

NIDA CTN Protocol 0064

**Assessing Long-term CTN-0049 Outcomes, HCV
Prevalence and Progression along the HCV Care
Continuum among HIV/HCV Co-infected Substance
Users in the U.S.**

Version 4.0

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1.0 LIST OF ABBREVIATIONS

ACTG	AIDS Clinical Trials Group
AD1	Adverse Events
AD2	Serious Adverse Events Summary
AD3	Serious Adverse Event Medical Reviewer
AE	Adverse Event
APRI	Aspartate aminotransferase/platelet Ratio Index
ART	Antiretroviral Therapy
ARTAS	Antiretroviral Treatment Access Study
AUDIT	Alcohol Use Disorders Identification Test modified
CAPI	Computer Assisted Personal Interview
CCC	Clinical Coordinating Center
CDC	Centers for Disease Control and Prevention
CF	Care Facilitator
CFI	Care Facilitation Intervention
CI CM	Confidence Interval Contingency Management
CoC	Certificate of Confidentiality
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DAA	Direct-acting Antiviral Agent
DHHS	Department of Health and Human Services DM Data Monitoring
DSC	Data and Statistics Center
DSMB	Data and Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
ICH	International Conference of Harmonization
IDU	Injection Drug Use or Injection Drug User
IRB	Institutional Review Board
ITT	Intent-To-Treat
LI	Lead Investigator
LN	Lead Node
NIDA	National Institute on Drug Abuse
PDV	Protocol Deviation
PI	Principal Investigator

PN	Patient Navigation or Patient Navigator
POCT	Point-of-Care Test
PT	Participant
QA	Quality Assurance
RA	Research Assistant
RCT	Randomized, Controlled Trial
RNA	Ribonucleic Acid
RRTC	Regional Research and Training Center
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
SVR	Sustained Virologic Response

2.0 STUDY SYNOPSIS AND SCHEMA

STUDY OBJECTIVES:

This study will examine long-term outcomes of the CTN-0049 study, document HCV prevalence among the HIV-infected CTN-0049 sample, and evaluate the effectiveness of a Care Facilitation intervention in moving HIV/HCV co-infected substance users forward along the HCV care continuum.

STUDY DESIGN:

The CTN-0064 study leverages the existing research infrastructure and cohort of an ongoing randomized controlled trial (RCT), “CTN-0049,” which is briefly described here. CTN-0049 (“Project HOPE -- Hospital Visit as Opportunity for Prevention and Engagement for HIV-Infected Drug Users”) is a three-group RCT that is evaluating the most effective strategy to achieve HIV virologic suppression among HIV-infected substance users who were recruited from hospital settings. Between July 2012 and January 2014, a total of 801 HIV-infected hospitalized patients were recruited from 11 participating sites throughout the U.S. and randomized to one of the following three groups: 1) Patient Navigator intervention, 2) Patient Navigator plus Contingency Management intervention, and 3) Treatment as Usual. All CTN-0049 participants provided informed consent and completed baseline computer assisted personal interviews or CAPI (computer assisted personal interview: focusing on drug use, mental health, demographics and socio-economic factors, HIV care and drug treatment history) and blood draws (for HIV viral load and CD4 count). The two intervention groups received up to 11 patient navigation sessions over a 6-month period to actively assist participants in linking to HIV primary care and substance use treatment. Participants in all three groups completed follow-up assessments consisting of CAPI, blood draws, urine collection and breath analysis at approximately 6 and 12 months post-randomization. Medical records were reviewed to document receipt of HIV care and treatment during the study period. The CTN-0049 follow-up phase officially ended in April 2015 and the study closed (data locked) in June 2015. The incremental cost and cost-effectiveness of the CTN-0049 interventions will also be evaluated. CTN-0064 will leverage the CTN-0049 research infrastructure and cohort by utilizing the 11 participating CTN-0049 research teams to recruit their randomized participants into the CTN-0064 study.

CTN-0064 has two main components: **Component 1** is the baseline assessment for CTN-0064. It will also serve as a long-term follow-up assessment for CTN-0049 for those who consent to participate in CTN-0064. Participants who screen as HCV antibody positive in this baseline assessment will be invited to enroll in Component 2. **Component 2** is an RCT that will assess the effectiveness of a Care Facilitation intervention (compared to Control) in moving HIV/HCV co-infected substance users forward along the HCV care continuum. The study’s primary objective is based on Component 2 and will be operationalized as movement through a series of (potentially non-sequential) pre-defined, clinical steps along the HCV care continuum (including the ultimate step, sustained virologic response to treatment at 12 weeks post treatment completion [SVR12]) (AASLD/IDSA/IAS–USA). Secondary objectives will be to assess: 1) success at each step in the HCV care continuum, 2) engagement in substance use treatment, and 3) HIV viral suppression as well as 4) to examine other long-term outcomes of the CTN-0049 cohort.

All adults who were randomized into the CTN-0049 study and who were not documented as deceased who provided consent to be contacted about future studies in the CTN-0049 database (hereafter, referred to as the “CTN-0049 cohort”) will be actively recruited into the CTN-0064 study. However, because this study will employ active and passive recruitment strategies, any participant from the CTN-0049 study may be enrolled into CTN-0064. All participants will provide informed consent and complete Component 1, consisting of: 1) a computer assisted personal interview or CAPI (capturing history of HIV care, HCV testing and care, substance use and substance use treatment; mental health; demographics; and socio-economic factors), 2) HCV antibody screening (and HCV RNA testing, as applicable), 3) associated pre-/

post-HCV test information and counseling, 4) blood specimen collection via venipuncture, and 5) drug/alcohol toxicology screening (via urine evaluation). The blood specimens of all participants will be assessed for HIV viral load and CD4 count. The blood specimens for the subset of participants who screen as HCV antibody positive will be assessed for HCV RNA to determine if their HCV infection is active.

Participants who screen as HCV antibody positive will be randomized into Component 2 and assigned to one of two groups: 1) HCV Care Facilitation intervention or 2) Control. The Care Facilitation intervention group will receive up to 12 sessions during a 6-month intervention period. Follow-up visits with both groups will be conducted at approximately 6 and 12 months post-randomization. These visits will consist of CAPI, blood specimen collection, and drug/alcohol toxicology screening. Medical records will be reviewed to document HCV testing, receipt and use of HCV clinical evaluation, care and treatment (as applicable); and HIV care and treatment before and during the study period.

STUDY POPULATION:

As described above, the CTN-0049 cohort will be recruited into the CTN-0064 study. At the time of their enrollment in CTN-0049, participants were HIV-infected inpatients who reported (or had evidence in the medical record of) opioid and/or stimulant and/or heavy alcohol use within the prior 12 months. Additionally, almost all of them had detectable HIV viral loads at their CTN-0049 baseline visit.

Given the number of deaths and losses to follow-up in the CTN-0049 cohort, it is estimated that approximately 680 - 690 CTN-0049 cohort participants will participate in CTN-0064 Component 1, the long-term CTN-0049 follow-up assessment which doubles as the baseline assessment for CTN-0064 Component 2 for those CTN-0049 participants that consent for CTN-0064. The number of participants will vary by site (range of 18 – 105 per site) according to the number of CTN-0049 cohort participants accrued by site. Further, as many as 270 Component 1 participants (those who screen as positive for HCV antibody) will be randomized into CTN-0064's Component 2, the RCT.

ELIGIBILITY CRITERIA:

Site Eligibility Criteria: Participating sites will be those that participated in the CTN-0049 cohort. All 11 of the CTN-0049 sites will participate in study Component 1. Of these, eight will participate in study Component 2. Three will not participate in study Component 2 due to not having adequate numbers of CTN-0049 cohort participants available (attributed to low enrollment and/or high number of deaths) to recruit into Component 2. Refer to section 7.5 for a general description of sites.

Participant Eligibility Criteria: Since all study participants will be recruited from the CTN-0049 cohort, they will be 1) HIV-infected and 2) 18 years of age or older and 3) able to communicate in English. Additionally, to be eligible for Component 1, participants must: 4) provide informed consent, which includes being willing to provide sufficient locator information and to be tested for anti-HCV antibodies and, if antibody positive, tested for active HCV infection and 5) sign a HIPAA authorization form/medical record release form to facilitate medical record abstraction. Finally, to continue on to Component 2, they must: 6) provide sufficient locator information, 7) report living in the vicinity and being able to return for follow-up visits, 8) complete the baseline assessments 9) complete the baseline blood draw 10) screen as HCV antibody positive via study Component 1 and 11) agree to be randomized into Component 2.

TREATMENTS:

Component 1 consists of the rapid HCV test, HCV RNA test for those found to be HCV antibody positive, and brief pre-/post- HCV test information and counseling as described below. After screening HCV antibody positive, participants will continue to Component 2 where they will be randomized to one of two groups: 1) HCV Care Facilitation intervention or 2) Control. These groups are described below.

It is important to note the following for treatment context. Not all CTN-0049 cohort participants will be engaged in HIV primary care when they enroll in the CTN-0064 study. Given this, CTN-0064 will perform HCV screening and testing (in both groups) from the perspective of a local public health department or community-based clinic, not necessarily an HIV primary care clinic. Additionally, the HCV testing, evaluation and treatment landscape has changed dramatically in recent years due to advances in HCV testing and evaluation technologies and advances in HCV treatment regimens which can now halt disease progression and cure HCV in most persons (Shivkumar, Peeling, Jafari, Joseph, Pant Pai, 2012; Cooper, Lester, Thorlund, Druyts, El Khoury, Yaya, et al., 2013; Bacon, Gordon, Lawitz, Marcellin, Vierling, Zeuzem, et al., 2011; Lawitz, Gane, 2013). National recommendations also have changed; in addition to testing high-risk persons routinely, they also now call for expanded one- time HCV testing in “baby boomers.” Given these recent changes and information gathered from Site PIs about local testing and referral practices, our expectation is that the current standard of care for HCV testing, referral, evaluation and treatment varies across our participating sites. Therefore, we have constructed the HCV testing and pre-/post-test information/counseling activities that occur as part of Component 1 to reflect CDC-recommendations (Smith, Morgan, Beckett, Falck-Ytter, Holtzman, Teo, et al., (2012) and National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (U.S.). Division of Viral Hepatitis, Centers for Disease Control and Prevention (CDC), (2015)). Additionally, because we are conducting the initial HCV screening from a public health department clinic or community clinic perspective, this education/information will be delivered in a pragmatic manner in a predominantly didactic format.

