of financial strain asked participants the following question: “at the end of the month, do you have some money left over, just enough money, or not enough money?” The second financial strain question asked “how often is your income not enough for food, housing, or medications?” with response options of “never,” “once in a while,” “fairly often,” or “very often.” (Pearlin, Lieberman, Menaghan, & Mullan, 1981; Samuel et al., 2012; Szanton et al., 2008).

At baseline, participants also self-reported illicit drug use in the past 12 months and current medication-assisted treatment for opiate use (MAT). We reviewed medical records for the most recent urine toxicology screen in the past 12 months at the time of participant enrollment. The Patient Health Questionnaire (PHQ-9) was administered to all participants at baseline to assess for depressive symptoms (Kroenke, Spitzer, & Williams, 2001). A safety protocol was in place for participants who scored greater than 10, indicating moderate (10-19) to severe (≥20) depressive symptoms. The medical record also was reviewed for a diagnosis of depression and other psychiatric diagnosis codes, such as bipolar disorder or schizophrenia.

**Perceived need.** Participants answered the Brief Hepatitis C Knowledge Scale to assess their baseline knowledge about HCV prevention, risk reduction, transmission, and treatment (Balfour et al., 2009). The Brief Hepatitis C Knowledge scale consists of 19 true/false items and has been validated in diverse populations (Balfour et al., 2009).

**Actual need.** HCV plasma RNA, HCV treatment history, and level of liver fibrosis were collected from the medical record at baseline. The most recent fibrosis
measure in the medical record was used. Fibrosis levels were obtained from either a liver biopsy, elastography (FibroScan), or FibroSure test and recorded by Metavir score, F0-F4. HCV genotype was added to the medical record abstraction at 6 months. Participants were asked to self-report the year of HIV diagnosis and whether they were currently taking antiretroviral therapy. The medical record was examined for most recent CD4 cell count, HIV viral load (categorized as undetectable [less than 20 copies/mL] or detectable [greater than or equal to 20 copies/mL]), and currently prescribed antiretroviral therapy regimen. Alcohol use in the past 6 months was collected via self-report at enrollment. Those who reported any alcohol use completed the Alcohol Use Disorders Identification Test (AUDIT) to identify harmful or hazardous drinking (Babor, Higgins-Biddle, Saunders, Monteiro, & Dependence, 2001). Participants who scored in Zone IV, suggesting alcohol dependence, were referred to their social worker for further counseling.

**Enabling resources.** Health insurance status and type (i.e., Medicaid, Medicare, private payer, Ryan White, and/or Maryland AIDS Drug Assistance Program) were obtained from the medical record at baseline.

**Use of health services.** All HCV care continuum outcomes were collected from the electronic medical record at 6 months (180 days) after study enrollment: 1) whether participants had received a referral to HCV specialty care, 2) whether an appointment in the viral hepatitis practice was ever scheduled, 3) whether the participant attended an HCV appointment, 4) if a prescription for DAAs was written, 5) if the participant started taking DAAs (initiated treatment), and 6) if the participant achieved an undetectable HCV plasma RNA (<15 copies/mL) within 6 months.
Statistical Analysis

Analyses were performed using 68 participants enrolled in the Care2Cure randomized controlled trial. Thirty-five participants were randomized to receive the NCM intervention and 33 were randomized to usual care. There were no differences in any participant characteristics between the NCM and usual care groups, hence descriptive statistics of demographic characteristics, HIV- and HCV-related health information, and substance use and psychiatric disorders, were generated for all participants. Participant characteristics were tested for normality and examined with means and standard deviations or medians and interquartile ranges accordingly. Participant characteristics were compared between the nurse case management intervention and usual care groups using chi-squared and Fisher’s exact tests for categorical variables, as appropriate, and t-tests and Mann Whitney U tests for continuous variables depending on analysis assumptions. A significance level of 0.05 was used for final analyses.

We evaluated the effect of select participant characteristics on HCV care continuum outcomes using logistic regression. We performed an analysis for each HCV care outcome separately (i.e., scheduled an appointment, attended an appointment, prescribed DAAs, and initiated DAAs). First, we conducted binary logistic regression with each characteristic of interest. Participant characteristics associated with the outcome with a p value of less than 0.2 were used to build the final models (Tabachnick & Fidell, 2012). We employed a stepwise forward method, described below. We used a correlation matrix to assess multicollinearity of the independent variables, and those with a correlation of greater than 0.6 were considered for removal from the model; a chi-
squared test was used to examine collinearity of binary variables. Randomization arm was controlled for in each model.

For the outcome of whether an HCV appointment was scheduled, binary logistic regression yielded \( p < 0.2 \) for the participant characteristics of: alcohol use, CD4 cell count, knowing someone who cured HCV, MAT use, baseline HCV RNA, and gender. These were entered stepwise into the model in order of smallest to largest \( p \) value and a likelihood ratio test was employed to evaluate significance of each added variable to the multivariable model. The final model for this outcome included alcohol use, CD4 count, and randomization arm.

The same method was used for each subsequent outcome. For attended an HCV appointment, participant characteristics with a \( p \) value less than 0.2 in binary logistic regression were, in order from smallest to largest: alcohol use, knowing someone who cured HCV, CD4 cell count, MAT use, and age. The final model for attended an appointment adjusted for alcohol use and randomization arm.

To determine characteristics associated with being prescribed DAAs, we entered the following covariates into a multivariable logistic regression using our forward stepwise method: knowing someone who cured HCV, alcohol use, MAT use, financial strain, race, being a caregiver, and CD4 cell count. The final model included knowing someone who cured HCV, alcohol use, MAT use, and randomization arm.

Finally, our covariates selected from binary logistic regression to predict DAA initiation included: knowing someone who cured HCV, financial strain, MAT use, CD4 cell count, gender, alcohol use, and race. The participant characteristics that added to the
final model were knowing someone who cured HCV, financial strain, and randomization arm.

Results

Sample characteristics

Table 1 summarizes the sample characteristics. The sample was predominantly middle-aged (mean=55 years), men (74%), and Black/African American (81%). Nearly half (41%) did not have a high school diploma or GED, and only 4% worked full or part time, with the rest receiving no income or government assistance. Seventy-percent reported not having enough money at the end of the month, and 72% had experienced financial strain that involved not enough money for housing, food, or medications. Nearly half (46%) reported any illicit drug use in the past 12 months, with 24% indicating they injected cocaine or heroin. Fifty-one percent were taking MAT for opiate use at the time of study enrollment. Depression was listed as a diagnosis in the medical record for 43% of participants, and 24% had another psychiatric illness other than depression or substance abuse, such as bipolar disorder or anxiety. Forty-one percent of participants drank alcohol within 6 months of enrollment; the median total AUDIT score was 3 (IQR 2-9).

Although all but 2 participants were prescribed ART, only 43% had an undetectable HIV viral load; the median CD4 cell count was 366 (IQR 197.5 – 652.5). At enrollment, 38 participants had a liver fibrosis measure in their record; of those, 37% were categorized as Metavir F0-F1 and 63% Metavir F2-F4. Most (88%) participants had HCV genotype 1, and 22% had been previously treated with either interferon or DAAs.
Factors Associated with HCV Care Continuum Outcomes

The HCV care continuum outcomes over our 6-month study period are depicted in figure 1. Seventy-four percent of participants were referred to the HCV practice by their primary care HIV providers, but 63% actually scheduled an appointment at the HCV practice during the 6-month period. Participants missed up to 5 scheduled HCV practice appointments during the study period (median 1; IQR 0-2). About half (48%) of participants attended at least one appointment at the HCV practice, yet only 29% were prescribed a DAA regimen. By the end of the 6 months, 18% initiated DAAs, and 13% had achieved HCV plasma RNA less than 15 copies/mL. Two participants were still taking DAAs at the end of the 6 month study period and one participant did not respond to HCV treatment.

Referred to HCV care and scheduled an appointment. No participant characteristics were associated with being referred by the primary care provider to HCV care in bivariate or multivariate analyses. Adjusting for CD4 cell count and randomization arm, participants who reported drinking alcohol had a 3.79 times greater odds of scheduling an appointment at the HCV specialty practice compared to those who reported no alcohol use in the past 12 months (p= 0.030). In this same adjusted analysis, an increase in CD4 cell count was associated with a greater odds of scheduling an HCV appointment (aOR 1.002; p=0.032).

Attended an appointment. Controlling for randomization arm, participants who drank alcohol were nearly four times more likely to attend an HCV appointment compared to those who did not report drinking alcohol in the past 12 months (aOR=3.79; p=0.018).
**Prescribed HCV treatment.** Participants who drank alcohol were also four times more likely to be prescribed DAAs within 6 months compared to those who do not drink alcohol (p=0.035), adjusting for knowing someone who had cured HCV, MAT use, and randomization arm. In this same model, knowing someone who had cured HCV was associated with five times greater odds of being prescribed DAAs compared to not knowing someone who had cured HCV (p=0.014). Additionally, participants who were taking MAT were 75% less likely to be prescribed DAAs compared to participants who do not take MAT (p=0.036).

**Initiated HCV treatment.** Knowing someone who had cured HCV increased the odds of initiating HCV treatment eight-fold, adjusting for knowing someone who had cured HCV and randomization arm (p=0.36). Experiencing financial strain (not enough money for basics such as housing, food, or medications) was associated with a 63% lower likelihood of initiating DAAs in this logistic regression model, although this was not statistically significant (p=0.052). All participants who initiated DAAs had genotype 1a or 1b.

**Discussion**

In this study describing the HCV care continuum among high-priority HIV/HCV co-infected individuals, we found that very few participants initiated treatment or achieved an HCV cure, despite the availability of DAAs. Alcohol use, higher CD4 cell count, and knowing someone who had cured HCV were associated with greater odds of succeeding in the HCV care continuum. MAT use decreased likelihood of being prescribed DAAs in our sample.
Alcohol use was a major predictor of engagement in HCV care across the continuum. These findings conflict with prior studies, which have reported that patients with a history of alcohol use had lower odds of specialty care follow up to HCV appointments and receipt of DAAs (Lin et al., 2017; Sims et al., 2017). However, we believe that our findings are meaningful and can likely be explained by patient motivation. We hypothesize that our participants who drank alcohol were more motivated to cure HCV and eliminate one of the stressors on their liver, potentially decreasing the combined effect from HCV and alcohol use. Given the high prevalence of alcohol use among persons with HCV, the overlapping epidemics of alcohol use and HCV need to be further explored, including motivations for engaging in HCV care and enhanced treatment pathways among persons who drink alcohol (Bhattacharya & Shuhart, 2003; Jamal et al., 2005; Khan & Yatsuhashi, 2000).

Knowing someone who had cured HCV was a significant predictor of being prescribed and initiating DAAs. Nearly half of persons living with HCV access their HCV information from friends and peers (Watson et al., 2007). But the impact of this information represents a flip from interferon-based treatment, when peer-based information focused on “horror stories” of interferon side effects, deterring individuals from starting HCV treatment (Swan et al., 2010). Now that the HCV cure message from peers is positive, there may be an opportunity to capitalize on social networks to eliminate HCV. HCV support groups are a meaningful way to facilitate HCV-information sharing and relationships among persons who have cured HCV and are considering curing HCV (Roose, Cockerham-Colas, Soloway, Batchelder, & Litwin, 2014). Peer education and peer navigator interventions that introduce patients to someone who has
been cured are a promising option (Arain et al., 2016; Roose et al., 2014). Peer support interventions are highly acceptable to patients and healthcare providers as long as peers are defined and selected carefully (Bonnington & Harris, 2017; Treloar et al., 2015). Future research could also examine the effect of peer referral programs to HCV care on treatment rates and outcomes.

Participants who reported taking MAT, such as methadone or buprenorphine, were less likely to be prescribed DAAs. To our knowledge, the relationship between taking MAT and engaging in HCV care has not previously been explored since the availability of DAAs. Individuals who take MAT have multiple competing priorities, including managing addiction and clinic visits to receive their dose of MAT as frequently as daily (Ball, Carroll, Canning-Ball, & Rounsaville, 2006; Shamsalinia, Norouzi, Fallahi-Khoshknab, Farhoudian, & Ghaffari, 2017). We postulate that this competing priority may explain why uptake of HCV care was lower in this population. Given that this population is both at risk for HCV transmission in the setting of ongoing drug use and also under direct observation of a healthcare provider, engaging people who take MAT in curing HCV is a critical opportunity. Clinical trials have demonstrated that DAAs remain over 90% effective among persons who are taking MAT (Dore et al., 2016; Grebely, Dore, et al., 2016). Studies have begun to look at models to treat HCV in the methadone maintenance setting with success (Akiyama et al., 2018; Alavi et al., 2013; Grebely, Alavi, et al., 2016; Schitz, Moser, Marchart, Haltmayer, & Gschwantler, 2016). Integrated substance abuse and HCV treatment programs are a promising approach to engage persons taking MAT in HCV care.
The results of this study must be considered in the context of its limitations. The number of participants who were prescribed and initiated DAAs was very small, resulting in large standard error for our estimates in those models, including alcohol use and knowing someone who cured HCV. Future studies will need to confirm the magnitude of these relationships with a larger sample. Furthermore, the study time period of 6 months contributed to the small proportion of participants who completed HCV treatment. Despite a high rate of HCV specialty care referral from primary HIV care providers, six months was not a sufficient time frame for patients to link to care and initiate treatment. A longer follow-up period would have likely improved our care continuum. However, these findings underscore the need for integrated HIV and HCV care and task shifting HCV care to non-specialty providers to eliminate the delay in linking to and following up with specialty care among patients who already attend primary HIV care (Jayasekera, Arora, & Ahmed, 2016; Yoo, Perumpail, Cholankeril, Jayasekera, & Ahmed, 2017). Finally, our co-located HIV and HCV practice may limit generalizability, but, considering the HCV care continuum gaps that exist in this high-level clinical setting, our findings remain relevant to clinical settings that do not have this capacity. Even with these limitations, this study provides an important description of the patient-level factors that predict engagement across the HCV care continuum in a high-priority population co-infected with HIV.

**Conclusion**

This study found that the HCV care continuum is still incomplete among PLWH. Our findings underscore the importance, and need for, integrated programs for the treatment of HIV, substance use, and HCV, as well as treatment pathways for persons...
who drink alcohol who are at high risk for liver disease but willing to cure their HCV.

