

# Nurse Case Management to Improve Hepatitis C Care in HIV Co-infection

NCT02707991

Study Protocol

May 8, 2017

## JHM IRB - eForm A – Protocol

### 1. Abstract

Hepatitis C virus (HCV) is a leading cause of liver cancer and HCV-related liver disease is among the most common causes of non-AIDS related death among people living with HIV (PLWH)<sup>1,2</sup>. One quarter of PLWH in the U.S. are co-infected with HCV, which leads to a 3-fold increase in progression to end stage liver disease and hepatocellular carcinoma<sup>2-5</sup>. HCV can be cured<sup>6</sup>, but less than half of PLWH with chronic HCV in the U.S. have linked to HCV care, and about 7% initiated treatment<sup>7-10</sup>. Poor treatment initiation rates historically have been due to low efficacy among PLWH, but HCV care now is at a turning point. We have the ability to substantially decrease HCV-related morbidity and mortality in PLWH with the availability of effective all-oral treatment<sup>11</sup>. As patients are funneled into HCV care, improving the process of linking to care and treatment preparation related to HIV medication modifications necessary for current HCV regimens is essential to maximize the lifesaving potential of available therapies among PLWH.

There are several barriers to linkage to HCV care and treatment. HCV is a “silent epidemic”<sup>12</sup> often presenting no symptoms for 20 years. Thus, perceived need for treatment is low among persons infected with HCV<sup>10,13-16</sup>. Knowledge about HCV and its available therapies is also low and lags behind new advancements in HCV treatment<sup>17-20</sup>. For PLWH who are linked to HCV care, drug interactions between new HCV therapies and HIV treatment regimens introduce a new barrier to HCV treatment initiation<sup>21,22</sup>. Up to 88% of PLWH will need to switch their HIV treatment regimen to avoid contraindicated drug interactions<sup>23</sup>. The April 8, 2015 updated 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<sup>21</sup>. But modifying HIV treatment regimens can have severe negative consequences, including decreased quality of life, increased symptom burden, and loss of viral suppression<sup>24</sup>. New approaches to modifying HIV treatment regimens are now crucial to smooth the transition into initiating HCV therapy for PLWH.

In similar settings and populations, nurse case management interventions have been shown to improve these outcomes<sup>25-31</sup>. However, few of these interventions have been rigorously tested in the context of HCV. Evidence supports combining existing intervention components from similar populations to improve HCV care. Strengths-based education<sup>25-31</sup>, patient navigation<sup>26,29,32</sup>, and reminder systems<sup>33-36</sup> improve knowledge and adherence to appointments. The addition of novel nurse-initiated referral and HIV/HCV drug interaction coordination has never been tested, but may further improve knowledge and motivation to engage in care and address this important barrier for PLWH<sup>22</sup>. Therefore, it is hypothesized that nurse case management consisting of nurse-initiated HCV referral, strengths-based HCV education, patient navigation, appointment reminders, and care coordination for HIV treatment modifications will improve linkage to HCV care and treatment initiation among PLWH.

### 2. Objectives

The specific aims of the proposed RCT are to:

1. Test whether a nurse case management intervention will **increase linkage** of persons with HIV/HCV co-infection to an HCV treatment pathway via the Viral Hepatitis Center compared to enhanced usual care  
*H0*: A higher proportion of those who are randomized to the intervention arm will attend the Viral Hepatitis Clinic or enroll in an HCV-treating clinical trial within 60 days of randomization compared to those who receive enhanced usual care.
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

*H0*: 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 enhanced usual care.

3. Describe the characteristics associated with uptake of HCV care among PLWH, controlling for covariates.

### 3. Background

Linkage to HCV care among people co-infected with HIV/HCV is poor. The greatest gap in the United States HCV care cascade begins between diagnosis and linkage to care<sup>7,8</sup>. Only 25% of PLWH with chronic HCV have attended an HCV appointment, and less than half of those have ever initiated HCV treatment<sup>7-9</sup>. A large cohort study in Baltimore found that only 21% of injection drug users with HCV had ever seen an HCV specialist<sup>10</sup>. At the Johns Hopkins Moore Clinic, less than half of patients who are referred to an HCV specialist by their primary care provider actually attend the scheduled specialty appointment.

The perceived threat of HCV and perceived need for HCV care among patients is low<sup>13</sup>. This perception, coupled with the fact that HCV is a “silent epidemic”<sup>12</sup>, places PLWH at great risk<sup>13-16</sup>. Qualitative studies describe that the absence of HCV-related symptoms leads to little interest in receiving HCV treatment<sup>16,18,19,37</sup>. This is exacerbated by a lack of knowledge about HCV and available therapies<sup>17-20</sup>; horror stories about interferon-related side effects and old ineffective treatments dominate conversations among peers with HCV despite these barriers being minimized with new all-oral therapy<sup>16,18-20</sup>. People with HCV also report low motivation to engage in HCV care due to competing demands from work, school or caregiving responsibilities<sup>13,38,39</sup>. Therefore, interventions to increase HCV knowledge and motivation, such as education, patient navigation, and appointment reminders are needed to improve linkage to HCV care.