Component 1 -- HCV testing: All participants at all 11 sites will complete 1) a computer assisted personal interview or CAPI (capturing history of HIV care, HCV testing and care, substance use and substance use treatment; mental health; demographics; and socio-economic factors), 2) HCV antibody screening (and HCV RNA testing, as applicable), 3) associated pre-/post-HCV test information and counseling, 4) blood specimen collection via venipuncture, and 5) drug/alcohol toxicology screening (via urine analysis). The blood specimens of all participants will be assessed for HIV viral load and CD4 count. The blood specimens for the subset of participants who screen as positive for HCV antibody will be assessed for HCV RNA to determine if their HCV infection is active.

HCV pre-/post-test information/counseling will be delivered via printed educational handout accompanied by a brief, manual-guided, didactic presentation of the information. The handout and presentation will encompass a brief orientation to the testing sequence for identifying current HCV infection and the meaning of possible results. Participants who screen as HCV antibody positive will also receive a reminder card with the date/time of their appointment to return to receive their HCV RNA results. Consistent with CDC recommendations, participants who are identified as having active HCV infection (HCV RNA positive) will be informed when they receive their RNA result about 1) HCV infection and treatment, 2) risk factors for disease progression, 3) preventive self-care and treatment options (e.g., protecting the liver from further harm through reducing or eliminating alcohol consumption, considering Hepatitis A and B vaccination, as applicable, and considering weight management or loss if overweight or obese), and 4) how to prevent HCV transmission. Also, at the time of receiving HCV RNA result, after holding a brief conversation with the HCV-infected participant to ascertain his/her true starting step along the HCV care continuum, study personnel will refer the participant to the next step in the HCV care continuum, i.e., they will refer the participant to the appropriate clinical appointment (e.g., HCV clinical evaluation, HCV care, HIV care). A brief alcohol screening will be conducted, and as needed, HCV-infected participants will be informed about available community resources for medical care including referral to local HIV primary care providers, substance use treatment and other social services and support.

Component 2 -- RCT: As previously mentioned, eight sites will participate in Component 2. Individuals who screen positive for HCV antibody via Component 1 will be randomized into Component 2 and

assigned to one of two groups: 1) HCV Care Facilitation intervention or 2) Control. It is important to note that Components 1 and 2 are overlapping for the eight sites, beginning at the point of randomization just after a participant screens as HCV antibody positive. For this reason, Component 2 encompasses only the post-randomization activities which differ as a function of their random assignment to the two RCT groups. These are: 1) the appointment reminder to prompt HCV antibody positive participants to return for HCV RNA results, 2) the method in which the HCV RNA pre-/post-test information/counseling is delivered and 3) the referral made to HCV RNA positive participants to link them to HCV clinical evaluation. These differences are described below.

Control Group:

1. After screening HCV antibody positive, participants in the control group will have an appointment made by (and with) study staff to receive their HCV RNA results. They will also receive a reminder card with the date/time of their appointment to return to receive their results. They will not receive any other reminders to return for the HCV RNA results.
2. The method in which study personnel deliver the pre-/post-HCV RNA test information/counseling will be didactic.
3. If HCV RNA positive, study personnel will provide a referral to the next step in the HCV care continuum, i.e., they will refer the participant to the appropriate clinical appointment (e.g., HCV clinical evaluation, HCV care, HIV care). The referral will consist of study personnel making an appointment for whatever is the participant's self-reported next step in the HCV continuum. Study personnel will make this attempt only during the study visit in which the participant learns that s/he is HCV RNA positive. If an appointment cannot be scheduled, study personnel will provide a written referral to the participant. If a participant attends the "next step" visit, the participant would be subject to whatever is the local standard of care at that clinic/agency from that point forward. Additionally, regardless of a participant attending the "next step" visit, sites will be encouraged to place the study test results in the participants' non-study medical record (likely at the HIV clinic). This could activate the local standard of care as well. For example, it is possible that if the test results are placed in the HIV clinic record and the participant has not made an appointment for an HCV clinical evaluation in a given timeframe, the HIV clinic would follow-up with the participant to schedule this appointment.
4. No appointment reminder calls or follow-up contact for a missed HCV or HIV appointment will be provided.

Care Facilitation (CF) Group:

1. After screening HCV antibody positive, participants in the intervention group will receive a reminder card with the date/time of their appointment to return to receive their HCV RNA results. Additionally, an HCV care facilitator will work individually with them to motivate them to return to retrieve the results.
2. The method in which study personnel deliver the pre-/post-HCV RNA test information/counseling will employ a motivational interviewing approach described in more detail in section 11.0.
3. If HCV RNA positive, the referral that study personnel provide will be a highly active referral to the next step in the HCV care continuum, i.e., they will work with the participant and with the clinical provider(s) to schedule the appropriate clinical appointment (e.g., HCV clinical evaluation, HCV care, HIV care) for the participant (or assist the participant in doing this). Multiple attempts to schedule the appointment will be made, as needed. The participant will be provided an appointment card for the scheduled clinical appointment. Additionally, the care facilitator will use a motivational interviewing approach to build an effective, working relationship with the participant, conduct a participant needs assessment, conduct a strengths assessment and encourage the participant to identify and use his/her strengths, abilities, and skills to move participants along the HCV care continuum.

4. Appointment reminder calls, texts or e-mails will be provided prior to the participant's HCV/HIV care or other "next step" visit; follow-up contact will be made for missed appointments; and transportation to/from HCV and HIV care and substance use treatment appointments will be provided, as needed.
5. The care facilitator will actively coordinate and link the participant to available community resources (e.g., mental health, legal assistance, housing agencies, food banks, support groups) through scheduling appointments, arranging transportation, and assisting the participant with completing any clinic registration, prior authorization (or other) paperwork that the agencies may require to access services, tests or medications as indicated.
6. Finally, the care facilitator will accompany the participant to key visits (e.g., HCV clinical evaluation, HIV primary care, substance use treatment visits).

SAFETY ASSESSMENT:

For the purposes of this study only adverse events (AEs) and serious adverse events (SAEs) related to the collection of biologic specimens will be captured and reported. The collection of these safety events will begin at the time of the specimen collection and continue through to the completion of that study visit. Psychological distress will be assessed at baseline and both follow-up visits through the Brief Symptom Inventory (BSI) form and monitored as needed per site local SOP. Assessment of suicidal risk will be conducted at baseline and both follow-up visits and collected on the Concise Health Risk Tracking - Self Report (CHRT-SR) form. Medical events related to underlying HIV disease, HCV disease and substance use (including admission to detoxification, elective hospitalizations for substance use treatment, or other substance use treatment) will not be collected as AEs. Instead, they will be collected on study-specific forms and followed throughout the trial. All of these events will be subject to ongoing monitoring by the study Executive Committee, including representatives from the lead nodes, NIDA and the CCC, and will be presented for DSMB review.

OUTCOME ASSESSMENTS:

HIV virologic suppression at the baseline is the Component 1 primary outcome. All-cause mortality will be counted as virologic failure. Forward movement along the HCV care continuum assessed 12 months post-randomization (among Component 2 participants) is the Component 2 primary outcome. To analyze this outcome, the HCV care continuum was broken into several (potentially non-sequential) measurable "steps" as detailed in section 8.1. There are four main secondary outcomes: 1) success at each step in the HCV care continuum, 2) engagement in substance use treatment, 3) HIV viral suppression and 4) long-term outcomes of the CTN-0049 cohort for those who provided consent to participate in CTN-0064. Additional secondary outcomes are described in sections 8.2 and 12.3.

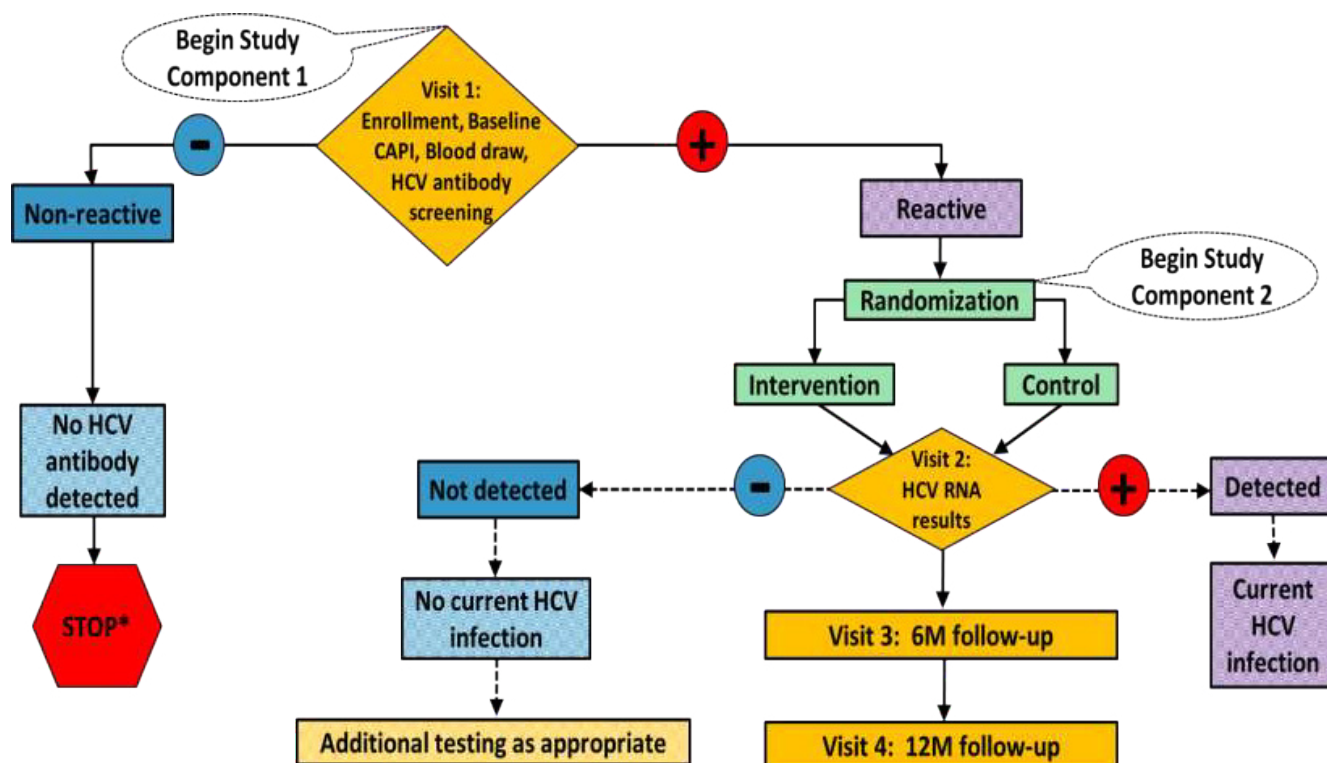
PRIMARY OUTCOME ANALYSIS:

The Component 1 primary outcome variable, HIV virologic suppression, will be measured as a binary variable: plasma HIV viral load (PVL) \leq 200 copies/mL (yes) and PVL $>$ 200 copies/mL or all-cause mortality (no). The Component 2 primary outcome variable, operationalized as the number of steps individuals move forward along the HCV care continuum, will be measured by a review of medical records and other evidence, e.g., bottle of HIV ART medication. Primary analyses will be performed under intent-to-treat (ITT) criteria. Because this study is recruiting only from an existing study population (CTN-0049 cohort), the ability to generalize the study conclusions may be limited. This study limitation will be noted when final results are reported.