Future interventions should capitalize on social networks to engage PLWH in HCV care.
References


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https://www.niddk.nih.gov/health-information/liver-disease/liver-transplant/definition-facts


https://doi.org/10.1097/MEG.0000000000000961


https://doi.org/10.1097/QAD.0b013e3282f10de9


Tables and Figures

Figure 1. Andersen’s Behavioral Model of Health Services Use applied to the hepatitis C care continuum
<table>
<thead>
<tr>
<th>Study Sample n=68</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean years (SD)</strong></td>
<td>55.03 (7.65)</td>
</tr>
<tr>
<td><strong>Female</strong></td>
<td>26 (38.24)</td>
</tr>
<tr>
<td><strong>Race/Ethnicity</strong></td>
<td></td>
</tr>
<tr>
<td>Black/African American</td>
<td>55 (80.88)</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>10 (14.71)</td>
</tr>
<tr>
<td>Native American/American Indian</td>
<td>1 (1.47)</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>2 (2.94)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>No high school diploma/No GED</td>
<td>28 (41.18)</td>
</tr>
<tr>
<td>High school graduate/GED</td>
<td>25 (36.76)</td>
</tr>
<tr>
<td>Some college or higher</td>
<td>15 (22.06)</td>
</tr>
<tr>
<td><strong>Primary income source</strong></td>
<td></td>
</tr>
<tr>
<td>Government assistance</td>
<td>56 (82.35)</td>
</tr>
<tr>
<td>No income</td>
<td>9 (13.24)</td>
</tr>
<tr>
<td>Work full- or part-time</td>
<td>3 (4.41)</td>
</tr>
<tr>
<td><strong>Health insurance</strong></td>
<td></td>
</tr>
<tr>
<td>Medicaid</td>
<td>58 (85.29)</td>
</tr>
<tr>
<td>Medicare</td>
<td>17 (25.00)</td>
</tr>
<tr>
<td>Private</td>
<td>1 (1.47)</td>
</tr>
<tr>
<td><strong>Financial strain</strong></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>14 (28.00)</td>
</tr>
<tr>
<td>Once in awhile</td>
<td>9 (18.00)</td>
</tr>
<tr>
<td>Fairly often</td>
<td>14 (28.00)</td>
</tr>
<tr>
<td>Very often</td>
<td>13 (26.00)</td>
</tr>
<tr>
<td><strong>CD4 cell count, median (IQR)</strong></td>
<td>366 (197.5 – 652.5)</td>
</tr>
<tr>
<td><strong>HIV viral load &lt;20 (undetectable)</strong></td>
<td>29 (42.65)</td>
</tr>
<tr>
<td><strong>Liver fibrosis – Metavir score</strong></td>
<td></td>
</tr>
<tr>
<td>F0-F1</td>
<td>14 (20.59)</td>
</tr>
<tr>
<td>F2-F4</td>
<td>24 (35.29)</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (44.12)</td>
</tr>
<tr>
<td><strong>HCV genotype</strong></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>44 (66.67)</td>
</tr>
<tr>
<td>1b</td>
<td>14 (21.21)</td>
</tr>
<tr>
<td>Other (2b, 3a, 4)</td>
<td>3 (4.56)</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (7.58)</td>
</tr>
<tr>
<td><strong>Previously treated for HCV</strong></td>
<td>15 (22.06)</td>
</tr>
<tr>
<td><strong>Knows someone who has cured HCV</strong></td>
<td>28 (41.18)</td>
</tr>
<tr>
<td><strong>Any illicit drug use, past 12 months</strong></td>
<td>31 (45.59)</td>
</tr>
<tr>
<td><strong>Injection drug use, past 12 months</strong></td>
<td>16 (23.53)</td>
</tr>
<tr>
<td><strong>Opiate substitution therapy, currently taking</strong></td>
<td>35 (51.47)</td>
</tr>
<tr>
<td><strong>Alcohol use, past 6 months</strong></td>
<td>28 (41.18)</td>
</tr>
<tr>
<td><strong>Depression</strong></td>
<td>29 (42.65)</td>
</tr>
<tr>
<td><strong>Other psychiatric illness</strong></td>
<td>16 (23.53)</td>
</tr>
</tbody>
</table>

*Financial strain – how often is your income not enough for food, housing, or medications?*

*Note: SD – standard deviation; IQR – interquartile range*
Figure 2: Six-Month Hepatitis C Care Continuum Outcomes

Six-Month Hepatitis C Care Continuum

- Referred to HCV care
- Scheduled appointment
- Attended appointment
- Prescribed DAAs
- Initiated DAAs
- Undetectable HCV RNA

Proportion of Participants
Table 2: Adjusted odds ratios of factors predicting HCV care continuum outcomes

Table 2. Adjusted odds ratios of factors predicting HCV care continuum outcomes (n=68)

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio, adjusted</th>
<th>p value</th>
<th>95% Confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Scheduled an appointment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count</td>
<td>1.002</td>
<td>0.032</td>
<td>1.00 – 1.00</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>3.792</td>
<td>0.030</td>
<td>1.14 – 12.61</td>
</tr>
<tr>
<td><strong>Attended an appointment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>3.786</td>
<td>0.016</td>
<td>1.29 – 11.13</td>
</tr>
<tr>
<td><strong>Prescribed direct acting antivirals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol use</td>
<td>4.178</td>
<td>0.035</td>
<td>1.10 – 15.80</td>
</tr>
<tr>
<td>Opiate substitution therapy</td>
<td>0.248</td>
<td>0.036</td>
<td>0.07 – 0.91</td>
</tr>
<tr>
<td>Know someone who cured HCV</td>
<td>5.238</td>
<td>0.014</td>
<td>1.40 – 19.55</td>
</tr>
<tr>
<td><strong>Initiated direct acting antivirals</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Financial strain</td>
<td>0.370</td>
<td>0.052</td>
<td>0.14 – 1.01</td>
</tr>
<tr>
<td>Knows someone who cured HCV</td>
<td>8.049</td>
<td>0.036</td>
<td>1.15 – 56.49</td>
</tr>
</tbody>
</table>

*a* adjusted for CD4 cell count, alcohol use, and randomization arm  
*b* adjusted for alcohol use and randomization arm  
*c* adjusted for alcohol use, opiate substitution therapy, knowing someone who cured HCV, and randomization arm  
*d* adjusted for knowing someone who cured HCV, financial strain, and randomization arm
CHAPTER 6: Lessons learned from a nurse case management clinical trial and implications for hepatitis C eradication in HIV care clinics

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Summary of Findings

The Care2Cure study demonstrated that nurse case management is an effective strategy to link persons co-infected with HIV to hepatitis C (HCV) care. Despite linking to care, few participants initiated HCV treatment during the six-month study period. We found no improvement in time to treatment initiation among participants who received nurse case management compared to participants who received usual care plus an HCV educational handout. Our research identified key facilitators to succeeding in HCV care continuum outcomes, including alcohol use and knowing someone who had cured HCV. A significant barrier to being prescribed direct acting antivirals (DAAs) for HCV treatment was taking medication-assisted treatment (MAT) such as methadone or buprenorphine.

This study enrolled a high-priority sample of individuals co-infected with HIV who are at increased risk for HCV-related morbidity and mortality (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018; Lo Re et al., 2014). The Care2Cure intervention components, consisting of nurse-initiated referral, strengths-based education, and care coordination and navigation, helped nearly half of participants to attend a specialty appointment for HCV treatment evaluation. Given that the majority of these participants had not been linked to HCV care within the era of all-oral DAAs, this is an important success. We enrolled and linked individuals to HCV care who had uncontrolled HIV, active drug and alcohol use, and significant socioeconomic disparities. Nonetheless, it is clear that linking patients to care alone is not sufficient to cure HCV; even if patients linked to care, many linked without ultimately receiving HCV treatment.
In the design of this study, we anticipated that drug-drug interactions between antiretroviral therapy (ART) and DAAs would be the greatest barrier to initiating HCV treatment, but found this was not the case in our setting. Many patients at the Bartlett Specialty Practice were switched to integrase inhibitor-based HIV treatment regimens pre-emptively in accordance with HIV treatment guidelines, thereby minimizing the potential for drug-drug interactions when considering HCV treatment (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2017). Instead, we found barriers at the provider level included non-referral to HCV care due to the belief the patient had too many missed visits or needed to stabilize their HIV and substance use first. At the system level, DAAs were not initiated due to insurance denial for having a detectable HIV viral load, liver fibrosis level less than Metavir F2, or ongoing prior authorization. Finally, at the patient level, our participants did not initiate HCV treatment due to loss to follow up, competing comorbidities such as cancer, or the decision to receive an HCV-positive kidney transplant before curing HCV.

Evaluation of the Nurse Case Management Intervention

The nurse case management intervention components showed mixed effects across the HCV care continuum. Figure 1 compares the HCV care continuum outcomes by randomization arm. Outcomes between the two groups were significantly different in the proportion of participants who scheduled an appointment for the HCV practice and attended the appointment at the HCV practice (linked to care).
Assisting a participant to schedule the appointment at the HCV practice was the most fruitful part of the intervention. The gap in proportion of participants who had an appointment scheduled between the intervention and control groups was highly significant (65% compared to 34%, respectively; p=0.007). This is in spite of both groups having nearly the same rate of referral to the HCV practice by their primary care HIV providers (77% compared to 70%, respectively). In addition, our HCV education and appointment reminders were successful in helping participants link to care. However, it is unclear whether the nurse-initiated referral had any effect, as the baseline referral rate to HCV care was high in our sample. Furthermore, we were unable to implement nurse-coordinated antiretroviral therapy modifications in response to drug-drug interactions. This is a testament to the high level of standard care provided at the Bartlett Specialty Practice. Yet the fact that our most successful intervention components were assistance
with scheduling appointments to the viral hepatitis practice, appointment reminders, and HCV education, shows that, while navigation is needed, a skilled clinician such as a registered nurse likely is not necessary to perform this intervention.

A major limitation of the Care2Cure intervention was its focus on linkage to care as a proxy for cure. Although we saw a positive difference in the proportion of participants who linked to care, indicating the intervention components were successful for their primary aim, very few participants started taking DAAs or achieved a cure. Follow-up procedures in our study protocol after linkage to care were specific to minimizing the effect of drug-drug interactions (Starbird et al., in press). Because participants in the nurse case management arm did not experience drug-drug interactions with ART and DAAs, no structured follow-up to help participants initiate HCV treatment and adhere to that treatment occurred through this study. Our findings indicate that interventions to improve HCV treatment uptake must span the entire continuum.

**Implications for Future Case Management for HCV Eradication**

In order to achieve the World Health Organization’s goal of HCV elimination as a public health threat by 2030 (World Health Organization, 2016), systems must be put in place to assist patients to navigate HCV specialty care, adhere to scheduled appointments, access curative medications, and succeed in taking those medications to achieve a cure. Case management has the potential to fill many of these needs. However, case management interventions must include optimal techniques to improve the entire continuum of care for HCV.

Based on the successes and failures of the Care2Cure study, I recommend the following approaches for clinics considering HCV eradication: 1) targeted case
management for high-priority patients that spans the care continuum; 2) patient navigation services, particularly for scheduling and keeping appointments; and 3) integrated HIV, HCV, and substance abuse care.

**Targeted comprehensive case management**

HIV and HCV are clearly overlapping epidemics. Not only is prevalence of HIV/HCV co-infection high, but the high-priority and hard-to-treat patients overlap as well. Case management that targets patients with known socioeconomic disparities, substance abuse, and uncontrolled HIV will also reach patients who are the highest priority to cure HCV. Therefore, funding in Ryan White-sponsored clinics should direct resources toward overlapping services for HCV case management.

Interventions to improve the HCV care continuum among persons co-infected with HIV need to be dosed continuously and ensure completion through the entire continuum of care. The Care2Cure study showed that we need to continue to support patients through initiating DAAs and beyond. If HIV care settings are going to eliminate HCV, comprehensive interventions that are structured to improve treatment initiation, follow-up, and medication adherence among these high-priority patients are necessary. Interventions to improve follow-up and decrease time to treatment initiation may include liver fibrosis staging at the time of HCV care referral to enhance perceived need for care among patients. Case managers can provide assistance with insurance approval and appeals, particularly by keeping patients engaged while waiting for insurance approval. Adherence support for taking DAAs and returning for follow-up evaluation, including required lab work, is also necessary is once treatment is initiated. In addition, the same
patient navigation strategies used to initially link patients to care should continue through every follow-up appointment.

**Patient navigation**

Interventions aimed at eliminating HCV should include patient navigation, including assistance obtaining referrals to specialty care, scheduling appointments, and keeping appointments. HIV case managers are in a strong position to monitor the chronic HCV status of their clients and ensure appropriate referrals are in place. Given that persons co-infected with HIV have been identified as a high-priority population to cure HCV, all HIV clinicians should be referring their HCV co-infected patients to receive evaluation and treatment for HCV (American Association for the Study of Liver Diseases & Infectious Diseases Society of America, 2018). Case managers should initiate this referral as needed with clinicians and follow up with their clients through HCV education emphasizing cure; prior studies have demonstrated the value of allied health professionals such as case managers in improving referral rates for cardiac management three-fold (Gravely-Witte et al., 2010).

Although scheduling specialty appointments associated with a referral is part of the standard check-out process in our practice, we found that an HCV practice appointment was not scheduled for most patients receiving usual care. Administrative policies may need to change to facilitate this process in the future. Additional reminders for staff, such as systematic prompts in the electronic medical record, should be integrated into clinic settings as had been done with colon cancer screening efforts (Baxter et al., 2017). Case managers can also follow up with clients to schedule these appointments, an approach the Care2Cure intervention successfully employed.
Once an appointment is scheduled, strategies need to be put in place to enable persons co-infected with HIV/HCV to attend the appointment. Competing priorities as well as socioeconomic barriers are prevalent in this population (Lin et al., 2017). We know from successful HIV care interventions that personalized appointment reminders in the form of text messages or phone calls can significantly improve show rates to clinical care (Farmer, Brook, McSorley, Murphy, & Mohamed, 2014; Finitis, Pellowski, & Johnson, 2014). This strategy was also a successful component of the Care2Cure study. In HIV primary care settings, case managers can include simple linkage to HCV care efforts in their workflow, such as appointment reminders, without substantial added time effort. Future research should further explore the role of HIV case managers in HCV care. Given that linkage to care alone is not enough to cure HCV, future research must also examine strategies to continue case management services through cure.

**Integrated care**

Getting referrals to specialty care, navigating scheduling specialty care appointments, and attending a specialty appointment are all barriers to engaging in HCV care that may be mitigated by integrating HCV treatment into HIV care settings. Recent studies have already found that primary care providers, including nurse practitioners and community-based physicians, can effectively treat HCV in hard-to-treat patients (Arora et al., 2011; Kattakuzhy et al., 2017; Miller, Fluker, Osborn, Liu, & Strawder, 2012). More evidence to support treating HCV using DAAs in an HIV clinic is needed. However, HIV primary care clinics are in an optimal position to manage HCV due to their high burden of HIV/HCV co-infection, infectious disease expertise, wraparound services including case management, and frequency of visits with their patients (Cachay et al., 2013).
Medicaid policies are relaxing to allow non-specialist providers to prescribe and manage HCV treatment, which will make this more feasible from a policy perspective (Maryland Department of Health, 2018).