HIV-HCV drug interactions will exist for up to 88% of PLWH<sup>23</sup>. HCV treatment guidelines no longer separate patients with HIV/HCV co-infection from those with HCV only because cure rates are similar in both groups (over 90%)<sup>21</sup>. Currently, the only difference in management of HCV in PLWH is the need to manage drug interactions<sup>40</sup>. Patel and colleagues (2015) conducted a cross-sectional study to determine the frequency of contraindicated drug-drug interactions when PLWH are prescribed HCV therapy. Examination of medication lists revealed that the prevalence of interactions was as high as 88.4% depending on the HIV and HCV regimens<sup>23</sup>. Based on these results, it is likely that a large proportion of PLWH who are initiating HCV treatment will have to modify their HIV treatment regimen. Modifying HIV treatment regimens can take months and deter PLWH from starting HCV treatment<sup>24</sup>. A prior study found that HIV combination antiretroviral therapy (ART) modifications can negatively impact quality of life and increase HIV symptom burden<sup>24</sup>. Therefore, new approaches to modifying ART that minimize barriers to HCV treatment initiation are urgently needed to smooth the transition for PLWH.

Interventions that increase perceived need and maximize enabling resources have the potential to improve the HCV care cascade for PLWH. Nurse case management (NCM) components used in similar contexts can be combined to achieve this improvement. Even in the era of interferon, brief HCV education alone significantly increased knowledge and linkage to HCV care by 14-25%<sup>25,29-31</sup>. Adding strengths-based NCM and care coordination improves linkage to HIV or HCV care by up to 30%<sup>26,27,29</sup>. Reminder systems using text and phone messages are also effective strategies to increase linkage to HIV care and substance use services in combination with other interventions<sup>33-36</sup>. Finally, the addition of care coordination for ART modification will further participants’ enabling resources and address this important new barrier for PLWH.

### 4. Study Procedures

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The proposed study is a single blinded, randomized controlled trial. The trial will evaluate a nurse case management intervention and determine differences in linking to HCV care (primary aim) and time to HCV treatment initiation (secondary aim) among persons co-infected with HIV. Patients with HIV and chronic HCV infection will be recruited from the Johns Hopkins University AIDS Service (JHUAS). After informed consent, participants will be randomized to a standard nurse case management protocol or enhanced usual outpatient care (100 per group), described below. Information flyers, provider referral, and targeted mailings will be used for recruitment.

## **Enrollment**

**Patient Population/Setting:** The Bartlett Specialty Practice (formerly the Moore Clinic for HIV Care) at the Johns Hopkins Hospital provides HIV primary care to approximately 3500 men and women over the age of 18 per year. The clinic serves a primarily adult, urban population, with approximately 80% of patients being African American. The average age of clinic patients is 49 years. Approximately 50% of patients with HIV are co-infected with HCV. In Maryland, HCV therapy currently must be managed by a hepatology, gastroenterology, or infectious disease specialist for Medicaid reimbursement<sup>41</sup>. The Viral Hepatitis Specialty Clinic, staffed with hepatologists and hepatitis-focused infectious disease physicians and nurse practitioners, is located within the Bartlett Specialty Practice. As of May 2015, 480 HIV/HCV co-infected patients at the Moore Clinic had *never* attended an appointment at the Viral Hepatitis Clinic; 90 patients never went to their scheduled appointments and 390 patients had never been scheduled for HCV care. In addition, a number of patients have not attended an appointment at the Viral Hepatitis Clinic in the era of all-oral therapy (including the past year). The median time between referral and available new patient appointment at the Viral Hepatitis Clinic is one week.

**Recruitment:** Patients will either 1) self-refer by contacting the research team after seeing flyers posted in the Bartlett Specialty Practice waiting room or in an exam room research binder; 2) be referred from their HIV provider in clinic; 3) self-refer after receiving a targeted letter in the mail; or 4) self-refer after finding the study on [clinicaltrials.gov](http://clinicaltrials.gov), [Trials @ Hopkins](mailto:Trials@Hopkins), or referral from the CFAR Hotline. Eligible prior study participants from the Principal Investigator's SUSTAIN study (NA\_00079147) who agreed to be contacted for future research (HIPAA form 3) will also be called. On a weekly basis, Bartlett Specialty Practice appointments will be reviewed electronically in EPIC to identify HIV/HCV co-infected patients scheduled for primary care visits. Letter notifications will be mailed to potentially eligible patients who have an upcoming appointment inviting them to contact the study team to participate in the research study. Daily, the primary HIV provider, registered nurse, or certified medical assistant will be approached to refer his or her eligible patients to the study. After the patient has contacted our research team to meet at the Bartlett Specialty Practice, a member of the study team will provide information regarding the study, answer any questions, and obtain informed consent. The PI will be available in person or via telephone to answer any questions when a student is present for the consent. Once enrolled, the study team will assign a study identification number (SIN) to the subject. This will be the primary mode of identification throughout the study. The SIN will appear on the consent form, the questionnaire, as well as all data collection forms. As part of the informed consent document, the participant will receive information on how to contact the investigators to discuss any of the nurse case management intervention components.