REGULATORY ISSUES:

The trial will be conducted in compliance with protocol, International Conference of Harmonization (ICH) guidelines for Good Clinical Practice (GCP), and applicable federal, state, and local regulatory requirements. The study will be registered in ClinicalTrials.gov.

3.0 STUDY FLOW CHART



*Baseline medical record abstraction of most recent HCV antibody and RNA tests should occur as soon as possible after the participant signs the informed consent form. If the participant tests non-reactive on the study HCV antibody test, yet his/her most recent HCV antibody or HCV RNA lab result from the medical record is positive, the study's HCV antibody negative result will be deemed as false negative and the participant will be treated as if his/her study HCV antibody test result was positive, that is a blood sample will be processed for HCV RNA to determine current infection status and the participant will be randomized if other eligibility criteria are met. Without the aforementioned medical record evidence, a participant whose study HCV antibody test is non-reactive will stop study participation after Visit 1.

4.0 INTRODUCTION

4.1 Background

HCV infection is a growing public health concern. The most current National Health and Nutrition Examination Survey (NHANES) data show that an estimated 2.7 million persons are infected in the U.S. (Denniston, Jiles, Drobeniuc, Kleven, Ward, McQuillan, et al., 2014). Because NHANES is a household survey conducted among noninstitutionalized civilians, it excludes high-risk populations such as incarcerated, homeless, and hospitalized individuals, nursing home residents, persons on active military duty, and immigrants. Therefore, the true prevalence of HCV in the U.S. is likely to be much higher (Chak, Talal, Sherman, Schiff, Saab, 2011). More than 10,000 HCV-related deaths occur annually, a mortality rate that surpassed HIV-related deaths in 2007 and is expected to double by 2020 (Burke, Cox, 2010; Ly, Xing, Kleven, Jiles, Ward, Holmberg, 2012). Morbidity and economic costs associated with HCV are expected to increase dramatically in the next 2 decades (Grebely, Raffa, Lai, Kraiden, Kerr, Fischer, et al., 2009). Of the 17,000 incident cases that occur in the U.S. annually (Ditah, Ditah, Devaki, Ewelukwa, Ditah, Njei, et al., 2014), only about one-quarter are symptomatic (Previsani, Lavanchy, 2011). Yet, 70-80% of new infections result in chronic carriage, and 20-25% of persons with persistent infection will develop liver disease that

manifests in cirrhosis, liver failure, or hepatocellular carcinoma (Previsani, Lavanchy, 2011). The strongest risk factor for HCV is (past or present) injection drug use. Estimated HCV prevalence among persons who inject drugs in the U.S. has ranged from 27 – 93%; this wide range is explained, in part, by variation in the duration of injection drug use and age of the populations studied (Chak, E., et al., 2011). Illicit non-injection drug use also has been associated with acquisition of HCV (Fischer, Powis, Firestone Cruz, Rudzinski, Rehm, 2008; Centers for Disease Control and Prevention (CDC), 2012; Macias, Palacios, Claro, Vargas, Vergara, Mira, et al., 2008; Scheinmann, Hagan, Lelutiu-Weinberger, Stern, Des Jarlais, Flom, et al., 2007) and reports of HCV prevalence in non-IDUs range from 2.3 to 35.3%, much higher than in the non-drug using population (Scheinmann, et al., 2007). Alcohol is among the most potent factors causing progression of HCV liver fibrosis (Safdar, Schiff, 2004; Harris, Gonin, Alter, Wright, Buskell, Hollinger, et al., 2001; Corrao, Arico, 1998; Hutchinson, Bird, Goldberg, 2005).

It is estimated that up to 30% of HIV-infected persons are HCV co-infected and the prevalence of co-infection among IDU ranges from 50-90% (Spradling, Richardson, Buchacz, Moorman, Finelli, Bell, et al., 2010; Sulkowski, Thomas, 2003; Vellozzi, Buchacz, Baker, Spradling, Richardson, Moorman, et al., 2011; Macias, et al., 2008). Since the introduction of HIV antiretroviral therapy, HCV-related liver disease has emerged as a leading cause of non-AIDS-related death in this population (Monga, Rodriguez-Barradas, Breaux, Khattak, Troisi, Velez, et al., 2001; Sulkowski, Thomas, 2003; Vellozzi, et al., 2011; Weber, Sabin, Friis-Moller, Reiss, El-Sadr, Kirk, et al., 2006; Lewden, Salmon, Morlat, Bevilacqua, Jougla, Bonnet, et al., 2005). Compared to individuals who are mono-infected with either HIV or HCV, co-infected individuals are at increased risk of (and accelerated progression to) end-stage liver disease, hepatocellular carcinoma, and progression of cirrhosis (Monga, et al., 2001; Kramer, Giordano, El-Serag, 2007; Pineda, Romero-Gomez, Diaz-Garcia, Giron-Gonzalez, Montero, Torre-Cisneros, et al., 2005; Soriano, Vispo, Labarga, Medrano, Barreiro, 2010; Sulkowski, Thomas, 2003; Tedaldi, Baker, Moorman, Alzola, Furhrer, McCabe, et al., 2003; Vellozzi, et al., 2011; Weber, et al., 2006). Co-infected individuals are more likely to have severe psychiatric illness and be active drug users, poor, and homeless creating significant barriers to successful uptake of potentially curative HCV care and treatment (Rosenberg, Drake, Brunette, Wolford, Marsh, 2005). HCV also may increase morbidity and mortality through chronic immune activation and HCV-related pro-inflammatory pathways which exacerbate risk for cardiovascular events, kidney disease, mental illness and cancer in this co-infected population (Soriano, et al., 2010; Zhu, Dhir, Soe, Green, Jiang, 2014). Further, evidence suggests that HCV increases the risk for progression to AIDS-related mortality (Holmberg, Spradling, Moorman, Denniston, 2013). Therefore, identification and treatment of HCV infection among HIV-infected individuals is both recommended and a priority (Vellozzi, et al., 2011).

The changing paradigm of HCV treatment now relies on direct-acting antiviral agents (DAA) to dramatically increase rates of sustained virologic response, SVR (SVR12 = aviremia 12 weeks after completion of antiviral therapy for chronic HCV), and is increasingly focused on replacing interferon-based therapies with all-oral antiviral treatments that are more tolerable, simpler to administer, and more likely to result in an SVR (Afdhal, Zeuzem, Schooley, Thomas, Ward, Litwin, et al., 2013). In some cases, a curative regimen can be taken once per day for as short a duration as eight weeks, with minimal side effects (Pollack, 2013). Concurrently, novel methodologies for non-invasive screening and staging are emerging that promise more timely and efficient diagnosis and treatment (Afdhal, et al., 2013). This coincides with CDC initiatives to simplify testing, improve awareness, and expand HCV screenings to include more than just high-risk individuals. Despite advances in HCV treatments (Afdhal, et al., 2013; Pollack, 2013) and testing technologies, and national guidelines recommending HCV testing for at-risk individuals and “baby boomers”, only one-half of those living with HCV in the U.S. had been diagnosed in 2013, translating to about 1.6 million undiagnosed infected persons (Holmberg, et al., 2013). Approximately one-third of infected persons were referred to care; only 7-11% initiated treatment and 5-6% achieved an undetectable viral load (Holmberg, et al., 2013). These gaps in the care continuum are likely larger

among drug users as most are not referred to HCV care.

Lack of success in linking persons to HCV care can be attributed to numerous patient, provider and systems-level barriers (Centers for Disease Control and Prevention (CDC), 2012; Butt, Paterson, McGuinness, 2008; Conrad, Garrett, Cooksley, Dunne, MacDonald, 2006; Evon, Simpson, Esserman, Verma, Smith, Fried, 2010; Khaw, Stobbart, Murtagh, 2007; Lally, Montstream-Quas, Tanaka, Tedeschi, Morrow, 2008; Lekas, Siegel, Leider, 2011; Swan, Long, Carr, Flanagan, Irish, Keating, et al., 2010; Treloar, Rhodes, 2009; Fraser, Treloar, 2006; Rosenberg, et al., 2005; Alavi, Grebely, Micallef, Dunlop, Balcomb, Day, et al., 2013; Grebely, Genoway, Raffa, Dhadwal, Rajan, Showler, et al., 2008; Johnson, Toliver, Mao, Oramasionwu, 2014; Khokhar, Lewis, 2007). Patient barriers include the disease's perceived stigma given its association with injection drug use (Butt, et al., 2008; Conrad, et al., 2006; Evon, et al., 2010; Khaw, et al., 2007; Lally, et al., 2008; Lekas, et al., 2011; Swan, et al., 2010; Treloar, et al., 2009; Fraser, et al. 2006); the long asymptomatic period that has contributed to diagnosed individuals believing that HCV has little impact on their health (Swan, et al., 2010; Alavi, et al., 2013; Grebely, et al., 2008; Khokhar, et al., 2007) and leading them to avoid or delay evaluation and treatment; and fear of liver biopsy and long-standing negative perceptions of treatments that may persist even in the new era of short-acting, more effective treatments with fewer side effects. Provider and other barriers include consideration of illicit drug use as a contraindication leading to denial of treatment, perceptions that illicit drug users may not adhere to HCV treatment or keep medical appointments, and long waiting periods for medical appointments in addition to the need for repeat HCV treatment visits (Centers for Disease Control and Prevention (CDC), 2012). Systems-level barriers to care include the lack of availability of specialized professionals and high treatment costs (Johnson, et al., 2014). This absence of, or substantially delayed, HCV care negatively impacts health outcomes of infected persons, increases health disparities, and facilitates ongoing HCV transmission. Thus, linkage to care and treatment is crucial to reducing the burden of disease (Centers for Disease Control and Prevention (CDC), 2012). Linkage to HCV care also provides the opportunity to link co- infected substance users to both HIV care and substance use treatment.