Moreover, we found that persons who are taking medication-assisted treatment for opiate use (MAT) are less likely to be prescribed HCV treatment than persons not taking MAT. We suspect that this disparity among persons taking methadone or buprenorphine is due to competing priorities and appointment burden. Patients who take MAT are already well engaged in healthcare – many visit a treatment center daily. If the current model of care does not support engaging these patients in HCV specialty clinic care, HCV treatment should be brought to the model that does fit their needs. Data are already emerging on the effectiveness of integrating HCV treatment into substance abuse care centers (Alavi et al., 2013; Grebely et al., 2016; Schitz, Moser, Marchart, Haltmayer, & Gschwantler, 2016). Benefits include the opportunity to cure an extremely high prevalence population with high likelihood of transmitting to others (Amon et al., 2008; Vos, Prins, & Kretzschmar, 2015), ease of directly observed therapy to maximize adherence (Schitz et al., 2016), and elimination of many barriers to accessing HCV care present in the current system of specialty care. Integrating HCV care services into syringe exchange programs should also be considered to improve the uptake of HCV cure among individuals and communities injecting drugs and is a major gap in existing research.

**Conclusion and Next Steps**

This research experience, complimented by my clinical practice, provided me with the opportunity to implement and critically evaluate a multicomponent nurse case management intervention to improve the HCV care continuum among persons co-
infected with HIV. Moving forward, my program of research will further examine the comparative and cost effectiveness of interventions to improve the continuums of care for persons with substance abuse, HIV, and HCV, particularly through integrated treatment settings. My goal is to develop, implement, and evaluate health systems that optimize care for these overlapping epidemics. I believe that the purpose of this work is to ensure the best decisions are the easiest decisions for patients to make – I hope that by providing strong evidence for systems of care that make being healthy easy, we can achieve HCV elimination as well as improve the wellbeing of persons affected by HIV and substance abuse.
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Observed Therapy of Chronic Hepatitis C With Interferon-Free All-Oral
Regimens at a Low-Threshold Drug Treatment Facility-a New Concept for
Treatment of Patients With Borderline Compliance Receiving Opioid Substitution
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APPENDIX

Study Instruments

Baseline Questionnaire

Participant Study ID

Interviewer Name
- Laura Starbird
- Jason Farley
- Demetrius Marcoulides
- Amit Dhir
- Michaela Bartheimass
- Jeffrey Eskra
- Lilly Su

Interview Date

Time questionnaire started
(Must be after time informed consent was obtained)

The first set of questions is about your basic demographic information

What gender do you identify with?
- Male
- Female
- Transgender
- Prefer not to answer

What race do you consider yourself to be?
- Black/African American or Black/African descent
- Caucasian/White
- Asian/Pacific Islander
- Native American/American Indian
- Biracial/Mixed Race
- Don’t know/Refuse
- Other (specify)

Specify other race

Do you also consider yourself to be Latino(e)?
- Yes
- No

The next few questions are about your education and work

How far did you go in school?
- No high school diploma and no GED
- High school graduate or GED
- Some college or vocational school
- College graduate or above

What is your primary source of income?
- Work full time
- Work part time
- Social Security
- Disability (SSD or SSDI)
- Supplemental Security Income (SSI)
- Pension/Retirement
- None
- Other (specify)
Specify other income source

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What is your total estimated yearly income from ALL sources?
- Less than $25,000
- $25,000 - $49,000
- $50,000 - $75,000
- More than $75,000

At the end of the month, do you have:
- Some money left over
- Just enough money
- Not enough money

How often is your income not enough for food, housing, or medications?
- Never
- Once in awhile
- Fairly often
- Very often

Are you the main caregiver for anyone (such as a child or an older or disabled adult)?
- Yes
- No

How many dependents do you have?

---

**These next questions are about your health history**

During the last 12 months, how would you describe your health?
- Excellent
- Good
- Fair
- Poor

You joined our study because you are a patient at the Moore Clinic. What year were you diagnosed with HIV?

Do you currently take HIV medications?
- Yes
- No

Have you ever taken hepatitis C medications?
- Yes
- No

When did you take hepatitis C medications?

---

Do you know someone who has cured their hepatitis C?
- Yes
- No

Have you ever gone to a hepatitis C support group?
- Yes
- No

Sometimes Johns Hopkins has studies that provide medications to treat hepatitis C. Are you interested in being referred to research studies that provide treatment for hepatitis C if you might be eligible?
- No
- Yes, but only trials with approved treatments (no investigational drugs)
- Yes, I am interested in trials with investigational (not FDA approved) treatments and approved treatments
These next questions ask about drug and alcohol use. Remember that all of your answers are confidential and will not be shared with anyone.

Have you used any street drugs in the last year? (such as heroin, cocaine, or painkillers)  
- Yes
- No

Which substances have you used in the last year?  
- IV heroin
- Intranasal (snort) heroin
- Smoked heroin
- IV cocaine
- Intranasal (snort) cocaine
- Smoked cocaine
- Crystal methamphetamine (Tina, Crank, Seed, IV Crystal, Snort Crystal)
- Pain killers (oxycodeone, OxyContin, Percocet, Dilauded, Vicodin)
- Benzodiazepines (Ativan, Xanax, Valium, Klonopin)  
(Select all that apply)

Do you currently take methadone, buprenorphine (suboxone), or other opiate replacement therapy?  
- Yes
- No

Have you drank alcohol in the past 6 months?  
- Yes
- No

The Alcohol Use Disorders Identification Test (AUDIT):  
Now I am going to ask you some questions about your use of alcohol beverages during this past year. By Alcoholic beverages, I mean beer, wine, vodka, etc.

How often do you have a drink containing alcohol?  
- Never
- Monthly or less
- 2 to 4 times a month
- 2 to 3 times a week
- 4 or more times a week

How many drinks containing alcohol do you have on a typical day when you are drinking?  
- 1 or 2
- 3 or 4
- 5 or 6
- 7, 8, or 9
- 10 or more

How often do you have six or more drinks on one occasion?  
- Never
- Less than monthly
- Monthly
- Weekly
- Daily or almost daily

How often during the last year have you found that you were not able to stop drinking once you had started?  
- Never
- Less than monthly
- Monthly
- Weekly
- Daily or almost daily

How often during the last year have you failed to do what was normally expected from you because of drinking?  
- Never
- Less than monthly
- Monthly
- Weekly
- Daily or almost daily
<table>
<thead>
<tr>
<th>Question</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?</td>
<td>Never, Less than monthly, Monthly, Weekly, Daily or almost daily</td>
</tr>
<tr>
<td>How often during the last year have you had a feeling of guilt or remorse after drinking?</td>
<td>Never, Less than monthly, Monthly, Weekly, Daily or almost daily</td>
</tr>
<tr>
<td>How often during the last year have you been unable to remember what happened the night before because you had been drinking?</td>
<td>Never, Less than monthly, Monthly, Weekly, Daily or almost daily</td>
</tr>
<tr>
<td>Have you or someone else been injured as a result of your drinking?</td>
<td>No, Yes, but not in the last year, Yes, during the last year</td>
</tr>
<tr>
<td>Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?</td>
<td>No, Yes, but not in the last year, Yes, during the last year</td>
</tr>
<tr>
<td><strong>AUDIT total score</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Patient Health Questionnaire (PHQ-9):**
These next questions are about your mood. Over the last 2 weeks how often have you been bothered by any of the following problems?

1. Little interest or pleasure in doing things
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day

2. Feeling down, depressed, or hopeless
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day

3. Trouble falling or staying asleep, or sleeping too much
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day

4. Feeling tired or having little energy
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day

5. Poor appetite or overeating
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day
6. Feeling bad about yourself -- or that you are a failure or have let yourself or your family down
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day

7. Trouble concentrating on things, such as reading the newspaper or watching television
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day

8. Moving or speaking so slowly that other people could have noticed? Or the opposite -- being so fidgety or restless that you have been moving around a lot more than usual
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day

9. Thoughts that you would be better off dead or of hurting yourself in some way
   - 0: Not at all
   - 1: Several days
   - 2: More than half the days
   - 3: Nearly every day

Total PHQ-9 Score

If total is 10-19, refer to primary care provider for further assessment.

If total is 20 or greater, STOP and notify primary care provider or urgent provider of the day.

Indicate action taken if applicable.

---

**The Brief Hepatitis C Knowledge Scale:**
This final set of questions are about hepatitis C. Answer each question “True” or “False.” This is just for our information; it is not a test.

<p>| People with hepatitis C can safely share their toothbrushes and razors with other people. | True | False |
| People with hepatitis C can safely take any herbal medicine. | True | False |
| People living with hepatitis C can damage their liver when they drink alcohol. | True | False |
| People who received a blood transfusion before 1991 may have been infected with hepatitis C. | True | False |
| There exists a hepatitis C vaccine that can be used to prevent people from getting infected with the hepatitis C virus. | True | False |
| It is a good idea for people living with hepatitis C to be vaccinated against hepatitis A and B. | True | False |</p>
<table>
<thead>
<tr>
<th>Statement</th>
<th>True</th>
<th>False</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studies show that more than 60% of people who inject street drugs with 'used needles' are infected with hepatitis C.</td>
<td></td>
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<tr>
<td>People can live with hepatitis C for many years without knowing that they have been infected with the virus.</td>
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<tr>
<td>There is some risk that hepatitis C can be given to someone by snorting cocaine with shared straws, rolled money, etc.</td>
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<tr>
<td>Some treatments for hepatitis C, such as interferon, can cause depression as a side effect in some patients.</td>
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<tr>
<td>Using 'new' (i.e. never used before) needles, syringes, and equipment reduces the risk of being infected with hepatitis C.</td>
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<tr>
<td>Babies born to hepatitis C pregnant women can be infected with hepatitis C at birth.</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis C can be given to someone during sexual intercourse.</td>
<td></td>
<td></td>
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<tr>
<td>Coughing and sneezing can spread hepatitis C.</td>
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<tr>
<td>Successful hepatitis C treatments can result in the hepatitis C virus being completely removed (or cleared) from one's blood.</td>
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<tr>
<td>The hepatitis C virus can be spread from shared kitchen cups, plates or utensils.</td>
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<tr>
<td>Once someone's hepatitis C virus has been completely treated and cleared, one cannot get re-infected with hepatitis C.</td>
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<td></td>
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<tr>
<td>People can get infected with hepatitis C from tattoos and body piercing.</td>
<td></td>
<td></td>
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<tr>
<td>Hepatitis C can be given by hugs or handshakes.</td>
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</tbody>
</table>

**Total Brief Hepatitis C Knowledge Score**

**Time baseline questionnaire completed**
## Baseline Medical Record Abstraction

<table>
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<th>Field</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Participant Study ID</td>
<td></td>
</tr>
<tr>
<td>Medical record screening date</td>
<td></td>
</tr>
<tr>
<td>Study team member completing record review</td>
<td>Laura Starbird, Jason Farley, Demetrius Marcouilides, Amit Dhir, Michaela Barthelmess, Jeffrey Eskra, Lilly Su</td>
</tr>
<tr>
<td>Most recent CD4 T-cell count</td>
<td></td>
</tr>
<tr>
<td>Most recent HIV RNA (HIV viral load)</td>
<td>Not detectable (&lt; 20), Detectable</td>
</tr>
<tr>
<td>Is the patient prescribed HIV medications?</td>
<td>Yes, No</td>
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<tr>
<td>Which HIV medications is the patient prescribed?</td>
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<tr>
<td>--------------------------------------------------</td>
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</tr>
<tr>
<td>Multi-class: Atripla (efavirenz, emtricitabine and tenofovir disoproxil fumarate)</td>
<td></td>
</tr>
<tr>
<td>Multi-class: Complera (emtricitabine, rilpivirine, and tenofovir disoproxil fumarate)</td>
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<tr>
<td>Multi-class: Stritol (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)</td>
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<tr>
<td>Multi-class: Triumeq (dolutegravir, abacavir, lamivudine)</td>
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<tr>
<td>NRTIs: Combin (lamivudine and zidovudine)</td>
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<tr>
<td>NRTIs: Embriva (emtricitabine, FTC)</td>
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<td>NRTIs: Eplvir (lamivudine, 3TC)</td>
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<td>NRTIs: Epzicom (abacavir and lamivudine)</td>
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<tr>
<td>NRTIs: Retrovir (zidovudine, azidothymidine, AZT, ZDV)</td>
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<tr>
<td>NRTIs: Trizivir (abacavir, zidovudine, and lamivudine)</td>
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<tr>
<td>NRTIs: Truvada (tenofovir disoproxil fumarate and emtricitabine)</td>
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<tr>
<td>NRTIs: Viread (tenofovir disoproxil fumarate, TDF)</td>
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<tr>
<td>NRTIs: Zerit (stavudine, d4T)</td>
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<tr>
<td>NRTIs: Zagen (abacavir sulfate, ABC)</td>
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<tr>
<td>NNRTIs: Edurant (rilpivirine)</td>
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<tr>
<td>NNRTIs: Intolerance (etravirine)</td>
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<tr>
<td>NNRTIs: Sustiva (efavirenz, EFV)</td>
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<tr>
<td>NNRTIs: Viramune (Immediate Release) (nevirapine, NVP)</td>
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<td>NNRTIs: Viramune XR (Extended Release) (nevirapine, NVP)</td>
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<td>PIs: Apitanz (tipranavir, TPV)</td>
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<tr>
<td>PIs: Kaletra (lopinavir and ritonavir, LPV/RTV)</td>
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<tr>
<td>PIs: Lexiva (fosamprenavir Caclium, FOS-APV)</td>
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<tr>
<td>PIs: Norvir (ritonavir, RTV)</td>
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<td>PIs: Prezista (darunavir)</td>
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<tr>
<td>PIs: Reyataz (atazanavir sulfate, ATV)</td>
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<tr>
<td>PIs: Viracept (nevirapine mesylate, NFV)</td>
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<tr>
<td>Other: Fuzeon (enfuvirtide, T-20)</td>
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<tr>
<td>Other: Sellestys (travirepil)</td>
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<td>Other: Isentress (raltegravir)</td>
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<td>Other: Tivicay (dolutegravir)</td>
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<tr>
<td>Other: Tybost (cobicistat, COBI)</td>
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<tr>
<td>Other: Vitekta (elvitegravir, EVG)</td>
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</tr>
<tr>
<td>Multi-class: Evotaz (atazanavir and cobicistat)</td>
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<table>
<thead>
<tr>
<th>Year of hepatitis C diagnosis</th>
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<td>--------------------------------</td>
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<table>
<thead>
<tr>
<th>Has the participant received hepatitis C treatment before?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
</tr>
<tr>
<td>No</td>
</tr>
<tr>
<td>Unknown</td>
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<table>
<thead>
<tr>
<th>Year of past hepatitis C treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>----------------------------------</td>
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</table>