**Eligibility:** Adults who are co-infected with HIV and HCV who have not attended an HCV-specific appointment in the past year will be enrolled in the proposed study. Specific eligibility requirements are detailed in inclusion/exclusion criteria below.

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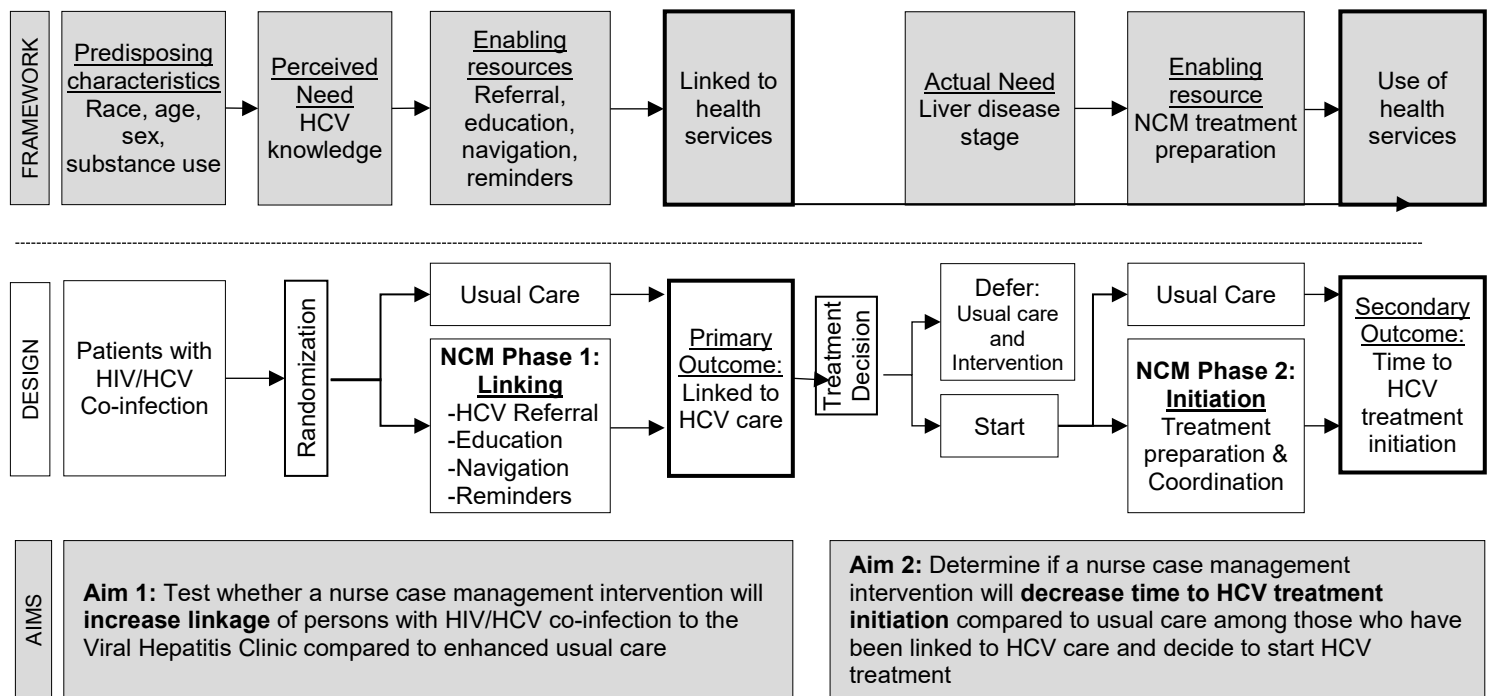
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**Participant Consent:** Once the participant contacts the study team through a study flyer, letter, clinical trials database, or provider referral, the study will be explained with an emphasis on the use of random assignment to study groups. The consent process will be completed in a private area of the Bartlett Specialty Practice. To account for low levels of literacy, the study materials have been developed on a 5<sup>th</sup> grade reading level. Participants will also be given the option to have the consent form read aloud in its entirety. The consent form will be maintained in the study files and participants will be given the option of taking a copy of the signed consent form with them. They will be informed that retention of the form may lead to a breach of confidentiality if the information is shared with someone who does not already know their HIV and/or HCV status.

**Assessment of Protocol Comprehension Prior to Signing Consent:** After the consent form is read by the participant or aloud, the study team member will evaluate comprehension with three protocol-specific 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? We will deem the participant to have an acceptable level of comprehension based on his/her ability to answer those questions.

**Allocation:** This RCT will be conducted and reported following the CONSORT clinical trial guidelines. The study design is pictured in Figure 1. After recruitment and informed consent, patients will be randomized to the nurse case management intervention group or to the usual care group electronically. Participants will be randomized in a 1:1 fashion using REDCap, a secure online data collection program, to ensure balanced, random assignment to the intervention and usual care groups. REDCap employs a simple randomization technique. This strategy will ensure that the study team has no a priori knowledge of group assignment when enrolling and randomizing study participants.