Effective strategies are needed for persons who are experiencing barriers to HCV care and the CDC suggests that they may benefit from the replication of effective linkage-to-care models (Centers for Disease Control and Prevention (CDC), 2012). Simulation modeling also has shown that interventions to improve progression along the HCV care continuum such as patient navigation (PN) and integrated case management are likely to be cost-effective strategies (Linaz, Barter, Leff, Assoumou, Salomon, Weinstein, et al., 2014).

Brief interventions (in particular, highly active linkage-to-care strategies) (Gardner, Metsch, Anderson-Mahoney, Loughlin, del Rio, Strathdee, et al., 2005; Molitor, Waltermeyer, Mendoza, Kuenneth, Aguirre, Brockmann, et al., 2006) have successfully linked persons newly diagnosed with HIV to primary care (Gardner, et al., 2005; Craw, Gardner, Marks, Rapp, Bosshart, Duffus, et al., 2008; Bradford, Coleman, Cunningham, 2007). In particular, highly active linkage-to-care strategies (Gardner, et al., 2008; Horstmann, Brown, Islam, Buck, Agins, 2010; Molitor, et al., 2006) such as the use of case managers (or patient navigators) in scheduling appointments, accompanying patients to clinic appointments, and following-up with patients, have been found to be effective. Drs. Lisa Metsch and Carlos del Rio participated in the development, implementation and evaluation of the CDC-funded multisite ARTAS (Antiretroviral Treatment Access Study) intervention, one of few published RCTs that demonstrated the efficacy of a brief PN approach (based on a strengths-based approach) in linking persons (including drug users and non-drug users) recently diagnosed with HIV to primary medical care (Gardner, et al., 2008). A brief PN intervention was compared with standard of care (passive referral) in linking recently diagnosed HIV-infected persons to medical care. Intervention participants received up to 5 sessions with

a PN over 90 days to facilitate linkage. ARTAS II replicated these results and demonstrated intervention effectiveness by using actual clinic personnel (Craw, et al., 2008).

Drs. Carmen Masson and David Perlman (Masson, Delucchi, McKnight, Hettema, Khalili, Min, et al., 2013) evaluated the efficacy of a hepatitis care coordination intervention vs. control to improve linkage to clinical evaluation of HCV among drug users in methadone maintenance. Both the intervention and control participants received 2 individual manual-guided sessions of HIV and viral hepatitis counseling and education reflecting what the CDC recommends for all drug users. The sessions were delivered differently across the 2 groups, with the intervention group receiving the sessions via a motivational interviewing style. Additionally, for a period of 6 months, intervention participants received motivational interviewing and enhanced case management assistance with off-site HCV evaluation. Case managers also assisted intervention participants with accessing psychiatric services, alcohol treatment and other social services. Intervention participants received an average of 11.3 sessions (SD=8.63 median 10 sessions); 65% of participants in the intervention group received an HCV evaluation compared to 37% in the control group (OR=4.10; 95% CI = 2.35, 7.17). HIV/HCV co-infected participants were more likely to receive an HCV evaluation than HCV mono-infected participants (OR=8.02; 95% CI = 2.81, 22.95).

Given the replicated success that the ARTAS intervention has demonstrated with linking HIV-infected individuals to HIV primary care and the success that the hepatitis care coordination intervention demonstrated with linking methadone maintenance patients to an HCV medical evaluation, we will adapt these efficacious interventions to facilitate HIV/HCV co-infected substance users' progression along the HCV care continuum.

5.0 OBJECTIVES

5.1 Primary Objectives

COMPONENT 1 (Long-term CTN-0049 follow-up): This study will examine the long-term primary outcome of the CTN-0049 study, HIV viral suppression.

Primary Hypothesis for Component 1: The rate of viral suppression (plasma HIV viral load of < 200 copies/mL) relative to non-suppression or all-cause mortality in the 3 CTN-0049 study groups will differ from each other at the CTN-0064 baseline visit.

Sub-hypothesis 1: The rate of virologic suppression (plasma HIV viral load of < 200 copies/mL) in the PN+CM group will be greater than that in the TAU group.

COMPONENT 2 (RCT): This study will evaluate the effectiveness of an HCV Care Facilitation intervention in moving HIV/HCV co-infected substance users forward along the HCV care continuum (compared with a Control group).

Primary Hypothesis for Component 2: The number of steps achieved along the HCV care continuum will differ between the two study groups over the 12 months of follow-up.

5.2 Secondary Objectives

Component 1 (Long-term CTN-0049 follow-up)

Using the CTN-0064 baseline data (self-report, medical record abstraction and biological data), the following CTN-0049 primary and secondary outcomes in participants who consented to the CTN-0064 protocol will be re-analyzed to evaluate latent and/or enduring effects of the CTN-0049 interventions:

1. HIV virological suppression, viral load, and CD4 T-cell count changes since CTN-0049 randomization, HIV Primary care visit attendance, ART adherence, rate of hospitalizations, and all- cause mortality.
2. Substance use frequency and severity and substance use treatment engagement and session attendance.
3. Selected mechanisms of action of the CTN-0049 interventions (i.e., mediators of intervention effect).
4. Potential characteristics associated with differential CTN-0049 treatment effectiveness (i.e., moderators of intervention effect).

While not a long-term CTN-0049 outcome, an additional secondary objective for Component 1 is to measure the point prevalence of HCV among the CTN-0049 cohort.

Component 2 (RCT)

The following objectives will be analyzed using the CTN-0064 baseline and longitudinal data (self-report, medical record abstraction and biological data):

1. To evaluate the effect of the Care Facilitation intervention on success at each step in the HCV care continuum.
2. To evaluate the effect of the Care Facilitation intervention on: HIV virological suppression and CD4 T-cell count changes at 12 months post-randomization; visit attendance; ART adherence; rate of hospitalizations; and all-cause mortality.
3. To evaluate the effect of the Care Facilitation intervention on: substance use frequency and severity; and substance use treatment engagement and session attendance.

4. To assess selected mechanisms of action of the Care Facilitation intervention (i.e., mediators of intervention effect).
5. To assess potential characteristics associated with differential treatment effectiveness (i.e., moderators of intervention effect).
6. To evaluate the incremental cost of the Care Facilitation intervention.

6.0 STUDY DESIGN

6.1 Overview

Study Component 2 is a 2-group randomized, prospective trial in which (known HIV-infected) CTN-0049 cohort participants who are determined to be co-infected with HCV will be randomized in 1:1 ratio to a Care Facilitation (CF) intervention vs. Control. Randomization will occur after informed consent, baseline assessments, collection of blood specimens, drug/alcohol toxicology testing and determination that the participant is HCV antibody positive. Participants assigned to the Care Facilitation group will meet with the CF interventionist and will complete up to 12 intervention sessions over the 6-month-long intervention period. Participants assigned to the Control group will receive referrals for further HCV evaluation (if HCV RNA positive) and other services, as needed. Follow-up visits will be conducted at approximately 6 and 12 months post-randomization. Participants who test as HCV RNA negative will be followed in the study per ITT criteria.

6.2 Duration of Study and Visit Schedule

Enrollment, HCV antibody screening, blood collection and baseline interview will ideally occur during a single visit. Additionally, for those determined to be HCV antibody positive, randomization and the initial intervention visit will ideally occur during this initial visit. Recognizing that participants may be recruited at various stages of HIV/HCV-related illness, this may not be possible. To allow maximum flexibility, these activities may occur over more than one visit, as needed, but should be completed as soon as possible after obtaining consent and before the participant attends his/her first HCV clinical evaluation/care appointment. Specific windows will be detailed in an SOP. The intervention duration will be 6 months with sessions ideally occurring twice monthly during the intervention period. However, the timing of intervention sessions will be flexible to meet the participants' needs. Follow-up visits will occur at approximately 6 and 12 months post-randomization. Therefore, the total duration of individual participation in the study is approximately 12 months. The estimated duration of each visit and study component is described in Section 9.0.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

By virtue of participating individuals being recruited from the CTN-0049 cohort, they will be:

1. HIV-infected and
2. 18 years of age or older
3. be able to communicate in English

Additionally, to be eligible for Component 1 they must:

4. provide informed consent, which includes being willing to provide sufficient locator information and to be tested for anti-HCV antibodies and, if antibody positive, tested for active HCV infection
5. sign a HIPAA form / medical record release form to facilitate medical record abstraction

Finally, to continue on to Component 2, they must:

6. provide sufficient locator information
7. report living in the vicinity and being able to return for follow-up visits
8. complete the baseline assessments
9. complete the blood draw¹
10. screen as HCV antibody positive² via study Component 1 and,
11. agree to be randomized in Component 2

7.2 Exclusion Criteria

Individuals will be excluded from participation if they:

1. have significant cognitive or developmental impairment
2. are terminated via site PI decision/discretion with agreement from study LI
3. are currently in jail, prison or any inpatient overnight facility as required by court of law or have a pending legal action which may prevent an individual from completing the study

Additionally, individuals may participate in Component 1, but will be excluded from Component 2 if they:

4. are currently on HCV therapy/medications at baseline based on self-report
5. have completed a course of HCV medications in the last 12 weeks based on self-report.

It should be noted that pregnancy is not an exclusion criterion. Therefore, sites may enroll pregnant women and/or follow-up with already enrolled women who become pregnant after enrollment in the study provided that they have local IRB approval to do so. This study uses the OraQuick HCV Rapid Antibody Test which has not been validated (performance characteristics have not been established) among adolescents under 15 years of age or among pregnant women.

7.3 Participant Recruitment

1 For sites only participating in component 1, if a blood specimen cannot be collected for any reason (e.g., vein is “dry”, participant is lost to follow-up, etc.) or the result of a collected specimen is not available (e.g., not enough specimen drawn, lab processing error, etc.), the study team may abstract and use non-study lab results (collected within 3 months of baseline) for the purpose of evaluating HIV viral load, CD4 and HCV RNA. Blood draws are required prior to randomization for those sites participating in component 2. However, if the result of the collected specimen is not available (e.g., not enough specimen drawn, lab processing error, etc.) and a new sample is not collected, the study team may abstract and use non-study lab results (collected within 3 months of baseline) for the purpose of evaluating HIV viral load, CD4 and HCV RNA.

2 Individuals who test HCV antibody negative via the study test, but who have evidence in the medical record that their most recent HCV antibody and/or HCV RNA test was positive will be considered as HCV antibody positive via study Component 1.