<table>
<thead>
<tr>
<th>Most recent HCV RNA (hepatitis C viral load)</th>
</tr>
</thead>
<tbody>
<tr>
<td>---------------------------------------------</td>
</tr>
<tr>
<td>Last known visit with a hepatitis C specialty provider</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Most recent fibrosis score</td>
</tr>
<tr>
<td>Current problem list diagnoses in addition to HIV/HCV</td>
</tr>
<tr>
<td>Is a toxicology screen available in the past 12 months?</td>
</tr>
<tr>
<td>Positive substances in the past 12 months</td>
</tr>
<tr>
<td>Insurance status</td>
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</table>
# Monthly Activity Log

## Participant Study ID

---

## Enter all encounters recorded for this participant during the designated month of study enrollment

<table>
<thead>
<tr>
<th>Date range for month reviewed</th>
<th>(mm/dd/yyyy - mm/dd/yyyy)</th>
</tr>
</thead>
</table>

## Study team reviewing record

- Laura Starbird
- Amit Dhir
- Demetrius Marcouliades
- Jason Farley
- Michaela Barthelmass
- Jeffrey Eskra
- Lilly Su

## Date of chart review

---

## Johns Hopkins Medicine Encounters

<table>
<thead>
<tr>
<th>Type of JHH encounters during specified period</th>
<th>In-person</th>
<th>Phone</th>
<th>Text</th>
<th>E-mail</th>
<th>No activities this month (Select all that apply)</th>
</tr>
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</table>

## Total number of JHH encounters this month

---

## Total duration of JHH encounters this month

- 10 minutes or less
- 11-30 minutes
- 31-60 minutes
- 1 to 5 hours
- More than 5 hours
JHH activities recorded this month

- Linkage to HCV Care Activities
- Referrals to Services or Clinics
- ART Adherence Support
- DAA Adherence Support
- Medication Management- drug interaction review
- Medication Management- ART change
- Medication Management- side effect evaluation
- Patient Education- HIV treatment/care/medication
- Patient Education- HCV treatment/care/medication
- Patient Education- lab results
- Patient Education- substance/alcohol use
- Patient Education- mental health
- Patient Education- life skills/navigating health care
- Patient Education- other
- Assistance Provided- financial/benefits/insurance
- Assistance Provided- food/nutrition
- Assistance Provided- transportation
- Assistance Provided- housing
- Assistance Provided- other
- Clinic Visit- primary care
- Clinic Visit- urgent care
- Clinic Visit- viral hepatitis
- Clinic Visit- psych
- Clinic Visit- other specialty
- Lab Draw
- Hospital Admission
- Emergency Visit
- Other Activity
- Pharmacy Visit
- Procedure

(Select all that apply; use "other" sparingly!)

Care2Cure Study Encounters (see contact log in participant study file)

Type of Care2Cure encounters during specified period

- In-person
- Phone
- Text
- E-mail
- No activities this month

(Select all that apply)

Total number of Care2Cure study encounters this month

Total duration of Care2Cure study encounters this month

- 10 minutes or less
- 11-30 minutes
- 31-60 minutes
- 1 to 5 hours
- More than 5 hours
<table>
<thead>
<tr>
<th>Care2Cure study activities recorded this month</th>
</tr>
</thead>
<tbody>
<tr>
<td>☐ Linkage to HCV Care Activities</td>
</tr>
<tr>
<td>☐ Referrals to Services or Clinics</td>
</tr>
<tr>
<td>☐ ART Adherence Support</td>
</tr>
<tr>
<td>☐ DAA Adherence Support</td>
</tr>
<tr>
<td>☐ Medication Management- drug interaction review</td>
</tr>
<tr>
<td>☐ Medication Management- ART change</td>
</tr>
<tr>
<td>☐ Medication Management- side effect evaluation</td>
</tr>
<tr>
<td>☐ Patient Education- HIV treatment/care/medication</td>
</tr>
<tr>
<td>☐ Patient Education- HCV treatment/care/medication</td>
</tr>
<tr>
<td>☐ Patient Education- lab results</td>
</tr>
<tr>
<td>☐ Patient Education- substance/alcohol use</td>
</tr>
<tr>
<td>☐ Patient Education- mental health</td>
</tr>
<tr>
<td>☐ Patient Education- life skills/navigating healthcare</td>
</tr>
<tr>
<td>☐ Patient Education- other</td>
</tr>
<tr>
<td>☐ Assistance Provided- financial/benefits/insurance</td>
</tr>
<tr>
<td>☐ Assistance Provided- food/nutrition</td>
</tr>
<tr>
<td>☐ Assistance Provided- transportation</td>
</tr>
<tr>
<td>☐ Assistance Provided- housing</td>
</tr>
<tr>
<td>☐ Assistance Provided- other</td>
</tr>
<tr>
<td>☐ Clinic Visit- primary care</td>
</tr>
<tr>
<td>☐ Clinic Visit- viral hepatitis</td>
</tr>
<tr>
<td>☐ Other Activity</td>
</tr>
<tr>
<td>☐ Pharmacy Visit</td>
</tr>
<tr>
<td>(Select all that apply; use &quot;other&quot; sparingly!)</td>
</tr>
</tbody>
</table>
60 Day Medical Record Review

Participant Study ID

Medical record review date

Study team completing record review
- Laura Starbird
- Jason Farley
- Demetrius Marcoulides
- Amit Dhir
- Michaela Barthelmass
- Jeffrey Eskra
- Lilly Su

Was a Viral Hepatitis Center (VHC - clinic or clinical trial) appointment scheduled within 60 days of the baseline study visit?  
- Yes
- No

Date of initial VHC appointment after baseline study visit

Did the patient attend one or more appointments at the VHC within 60 days of the baseline study visit?  
- Yes
- No

Decision to treat HCV
- Defer
- Start
- Unknown/no decision

Recommended DAA regimen according to hepatitis clinic visit note or medication list
- Zepatier (elbasvir 50 mg/grazoprevir 100 mg)
- Harvoni (ledipasvir 90 mg/sofosbuvir 400 mg)
- Viekira Pak (paritaprevir 150 mg/ritonavir 100 mg/ombitasvir 25 mg + dasabuvir 250 mg + RBV)
- simeprevir 150 mg + sofosbuvir 400 mg
- daclatasvir 60 mg + sofosbuvir 400 mg + RBV
- sofosbuvir 400 mg + RBV + PEG-IFN
- other

Specify other regimen:

Is an HIV treatment modification indicated?  
- Yes
- No

(If YES, nurse case manager contact for Phase 2)

Nurse Case Manager Phase 2 eligibility notes

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# 6 Month Medical Record Abstraction

<table>
<thead>
<tr>
<th>Participant Study ID</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<table>
<thead>
<tr>
<th>Medical record screening date</th>
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</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Study team member completing record review</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Laura Starbird</td>
</tr>
<tr>
<td>2. Jason Farley</td>
</tr>
<tr>
<td>3. Demetris Marcoulides</td>
</tr>
<tr>
<td>4. Amit Dhir</td>
</tr>
<tr>
<td>5. Michaela Barthelma</td>
</tr>
<tr>
<td>6. Jeffrey Eska</td>
</tr>
<tr>
<td>7. Lilly Su</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Most recent CD4 T-cell count</th>
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</thead>
<tbody>
<tr>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Most recent HIV RNA (HIV viral load)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Not detectable (&lt; 20)</td>
</tr>
<tr>
<td>2. Detectable</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Is the patient prescribed HIV medications?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Yes</td>
</tr>
<tr>
<td>2. No</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Which HIV medications is the patient prescribed?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Multi-class: Atripla (efavirenz, emtricitabine and tenofovir disoproxil fumarate)</td>
</tr>
<tr>
<td>2. Multi-class: Complera (emtricitabine, rilpivirine, and tenofovir disoproxil fumarate)</td>
</tr>
<tr>
<td>3. Multi-class: Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate)</td>
</tr>
<tr>
<td>4. Multi-class: Trulomeq (dolutegravir, abacavir, lamivudine)</td>
</tr>
<tr>
<td>5. NRTIs: Combivir (lamivudine and zidovudine)</td>
</tr>
<tr>
<td>6. NRTIs: Emtriva (emtricitabine, FTC)</td>
</tr>
<tr>
<td>7. NRTIs: Epivir (lamivudine, 3TC)</td>
</tr>
<tr>
<td>8. NRTIs: Epzicom (abacavir and lamivudine)</td>
</tr>
<tr>
<td>9. NRTIs: Retrovir (zidovudine, azidothymidine, AZT, ZDV)</td>
</tr>
<tr>
<td>10. NRTIs: Trizivir (abacavir, zidovudine, and lamivudine)</td>
</tr>
<tr>
<td>11. NRTIs: Truvada (tenofovir disoproxil fumarate and emtricitabine)</td>
</tr>
<tr>
<td>12. NRTIs: Viread (tenofovir disoproxil fumarate, TDF)</td>
</tr>
<tr>
<td>13. NRTIs: Zent ( stavudine, d4T)</td>
</tr>
<tr>
<td>14. NRTIs: Ziagen (abacavir sulfate, ABC)</td>
</tr>
<tr>
<td>15. NNRTIs: Edurant (rilpivirine)</td>
</tr>
<tr>
<td>16. NNRTIs: Intonel (etravirine)</td>
</tr>
<tr>
<td>17. NNRTIs: Sustiva (efavirenz, EFV)</td>
</tr>
<tr>
<td>18. NNRTIs: Viramune (Immediate Release)(nevirapine, NVP)</td>
</tr>
<tr>
<td>19. NNRTIs: Viramune XR (Extended Release (nevirapine, NVP)</td>
</tr>
<tr>
<td>20. PIs: Aptivus (tipranavir, TPV)</td>
</tr>
<tr>
<td>21. PIs: Kaletra (lopinavir and ritonavir, LPV/RTV)</td>
</tr>
<tr>
<td>22. PIs: Lexiva (Fosamprenavir Calcium, FOS-APV)</td>
</tr>
<tr>
<td>23. PIs: Norvir (ritonavir, RTV)</td>
</tr>
<tr>
<td>24. PIs: Prezista (darunavir)</td>
</tr>
<tr>
<td>25. PIs: Reyataz (atazanavir sulfate, ATV)</td>
</tr>
<tr>
<td>26. PIs: Viracept (nelfinavir mesylate, NFV)</td>
</tr>
<tr>
<td>27. Other: Fuzenon (efavirenz, T-20)</td>
</tr>
<tr>
<td>28. Other: Selzentry (maraviroc)</td>
</tr>
<tr>
<td>29. Other: Isentress (raltegravir)</td>
</tr>
<tr>
<td>30. Other: Tivicay (dolutegravir)</td>
</tr>
<tr>
<td>31. Other: Tybost (cobicistat, COBI)</td>
</tr>
<tr>
<td>32. Other: Vitekta (elvitegravir, EVG)</td>
</tr>
<tr>
<td>33. Multi-class: Evotaz (atazanavir and cobicistat)</td>
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<tr>
<td>34. Multi-class: Prezcoxiv (darunavir and cobicistat)</td>
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<tr>
<td>Question</td>
</tr>
<tr>
<td>-------------------------------------------------------------------------</td>
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<tr>
<td>Were any changes made to the prescribed HIV regimen since enrollment?</td>
</tr>
<tr>
<td>Is a referral to Infectious Disease for chronic hepatitis C entered in Epic for the patient?</td>
</tr>
<tr>
<td>Reason patient was not referred to HCV care (per HIV provider):</td>
</tr>
<tr>
<td>Stabilize HIV treatment</td>
</tr>
<tr>
<td>Decrease drug use</td>
</tr>
<tr>
<td>Decrease alcohol use</td>
</tr>
<tr>
<td>Missed visits/not established in HIV care</td>
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<tr>
<td>No response from provider</td>
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<tr>
<td>Other</td>
</tr>
<tr>
<td>Control group/HCV not addressed by provider</td>
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<tr>
<td>Specify other reason:</td>
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<tr>
<td>Was a Viral Hepatitis Center appointment scheduled within 6 months of enrollment?</td>
</tr>
<tr>
<td>Total number of scheduled VHC appointments in the past 6 months</td>
</tr>
<tr>
<td>Did the patient attend a VHC appointment within 6 months of enrollment?</td>
</tr>
<tr>
<td>Total number of VHC appointments attended in the past 6 months</td>
</tr>
<tr>
<td>Overall show rate from Epic appointment desk (%)</td>
</tr>
<tr>
<td>Was a prescription written for HCV treatment within 6 months of enrollment?</td>
</tr>
<tr>
<td>Date HCV prescription was written</td>
</tr>
<tr>
<td>Did the patient start taking HCV treatment within 6 months of enrollment?</td>
</tr>
<tr>
<td>Date of first dose of HCV treatment</td>
</tr>
<tr>
<td>HCV treatment initiation barriers:</td>
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<tr>
<td>Wait for transplant</td>
</tr>
<tr>
<td>Insurance denial - HIV viral load detectable</td>
</tr>
<tr>
<td>Insurance denial - substance use</td>
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<tr>
<td>Insurance denial -</td>
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<tr>
<td>Specify other barrier(s):</td>
</tr>
<tr>
<td>Most recent HCV RNA (hepatitis C viral load) (if &quot;undetectable,&quot; enter &quot;0&quot;)</td>
</tr>
<tr>
<td>HCV genotype:</td>
</tr>
<tr>
<td>-------------------------------</td>
</tr>
<tr>
<td>Most recent fibrosis score</td>
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<tr>
<td>Current diagnoses in addition to HIV/HCV</td>
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<td>Is a toxicology screen available in the past 12 months?</td>
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<tr>
<td>Positive substances in the past 12 months</td>
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<td>Insurance status</td>
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# NCM Phase 1

<table>
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<td>Participant Study ID</td>
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<tr>
<td>Date intervention initiated</td>
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</tr>
<tr>
<td>Initiated HCV referral</td>
<td>Yes</td>
</tr>
<tr>
<td>Initiated HCV referral</td>
<td>No</td>
</tr>
<tr>
<td>HCV referral to clinical care or trial?</td>
<td>Clinical care</td>
</tr>
<tr>
<td>HCV referral to clinical care or trial?</td>
<td>Clinical trial</td>
</tr>
<tr>
<td>Which clinical trial was the participant referred to?</td>
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</tr>
<tr>
<td>Referral Notes</td>
<td></td>
</tr>
<tr>
<td>Strengths-based education notes</td>
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<tr>
<td>Time spent on education</td>
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</tr>
<tr>
<td>Appointment scheduled with HCV provider or clinical trial coordinator</td>
<td>Yes</td>
</tr>
<tr>
<td>Appointment scheduled with HCV provider or clinical trial coordinator</td>
<td>No</td>
</tr>
<tr>
<td>Select referrals made to other services</td>
<td>Social Work</td>
</tr>
<tr>
<td>Select referrals made to other services</td>
<td>Primary Care</td>
</tr>
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<td>Select referrals made to other services</td>
<td>Psych</td>
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<td>Select referrals made to other services</td>
<td>Pharmacy</td>
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<td>Select referrals made to other services</td>
<td>Nurse</td>
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<tr>
<td>Select referrals made to other services</td>
<td>Other</td>
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<tr>
<td>Select referrals made to other services</td>
<td>(Select all that apply)</td>
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<tr>
<td>Patient Navigation notes</td>
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<tr>
<td>Total time spent with patient in Phase 1 NCM visit</td>
<td>(minutes)</td>
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### NCM Phase 2

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<table>
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<th>Was the participant contacted for a follow up NCM visit?</th>
<th>Yes</th>
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<table>
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<tr>
<th>Scheduling notes for phase 2 follow up</th>
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<tr>
<th>Personalized drug-drug interactions chart given to patient</th>
<th>Yes</th>
<th>No</th>
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<table>
<thead>
<tr>
<th>Follow-up appointment with HIV provider navigated</th>
<th>Yes</th>
<th>No</th>
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</table>

<table>
<thead>
<tr>
<th>DHHS table sent to provider</th>
<th>Yes</th>
<th>No</th>
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</thead>
</table>

<table>
<thead>
<tr>
<th>Drug-drug interactions education notes</th>
<th></th>
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</tbody>
</table>
HEPATITIS C

General Information

What is hepatitis?