**Blinding:** The study allocation will be single-blinded; no direct communication will occur between the nurse case manager and the HCV provider to avoid influencing the HCV management of the patient. The intervention will support the HIV provider and patient without influencing the HCV provider's decisions. The study team member completing data collection for the study outcomes will also be blinded to randomization to minimize bias in the results.

**Figure 1.** Integrated study flow and conceptual framework

\*HCV=hepatitis C virus; NCM=nurse case management; ART=HIV antiretroviral therapy

### Data Collection Measures:

The baseline characteristics questionnaire used in the proposed study has been thoroughly evaluated with over 1000 subjects (over 50% with HIV). The current study team has used this questionnaire with study participants in the Moore Clinic<sup>42</sup>. Questions have been added or removed as applicable to this study and patient population. If a participant reports any alcohol use in the past 6 months on the questionnaire, the Alcohol Use Disorders Identification Test (AUDIT) will also be administered<sup>43</sup>. 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<sup>44</sup> to the mid-0.90s<sup>43</sup>. In a primary care setting, the AUDIT is intended to be administered by a nurse or social worker<sup>43</sup>, and will be administered by a registered nurse in the proposed study. The research nurse case manager will counsel 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, will be referred to their Bartlett Specialty Practice social worker to discuss further counseling and treatment options.

The 19-item Brief Hepatitis C Knowledge Scale (Cronbach's  $\alpha=0.87$ ) will also be administered to measure baseline HCV knowledge<sup>45</sup>. The Brief HCV Knowledge Scale includes a comprehensive list of items in its single factor 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 different socioeconomic and demographic backgrounds. It uses a simple true/false/don't know scoring system.

Depression can be associated with engagement in health services; therefore, the Patient Health Questionnaire (PHQ-9) will be administered. The PHQ-9 will be scored immediately. Participants scoring 10-19, indicating moderate depression, will be referred to their primary care provider for further follow up. Those

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with scores of 20 or greater (severe) will be 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 is continued.

All questions in the protocol will be asked in a private area and can be administered by a study team member in 30-45 minutes. In addition to the subject questionnaire, each instrument contains a section for the research team to interrogate the patient's medical record to verify specific pieces of the medical history. These variables of interest include:

- CD4+ T cell count
- HIV viral load
- Prescribed HIV treatment
- Year of HCV diagnosis
- HCV RNA
- Fibrosis score
- HCV genotype
- HCV referral history
- HCV appointment history
- HCV treatment initiation barriers
- Hopkins appointment no-show rate

In addition to baseline and outcome data collection, monthly activity logs will be collected for each study participant, independent of allocated study arm. The type, quantity, and content of all encounters with a study participant in the Johns Hopkins system will be 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 will also be recorded to define the dose of the intervention. Data will be collected from the study participant's Epic record and the interventionist's notes.

**Enhanced Usual Care:** After randomization into the enhanced usual care arm, the nurse case manager will provide participants with the CDC HCV Fact Sheet<sup>46</sup> and phone number for the CFAR Research Study Hotline. Participants will then be referred to the usual clinic appointment check-out process. To check-out of Bartlett Specialty Practice appointments, participants return to the front desk with a paper billing page and printed appointment referrals if applicable. The administrative staff closes the appointment encounter and gives the patient the phone number for the Johns Hopkins Hospital central scheduling phone line to schedule referral-based appointments. Patients are responsible for calling central scheduling to set up the specialty appointment. If an appointment is scheduled, all patients receive an automated appointment reminder call 2 days before the scheduled appointment from Johns Hopkins Hospital. Patients at the Bartlett Specialty Practice have access to nurse case managers and social workers assigned by their primary providers. 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 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 the proposed study seeks to fill.

### **Nurse Case Management Intervention Phase 1 – Linking to Care:**

Following informed consent, randomization, and completion of the baseline questionnaire, participants allocated to the intervention group will receive the first phase of the nurse case management (NCM) intervention (Table 1). This phase of the intervention will increase linkage to HCV care through NCM consisting of nurse-initiated referral, strengths-based HCV education, patient navigation, and HCV appointment reminders. The research nurse case manager will initiate an HCV referral for participants randomized to the

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intervention group via the electronic health record. This will send a cue to the HIV provider to approve the referral and minimize the barrier of non-referral by the provider. Participants will then receive brief strengths-based HCV education<sup>47</sup>. Strengths-based education can improve knowledge and motivation to achieve health-related goals in PLWH<sup>26,27,47</sup>. The research nurse case manager will help participants identify their strengths within the context of engaging in HCV care, including social support and engagement in HIV primary care<sup>48-50</sup>. HCV education will include transmission, symptoms, treatment, and risk reduction. 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, mental health services, and the Johns Hopkins "Cure Club" HCV support group<sup>51</sup>.