Recruitment

Based on our recent work with this cohort, we conservatively estimate that 90% of the (non-deceased) CTN-0049 cohort will return to take part in study Component 1. Based on the prevalence of HCV among HIV-infected individuals (approximately 30%) and substance users (up to 90% in IDU), we estimate that 20-40% of the CTN-0049 cohort will test HCV antibody positive and be randomized into study Component 2. We estimate that it will take sites approximately 4-5 months to locate and recruit the CTN-0049 cohort participants into this study. Therefore, the average weekly enrollment rate across all 11 sites is expected to be 3-4 participants/week/site. The average weekly randomization rate across all eight sites participating in Component 2 is expected to be 1-2 participants/week/site.

Sites will actively recruit cohort participants into the CTN-0064 study using locator information collected in the CTN-0049 study to contact them. Additionally, sites are encouraged to use passive recruitment strategies such as posting flyers in designated areas where cohort participants are likely to see them (e.g., HIV primary care clinic, hospital from which they were recruited in CTN0049, etc.) and/or posting advertisements in the local paper. Such passive recruitment strategies may result in recruitment of CTN-0049 participants who did not provide consent to be contacted about future studies; these CTN-0049 participants are welcome to enroll in the CTN-0064 study.

In the event that a CTN-0049 cohort participant has moved to a location that is in close proximity to another participating site, it is possible (and preferable) for the individual to be referred/transferred to that site, that is, be enrolled as a participant at the other participating site. Sites should seek local IRB approval to make such recruitment referrals/transfers.

Because CTN-0049 follow-up visits were completed between January 2013 and April 2015, the locator information collected during the CTN-0049 study may no longer be working/active for some participants. Therefore, sites are encouraged to obtain local IRB permission via HIPAA recruitment waiver of authorization and/or waiver of consent and/or other mechanism to abstract CTN-0049 cohort participants' medical records to determine their current contact information for use in recruiting them into the CTN-0064 study.

7.4 Number of Community Treatment Program/Sites

All 11 of the CTN-0049 sites will participate in study Component 1. Of the 11 sites, eight will participate in study Component 2. Three will not participate in study Component 2 due to their having too few CTN-0049 cohort participants (due to low enrollment and/or high number of deaths) to recruit into Component 2.

7.5 Rationale for CTP Selection and Overview of CTP Characteristics

The Community Treatment Programs (CTPs) are those that participated in CTN-0049. They are located in cities that are HIV epicenters, with a high prevalence of substance use among HIV-infected inpatients. Additionally, they are experienced in conducting multi-site research/clinical studies.

In preparation for CTN-0064, our study team conducted a brief, two-part Site Characterization survey in February/March of 2015 of the eight CTN-0049 CTPs that will participate in study Component 2. The goals of the survey were to: 1) describe the current HCV care landscape with respect to HCV clinical evaluation, care and treatment, including where HIV/HCV co-infected patients are tested, evaluated and treated for HCV, and the process and timeframe to receive an HCV clinical evaluation and obtain HCV treatment; and 2) describe physicians' perceptions of barriers to moving HIV/HCV co- infected patients forward along the HCV care continuum.

In one survey, we asked the Site Principal Investigators (who are HIV and/or Infectious Diseases physicians) to work with their local health department or a community-based clinic that provides HCV testing in their community to complete the survey. We received completed questionnaires from seven of eight Site Principal Investigators (PI). Collectively, they reported that HCV testing, referral and pre-/post-test information/counseling practices vary widely across and within their communities, and even within clinics practices are often clinician-specific. Most (five) Site PIs reported that at least some of the departments of health or community-based clinics within their communities provide anti-HCV antibody testing via OraQuick HCV Rapid Antibody Test and most (five) reported that these clinics perform on-site HCV RNA testing. Systems used to routinely remind clients to retrieve their HCV RNA test results varied from no reminder to reminders by phone call, text or e-mail. Additionally, methods of referral to HCV clinical evaluation (for clients with active HCV infection) varied from passive referral to actively scheduling the clinical evaluation appointment for the client. Pre-/post-test information/counseling for the anti-HCV antibody test ranged in duration from 1-30 minutes, varied in format from providing written materials to verbal explanation, and varied in content from addressing basic information about HCV and the meaning of test results to HCV transmission prevention and connection to HCV care. Pre-/post-test information/counseling for the HCV RNA test varied in duration (1-30 minutes), format and content in a similar fashion to that provided for the antibody test.

In a second survey, we asked the Site PIs to work with their local HCV provider(s)/agencies that treat the majority of their HIV/HCV co-infected patients, as needed, to complete the survey. We received results from all eight Site PIs. Collectively, the HIV primary care clinics with which they are affiliated provide HIV primary care to approximately 29,622 unduplicated HIV-infected patients annually of which approximately 6,751 (or 23%) are estimated to be co-infected with HCV (Table 1).

Table 1: Site Characteristics

Site	# HIV Unduplicated HIV-infected Patients/ annually	% HIV/ HCV Co-infected	HIV Clinic Provides HCV Treatment On-site (in HIV Clinic)	HIV Clinic Provides On- site Drug/Alcohol Treatment
1	1400	36%	Yes	suboxone and counseling only
2	1831	33%	Yes	No
3	2500	30%	Yes	Yes
4	2700	30%	Yes	Yes
5	5000	14%	No	Yes
6	5000+	18%	Yes	Yes
7	5300	30%	Yes	No
8	5891	15%	Yes	Yes

HIV Treatment and Referral Processes for New Patients

Not all CTN-0049 cohort participants will be engaged in HIV primary care when they enroll in the CTN-0064 study. Additionally, most of the Site PIs report that clinicians typically want to see that an HIV/HCV co-infected patient is HIV virally suppressed or has demonstrated ability to adhere to HIV antiretroviral therapy (ART) before initiating HCV treatment. Therefore, we view engagement in HIV care as a critical component of the HCV care continuum for HIV/HCV co-infected patients. As such, we queried site PIs about the HIV treatment and referral processes for new patients.

When asked how long it takes for a new patient to be seen for an initial HIV primary care appointment in their affiliated HIV primary care clinic, five Site PIs reported that, on average, it takes less than one

month for a new patient to be seen; three Site PIs reported that it takes 1-2 months for a new patient to be seen. Six Site PIs reported that once a co-infected patient completes an initial HIV primary care visit, it takes an HIV clinician approximately 1-4 weeks to offer an ART prescription; two Site PIs reported that it takes less than 1 week. The majority of Site PIs reported that once an ART prescription is offered, it takes a co-infected patient (for whom ART is clinically indicated) less than 1 week to start taking ART, whether or not the patient is a substance user; two Site PIs reported that it takes 1-4 weeks.

Where HCV Treatment for HIV/HCV Co-infected Patients is provided

Seven of the eight affiliated HIV primary care clinics provide HCV treatment on-site (directly within the HIV clinic). The one that does not provide HCV treatment within the HIV clinic provides HCV treatment co-located on a separate floor from the HIV clinic and on a different clinic day. Of the seven HIV clinics that provide on-site HCV treatment, five have one or more specific HIV clinicians who treat HCV (two also have an on-site viral hepatitis specialist or HCV expert); in two of the HIV clinics all HIV clinicians treat HCV.

HCV Treatment and Referral Processes

When asked about treatment and referral processes, the majority of Site PIs (six) reported that HCV treatment is not offered to everyone with HIV/HCV co-infection (regardless of cirrhosis or stage of liver disease). Seven indicated that it is strongly preferred or required that patients have a suppressed HIV viral load (or be able to adhere to ART) to be offered HCV treatment. Additionally, when asked if patients who use drugs and/or heavy alcohol are offered HCV treatment, six Site PIs responded that “it depends”; some reported that a period of abstinence is required while others indicated that the decision to offer treatment hinges on whether or not the patient is capable of being adherent to medications. Four Site PIs indicated that presence of cirrhosis or advanced fibrosis is taken into consideration when offering HCV treatment (or a referral for HCV treatment).

Site PIs whose affiliated HIV primary care clinics provide HCV treatment on-site, but also refer some co-infected patients out for HCV treatment reported that the average wait time for a co-infected patient to be seen by an off-site HCV treating provider ranges from less than 1 month to up to 5 months. The one Site PI who reported that his/her affiliated HIV clinic does not provide HCV treatment indicated that the average wait time for an HIV/HCV co-infected patient to be seen by an HCV treating provider is less than 1 month.

When asked to estimate the average time that it takes to assess that a patient should be treated (as opposed to being monitored off treatment) once a patient completes an initial visit with an HCV treating provider, five Site PIs reported that the average time is less than 1 month; two reported that it takes 1-2 months and one reported that it takes more than 4 months to assess that a patient should be treated.

When asked about the diagnostic tests performed as part of the HCV clinical evaluation provided to HIV/HCV co-infected patients prior to initiating HCV treatment, all eight Site PIs reported obtaining HCV genotype and HCV viral load before initiating HCV treatment. Six Site PIs reported obtaining an ultrasound for assessment of liver cirrhosis for 5 – 100% of co-infected patients; six reported obtaining a FibroScan (transient elastography) for 25 – 100% of co-infected patients; six reported obtaining a FibroSURE for <5 - 85% co-infected patients; five reported obtaining a liver biopsy for <5 - 60% of co-infected patients; five reported obtaining a FIB-4 (fibrosis-4 index); and four Site PIs reported obtaining an APRI (aspartate aminotransferase/platelet ratio index).

Again, specific criteria used in deciding if HCV treatment is offered (or if a referral for HCV treatment is made) largely includes that the patient is HIV virally suppressed or has demonstrated the ability to adhere to ART before initiating HCV treatment. While less of a deciding factor, some Site PIs reported that active substance use (particularly injection drug use) also may be considered in that they want to ensure that the patient is able to adhere to the treatment regimen.

Four Site PIs reported that once it is assessed that a co-infected patient should be treated (as opposed to being monitored off treatment), the average time that it takes the treating clinician to offer HCV treatment is less than one month; three Site PIs reported that it takes 1 – 2 months; and one Site PI reported that the average time it takes the treating clinical to offer HCV treatment is 3 – 4 months.

The average wait time with an HCV treating provider before a co-infected patient starts HCV treatment once it has been assessed that a patient should be treated (as opposed to being monitored off treatment) was reported by four Site PIs to be less than one month; three Site PIs reported that the average wait time is 1 – 2 months; and one Site PI reported an average wait time of 3 – 4 months.