‘Hepatitis’ means inflammation of the liver. The liver is a vital organ that processes nutrients, filters the blood, and fights infections. When the liver is inflamed or damaged, its function can be affected.

Heavy alcohol use, toxins, some medications, and certain medical conditions can cause hepatitis. However, hepatitis is most often caused by a virus. In the United States, the most common types of viral hepatitis are Hepatitis A, Hepatitis B, and Hepatitis C.

How is Hepatitis C spread?

Hepatitis C is usually spread when blood from a person infected with the Hepatitis C virus enters the body of someone who is not infected. Today, most people become infected with Hepatitis C by sharing needles, syringes, or any other equipment to inject drugs. Before widespread screening of the blood supply in 1992, Hepatitis C was also spread through blood transfusions and organ transplants. While uncommon, poor infection control has resulted in outbreaks in healthcare settings.

While rare, sexual transmission of Hepatitis C is possible. Having a sexually transmitted disease or HIV, sex with multiple partners, or rough sex appears to increase a person’s risk for Hepatitis C. Hepatitis C can also be spread when getting tattoos and body piercings in unlicensed facilities, informal settings, or with non-sterile instruments. Also, approximately 6% of infants born to infected mothers will get Hepatitis C. Still, some people don’t know how or when they got infected.

What is Hepatitis C?

Hepatitis C is an infection of the liver that results from the Hepatitis C Virus. Acute Hepatitis C refers to the first several months after someone is infected. Acute infection can range in severity from a very mild illness with few or no symptoms to a serious condition requiring hospitalization. For reasons that are not known, about 20% of people are able to clear, or get rid of, the virus without treatment in the first 6 months.

Unfortunately, most people who get infected are not able to clear the Hepatitis C virus and develop a chronic, or lifelong, infection. Over time, chronic Hepatitis C can cause serious health problems including liver disease, liver failure, and even liver cancer.

What are the symptoms of Hepatitis C?

Many people with Hepatitis C do not have symptoms and do not know they are infected. If symptoms occur, they can include: fever, feeling tired, not wanting to eat, upset stomach, throwing up, dark urine, grey-colored stool, joint pain, and yellow skin and eyes.

When do symptoms occur?

If symptoms occur with acute infection, they can appear anytime from 2 weeks to 6 months after infection. If symptoms occur with chronic Hepatitis C, they can take decades to develop. When symptoms appear with chronic Hepatitis C, they often are a sign of advanced liver disease.

Continued on next page
How would you know if you have Hepatitis C?

The only way to know if you have Hepatitis C is to get tested. Doctors use a blood test, called a Hepatitis C Antibody Test, which looks for antibodies to the Hepatitis C virus. Antibodies are chemicals released into the bloodstream when someone gets infected. Antibodies remain in the bloodstream, even if the person clears the virus.

A positive or reactive Hepatitis C Antibody Test means that a person has been infected with the Hepatitis C virus at some point in time. However, a positive antibody test does not necessarily mean a person still has Hepatitis C. An additional test called a RNA test is needed to determine if a person is currently infected with Hepatitis C.

Who should get tested for Hepatitis C?

Testing for Hepatitis C is recommended for certain groups, including people who:

- Were born from 1945 – 1965
- Received donated blood or organs before 1992
- Have ever injected drugs, even if it was just once or many years ago
- Have certain medical conditions, such as chronic liver disease and HIV or AIDS
- Have abnormal liver tests or liver disease
- Have been exposed to blood from a person who has Hepatitis C
- Are on hemodialysis
- Are born to a mother with Hepatitis C

Can Hepatitis C be treated?

Yes. However, treatment depends on many different factors, so it is important to see a doctor experienced in treating Hepatitis C. New and improved treatments are available that can cure Hepatitis C for many people.

How can Hepatitis C be prevented?

Although there is currently no vaccine to prevent Hepatitis C, there are ways to reduce the risk of becoming infected with the Hepatitis C virus:

- Avoid sharing or reusing needles, syringes or any other equipment to prepare and inject drugs, steroids, hormones, or other substances.
- Do not use personal items that may have come into contact with an infected person’s blood, even in amounts too small to see, such as razors, nail clippers, toothbrushes, or glucosamine monitors.
- Do not get tattoos or body piercings from an unlicensed facility or in an informal setting.

For more information

Talk to your health professional, call your health department, or visit www.cdc.gov/hepatitis.
Hepatitis C Basics

What is hepatitis C? — Hepatitis C is a disease that harms the liver. The liver is a big organ in the upper right side of the belly. A virus causes this disease. The virus is called the hepatitis C virus. It spreads from person to person through contact with blood. This can happen in a few ways, like sharing drug needles or having sex.

What are the symptoms of hepatitis C? — Most people with hepatitis C have no symptoms. When symptoms do occur, they can include:

- Feeling tired or weak
- Lack of hunger
- Nausea
- Muscle or joint aches
- Weight loss

In most cases, hepatitis C lasts for many years. That can lead to liver scarring, called “cirrhosis.” Many people with cirrhosis have no symptoms. When symptoms do occur, they can include:

- Swelling in the belly and legs, and fluid build-up in the lungs
- Bruising or bleeding easily
- Trouble taking in a full breath
- Feeling full in the belly
- Yellowing of the skin or whites of the eyes, called jaundice
- Confusion that can come on suddenly
- Coma

How did I get the disease? — You can catch the hepatitis C virus if you have contact with the blood of someone who is infected. This can happen if you:

- Share drug needles or cocaine straws
- Use infected needles for tattooing, acupuncture, or piercings
- Share toothbrushes, razors, or other things that could have blood on them
- Get a blood transfusion before 1990 (when the way blood was handled changed)
- Have sex with someone who is infected

A pregnant woman who is infected can also give hepatitis C to her baby.

Some people who have hepatitis C do not remember how they were infected. In the United States, many people with hepatitis C were born between 1945 and 1965. If you were born during these years, your doctor might want to test you for hepatitis C even if you did not do any of the things that put you at risk of infection.
Is there a test for hepatitis C? — Yes. Your doctor might order a few tests:

- Blood tests can show:
  - If you have hepatitis C
  - What type of the virus you have (there are at least 6 types)
  - Which treatment will work best for you

If you have hepatitis C, your doctor will also want to know if you have any liver scarring. Ways to check for scarring include:

- Blood tests
- Liver scan – This is a type of imaging test that can show how much scarring you have.
- Biopsy – For this test, a doctor puts a needle into your liver and takes out a small sample of tissue. The sample will show how bad the damage is. Not everyone needs this test.

How is hepatitis C treated? — Treatment depends on what type of hepatitis C you have. There are different medicines to treat hepatitis C. Some of them only work on certain forms of the hepatitis C virus. Treatment usually lasts 2 to 6 months.

Is there anything I can do to protect my liver? — Yes, you can:

- Avoid alcohol.
- Maintain a healthy weight.
- Get vaccinated for hepatitis A and B.
- Get vaccinated for pneumonia, the flu, and other diseases.
- Ask your doctor or nurse before taking any over-the-counter pain medicines (these medicines can sometimes damage the liver).
- Avoid marijuana.

What if I want to get pregnant? — If you want to get pregnant, talk to your doctor or nurse first. About 1 in 20 women who have hepatitis C pass the virus on to the baby during pregnancy. That number goes up in women who are also infected with HIV.

What will my life be like? — Many people with hepatitis C are able to live normal lives. Treatment can cure the disease in many cases.

If you have hepatitis C, it is still safe to:

- Hug, kiss, and touch other people (but you can spread the infection through sex)
- Share forks, spoons, cups, and food
- Sneeze or cough
- Breastfeed
Standard Operating Procedures

Recruiting Study Participants

1. Purpose:
   a) The purpose of this SOP is to ensure the adequacy of the recruitment of adult study participants in the Care2Cure Study in regards to the study protocol and ethical guidelines as required by this institution.
   b) All persons who are responsible for participant recruitment in the Care2Cure Study must abide by the SOP put forth below.

2. Who may recruit study participants:
   a) Any person listed on this institution’s IRB application specific to the study protocol as being approved to obtain consent may participate in recruiting study participants. These may include the principal investigator (PI), Co-investigator(s), Research Nurse(s), and Research Assistant(s) (RA) where applicable.
   b) Any person approved to recruit study participants on the protocol application must have the appropriate human subjects training certificates as outlined by this institution’s requirements.
   c) Any person recruiting study participants must have a minimum of EPIC View Only access to view patient charts per the approved protocol for eligibility criteria.

3. Steps to recruit study participants:
   a) Medical Record Review: Every week, a research team member will review the Moore Clinic schedule to identify potentially eligible study participants per the approved HIPAA IRB Form 4.
      i) Log into EPIC selecting JHH MOORE CLINIC [110107468] as Department
      ii) Select the JHH MOORE Clinic schedule and the desired date to review
      iii) Starting with the first patient, click on each patient and select “SnapShot” in the Schedule toolbar to review the patient record for the following eligibility criteria:

         (1) **HIV Infection**: Eligible patients must have HIV. In the SnapShot activity bar, the Problem List must have a diagnosis of “HIV” or “AIDS”
(2) **Chronic Hepatitis C Infection**: Eligible patients must have current chronic hepatitis C virus infection. In the SnapShot activity bar, the Problem List must have a diagnosis of “Hepatitis C, chronic” AND under the Chart Review activity bar Labs tab, the most recent “Hepatitis C Virus, Quant PCR” must be detectable (≥15).

(3) **Current Patient at the Moore Clinic**: Eligible patients must have attended one or more appointment at the Moore Clinic in the past year. In the Chart Review activity bar Encounters tab, the date of the most recent “Office Visit” at “JHH MOORE” must be less than 12 months from the date of study enrollment.

(4) **Not Linked to the Blalock Specialty Clinic**: Eligible patients must have no attended visit at JHH M-HEP in the past year. In the Chart Review activity bar Encounters tab, search for an encounter at “JHH M-HEP.” If no encounter exists, the patient is eligible. If an encounter does exist, the date of the most recent “Office Visit” at “JHH M-HEP” must be greater than 12 months from the date of study enrollment.

iv) All four eligibility criteria above must be met to consider the patient for study participation. If one or more of the above criteria are not met, move to the next patient on the schedule.

v) If all four criteria above are met, review the Care2Cure Pre-Screened Patients Not Enrolled list to ensure the patient has not previously refused participation. If the patient is on this list, move to the next patient on the schedule.

vi) Record the patient’s name, date of birth, and address as well as Moore Clinic appointment time and provider on the Recruitment Screening Log for that day and proceed to steps b) and c).

b) **Mail IRB-approved recruitment letters**: Letter notifications will be mailed to potentially eligible participants who have an upcoming appointment inviting them to contact the study team to participate in the research study. Letters will be sent to patients who are listed on the Recruitment Screening Log and have met the initial inclusion criteria outlined in part a) above.

i) The study team member will write the patient’s name and appointment date and time on the IRB-approved recruitment letter. The research study team will never indicate on this letter that the appointment is scheduled at the Moore Clinic to protect the patient’s privacy.

ii) The study team will address and stamp an envelope, insert the recruitment letter, and place in a mailbox at least 3 business days before that scheduled appointment.

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iii) The study team member will initial the “Letter Sent” box on the Recruitment Screening Log once complete.

c) Notify providers: Daily, the primary HIV provider will be approached to refer his or her eligible patients to the study. Prior to the start of the clinic session (morning or afternoon), a study team member will give each provider listed on the Recruitment Screening Log a list of his/her patients that may qualify for the study and request that the provider refer the patient to the study. One copy of the In-Clinic Recruitment Letter will be left with the provider for each eligible patient.

d) Telephone inquiries: Potentially eligible participants may call the study phone number after seeing it on a mailed letter, study flyer, clinicaltrials.gov or Trials@Hopkins. Potentially eligible participants may also be referred to the study phone number from the CFAR Study Hotline. In this case, the study team member will return the person’s phone call using the IRB-approved telephone script.

4. SOP Review and Revision

a) This SOP will be reviewed by the research team annually to ensure compliance with the protocol and institution guidelines

b) This SOP will be reviewed and approved by the PI and considered in effect upon their signature and dating of the SOP

c) All study team members will review this SOP annually and sign a training log to ensure consistency in recruiting Care2Cure study participants.

Laura Starbird

(Principal Investigator) May 3, 2016

(Date)
Obtaining Written Informed Consent for Research Studies

1. Purpose:
   a) The purpose of this SOP is to ensure the adequacy of the informed consent process for research in adults in regards to the federal legal and ethical guidelines and as required by this institution.
   b) All persons who are responsible for obtaining written informed consent for human subjects research must abide by the SOP put forth below.

2. Who may obtain written informed consent:
   a) Any person listed on this institution’s IRB application specific to the study protocol as being approved to obtain consent may obtain consent. These may include the principal investigator (PI), Co-investigator(s), Research Nurse(s), and Research Assistant(s) (RA) where applicable.
   b) Any person approved to obtain consent on the protocol application must have the appropriate human subjects training certificates as outlined by this institution’s requirements.