Linkage to care will be defined as attendance at one or more appointment within the HCV treatment pathway via the Viral Hepatitis Center, including either traditional clinical care at the Bartlett Specialty Practice or an HCV treatment-providing clinical trial within the Viral Hepatitis Center. This will ensure that participants enrolled in the Care2Cure study have the opportunity to engage in HCV treatment in all pathways offered by the Viral Hepatitis Center and inherent in Johns Hopkins Hospital's standard of care as an academic institution and research center. Independent of randomization allocation, all study participants will be asked in the baseline characteristic questionnaire if he/she would like to be referred to a clinical trial, with the option to refuse or opt out of trials for non-FDA approved treatments. Based on this participant preference, eligibility for actively recruiting clinical trials at the Viral Hepatitis Center will be assessed. Participants will then be referred by the study nurse case manager to either traditional care at the Bartlett Specialty Practice, a clinical trial with no investigational drug, or a clinical trial with an investigational drug, as eligible and available.

Multiple strengths support this approach to the outcome of linkage to care. In Maryland, patients must have a Metavir score greater than or equal to 2 to receive HCV treatment (Maryland Department of Health and Mental Hygiene, 2015). Linking patients to clinical trials that offer treatment to patients in all stages of liver disease, including F0 and F1, removes this barrier to treatment. This approach also minimizes selection bias. Participants who choose to receive HCV treatment through a trial may be different than those who seek care through the traditional clinical pathway; the Care2Cure study will include both.

Because appointment scheduling is a known barrier to linkage to care, patient navigation will include either a) calling central scheduling during the visit so the research nurse case manager can navigate participants through the Viral Hepatitis Clinic scheduling process<sup>17,20,52</sup> or b) calling a clinical trial recruitment number to link eligible participants with an HCV-treating clinical trial. Participants also will be encouraged to call the Care2Cure research nurse case manager for needs relating to linking to HCV care throughout the study period. All contacts and amount of time spent with the study participants will be recorded by the research nurse. 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. A plan for contacting participants for personalized appointment reminder will be made, including the best mode of contact (phone, text, or email) and time of day. Participants will be contacted 1 day before their scheduled Viral Hepatitis Center appointment (either at the Bartlett Specialty Practice or a clinical trial) for an appointment reminder in addition to the automated JHH reminder 2 days before the appointment<sup>53</sup>. If the scheduled Viral Hepatitis Center appointment is greater or equal to 2 weeks (10 business days) from the date of the baseline visit, participants will also be contacted one week before the appointment for a reminder.

The medical record will be reviewed 60 days after the baseline visit to verify whether the participant was registered for one or more Viral Hepatitis Clinic appointment since randomization if referred to the Bartlett Specialty Practice HCV provider. If the participant was referred to a clinical trial, attendance at a study appointment will be confirmed with that study coordinator.

### **Nurse Case Management Intervention Phase 2 – Treatment Initiation:**



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This phase of the intervention will decrease time to HCV treatment initiation by using a nurse case manager to coordinate communication about antiretroviral therapy (ART) modifications between the patient, HCV provider documentation, and HIV provider. Participants who are enrolled in another clinical trial will not be included in this phase. Participants in clinical trials that provide medication (such as the CHAMPS study or an investigational drug trial) will receive an intervention to initiate HCV treatment within that trial. These participants are expected to follow a different timeline than clinical patients and face different challenges. Therefore, this phase will include a subgroup of consented Care2Cure study participants who link to an appointment at the Bartlett Specialty Practice HCV provider.

After the participant attends the Viral Hepatitis appointment, the research nurse case manager will review 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 will be single-blinded; no direct communication will occur between the research team and the HCV provider to avoid influencing the HCV management of the patient. The intervention will support the HIV provider and patient without influencing the HCV provider's decisions. Using a Phase 2 Algorithm, the research nurse case manager will identify participants who have a decision to start treatment indicated in the HCV visit note. The anticipated HCV therapy regimen(s) in the clinic note will be 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 will contact the participant via his/her preferred contact method to schedule a follow-up NCM visit. At this visit, the participant will be given a modified one-page drug interaction sheet tailored to his/her ART regimen. The research nurse case manager will also send a secure email to the participant's HIV provider notifying him/her of the potential need for ART modification. This email will include 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. The research nurse case manager will coordinate 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 scheduled HIV primary care visit.

To measure the effectiveness of NCM Phase 2, the electronic medical record will be reviewed 6 months after the enrollment visit. The study team will record whether a change in ART was made during the study period (yes/no). We will also determine if a prescription for HCV therapy was written during the study period, and the time to initiation of that prescribed treatment. 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<sup>21</sup>; 4) HCV-related blood tests and imaging, and 5) uncontrollable factors such as appointment cancellations, rescheduling, and reimbursement.

**Table 1. Nurse Case Management Intervention and Study Visit Schedule**

	Enrollment	Before HCV appt.	HCV appt.	NCM visit	ART change appt. <sup>a</sup>	6 months
<b>Administrative and Data Collection Procedures</b>						
Informed Consent	X					
Baseline questionnaire	X					
Randomization	X					
Medical record abstraction: Linkage to care			X			
Medical record abstraction: Treatment initiation						X
Exit Interview						X

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NCM Phase 1: Linking to Care						
Nurse-initiated Referral	I					
Strengths-Based Education <sup>25,26,28-31,53</sup>	I					
Patient Navigation <sup>26,29,32</sup>	I	I <sup>b</sup>				
Appointment Reminders <sup>33-36</sup>		I <sup>c</sup>				
NCM Phase 2: Treatment Initiation <sup>d</sup>						
Care Coordination of ART Modification <sup>22,23,51</sup>			I	I	I	