The average wait time to get HCV medications as reported by seven Site PIs is 1 – 2 months; one Site PI reported that it averages 2 – 3 months. All Site PIs reported that they work with “specialty pharmacies,” pharmaceutical companies or utilize “Compassionate Use” to secure HCV medications for their co-infected patients.

Few Site PIs reported that HIV/HCV co-infected patients are offered Pegylated interferon + ribavirin + one oral direct-acting antiviral agent (DAA). One Site PI reported that this regimen is offered to 70- 80% of co-infected patients; another reported that it is offered to less than 3%. These Site PIs estimated that only 10% of patients who are offered this regimen actually start it and of those who start it only 10% are estimated to complete the regimen.

Six Site PIs reported that 85-100% of co-infected patients are offered two oral DAAs. Most estimated that 90-100% of patients who are offered this regimen actually start it (one Site PI estimated that 66-70% start it) and of those who start the two oral DAA regimen, 90-100% complete it; one Site PI estimated that 80% complete this regimen.

Insurance Coverage among HIV/HCV Co-infected Patients

When asked about insurance coverage for two oral DAAs, five PIs indicated that most co-infected patients do have insurance (private or Medicaid) that covers the use of two oral DAAs; two PIs indicated that most do not have this coverage; and one PI indicated that coverage is “to be determined” because the insurance plans are currently defining eligibility criteria. Further, Site PIs reported that most insurance plans and/or Medicaid have restrictions or special circumstances regarding their coverage of two oral DAAs such as the patient needing to meet clinical eligibility (e.g., have evidence of advanced fibrosis or cirrhosis) or demonstrate being drug free via negative urine toxicity screen. Six PIs reported that the above insurance also covers pegylated interferon + ribavirin + one oral DAA, again, typically for patients with advanced liver disease.

Barriers to Providing HCV Treatment to HIV/HCV Co-infected Patients

The most frequently identified (recognized by seven Site PIs) patient-level barriers to linking HIV/HCV co-infected individuals to HCV treatment were: patients not showing up to scheduled appointments, mental illness interfering with follow-up, substance abuse interfering with follow-up, and other competing life priorities interfering with follow-up. Financial reasons (e.g., cost of co-pays, medications, etc.) and patients not believing their HCV infection is a health risk also were frequently identified as patient-level barriers (recognized by six and four Site PIs, respectively).

The most frequently identified clinic/system-level barriers to linking HIV/HCV co-infected individuals to HCV treatment were: insurance not covering two oral DAAs (recognized by five Site PIs); too much paperwork (recognized by four Site PIs); and not enough clinic appointments, clinic staff and/or clinicians tending to avoid prescribing HCV medications to known substance users (unless they show evidence of cutting down or going into rehab), cost (e.g., co-pays, medication costs), and insurance covering interferon/ribavirin, but providers preferring to wait to see if oral DAAs become more widely available (all recognized by three Site PIs).

8.0 OUTCOME MEASURES

8.1 Component 1 - Primary Outcome Measure

The Component 1 primary outcome variable is binary: HIV viral suppression (≤ 200 copies/ml), as determined by blood draw (or medical record abstracted non-study lab result, as needed) at the baseline visit versus presence of viral load > 200 copies/ml or death (all-cause mortality).

8.2 Component 2 - Primary Outcome Measure

As part of Component 1, all participants will be screened for HCV antibody and (if antibody positive) assessed for active HCV infection for the purpose of documenting baseline HCV prevalence in the sample. We recognize, however, that at the time participants enter the study, some participants may already be aware of their active HCV infection and (potentially) have advanced further through the HCV care continuum. To accurately assess the Component 2 primary outcome, we will determine the participant's true start point/step on the HCV care continuum. For the purpose of analyzing the Component 2 primary outcome, we will devise an algorithm to determine the start step that relies on medical record data (including pharmacy data, as applicable). The algorithm will be detailed in the Statistical Analysis Plan. Despite following an algorithm, there may be times when our team does not reach consensus about the true start step. Such cases will be referred to an independent committee for adjudication.

Because the Component 2 primary outcome is operationalized as forward movement along the HCV care continuum, we have identified several (not necessarily sequential) measurable "steps" along this continuum, each contributing to the coding algorithm for the Component 2 primary outcome variable. Specifically, the Component 2 primary outcome variable is calculated as the number of steps completed on the HCV care continuum by the 12 month follow-up. The number of steps possible for a given case may depend on the number of steps already completed by the baseline assessment³. It is important to note that because our entire study sample is HIV-infected, HIV treatment engagement is considered relevant to HCV treatment. Therefore, we include two HIV-related steps (2 and 3) within this continuum. In the event that our algorithm is unclear on whether or not a particular Component 2 outcome was achieved post-randomization, it will be adjudicated by an independent committee at the end of the trial.

Note: All steps measured via medical record abstraction unless stated otherwise.

1. Receipt of HCV RNA result -- result received within 3 months after enrollment (from study test or non-study test conducted after enrollment) measured via study CRF (HRR, AUH)
2. HIV primary care visit -- completion of 1 medical visit in which HIV is addressed or 1 visit with an HIV or infectious disease provider (excluding visits in which only HCV is addressed) (AUM)
3. Initiated HIV ART -- presence of one or more of the following (ARS, ARV):
 - a. Participant supplies his/her bottle of HIV ART medication with an active date on it OR
 - b. Presence of clinician documentation that the participant started HIV ART (e.g., clinician note, medication log, prescription, etc.) OR
 - c. Evidence in pharmacy record that HIV ART was dispensed
4. HCV evaluation -- presence of one of the following (AUH, AUL):
 - a. clinician note documenting evaluation of liver status/assessment of liver disease status OR
 - b. liver biopsy OR

³ Calculation of steps 2 and 3 depends on assessed start step (number of steps already completed by the baseline visit) according to step-specific timeframes outlined in the Statistical Analysis Plan.

- c. FibroScan OR
- d. sero-marker with score (e.g., FIB-4 or FibroSURE or APRI or FibroSpect II)
- 5. HCV treatment offered and declined or prescription process initiated (AUH):
 - a. Presence of a clinician note stating that participant should be on HCV medication, but participant declined OR
 - b. Evidence that the process for securing a prescription for HCV treatment was started (e.g., letter of compassion written, patient statement for insurance provider regarding not using drugs/alcohol written, prescription, etc.)
- 6. HCV treatment initiated (AUH, HCM):
 - a. Presence of clinician documentation that the participant started HCV medication (e.g., clinician note, medication log, etc.) OR
 - b. Evidence in pharmacy record that HCV medication was dispensed
- 7. Course of HCV treatment completed (AUH, CLD, HCM):
 - a. Presence of clinician documentation that the participant completed course of HCV medication (e.g., clinician note, medication log, etc.) OR
 - b. Evidence in pharmacy record that enough HCV medication was dispensed (AUH) to meet the prescribed duration of treatment (HCM) AND evidence of an undetectable HCV viral load (AUH, CLD) following the calculated treatment completion date
- 8. SVR12 (sustained virologic response) achieved at 12 or more weeks after treatment completion (AUH, CLD):
 - a. Presence of clinician documentation that the participant achieved SVR12 (e.g., clinician note) OR
 - b. Evidence of treatment completion followed by an undetectable HCV viral load at least 12 weeks after treatment completion.

8.3 Secondary Outcome Measures

Secondary outcomes include those related to HCV, those related to HIV and those related to substance use. These will be used to evaluate the effect of the Care Facilitation intervention. For each secondary outcome listed, the data type and source are indicated in parentheses.

HCV Related Secondary Outcome (Component 1)

Point prevalence of HCV among the CTN-0049 cohort (binary; CLD/medical record abstraction, AUH)

HCV Related Secondary Outcomes (Component 2)

- 1. Specific Steps on the HCV Care Continuum
 - a. Receipt of HCV RNA result (binary; self-report, AUS, HRR; medical record abstraction, AUH)
 - b. HCV evaluation (binary; self-report, AUS/medical record abstraction, AUH, AUL) with an indicator of any of the following through self-report/medical abstraction: liver function assessment by clinician (note that documents evaluation), liver biopsy, FibroScan, sero-marker with score (FIB-4, FibroSURE, APRI, FibroSpect II)
 - c. HCV treatment offered (binary; self-report, AUS/medical record abstraction, AUH)
 - d. HCV treatment initiation (binary; self-report, AUS/medical record abstraction, AUH, HCM)
 - e. HCV treatment completion (binary; self-report, AUS/laboratory assay, CLD/medical record abstraction, AUH, HCM)

- f. Sustained virologic response (binary; laboratory assay, CLD/medical record abstraction, AUH/self-report, AUS)
2. HCV-specific mortality (binary; medical record abstraction, DTH)

HIV Related Secondary Outcomes (Components 1 and 2)

1. HIV viral suppression (suppression binary defined as viral load \leq 200 copies/ml (yes) vs. viral load $>$ 200 copies/ml or all-cause mortality (no); viral load continuous; laboratory assay, CLD/medical record abstraction, AUM)
2. Initiated ART (binary; prescription bottle, ARS/medical record abstraction, ARV)
3. CD4 cell count (continuous; laboratory assay, CLD/medical record abstraction, AUM)
4. HIV care visit attendance (count; self-report, AUS/medical record abstraction, AUM)
5. Medication adherence (count, binary; self-report, ADH)
6. Inpatient hospitalizations (count; self-report, SUD, SDB/medical record abstraction, SUD, SDB)
7. All-cause mortality (binary; self-report/medical record abstraction/National Death Index, DTH)
8. HIV-related mortality (binary; medical record abstraction or National Death Index, DTH)

Substance Use Related Secondary Outcomes (Components 1 and 2)

1. Substance use frequency (count; self-report ASD and binary; self-report, SUB/; laboratory assay, ETG, UDS)
2. Substance use severity (continuous, self-report, DST, AUD, AUC)
3. Substance use treatment engagement (binary; self-report, ASD, ADM, SUD, SDI)
4. Number of alcohol and drug treatment sessions (count; self-report, SUD)

8.4 Tertiary Analyses: Mediators and Moderators of Outcomes

1. HIV Viral Suppression and HCV Care Continuum Moderators: psychological distress (continuous; BSI questionnaire), housing instability (categorical; ADM questionnaire), food insecurity (continuous; HFI questionnaire), health literacy (continuous; HLT questionnaire), medical mistrust (continuous; MMT questionnaire), perceived health status (continuous; SFM questionnaire), renal and liver function status (continuous; medical record abstraction, AUM).
2. HIV Viral Suppression and HCV Care Continuum Mediators: medication self-efficacy (continuous; separate questionnaires for HIV [HTA] and HCV [HSE]), physician-patient relationship (continuous; PPR, PPH questionnaires), access to care (continuous; ATC questionnaire), social support (continuous; STS questionnaire), substance use (binary; SUB and continuous; ASD questionnaire, DAST10 [DST], modified AUDIT [AUD, AUC]), psychological distress (continuous; BSI questionnaire), perceived health status (continuous; SFM questionnaire).
3. CD4 Count Moderators: HIV viral suppression status (binary; CLD, AUM), HIV viral load (continuous; CLD, AUM).
4. HCV Specific Mediators/Moderators: HCV knowledge (continuous; HKQ questionnaire), HCV stigma (continuous; EIS questionnaire), community cohesion (continuous; CCS questionnaire), measure of unmet need for drug/alcohol treatment (continuous; neighborhood level, LIF), concentrated disadvantage (continuous; neighborhood level, LIF), racial/ethnic residential segregation (continuous; neighborhood level, LIF).
5. HIV Specific Mediators/Moderators: HIV-related cognitive problems (continuous; IDS).
6. Drug Use Mediators/Moderators: Readiness for drug treatment (continuous; RST Questionnaire), social support (continuous; STS Questionnaire), measure of unmet need for drug/alcohol treatment (continuous; neighborhood level, LIF).