3. Steps to obtaining written informed consent:
   a) Informed consent may occur either prior to the enrollment visit for a study, or on the day of the baseline enrollment visit. When informed consent occurs is at the discretion of the study team member and may be dependent on:
      i) Time: Written informed consent will occur at a time that ensures the participant has adequate opportunities to review the informed consent, ask questions pertaining to risks and procedures, and make an informed decision to participate in the study.
      ii) Location: Written informed consent will occur in a private location that ensures confidential health and other private information will not be disclosed.
   b) A study team member may be approached by potential participants at any routine clinic visit for interest in study participation or called to schedule an enrollment visit.
   c) The study team member will screen for eligibility prior to obtaining informed consent from the interested patient.
i) The study team member will confirm the patient’s name and date of birth and locate the matching patient record in EPIC.

ii) The study team member will check the record for the following criteria:

1) HIV infection (present in problem list)

2) Chronic HCV infection (present in problem list and most recent HCV RNA ≥15)

3) Moore Clinic Patient (registered encounter at Moore Clinic [JHH MOORE] ≤ 1 year from current date)

4) No attended Viral Hepatitis Clinic appointment in past year (no registered encounter at JHH M-HEP within 1 year of current date)

iii) Only those patients who meet all criteria (1) through (4) will be included in this study. The study team will thank any patients who do not meet these criteria for their interest and notify them that they are not eligible at this time.

d) Once interest in the study has been ascertained, a copy of the most currently approved informed consent may be provided to the participant to allow him/her to review it at his/her leisure and to formulate questions in response to the study procedures.

e) The study team member will ensure that the participant has an adequate understanding of the English language.

f) The informed consent process will occur in a private area of the Moore Clinic. This includes a private room or sectioned off area where other patients are out of hearing range. The participant may choose to bring a family member or confidant into the room. This is at the discretion of the participant.

g) The study team member will read through each section of the most currently IRB-approved written informed consent form with the participant

i) The study team member will read at a slow and steady pace to allow for processing of information

ii) The study team member will stop at the end of each section of the informed consent to assess for understanding and to see if the participant has any questions or concerns about the study
iii) The participant will be encouraged to ask questions and clarify his/her role in the study

iv) The participant will be asked the following three comprehension assessment questions:

1. What are the problems we are trying to improve?
2. How does this study plan to improve these problems?
3. How will you be assigned to the different options in this study?

h) The participant will be informed that he/she is under no obligation to sign the informed consent and participate in the study, that participation is strictly voluntary, and that he/she may withdraw consent and discontinue participation in the study at any time and at no consequences to him/herself or his/her healthcare.

i) The participant and the study team member will sign, date, and time 2 copies of the informed consent once all questions have been answered and all concerns have been addressed.

j) One copy of the signed informed consent will be provided to the participant for his/her records.

k) The study team member will ensure the participant knows where to locate on the informed consent information pertaining to:

i) How to contact the study team members

ii) How to contact the PI of the study team

l) The signed informed consent will be scanned and uploaded into EPIC within 5 business days of obtaining said signature per this institution’s regulations (410-367-7382).

m) The original signed written informed consent will be stored in the participant’s folder specific to this study and stored per this institution’s guidelines.

n) The study team member will record receipt of written informed consent on the Care2Cure Baseline Study Visit checklist.
If at any time the written informed consent form changes for the study, a study team member must obtain a new signature on the revised consent following the procedures outlined above.

4. SOP Review and Revision

   a) This SOP will be reviewed by the research team annually to ensure compliance with all institution guidelines and federal regulations.

   b) This SOP will be reviewed and approved by the PI and considered in effect upon their signature and dating of the SOP.

   c) All study team members will review this SOP annually and sign a training log to ensure compliance and consistency in obtaining written informed consent for study participation.

Laura Starbird  March 8, 2016
(Principal Investigator) (Date)
Completing Baseline Data Collection and Randomization

1. Purpose:
   
a) The purpose of this SOP is to ensure the adequacy of the baseline data collection process for research in adults in the Care2Cure Study in regards to the study protocol and ethical guidelines as required by this institution.

b) All persons who are responsible for data collection in the Care2Cure Study must abide by the SOP put forth below.

2. Who may obtain baseline data:
   
a) Any person listed on this institution’s IRB application may collect data from participants. These may include the principal investigator (PI), Co-investigator(s), Research Nurse(s), and Research Assistant(s) (RA) where applicable.

b) Any person approved to collect data on the protocol application must have the appropriate human subjects training certificates as outlined by this institution’s requirements.

3. Steps to complete baseline questionnaire data collection:
   
a) All data collection must occur after written informed consent has been obtained, either on the day of the informed consent or at a scheduled baseline study visit after the date of informed consent. When baseline data collection occurs is at the discretion of the study team member and may be dependent on:

   i) Time: Data collection will occur at a time that ensures the participant has adequate opportunities to answer the complete set of questionnaires.

   ii) Location: All questionnaire data collection will occur in a private location that ensures confidential health and other private information will not be disclosed.

b) The baseline data collection process will occur in a private area of the Moore Clinic. This includes a private room or sectioned off area where other patients are out of hearing range. The participant may choose to bring a family member or confidant into the room. This is at the discretion of the participant. Data collection may occur over the telephone only with approval of the PI.

c) Once written informed consent has been confirmed, the study team member will open the REDCap app on the study-designated iPad. Note: if the REDCap
When the database is inaccessible, the study team member will use a backup paper baseline data questionnaire and enter the responses into REDCap within 48 hours.

i) The study team member will create a unique study identification number (SIN) for the participant and create a new study participant in REDCap.

   (1) To generate the 5-digit SIN, the study team member will use the patient’s first and last initial followed by the enrollment number in the study. For example, the first participant enrolled in the study, named John Smith, will be given the SIN of JS001; the 134th participant, named Jane Doe, will be given the SIN JD134.

ii) The study team member will read through each section of the baseline questionnaire in REDCap aloud and enter the participant’s responses as answered directly into the REDCap database.

   (1) The study team member will assure the participant that he/she does not have to answer any question he/she does not want to and may stop the questionnaire at any time

   (2) The study team member will read at a slow and steady pace to allow for accurate responses

   (3) The participant will be encouraged to ask questions to clarify items

   (4) The study team member will stop at the end of each questionnaire to see if the participant has any questions or concerns about his/her responses

   (5) The study team member will ask the participant to clarify any responses that do not match previous responses or indicate the item was misunderstood

iii) The study team member will record completion of the baseline questionnaire on the Care2Cure Baseline Study Visit checklist.

4. Randomization of the participant:

   a) After the baseline questionnaire data has been collected, the study team member will randomize the participant to the control or intervention arm using REDCap
i) The study team member will explain the process of randomization to the participant and ensure the participant understands that he/she may be assigned to either group.

ii) The study team member will navigate to the “Demographics” form in REDCap and select “Randomize.” Confirmation that this action is intentional is required by REDCap.

iii) The study team member will confirm randomization in REDCap and note the assignment on the Care2Cure Baseline Study Visit checklist.

iv) The study team member will refer all participants allocated to the Intervention Arm to the study nurse case manager for intervention.

v) The study team member will provide all participants allocated to the Control Arm with the CDC Hepatitis C Fact Sheet and indicate receipt on the Care2Cure Baseline Study Visit checklist.

5. Baseline medical record data abstraction

a) Medical record data abstraction will be completed by the study team member after written informed consent has been obtained. When baseline medical record data abstraction occurs is at the discretion of the study team member and may be dependent on:

i) Time: Medical record abstraction will occur at a time that ensures the study team member has the ability to complete all items in the baseline abstraction.

ii) Participant scheduling: Timing of medical record abstraction may be dependent on the schedule of the participant, and the study team member may choose to abstract baseline medical record data before or after completing the baseline patient questionnaire, before or after randomization, or after the phase 1 baseline visit is completed. The participant does not have to be present for medical record abstraction to occur.

b) The study team member will complete the baseline medical record data abstraction form in REDCap using EPIC.

i) The study team member will verify the participant’s REDCap record and EPIC record match to ensure accurate data collection.

6. SOP Review and Revision
a) This SOP will be reviewed by the research team annually to ensure compliance with the protocol and institution guidelines

b) This SOP will be reviewed and approved by the PI and considered in effect upon their signature and dating of the SOP

All study team members will review this SOP annually and sign a training log to ensure consistency in collecting baseline data for Care2Cure study participants.

Laura Starbird  
April 22, 2016  
(Principal Investigator)  (Date)
Distributing Research Study Participant Compensation

1. Purpose:
   a) The purpose of this SOP is to ensure the adequacy of the distribution of compensation for participation in research as required by this institution.
   b) All persons who are responsible for distributing compensation for human subjects research must abide by the SOP put forth below.

2. Who may distribute compensation for study participation:
   a) Any person listed on this institution’s IRB application as approved to interact with study participants may distribute compensation for research participation. These may include the principal investigator (PI), Co-investigator(s), Research Nurse(s), and Research Assistant(s) (RA) where applicable.

3. Steps to distributing compensation for research study participation:
   a) The study team will provide compensation for research study participation after the baseline study visit and after the phase 2 nurse case management study visit, if applicable.
   b) After informed consent, the baseline questionnaire, and randomization have been completed, each study participant, regardless of randomization arm, will receive $10 for his/her participation in the study.

   i) First, the study team member will ensure the required fields of the Petty Cash Voucher form are complete. Required fields include:

   (1) Date
   (2) Received by [study participant name]
   (3) Description/purpose [Care2Cure study participation]
   (4) SSN (last 4 digits) [of participant]
   (5) Participant Phone Number
   (6) Total Amount [$10.00]
   (7) Dollar Amount in Words [ten dollars]
   (8) Recipient Signature [participant signature of receipt]
ii) The study team member, if not Laura Starbird (L.S.), will route this form to L.S. within 7 days for the remaining required fields:

(1) Cost Center or Internal Order
(2) Approver Signature [L.S.]
(3) Approved By [L.S.]
(4) Approver Phone Number [L.S.]

iii) L.S. will return this form to Patrice Hamilton in Student Accounts within 30 days.

c) If a study participant is eligible and returns for a Phase 2 NCM study visit, he/she will receive a second compensation for $10 at the end of that visit, following the procedure listed above.

d) No study participant will receive more than $20 total for participation.

4. SOP Review and Revision

a) This SOP will be reviewed by the research team annually to ensure compliance with all institution guidelines

b) This SOP will be reviewed and approved by the PI and considered in effect upon their signature and dating of the SOP

c) All study team members will review this SOP annually and sign a training log to ensure compliance and consistency in distributing compensation for study participation.

Laura Starbird   May 4, 2016
(Principal Investigator) (Date)
Care2Cure Phase 1 Nurse Case Management Intervention Manual

5. Purpose:
   a) The purpose of this SOP is to ensure the adequacy of the intervention delivery for research in adults in regards to the federal legal and ethical guidelines and as required by this institution and to ensure consistency in the intervention for scientific validity.

   b) All persons who are responsible for delivering the Care2Cure nurse case management (NCM) intervention must abide by the SOP put forth below.

6. Who may deliver the NCM intervention:
   a) A registered nurse listed on this institution’s IRB application specific to the study protocol as being approved to deliver the intervention may do so. These may include the principal investigator (PI), Co-investigator(s), and Research Nurse(s).

   b) Any person approved to deliver the intervention must have the appropriate human subjects training certificates as outlined by this institution’s requirements.

   c) Any person approved to deliver the intervention outlined in this SOP must have a current Registered Nurse (RN) license in the state of Maryland.

7. Identifying participants to receive Phase 1 of the intervention:
   a) The interventionist will be notified of a participant enrolled in the intervention arm either by a study team member conducting randomization during the baseline visit or by conducting randomization at the baseline visit him/herself

   b) The interventionist will confirm a participant’s eligibility to receive the intervention prior to administration

      i) The interventionist will confirm that the participant has signed a written informed consent prior to delivering the intervention

      (1) All study participants will have a signed and dated informed consent in his/her study file (see Written Informed Consent SOP)

      ii) The interventionist will confirm that the participant has been randomized to the intervention arm in the participant’s REDCap file
iii) The interventionist will confirm that the Baseline Questionnaire has been completed in REDCap (or on paper in the case that REDCap is down) so that the study participant’s baseline responses are not influenced by the intervention.

8. Steps to deliver Phase 1 of the NCM intervention:

a) All in-person intervention delivery will occur in a private area of the Moore Clinic or Blalock Specialty Clinic. This includes a private room or sectioned off area where other patients are out of hearing range. The participant may choose to bring a family member or confidant into the room. This is at the discretion of the participant.

b) Referral to the Viral Hepatitis Clinic

i) A referral to the Viral Hepatitis Clinic should be confirmed or entered first so that a new order can be approved by the participant’s Moore Clinic provider or the Principal Investigator if necessary.

ii) The interventionist will check the participant’s medical record to determine if a referral to the Viral Hepatitis Clinic (VHC) has been made.

   (1) Go to the patient’s Appointment Desk (“Appts” icon in top toolbar)
   (2) Select the “Orders” tab
   (3) Look for an Ambulatory order to Infectious Disease with a diagnosis (dx) including “hepatitis c”

iii) If a referral is present in the participant’s EPIC record according to above steps, skip to step c) Strengths-Based Education.

iv) If no referral is present in the EPIC record, the interventionist will order a referral in the participant’s EPIC record

   (1) Go to the patient’s Encounter entry (“Encounter” stethoscope icon in top toolbar)
   (2) Select the correct patient by confirming name, date of birth, and medical record number
   (3) Click “New” to create a new encounter
   (4) Choose “Orders Only” under Type
   (5) Ensure correct department is selected (JHH Moore Clinic)
(6) Click “Accept”

(7) In the left activity bar, choose “Order Entry”

(8) Enter “Ambulatory referral to Infectious Disease” in New Order field

(9) Specify Reason for consult: hepatitis C, chronic

(10) Associate diagnosis with order: Chronic hepatitis C without hepatic coma [B18.2]

(11) Click “Sign Orders” green checkmark icon

(12) Enter Principal Investigator as Authorizing Provider. The order will then be routed to the Authorizing Provider for second sign.

c) **Strengths-Based Education:**

   i) This aspect of the intervention is based on the concepts of Strengths-Based Nursing (Gottlieb, 2014) and Strengths-Based Case Management (Craw et al., 2010).