X=all participants; I=intervention arm only; appt.= appointment; NCM=nurse case management; <sup>a</sup>ART change appointment with HIV provider; <sup>b</sup>Participants will be encouraged to call the research nurse case manager for needs relating to linking to HCV care and initiating HCV treatment; <sup>c</sup>Appointment reminders will occur 1 day and 1 week (if applicable) before HCV appointment; <sup>d</sup>Includes participants from Phase 1 who link to an HCV provider only

### **Exit Interview (Intervention and Control Participants):**

At the time of the 6-month medical record review to evaluate the study outcomes, participants in both groups will be called by a study team member other than the research nurse case manager to complete an exit interview. The purpose of this interview is to identify barriers that participants in both groups encountered in linking to HCV care and initiating therapy during the study period, as well as to measure the intervention group's perception of the content, quality, and quantity of the intervention delivered by the research nurse case manager. This interview will also help to explain the acceptability and of the intervention as well as its success or failure among patients in the intervention group.

Participants will be asked to answer a short survey with the opportunity to provide an open-ended response to explain their answer or give additional feedback about the intervention and participation in the study. A separate survey will be given to the control and intervention groups. The Nurse Case Management group will be asked about overall feedback about participation in the study, barriers to linking to HCV care and treatment initiation, and evaluation of the interventionist. The Enhanced Usual Care group will receive the same questions about overall feedback and barriers, but without the evaluation of the interventionist questions, so that comparisons can be made between the two groups about satisfaction with participation in the study and barriers to linking to and engaging in HCV care.

### **Study Timeline**

The following 3-year study timeline provides an overview of the study preparation period, enrollment and follow-up (Table 2).

Table 2: Timeline				
Year	First 6 months	Second 6 months	Year 2	Year 3
Task	Preparation	Enrollment	Enrollment	Follow-Up
IRB Process				
Identify/Train Research Assistants				
Recruitment/Informed Consent/Screening				
NCM Intervention and Study Visits				
Medical Record Review of Outcomes				

Data Entry and Statistical Analysis				
Present at Meetings and Publish Data				

**Study Duration:** Final data collection for each participant will occur 6 months after the date of enrollment (Table 1). Participants will be asked to complete a maximum of two study visits. Participants in both groups will have a baseline study visit consisting of informed consent, baseline questionnaire, and medical record review. Participants in the enhanced usual care group will receive the CDC HCV Fact Sheet at this time and require no further follow-up visits. Participants in the NCM intervention group will receive intervention Phase 1 at the time of the baseline visit. A second visit will occur for participants in the intervention group who are included in Phase 2 after 60 days to coordinate ART modifications with the nurse case manager, as described under Phase 2 – Treatment Initiation above. After 6 months, the study team will review the medical record for final data collection. Participants will be contacted via their preferred method at 6 months to respond to an exit survey, which may take place over the phone.

## 5. Inclusion/Exclusion Criteria

### *Inclusion Criteria*

- HIV infection: This study is examining linkage to HCV care and treatment, with a focus on ART modifications among people living with HIV; therefore, participants must have an HIV diagnosis. People with HIV have a different, accelerated HCV disease course than those with HCV only. People with HIV also have different levels of engagement in healthcare and resources to attend healthcare than the general population due to Ryan White policies. Finally, barriers to engaging in HCV care historically have been different among people with HIV due to particularly low efficacy of HCV treatment options.
- Chronic HCV infection: This study aims to improve linkage to HCV care and treatment in those who need it; therefore, all participants must be chronically infected with HCV. Acute HCV infection is not included in this study because its management and the treatment course are vastly different.
- Age 18+: Most HIV-positive patients at the Bartlett Specialty Practice are over the age of 25 years. Children under the age of 18 years will not be included because management of HCV is different in this population, who does not receive care at the historical Moore Clinic.
- Did not attend appointment with a viral hepatitis provider at Viral Hepatitis Clinic/Bartlett Specialty Practice in past year: The primary goal of this study is to improve linkage to HCV care among those who are not engaged in care; therefore, anyone who has not had a visit at the HCV clinic in the past 1 year will be considered not linked to care because they have not been assessed by an HCV-specific provider in the all-oral era of HCV treatment.
- Ability to speak English: The study team has limited resources to create study materials and provide the nurse case management intervention in multiple languages. The clinic population is primarily African American and Caucasian patients, with few patients speaking no English.
- At least one visit at the Moore HIV Clinic or Bartlett Specialty Practice in the past year: This study aims to test an intervention that can be used in an HIV primary care clinic setting. Participants will be recruited from their regularly scheduled HIV clinic appointments; therefore, those who have been to the clinic in the past year will be considered active clinic patients.

### *Exclusion Criteria*

- Pregnancy: Women who are pregnant will be excluded from this study because treatment of pregnant women with direct acting antivirals and/or ribavirin is not recommended.