9.0 STUDY PROCEDURES

9.1 Study Enrollment Procedures

As previously outlined in section 2.0, all CTN-0049 cohort participants (all adults who were randomized into the CTN-0049 study and who were not documented as dead and who provided consent to be contacted about future studies in the CTN-0049 database) will be actively recruited into the CTN-0064 study. If interested in taking part in the study, they will be invited to attend a baseline visit. At the baseline visit, they will be enrolled in the study prior to participating in study activities. Enrollment consists of providing written informed consent for study participation, passing a consent quiz, signing a HIPAA authorization form to facilitate medical records abstraction to verify recent HCV testing and care/treatment (as applicable) and recent HIV care and completing a locator information form. After signing the consent and HIPAA authorization/medical records release form(s), participants will be offered copies of the form(s) to keep for their records. Re-enrollment of an individual who initially screen fails will be permitted, but may be restricted (per Site PI decision/discretion with agreement from study LI) to those individuals who initially reported recent exposure to HCV.

Informed Consent Process

Study procedures and the potential risks and benefits of participating in the trial will be explained. We also will obtain permission to audio record intervention sessions for intervention fidelity monitoring purposes. Given the multi-site nature of the trial, it is possible that ancillary studies will be proposed before or after the study begins recruitment. For this reason, during the informed consent process, we also will seek permission to contact the participant in the future about other study opportunities. Staff will be available to answer questions about the consent form while participants are reviewing it. Prior to signing the consent form, the participant must pass a brief consent quiz to illustrate comprehension of the study activities. After passing the quiz and signing the consent form, participants will be offered a copy of the forms to keep for their records. The informed consent process and quiz will take approximately 20 and 5 minutes to complete, respectively.

HIPAA Authorization and Medical Record Release Forms

Participants will complete HIPAA Authorization and/or medical record release forms throughout the study (as applicable) to grant permission to study staff to review their HCV and HIV care and treatment medical records. After an individual provides informed consent for screening and HIPAA authorization, records may be reviewed back to the time of CTN-0049 randomization to ascertain information about HIV and HCV care and treatment that occurred since their participation in CTN-0049. Some records may be reviewed back even further to ascertain previous HCV testing and genotype/subtype. The purpose of medical records review is to document information needed to evaluate primary and secondary outcomes, including determining which “steps” on the HCV care continuum participants may have completed prior to their CTN-0064 study participation. Specifically, we will abstract medical record information to corroborate and/or supplement participants’ self-report of information including, but not limited to the following: HCV testing, HCV clinical evaluation (e.g., clinical information concerning liver function, renal function, etc.), utilization of HCV related diagnostic tests, HCV care and treatment, utilization of HIV primary care and treatment, HIV viral load and CD4 count, and filling of HIV medication prescriptions. Other clinical information concerning participants’ medical and psychiatric status (e.g., evidence of end stage/decompensated liver disease [ascites, encephalopathy, hepatocellular carcinoma], diagnosis of cirrhosis, diagnosis of any opportunistic infections/cancers, prescriptions for oral mood stabilizers or antipsychotic medications) will be abstracted to enable investigators to better characterize comorbidities of the study sample and to use as covariates in analyses. Records review/abstraction will occur

throughout the study (as needed) and up to 18 months post-randomization. Completion of the HIPAA and/or medical record release form(s) will take approximately 10 minutes.

Because approximately 11% of the CTN-0049 study sample was deceased by the end of the CTN- 0049 study, the investigative team expects that some CTN-0049 participants will have died since completing that study. Because all-cause, HIV-specific and HCV-specific mortality are all CTN-0064 secondary outcomes, the investigative team is interested in gathering as much data as possible on CTN-0049 study participants who died after completing CTN-0049. This includes all CTN-0049 participants who died prior to being enrolled in the present (CTN-0064) study as well as those who die post-enrollment. Therefore, sites are encouraged to obtain local IRB permission via HIPAA authorization – Investigator Certification for Research with Decedent Information (or other mechanism, as needed) to perform medical record abstraction for all CTN-0049 participants who died prior to enrolling in the CTN-0064 study. Section 164.512 of the Privacy Rule also establishes specific PHI uses and disclosures that a covered entity is permitted to make for research without an Authorization, a waiver or an alteration of Authorization, or a data use agreement. These limited activities are the use or disclosure of PHI preparatory to research and the use or disclosure of PHI pertaining to decedents for research. Case report forms to be completed for these decedents are the “general assessments” (medical record) and service utilization emergency department and inpatient hospital modules (medical record) listed at the bottom of the Assessments Timetable in section 10.4 of this protocol which ascertain information about access to and utilization of HIV care, HCV care, liver care and medications to treat HIV and HCV. The Death case report form will also be completed. Additionally, a National Death Index search will be performed and include decedents as well as all cohort participants who were lost to follow-up, i.e., those who were never located for enrollment into CTN 0064 and those who enrolled in CTN 0064 yet did not return for follow-up visits.

Locator Information Form

After completing the informed consent process, participants will complete a locator information form which will be used to contact them to remind them of follow-up visits (as applicable), to locate participants who cannot be found (as needed), and to notify participants of the overall study results at the conclusion of the study (as desired). For participants who provide informed consent to be contacted about future studies, the locator information form will also be used to find and contact them in the future for this purpose. When completing this form, participants will provide their names, addresses, and telephone numbers as well as contact information for at least one other person. Permission will be requested to obtain locating information from additional agencies and publicly accessible databases or search engines including, but not limited to, Medicare/Medicaid and social security offices, department of motor vehicles, local jail logs, white pages, Facebook, etc. Locator information will be updated at the 6-month follow-up visit and at any other time during the study, as needed. The locator information form will take approximately 15 minutes to complete.

9.2 Baseline Interview

After the enrollment process is complete and a brief rapport-building discussion between the interviewer and participant has taken place, the study interviewer will prepare a new data record for the participant and the baseline assessments will be administered through CAPI. The Site PIs have experience in the use of CAPIs from their previous studies. The CAPI system displays each assessment question on a computer monitor, allowing the interviewer to read the questions and then enter the participants' responses directly into the computer. The baseline assessments will include, but not be limited to questions on participant demographics; prior HCV testing, evaluation, and utilization of HCV care and treatment (as applicable); HIV care and treatment; HIV medication adherence; substance use and

treatment; and co-morbid conditions such as depression, etc. (see section 10.0 for a detailed description and timetable of measures). The baseline CAPI will take approximately 1-2 hours to complete.

9.3 HCV Screening AND Testing for Active HCV

As outlined in section 2.0, HCV screening and testing will be performed from a health department clinic or community clinic perspective. The CDC-recommended testing sequence for identifying current HCV infection consists of initial HCV antibody testing (either rapid or laboratory-conducted assay) followed by HCV RNA assay for all positive antibody tests (Centers for Disease Control and Prevention (CDC), 2013). For study efficiency, we will perform initial HCV antibody testing via the OraQuick HCV Rapid Antibody Test. It is the only FDA-approved point-of-care test (POCT) for use with whole blood samples obtained through venipuncture or fingerstick. Additionally, the FDA granted a Clinical Laboratory Improvements Amendments (CLIA) waiver for the test in 2011, indicating that the test is easy to perform with a negligible chance of error. Further, its sensitivity and specificity are high and comparable to other laboratory-conducted assays (Khuroo, Khuroo & Khuroo, 2015; Cha et al., 2013; Shivkumar et al., 2012).

One review of 18 meta-analyzed studies evaluating the diagnostic accuracy of several rapid diagnostic tests (RDTs) and POCTs to screen for HCV found that POCTs of blood (serum, plasma, or whole blood) have high accuracy; the pooled sensitivity in POCTs of whole blood was 98.9% ([95% CI, 94.5% to 99.8%]) and the pooled specificity was 99.5% ([CI, 97.5% to 99.9%]) (Shivkumar, et al., 2012). A more recent review and meta-analysis of 30 POCTs to screen for HCV (in serum, plasma, whole blood or oral fluid) suggested high pooled accuracy for all studies; the overall pooled sensitivity, specificity, positive likelihood-ratio, negative likelihood-ratio and diagnostic odds ratio for all tests were 97.4% (95% CI: 95.9–98.4), 99.5% (99.2–99.7), 80.17 (55.35–116.14), 0.03 (0.02–0.04), and 3032.85

(1595.86–5763.78), respectively (Khuroo et al., 2015). Some studies not included in these meta-analyses have found lower sensitivities and specificities in various high and low risk populations (Scalioni et al., 2014; Fisher et al., 2015). Additionally, these and several studies have demonstrated that the OraQuick HCV Rapid Antibody Test has the highest sensitivity and specificity compared to other rapid screening assays for the detection of antibodies to HCV (Smith et al., 2011(a); Scalioni et al., 2014; Khuroo et al., 2015; Fisher et al., 2015). Of seven POCTs evaluated in their meta-regression model, Khuroo et al., (2015) found that OraQuick had the highest test sensitivity and specificity and even performed better than a third generation enzyme immunoassay in seroconversion panels (Khuroo et al., 2015).