   (1) The goal of strengths-based nursing is to encourage empowerment and self-efficacy while promoting health behavior. Strengths-based nursing focuses on the concepts of person-centered care, health promotion, collaborative partnerships, and empowerment

   (2) Similarly, strengths-based case management is a CDC model designed to help clients identify needed resources to resolve the various individual and structural barriers to medical care. Clients identify their own strengths, abilities, and assets to overcome barriers and accomplish specific goals. The process of identifying and reinforcing personal strengths enables clients to appreciate their own past self-efficacy, enhances motivation, and prepares them for identifying and achieving goals

   (3) Principles of Strengths-Based Case Management

      (a) Encourage clients to identify and use their strengths, abilities, and assets to accomplish goals

      (b) Recognize and support client control over goal-setting and the search for needed resources

      (c) Establish an effective working relationship with the client
(d) View the community as a resource and identify informal sources of support (family members, friends, neighbors, support groups, etc.)

   ii) **HCV Education:** The nurse case manager will review key hepatitis C terms and concepts with the participant. The *Hepatitis C Basics* patient education handout will be used as a guide. Key areas that must be discussed within the educational part of this intervention per the Hepatitis C Basics guide include:

   (1) Transmission
   (2) Symptoms
   (3) Treatment
   (4) Risk Reduction

   iii) **Strength Identification:** The research nurse case manager will help participants identify their strengths within the context of engaging in HCV care. This will include a focus on the study participant’s current engagement in HIV care as a strength, and discussion of social support. Other strengths may be identified by the study participant.

   iv) **Identifying Barriers:** Participants will also identify barriers to linkage to care and form a plan with the research nurse case manager to minimize these barriers; this may include referrals to benefits counseling, substance use services, mental health care, and the Johns Hopkins “Cure Club” HCV support group

   (1) The interventionist will document any referrals made to other services in the NCM Phase 1 instrument in REDCap.

   v) The study participant will be encouraged to ask questions throughout the intervention administration. The research nurse case manager will ask the participant open ended questions to confirm comprehension of the four areas of hepatitis C basics. At the completion of the education portion of the intervention, the research nurse case manager will ask the participant what questions he/she has and encourage the participant to contact the study nurse case manager with questions related to hepatitis C care.

**d) Patient Navigation**

i) Because appointment scheduling is a known barrier to linkage to care, patient navigation will include calling central scheduling during the visit so the research nurse case manager can navigate participants through the Viral Hepatitis Clinic scheduling process. Participants also will be encouraged to call the research nurse case
manager for needs relating to linking to HCV care and initiating HCV treatment throughout the study period. All contacts and amount of time spent with the study participants will be recorded by the research nurse.

ii) The interventionist will confirm that an order for a referral to a hepatitis specialty provider is present in the patient’s medical record by following the steps outlined in b) ii) above.

iii) If a referral has not been approved by the end of the baseline study visit, the interventionist will make this note in the REDCap record under “Phase 1 NCM Referral Notes” and leave that questionnaire “incomplete” to cue the interventionist to return to it.

(1) The interventionist will notify the participant that the referral to the hepatitis clinic is still pending, and ask the participant if it is ok to call him/her when the referral is approved to help schedule the appointment

(a) If yes, the interventionist will make a note in the REDCap scheduler to check the patient record the next day for a signed order. If there order has not been signed, the interventionist will add another scheduler reminder, continuing this process until an order is approved or for 5 business days, whichever is longer. The interventionist will document the outcome under “Phase 1 NCM Referral Notes” in REDCap.

(b) If no, the interventionist will tell the participant that he/she will be responsible for ensuring an appointment is scheduled and document this decision under “Phase 1 NCM Patient Navigation Notes.”

iv) After a referral has been confirmed, the interventionist will assist the study participant in calling the central scheduling line to schedule an appointment at JHH M-HEP. This may include a) supporting the participant while he/she calls 410-955-5000 on his/her own cell phone; b) supporting the participant while he/she calls 410-955-5000 on the study cell phone through Google Voice; c) calling 410-955-5000 with the participant at his/her side.

(1) If the referral is confirmed after the baseline visit and the study participant agreed to be contacted about the referral in iii) (1) (a) above, the interventionist will call the study participant to notify him/her that he/she has been referred to the hepatitis clinic. The
interventionist will provide the study participant with the phone number 410-955-5000 and encourage the participant to call immediately to schedule an appointment. The interventionist may also offer to call 410-955-5000 on behalf of the participant. This is at the discretion of the study participant.

v) The interventionist will document the scheduling outcome and any deviations under “Phase 1 NCM Patient Navigation Notes” in REDCap.

vi) The interventionist will add the scheduled appointment to the REDCap scheduler and input dates for appointment reminders per the procedure outlined in section e) below.

e) **Plan for appointment reminders**

   i) Participants will receive a personalized HCV appointment reminder in addition to the automated phone reminder all patients receive through the Johns Hopkins Hospital usual care system.

   ii) The interventionist will make a plan for contacting the participant for personalized appointment reminder(s) according to the study participant’s preferences.

      (1) The interventionist will verify the participant’s demographic information under the “Demographics” instrument in REDCap, including primary contact phone number and type, message preferences, alternate modes of contact, and preferred time of day.

      (a) Effort will be made to obtain more than one method of contacting the participant.

      (b) If a participant indicates a desire to receive a text message or email, he/she must sign the Authorization to be contacted by Text/Email. This authorization should be kept in the study participant’s master file.

   iii) Participants will be contacted 1 day before their scheduled Viral Hepatitis Clinic appointment for an appointment reminder in addition to the automated reminder 2 days before the appointment.

      (1) At the NCM Phase 1 study visit, the interventionist will add an event to the REDCap Calendar indicating the Participant Study ID, Date (1 business day before the scheduled JHH M-HEP appointment), and Note “1-day appt reminder.”
(a) A Time may be added if the study participant has indicated a specific time he/she desired to be contacted. This is optional.

(b) A contact method may be added to the Notes field if the study participant has indicated a preferred method other than what is listed in the Demographics instrument. This is optional.

iv) If the scheduled Viral Hepatitis Clinic appointment is greater than or equal to 2 weeks (10 business days) from the date of the NCM Phase 1 visit, participants will also be contacted one week before the appointment for a reminder.

1. The interventionist will add an event to the REDCap Calendar indicating the Participant Study ID, Date (5 business days before the scheduled JHH M-HEP appointment), and Note “1-wk appt reminder.”

v) The interventionist will check the REDCap Calendar every business day and complete the appointment reminders listed.

vi) To complete an appointment reminder by phone, the interventionist will call the study participant’s preferred phone number at the specified time of day, if applicable.

1. The interventionist will identify him/herself as a nurse from the Care2Cure study at Johns Hopkins and confirm he/she is speaking to the study participant.

2. The interventionist will state that he/she is calling to remind the study participant that he/she has an appointment [tomorrow/next week] at the Blalock Specialty Clinic at [time].

3. The interventionist will ask the participant if he/she plan to attend and refer him/her to central scheduling at 410-955-5000 if he/she needs to reschedule.

4. The interventionist will offer to answer any questions, reiterate that hepatitis C can be cured, and leave the study contact information with the participant.

vii) To complete an appointment reminder by text message, the interventionist will send a text message to the participant’s specified cell phone that reads “Hi! This is Laura from the Care2Cure study. You have an apt at Johns Hopkins [tomorrow/next week] at [time]. Text or call 443-961-7015 if you have questions.”

9. SOP Review and Revision
a) This SOP will be reviewed by the research team annually to ensure fidelity to the intervention protocol and compliance with institution and federal regulations

b) This SOP will be reviewed and approved by the PI and considered in effect upon their signature and dating of the SOP

c) All interventionists will review this SOP annually and sign a training log to ensure fidelity and consistency in delivering the intervention.

Laura Starbird
(Principal Investigator)

May 3, 2016
(Date)
Phase 1 (Linkage to Care) Outcome Data Collection

10. Purpose:

   a) The purpose of this SOP is to ensure the adequacy of the outcome data collection process for research in adults in the Care2Cure Study in regards to the study protocol and ethical guidelines as required by this institution.

   b) All persons who are responsible for data collection in the Care2Cure Study must abide by the SOP put forth below.

11. Who may obtain outcome data:

   a) Any person listed on this institution’s IRB application may collect data from the medical record of participants. These may include the principal investigator (PI), Co-investigator(s), Research Nurse(s), and Research Assistant(s) (RA) where applicable.

   b) Any person approved to collect data on the protocol application must have the appropriate human subjects training certificates as outlined by this institution’s requirements.

   c) Outcomes may **not** be collected from the medical record by the interventionist; this is to ensure that the interventionist does not influence the results of the intervention.

   d) The study team member collecting outcome data from the medical record must be **blinded** to the randomization allocation of the participant to minimize bias in the results. This includes a study team member who was not involved in the randomization of the participant or administering any of the intervention components and is unaware of which group the participant has been assigned to.

12. Steps to complete follow up outcome data collection for Phase 1 (Linkage to Care):

   a) Outcome data collection for Phase 1 will occur 60 days (± 48 hours) after randomization according to the study calendar in REDCap.

   b) Outcome data collection will occur electronically in the EPIC medical record and be recorded into the REDCap database.

   c) The study team member will locate the participant’s electronic medical record and cross-check with the REDCap record to ensure the correct record is being examined and the data is entered into the correct REDCap participant record.
d) Once the correct record has been confirmed, the study team member will access the “Chart Review” section in the EPIC record.

e) Under the “Chart Review” section, the “Encounters” tab will be selected.

f) The study team member will assess all encounters since randomization (60 days) and determine if the patient attended a clinic visit at the Viral Hepatitis Clinic [JHH M-HEP] during that time.

g) The study team member will record the result of attendance at the Viral Hepatitis Clinic since randomization (yes or no) in the REDCap Phase 1 Outcome form.

13. SOP Review and Revision

a) This SOP will be reviewed by the research team annually to ensure compliance with the protocol and institution guidelines.

b) This SOP will be reviewed and approved by the PI and considered in effect upon their signature and dating of the SOP.

c) All study team members will review this SOP annually and sign a training log to ensure consistency in collecting outcome data for Care2Cure study participants.

Laura Starbird  March 8, 2016
(Principal Investigator)  (Date)
**Care2Cure Phase 2 Nurse Case Management Intervention Manual**

14. **Purpose:**

   a) The purpose of this SOP is to ensure the adequacy of the intervention delivery for research in adults in regards to the federal legal and ethical guidelines and as required by this institution and to ensure consistency in the intervention for scientific validity.

   b) All persons who are responsible for delivering the Care2Cure nurse case management (NCM) intervention must abide by the SOP put forth below.

15. **Who may deliver the NCM intervention:**

   a) A registered nurse listed on this institution’s IRB application specific to the study protocol as being approved to deliver the intervention may do so. These may include the principal investigator (PI), Co-investigator(s), and Research Nurse(s).

   b) Any person approved to deliver the intervention must have the appropriate human subjects training certificates as outlined by this institution’s requirements.

   c) Any person approved to deliver the intervention outlined in this SOP must have a current Registered Nurse (RN) license in the state of Maryland.

16. **Steps to determine eligibility for Phase 2:**

   a) The study team member will use the *Follow Up: 60-Day Medical Record Review Algorithm* worksheet to determine a participant’s eligibility for Phase 2 of the study.

   b) The study team member will identify if a participant attended a Viral Hepatitis Clinic appointment within 60 days of randomization using the steps outlined in step 3 of the *Phase 1 (Linkage to Care) Outcome Data Collection SOP* and as recorded in REDCap.

   c) If a participant attended a Viral Hepatitis Clinic appointment (outcome of “yes” to Phase 1), the study team member will open the details for that encounter, or all encounters during the 60 day period if more than one.

   d) The study team member will assess the encounter detail for a decision about initiating hepatitis C treatment (start, defer, or unknown).
(1) “Start” is defined as a documented decision by the hepatitis provider that initiating hepatitis C treatment has been discussed with the patient and steps to start treatment will be initiated. These steps may include writing a prescription for HCV therapy, ordering additional tests (i.e. genotype or measure of fibrosis) so the correct regimen can be prescribed, referrals to resources to get the patient ready to start (i.e. primary care and/or HIV provider, social work, nursing, pharmacy, mental health).

(2) “Defer” is defined as a documented decision by the hepatitis provider that the steps to start treatment will not be initiated and the patient will require additional time before hepatitis C treatment can be considered or the patient is ineligible for hepatitis C treatment.

(3) “Unknown” should only be selected if there is no clearly documented decision in the participant’s medical record. If “unknown,” a second study team member will assess the encounter details to ensure a decision cannot be determined and that participant is ineligible for Phase 2.

ii) The interventionist or unblinded study team member may complete eligibility screening for the participant only after the outcome for Phase 1 has been documented by a blinded study team member.

e) A participant with the decision to “defer” or “unknown” is ineligible for Phase 2. This decision will be recorded on the Follow Up: 60-Day Medical Record Review Algorithm worksheet and in REDCap.

f) A participant with the decision to “start” is eligible for Phase 2. This decision will be recorded on the Follow Up: 60-Day Medical Record Review Algorithm worksheet and in REDCap.

i) The study team member will refer all participants with the decision to “start” to the study nurse case manager for participation in Phase 2, regardless of randomization.

ii) The interventionist will determine if the participant has been randomized to the control or intervention arm in REDCap.

(1) If a participant is eligible for Phase 2 but in the control arm, no further intervention will take place. Monthly and 6-month data collection will continue for this participant.
(2) If a participant is eligible for Phase 2 and in the intervention arm, continue to Step 4.

17. Scheduling the follow up nurse case management visit for Phase 2:

   a) The research nurse case manager will contact the participant via his/her preferred contact method to schedule a follow-up NCM visit.
      i) Preferred contact method can be determined in the Demographics instrument in REDCap.

   b) Up to three attempts will be made to contact the study participant for a Phase 2 study visit. The interventionist may only leave a message if indicated in the Demographics form.

   c) When contact is made, the interventionist will identify him/herself as a nurse from the Care2Cure study. The interventionist will tell the study participant that he/she is eligible for the second part of the study. If the study participant agrees, the interventionist will schedule an appointment with the participant to return to Johns Hopkins Hospital.

   d) The scheduled appointment will be recorded on the Calendar in REDCap with the study participant ID, date, time, and “Phase 2” typed in the Notes field.

18. Preparation for the Phase 2 NCM visit:

   a) Prior to the scheduled Phase 2 study visit, the interventionist will review any notes related to HCV since study enrollment and the participant’s medication list, if applicable, to determine the anticipated HCV therapy regimen to be initiated by the study participant.

   b) The anticipated HCV therapy regimen(s) in the clinic note or medication list will be assessed for potential drug-drug interactions with the participants’ current HIV antiretroviral therapy regimen.
      i) The interventionist will use Table 12 in the DHHS Guidelines: Concomitant Use of Selected HIV Drugs and FDA-Approved HCV Drugs for Treatment of HCV in HIV-Infected Adults as well as hepdruginteractions.org to determine the presence and extent of potential drug interactions.
      ii) If a potential drug interaction exists, the interventionist will select the appropriate HIV-HCV Interactions patient education handout based on the study participant’s current ART regimen (PI-based, NNRTI-
based, INSTI-based, or single pill combination) and place it in the participant’s study file.

iii) If a potential drug interaction exists, the interventionist will also notify the study participant’s primary HIV provider.