- Emergency medical care needed: If a potentially eligible patient requires emergency medical care at the time of the HIV clinic appointment, the study team will not enroll this patient in the study so that the patient can receive necessary care. The patient will be able to contact the study team at a later date if interested in the study.
- Unable to provide informed consent: Patients who are independently unable to provide informed consent will be excluded from this study to minimize the risk of coercion by the study team or other third parties.

## 6. Drugs/ Substances/ Devices

N/A

## 7. Study Statistics

### Analysis:

Data will be cleaned and efforts made to minimize the effects of missing data. All provider visits at Johns Hopkins are registered in the electronic medical record, so absence of a registered appointment during the study period will be considered non-attendance for the primary outcome variable. A computer-based data collection method will be used for data collection of independent variables in attempt to minimize missing data. Exploratory and descriptive analysis will be completed for all study variables. Variables will be tested for normality and examined with means and standard deviations or medians and interquartile ranges accordingly. Baseline characteristics comparing the two groups (usual care vs. 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. All tests will be two-tailed and analyzed by intention-to-treat.

**Primary Outcome:** The primary outcome is linkage to care, measured by attendance at the Viral Hepatitis Center (either traditional care or an HCV-treating clinical trial) within 60 days of randomization (yes/no). This hypothesis will be tested using a two-sample z-test for the difference in independent proportions comparing the intervention to usual care groups.

**Secondary Outcome:** The secondary outcome is time to HCV treatment initiation, measured by the number of days from randomization to the date HCV treatment is initiated according to the medical record. Kaplan Meier estimates will be conducted to compare time to HCV treatment initiation between participants in the intervention group and the usual care group, and a log-rank test will be used to test the difference. Covariates (age, sex, race/ethnicity, HCV knowledge, substance use, fibrosis score, CD4+ T cell count, HIV viral load, care giving responsibilities, and participation in Cure Club) 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.

**Exploratory Analysis:** Binary logistic regression will be used to determine an effect on linkage to care controlling for differences in age, sex, race/ethnicity, HCV knowledge, substance use, fibrosis score, CD4+ T cell count, HIV viral load, care giving responsibilities, and participation in Cure Club. A correlation matrix will be used to assess multicollinearity of the independent variables, and those with a correlation of greater than 0.6 will be considered for removal from the model. The remaining covariates will be entered into the model first, followed by the independent variable of interest (intervention vs. usual care). To evaluate how much predictive

power was added to the model by adding the variable(s) of interest, the change in likelihood ratio test will be evaluated<sup>54</sup>.

**Exit Interview:** Descriptive statistics will be used to examine the overall satisfaction of participants in the study. One-way frequency analysis will describe the intervention group's perceptions of the intervention and the interventionist to inform future studies. Participant responses to the barriers to linking to HCV care and initiating therapy will be grouped into categories and compared between the intervention and control group using a categorical Chi-Square test to determine if there is any difference in quantity and category of barriers to accessing care.

### **Sample Size Justification:**

Currently, 40% of new Viral Hepatitis Clinic appointments are attended by patients. Based on prior studies testing the intervention components in similar populations, including persons living with HIV and/or substance use disorders, it is expected that the intervention will improve the primary outcome of linkage to care by 18-30%<sup>26,53</sup>. Although the effect size is not known in the context of HCV, we estimate an improvement in linkage of 20% (i.e., 60% attendance [0.60] in the NCM group compared to 40% attendance [0.40] in the usual care group) based on these prior studies. Using these figures and a two-tailed test with an alpha of 0.05, a conservative estimate of the total sample size required to achieve 80% power is 97 per group, or a total of 194 participants (G\*Power 3.1.9.2). With a sample size of 100 participants in each group, there should be an adequate number of participants to detect a difference in proportion of linkage to care for the primary aim.

For Phase 2, participants with successful linkage to clinical care from Phase 1 (those who attend  $\geq 1$  appointment at the Viral Hepatitis Clinic within 60 days) will be included. Therefore, the eligible sample size will be less than 40-60% of the original sample size because a linkage to care proportion of 0.40-0.60 is expected, and some participants will link to a clinical trial and not be included in this outcome. This is a secondary outcome and estimated effect size is unknown. However, with 100 participants in this group (half of the total sample size), we will have 90% power to detect a hazard ratio of 2.

## **8. Risks**

### **Potential Risks:**

Potential risks of this study include loss of confidentiality, time involvement, fatigue, distress, and embarrassment because of the nature of some of the questions. There are no physical risks to participants who receive the nurse case management intervention. All participants will be informed about the potential risks of participating.

Questioning participants about socially stigmatized conditions accompanied by low level of knowledge among the general population, such as HIV and HCV, is sensitive. There is a risk that a participant is not aware of his or her HCV diagnosis at the time of enrollment; however, participants will be told about the study by their primary HIV provider or self-referred from study flyers that list current chronic HCV infection in the eligibility criteria. Therefore, it is unlikely that a participant will be unaware of an HCV diagnosis at the time of study enrollment. While learning about HCV and HCV-related liver disease may be distressing to participants, studies evaluating HCV educational interventions have not reported any negative effects of providing HCV education to persons with chronic HCV and have demonstrated that HCV education improved patient outcomes<sup>33-35</sup>. The research nurse case manager will emphasize participants' strengths, benefits of HCV treatment, and HCV cure. The study's research nurse also has experience providing education about HCV to

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newly diagnosed patients. In the event that participants become distressed or uncomfortable during a study visit, the study team will stop the study and the participants' primary HIV provider will be called to assess the participant. Participants will be allowed to withdraw from the study at any time.

Initiating a discussion about drug interactions and the need to make modifications to an ART regimen could turn participants away from HCV care if they do not want to make a modification. However, the purpose of this intervention is to foster a supportive environment to make these modifications easier for the patient. Participants would eventually be approached by the HCV or HIV provider with the need for ART modification regardless of participation in this study in order to initiate HCV therapy; therefore, this study is not expected to generate any additional risks of distress or loss to follow-up than usual care, and may decrease distress associated with this process due to supportive and timely care coordination.

### **Protection against Risks:**

All study team members will continue to comply with Johns Hopkins and federal human subjects research requirements. All participants will be informed about the potential risks in participating and notified that they can withdraw from the study at any time without penalty.

**Confidentiality:** After participants have completed the necessary consent process and have agreed to enrollment, they will be assigned a unique study identification number. This number will be used to label all study documents. A key for linking participants with their IDs will be necessary to access and link appropriate medical records data to the study ID number. This list will be kept separately from all other study materials in a locked cabinet in a locked office in the School of Nursing. Participants' names will not appear on any records or data collection forms.

As noted, all research information will be kept in locked cabinets, in a secure locked office in the School of Nursing. Access to identifying information will be limited to the approved study team. Participants will be advised of the precautions that will be taken to preserve confidentiality during the consent process. Data with identifiers will not be permitted outside of the Johns Hopkins campus.

All de-identified data collected from study questionnaires and medical record abstraction will be entered into a password protected and encrypted data management system known as REDCap (Research Electronic Data Capture)<sup>62</sup>. This is a university developed system that will allow direct online data capture into a password protected, secured server at Johns Hopkins. The development of the database and security of the data and storage are supported by The Johns Hopkins University School of Public Health, a REDCap Consortium member. The database also will provide a reminder system for data entry, facilitate accurate data collection, and ensure confidence in data integrity.

**Data Security:** The REDCap application is hosted on servers administered by the Data Informatics Services Core (DISC) of the Johns Hopkins Biostatistics Center (JHBC). The JHBC servers are protected by both a hardware firewall and a web application firewall. In addition, they have multi-level intrusion detection, network security audits, and secondary hardware on standby for immediate replacement. JHBC administrators connect to the REDCap servers for system administration using a VPN connection and a two-factor authentication method. All data transmitted between the client browser and REDCap web servers are encrypted using an SSL connection. JHBC system administrators regularly monitor server logs and services to ensure that the servers are secured. To access the REDCap website, all users of the REDCap system must have a valid username and password which is generated and maintained by the JHBC administrators on the REDCap server. Each user account has rights that can be granted or denied including: data import, data export, data comparison, data logging, file repository access, user rights assignment, data access groups assignment, lock/unlock records, and super user. In addition, they can be granted read, edit or no data entry rights for each data entry form.

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**Participant Distress:** All study visits will take place in private areas within the Bartlett Specialty Practice. Procedures for asking sensitive questions have been developed for previous research by Dr. Farley and Dr. Sulkowski with this population. Distress is unlikely, but may arise during the survey or education; in the case that a participant becomes distressed during a study visit, the research nurse's experience providing care to this population will allow her to effectively approach any such situations. In addition, the participant's HIV primary provider will be available, since recruitment takes place during a regular visit. Further support will be provided by the PI and Co-PI, who are clinicians active in clinical care of people living with HIV and HCV. The study team will be available to participants by phone or email in case participants have further questions or concerns.

### **Plan for Reporting Unanticipated Problems or Study Deviations**

**Data Safety and Monitoring Plan:** A group of designated Johns Hopkins faculty will have responsibility for monitoring and oversight of protocol events for this research. This includes Laura Gitlin, PhD (School of Nursing), Mark Sulkowski, MD (School of Medicine), Chakra Budthathoki, PhD (School of Nursing), and Haera Han, PhD, RN (School of Nursing). The study team will meet biweekly to review recruitment progress, any issues related to data collection, and to ensure that all concerns related to intervention delivery are handled appropriately. Any unanticipated problems or study deviations will be reported to Dr. Farley immediately. If there is any concern raised by a participant that the study team cannot address, assistance will be sought through the Institutional Review Board.

## **9. Benefits**

There may be no direct benefit to the subjects in this study; however, information obtained in this study may inform research and practice so that the most effective linkage to care and treatment approach is integrated into the care of this population to decrease morbidity and mortality related to HIV/HCV co-infection. Given the interaction with participants, it is possible that a participant may benefit from more timely evaluation and/or treatment of HCV.

## **10. Payment and Remuneration**

Enrolled participants in both the enhanced usual care and intervention groups will receive a \$20.00 gift card after completion of the baseline study visit. We will offer a second gift card of \$20.00 to participants in the intervention arm on completion of the phase 2 nurse case management visit.

## **11. Costs**

There are no direct costs to the patient in this study.

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