(1) The interventionist will send a secure message to the Moore Clinic provider’s [Epic Inbox or email] to notify him/her of the potential need for ART modification. This message will include an attachment of the latest DHHS Concomitant Use of Selected HIV Drugs and FDA-Approved HCV Drugs for Treatment of HCV in HIV-Infected Adults table 12. The table will serve as a decision-making aid for the HIV provider to modify the ART regimen if needed.

(2) The message will follow the Phase 2 Provider Message Template.

19. Steps to deliver the Phase 2 intervention at the follow up NCM visit:

a) All in-person intervention delivery will occur in a private area of the Moore Clinic or the Blalock Specialty Clinic. This includes a private room or sectioned off area where other patients are out of hearing range. The participant may choose to bring a family member or confidant into the room. This is at the discretion of the participant.

b) This intervention is designed to support the HIV provider and patient at the HIV clinic level without influencing the HCV provider’s decisions. Therefore, the study team will not interact directly with the assigned provider at the Blalock Specialty Clinic about patient-specific matters.

c) The NCM Phase 2 visit will involve assessment of strengths and barriers to initiating HCV therapy and development of a patient-centered plan following the strengths-based model described in the Care2Cure Phase 1 Nurse Case Management Intervention Manual.

   i) The interventionist will ask the study participant what questions he/she has following the appointment at JHH M-HEP and reinforce hepatitis C education.

   ii) Strength Identification: The research nurse case manager will help participants identify their strengths within the context of initiating HCV care. This will include a focus on the study participant’s current engagement in HIV care and linkage to the Blalock Specialty
Clinic as strengths. Other strengths (i.e. social support, treatment adherence) may be identified by the study participant.

iii) Identifying Barriers: Participants will also identify barriers to initiating HCV treatment and form a plan with the research nurse case manager to minimize these barriers; this may include referrals to benefits counseling, pharmacy, substance use services, mental health care, and the Johns Hopkins “Cure Club” HCV support group.

(1) The interventionist will document any referrals made to other services in the NCM Phase 2 instrument in REDCap.

iv) If a modification of ART is indicated because a contraindicated drug-drug interaction exists as determined by Step 5 above, NCM Phase 2 will also include targeted education about drug interactions and modification.

(1) The research nurse case manager will give the participant the one-page HIV-HCV Drug Interactions handout that has been tailored to his/her ART regimen.

(2) The interventionist will review this handout with the participant, including the different levels of drug interactions (green, yellow and red).

(3) The interventionist will review when the study participant’s next scheduled appointment with his/her HIV provider is. If the next appointment is greater than 1 month from the current date, the interventionist will give the study participant the option of trying to schedule a sooner appointment to discuss ART modification.

(a) The research nurse case manager will help the study participant navigate scheduling an ART modification appointment with the HIV provider by a) supporting the participant while he/she calls 410-955-5000 on his/her own cell phone; b) supporting the participant while he/she calls 410-955-5000 on the study cell phone through Google Voice; or c) calling 410-955-5000 at his/her side.

v) The study participant will be encouraged to ask questions throughout the intervention administration. The research nurse case manager will ask the participant open ended questions to confirm comprehension of the material discussed, particularly around drug
interactions and ART modification. At the completion of the visit, the research nurse case manager will ask the participant what questions he/she has and encourage the participant to contact the study nurse case manager with questions related to hepatitis C care.

20. SOP Review and Revision

a) This SOP will be reviewed by the research team annually to ensure fidelity to the intervention protocol and compliance with institution and federal regulations

b) This SOP will be reviewed and approved by the PI and considered in effect upon their signature and dating of the SOP

c) All interventionists will review this SOP annually and sign a training log to ensure fidelity and consistency in delivering the intervention.

Laura Starbird
(Principal Investigator) May 4, 2016

(Principal Investigator) (Date)
Phase 2 (Treatment Initiation) Outcome Data Collection

21. Purpose:
   a) The purpose of this SOP is to ensure the adequacy of the outcome data collection process for research in adults in the Care2Cure Study in regards to the study protocol and ethical guidelines as required by this institution.
   b) All persons who are responsible for data collection in the Care2Cure Study must abide by the SOP put forth below.

22. Who may obtain outcome data:
   a) Any person listed on this institution’s IRB application may collect data from the medical record of participants. These may include the principal investigator (PI), Co-investigator(s), Research Nurse(s), and Research Assistant(s) (RA) where applicable.
   b) Any person approved to collect data on the protocol application must have the appropriate human subjects training certificates as outlined by this institution’s requirements.
   c) Outcomes may not be collected from the medical record by the interventionist; this is to ensure that the interventionist does not influence the results of the intervention.
   d) The study team member collecting outcome data from the medical record must be blinded to the randomization allocation of the participant to minimize bias in the results. This includes a study team member who was not involved in the randomization of the participant or administering any of the intervention components and is unaware of which group the participant has been assigned to.

23. Steps to complete follow up outcome data collection for Phase 2 (Treatment Initiation):
   a) Outcome data collection for Phase 2 will occur 6 months (± 48 hours) after randomization according to the study calendar in REDCap.
   b) Outcome data collection will occur electronically in the EPIC medical record and be recorded into the REDCap database.
c) The study team member will locate the participant’s electronic medical record and cross-check with the REDCap record to ensure the correct record is being examined and the data is entered into the correct REDCap participant record.

d) Once the correct record has been confirmed, the study team member will complete the 6-month Follow up Medical Record Abstraction in REDCap using the participant’s EPIC medical record.

e)

24. SOP Review and Revision

a) This SOP will be reviewed by the research team annually to ensure compliance with the protocol and institution guidelines

b) This SOP will be reviewed and approved by the PI and considered in effect upon their signature and dating of the SOP

c) All study team members will review this SOP annually and sign a training log to ensure consistency in collecting outcome data for Care2Cure study participants.

Laura Starbird ________________________________ March 8, 2016

(Principal Investigator) (Date)
CURRICULUM VITAE

Part I

PERSONAL DATA

Laura E. Starbird, MS, RN, PHNA-BC
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lstarbi1@jhu.edu

EDUCATION

2013 – Present  PhD candidate, Johns Hopkins School of Nursing, Baltimore, MD
2012  MS in Advanced Practice Public Health Nursing, Minor in HIV/AIDS, University of California, San Francisco, CA
2009  BSN, Magna Cum Laude, Saint Anselm College, Manchester, NH

LICENSURE AND CERTIFICATION

2013 – Present  RN  Maryland Board of Nursing #R207824
2012 – Present  PHNA-BC  American Nurses Credentialing Center #2012011884
2012 – 2014  CNS  California Board of Registered Nursing #3886 (inactive)
2009 – Present  RN  Massachusetts Board of Registration in Nursing #RN2260329

PROFESSIONAL EXPERIENCE

2016 – 2018  Lecturer, Johns Hopkins School of Nursing, Baltimore, MD
2013 – 2017  Study Coordinator, Stop Community MRSA Colonization among Patients, Johns Hopkins University School of Nursing, Baltimore, MD
2014  Research Assistant, Hepatitis C Treatment Candidacy in the Age of Highly Acting Antivirals, University of California, San Francisco, CA
2012 – 2013  Research Assistant, Investigating Patient Attitudes toward Hepatitis C, Housing and Urban Health, San Francisco, CA
2011 – 2013  HIV Health Education Nurse, San Francisco Department of Public Health, San Francisco, CA

2011 – 2013  Graduate Research Assistant, San Francisco Health Improvement Partnership, San Francisco, CA

2011 – 2012  Triage Nurse, San Francisco Department of Public Health, San Francisco, CA

2009 – 2010  Staff Nurse, General Medicine, Brigham and Women’s Hospital, Boston, MA

2007 – 2009  Licensed Nursing Assistant, Intensive Care Unit, Elliot Hospital, Manchester, NH

HONORS AND AWARDS

2016  Graduate Scholarship, Sigma Theta Tau International, Epsilon Tau-at-Large Chapter

2016  Dean’s Travel Award, Johns Hopkins University School of Nursing

2015 – 2016  Henry Spencer Scholarship, Nurses Educational Funds, Inc.

2015  Student Poster Award, Association of Nurses in AIDS Care

2015  Johns Hopkins Professional Development Award

2015  Hartford Foundation Scholarship, Center for Innovative Care in Aging, Johns Hopkins University

2014 – 2016  Johns Hopkins University School of Nursing Graduate Assistantship

2013 – 2014  Johns Hopkins University School of Nursing Scholarship

2010 – 2011  Professional Nurse Traineeship Award, UCSF, US Dept. of HHS

2009  Sigma Student Scholarship Travel Award, Epsilon Tau Chapter

2008  Sigma Theta Tau International Honor Society for Nursing Induction

2008  Dorothy M. Goodwin Nursing Scholarship, Elliot Hospital

2005 – 2009  Helene Morgan Babcock Memorial Trust Scholarship

2005 – 2009  Presidential Scholar, Dean’s List, Saint Anselm College
RESEARCH

Research Grants


2016-2017 Nurse Case Management to Improve the Hepatitis C Care Continuum in HIV Co-infection: A Randomized Controlled Trial. PI: Starbird; CANS/SNRS Dissertation Research Grant. Total direct costs $5,000.

2016-2017 Nurse Case Management to Improve Hepatitis C Care in HIV Co-infection: A Randomized Controlled Trial (Care2Cure). PI: Starbird; Sigma Theta Tau International/Association of Nurses in AIDS Care. Total direct costs $2,500.


PRACTICE

Practice & Educational Grants

2015-2016 Interdisciplinary Doctoral Student Professional Development Speaker Series. Project Director: L. Starbird; Johns Hopkins University Alumni Association Student Grants Program. Total direct costs $750.

2013 An Innovative Intervention for Sustaining HIV Treatment Adherence. Project Director: L. Starbird, Southeast Health Center HIV Care Program; ViiV Healthcare Positive Action Community Grant. Total direct costs $2,800.

2012 Incentives for HIV Treatment Adherence. Project Director: L. Starbird, Southeast Health Center HIV Care Program; Gilead U.S. Corporate Grant: Community and Patient Education. Total direct costs $2,500.

Clinical Protocols

Clinical Service

2016-Present  Clinical Volunteer Coordinator, Baltimore City Health Department Needle Exchange Program, Baltimore, MD

2009  Volunteer Nurse Clinician, Centre for Maasai Development, Saikeri Village, Ngong, Kenya

SCHOLARSHIP

Peer Reviewed Publications (*Data Based)


Han, H., Hong, H., **Starbird, L.E.,** Ge, S., Ford, A., Renda, S., Sanchez, M., Stewart, J. (in press). A systematic review of eHealth literacy in people living with HIV. *Journal of Medical Internet Research.*


Manuscripts under Review (*Data Based)

Manuscripts in Preparation for Submission (*Data Based)


**Starbird, L.E.**, Budhathoki, C., Sulkowski, M.S., Han, H., Reynolds, N., Farley, J.F. Nurse case management to improve the hepatitis C care continuum in HIV co-infection: the Care2Cure Study.

**Starbird, L.E.**, Han, H., Budhathoki, C, Irvin, R., Farley, J.F., Predictors of engaging in hepatitis C treatment across the continuum among high-priority HIV co-infected patients.

**Starbird, L.E.**, DiMaina, C., Nkimbeng, M., Han, H. A systematic review of interventions to minimize transportation barriers among people with chronic diseases.


Conference Meetings & Presentations (*Data Based)

International


National


**Starbird, L.E.**, Teeter, T., McArthur, J., Brinkley, S., Katzianer, J., Nolan, K. Eliminating HCV through a Multidisciplinary Clinical Pathway for


Regional


Local


**PROFESSIONAL ACTIVITIES**

2015 – 2016 President, Johns Hopkins School of Nursing Doctoral Student Organization
2015 – Present Council for the Advancement of Nursing Science  
2015 – Present Southern Nursing Research Society  
2012 – Present American Public Health Association, Public Health Nursing Sector  
2012 – Present Association of Nurses in AIDS Care  
2012 – 2013 San Francisco Department of Public Health HIV Quality Improvement Committee  
2011 – 2013 Southeast Health Center Quality Improvement Committee  
2008 – Present Sigma Theta Tau International Honor Society of Nursing, Epsilon Tau-at-Large (Delegate, 2008-2009) and Nu Beta Chapter  

Peer Review Activities  

2016 - Present Peer Reviewer, *Journal of the Association of Nurses in AIDS Care (JANAC)*  
2015 Ad Hoc Journal Article Review with Dr. Jason Farley for *Journal of the Association of Nurses in AIDS Care (JANAC)*  
2014 - 2015 Ad Hoc Journal Article Review with Dr. Jason Farley for *PLOS ONE*  

**EDUCATIONAL ACTIVITIES**  

2016 – Present Co-Course Coordinator, *Population Health Leadership* (MSN students), Johns Hopkins University School of Nursing  
2016 Teaching Assistant, Health Promotion and Risk Reduction Across the Lifespan (MSN students), Johns Hopkins University  
2015 Teaching Assistant, Teaching Strategies in Nursing (MSN & DNP students), Johns Hopkins University  
2015 Teaching Assistant, Program Development and Evaluation in Health Care (interdisciplinary Master's-level students), Johns Hopkins University  
2015 Teaching Assistant, *Nursing for Adult Health I* (BSN students), Johns Hopkins University  
2014 – 2015 Tutor, *Biostatistics* (PhD students), Johns Hopkins University  
2013 Teaching Assistant, *Global Tuberculosis Clinical Management and Research,* (interdisciplinary massive open online course), Johns Hopkins University  
2011 – 2012 Teaching Assistant, *Theories of the Health Policy Process* (MSN students), University of California, San Francisco  
2007 – 2009 Tutor, *Biochemistry* (BSN students), Saint Anselm College  
2007 – 2009 Tutor, *Anatomy & Physiology* (BSN students), Saint Anselm College  

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**ACADEMIC SERVICE**

2017  
Interprofessional Education Faculty Mentor, Johns Hopkins Schools of Medicine and Nursing with Notre Dame of Maryland University School of Pharmacy

2016 – 2017  
Nurse Faculty for the Future Student Advisory Committee, Johns Hopkins School of Nursing

2014 – 2017  
School of Nursing Ambassador, Developing Behavioral Interventions: A Summer Research Institute, Johns Hopkins University

2010 – 2012  
Student Representative, Student Feedback Committee on MS Revised Curriculum, University of California, San Francisco

2008 – 2009  
Student Representative, Curriculum Development Committee, Saint Anselm College

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Laura Elizabeth Starbird  
Born September 18, 1986  
Nashua, New Hampshire, USA