The OraQuick test is read between 20 to 40 minutes after sample collection and the result is either reactive or nonreactive. Participants whose test result is reactive will undergo subsequent testing to confirm whether they have current/active vs. resolved HCV infection. HCV RNA in blood is a marker for HCV viremia and is detected only in individuals who have current HCV infection. Therefore, a quantitative HCV RNA test will be performed to determine if the participant whose HCV rapid antibody test was reactive has current/active HCV infection. Adapted from the CDC's guidance on HCV testing for clinicians and laboratory staff (Centers for Disease Control and Prevention (CDC), 2013), Table 2 provides an overview of the interpretations of the HCV antibody test result and (as applicable) the HCV RNA test result and further action (or next steps).

Table 2: Interpretation of results of tests for Hepatitis C virus (HCV) infection and further actions

Test outcome	Interpretation	Further action
HCV antibody nonreactive	No HCV antibody detected	<p>Explain HCV antibody test results. Specimen can be reported as nonreactive for HCV antibody.</p> <p>Because there is a small chance that the result could be false negative and the study calls for retrospective medical records abstraction, study personnel will perform baseline abstraction as soon as possible to determine if there are any previous positive HCV antibody or HCV RNA results in the medical record. If not, no further action is required. Participant does not qualify for study Component 2.</p> <p>If the most recent HCV antibody and/or HCV RNA result from the medical record is positive, then an HCV RNA test to identify current infection will be performed and the participant (if from an RCT site) will be randomized into study Component 2.</p> <p>If recent HCV exposure (within past 6 months) in person tested is suspected, advise the participant to be re-tested in the community; provide a list of local testing agencies.</p> <p>For persons who are immunocompromised, testing for HCV RNA can be considered; referrals for future testing in the community may be provided.</p>
HCV antibody reactive	Preliminary positive/ Presumptive HCV infection	Explain HCV antibody test results. A repeatedly reactive result is consistent with current HCV infection, or past HCV infection that has resolved, or biologic false positivity for HCV antibody. An HCV RNA test to identify current infection will be performed and the participant will be randomized..
HCV antibody reactive HCV RNA Detected	Current HCV infection	Explain results of HCV RNA test. Provide participant with appropriate counseling and link person tested to medical care and treatment. The Care Facilitation intervention group participants will receive post-test information/counseling and active linkage to HCV care as described in section 11.0; Control group participants will receive post-test information/counseling and referral to HCV care as described in section 11.0.
HCV antibody reactive HCV RNA not detected	No current HCV infection	<p>Explain results of HCV RNA test. Participant has cleared the virus and is considered HCV negative. No further action required in most cases. The participant will continue to participate in Component 2.</p> <p>In certain situations[§] follow up with HCV RNA testing and appropriate counseling in the community is recommended.</p>

[§] If the person tested is suspected of having HCV exposure within the past 6 months, or has clinical evidence of HCV infection.

With up to 690 CTN-0049 cohort participants being tested, some biologic false positive and false negative HCV antibody results may occur. Several studies have examined the association between HIV positivity and false negative and/or false positive rapid test results and found mixed results. Some have shown an association between HIV positivity and false rapid results with certain HCV rapid tests (e.g., Chembio and MedMira), but did not show this association using the OraQuick test (Smith et al., 2011(a); Smith et al., 2011 (b); Cha et al., 2013; Khuroo et al., 2015). One study (Fisher et al., 2015) showed an association between HIV positivity and false negative HCV antibody results in seven out of eight POCTs, including the OraQuick test; the authors suggest that the association may be due to a reduction in antibody production.

During the study consent process, HCV testing consent process (as applicable) and the testing and counseling sessions (in both groups), participants will be advised of the possibility and meaning of false positive and false negative antibody results. Study sites will follow the local/state standard for reporting positive HCV results, and participants will be notified of these guidelines as part of the informed consent process. Additionally, participants receiving an HCV antibody-positive and HCV RNA-negative test result will be referred for risk-reduction counseling and testing in the community.

Because the study performs retrospective medical record abstraction from the point of baseline, sites will have a unique opportunity to determine if the study HCV antibody test result is false negative. Therefore, baseline medical record abstraction of previous HCV antibody and HCV RNA tests will occur as soon as possible after the participant signs the informed consent form. If the participant tests non-reactive on the study HCV antibody test, yet has a positive HCV antibody or RNA lab result in the medical record, the study's HCV antibody negative result will be deemed as false negative and the participant will be treated as if his/her study HCV antibody test result was positive; that is a blood sample will be processed for HCV RNA to determine current HCV infection status and (if an RCT site participant) the participant will be randomized if other eligibility criteria are met. Ideally, the determination of the false negative result will occur during the baseline visit. If baseline abstraction cannot occur during the baseline visit and positive HCV RNA lab results are later abstracted, the participant will be asked to return to the study for collection of blood for HCV RNA processing (as needed) and (if an RCT site participant) randomization if other eligibility criteria are met.

9.4 Collection of Biologic Specimens

We will collect blood specimens⁴ at the baseline, 6-month and 12-month follow-up visits to 1) determine active HCV infection (at baseline) 2) evaluate the HCV SVR primary outcome (as applicable) 3) evaluate the secondary outcome, HIV virologic suppression, and 4) measure CD4 count. We will also perform toxicology screening (via urine evaluation) during the baseline and follow-up visits to characterize substance use over time. CD4, viral load and toxicology results will be filed in the study record. Additionally, sites are encouraged to file a copy of the results in participants' non-study medical records.

For maximum flexibility and to minimize participant burden related to time dedicated to the baseline visit and number of times that blood is drawn (via fingerstick and phlebotomy), sites may collect the baseline blood specimen prior to or as part of performing the HCV rapid antibody test. If the baseline blood specimen is collected prior to the HCV rapid antibody test result being available, the "extra" blood for

⁴ For sites only participating in Component 1, in the event that a blood specimen cannot be collected for any reason (e.g., vein is "dry", participant is lost to follow-up, etc.) or the result of a collected specimen is not available (e.g., not enough specimen drawn, lab processing error, etc.), the study team may abstract and use non-study lab results (collected within 3 months of baseline) for the purpose of evaluating HIV viral load, CD4 and HCV RNA. Blood draws are required prior to randomization for those sites participating in Component 2. However, if the result of the collected specimen is not available (e.g., not enough specimen drawn, lab processing error, etc.) and a new sample is not collected, the study team may abstract and use non-study lab results (collected within 3 months of baseline) for the purpose of evaluating HIV viral load, CD4 and HCV RNA.

HCV RNA processing will be drawn at the time that the blood for HIV viral load and CD4 count is drawn. If the rapid antibody test result comes back as nonreactive, the blood drawn for HCV RNA processing will be discarded per sites' local procedures.

9.5 Randomization

Participants will be randomized in a 1:1 ratio to one of the two treatment groups. Randomization will be stratified by site, CTN-0049 treatment assignment, and self-report of currently being in HIV care and taking HIV ART (i.e., participant has attended an HIV primary care visit within the last 6 months [yes/no] and participant reports currently taking HIV ART [yes/no]; in care and on ART defined as "yes" on both conditions). The randomization procedure will be conducted in a centralized process through the Data and Statistics Center (DSC). Specifically, the DSC statistician will create randomization schedules for each site. The randomization schedules will be of a randomized-block nature to ensure relative equality of assignment across condition during the recruitment period. The block size also will be randomized to prevent the potential for study personnel guessing the next assignment which sometimes happens with a fixed block-size. After the participant is determined to be HCV antibody positive and meet other protocol-specified eligibility criteria, a designated study staff member will perform the randomization. Randomization for each participant is done over the Internet using the Enrollment Module in Advantage eClinical.

The DSC statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. If a participant drops out of the study at any point after randomization, the randomization slot will not be re-allocated to a new patient due to the intent-to-treat nature of the study.

9.6 Treatment

Study Interventions

The two treatment groups are: 1) Care Facilitation intervention and 2) Control. Details of the two groups are described in Section 11.0.

Discontinuation

All participants will be followed for the duration of the study (12 months) unless they withdraw consent, die, or the investigator or sponsor decides to discontinue their enrollment for any reason. Reasons for the investigator or sponsor terminating a participant from the study may include, but are not limited to, the participant becoming a threat to self or others, lack of funding, or DSMB early termination of the study for safety or effectiveness reasons.

Follow-Up

Follow-up visits will be conducted at approximately 6 and 12 months post-randomization. Specific windows will be detailed in an SOP prior to study commencement. Follow-up visits will involve CAPIs and the collection of blood and urine. Ideally, all follow-up visits will take place at designated research offices/locations at each participating site. However, if it is not possible for participants to come to the designated research location, follow-up visits may be conducted in the field at mutually agreed upon locations (e.g., participant's home, clinic, etc.). If an in-person visit is not possible, the visit(s) may be conducted by telephone after obtaining Lead Team permission. Compensation for telephone and other incomplete visits (e.g., those in which biological specimens are not collected) will be pro-rated. While permissible, completing follow-up visits by telephone is discouraged (last resort) because

biologic outcome data and new medical record releases to facilitate abstraction of outcome data (e.g., completion of HCV care continuum steps) may be missing in these cases. To minimize missing data due to telephone interviews (or other reasons), sites may, with local IRB permission, pay for the participant to have his/her blood drawn at a local lab and/or pay for the shipment of signed medical record releases or medical records.

In the event that a participant moves to a location that is in close proximity to another participating site, it is possible (and preferable) for the participant to be transferred to that site (i.e., be enrolled as a participant at that site) to complete remaining study activities in person. Sites may seek local IRB approval to make such participant transfers.

9.7 Compensation

Participants will be compensated for their time and effort for baseline and follow-up visits. Participants may receive a maximum amount of up to approximately \$130 (or amount approved by Lead Team and local site IRB) for completing the following non-intervention related activities: baseline visit (including HCV rapid screening test), 6-month follow-up visit, 12-month follow-up visit, and up to two check-in contacts in which the participant contacts study staff prior to follow-up visits to verify locator information and confirm his/her visit appointment. The specific amounts and format (e.g., cash, debit card, voucher, etc.), and distribution schedule will be determined by the participating site with the approval of the Lead Investigator or co-Lead Investigators and the corresponding IRB(s) of record. Participants in the Care Facilitation group may receive up to approximately \$120 (or amount approved by Lead Team and local site IRB) for completing up to 12 intervention sessions. Additionally, they may be transported to/from intervention visits as described in section 11.0.

10.0 STUDY ASSESSMENTS AND INSTRUMENTS

The selected assessment battery attempts to balance the value of comprehensive data against the costs of data collection in terms of staff time, financial cost, and assessment reactivity. Therefore, assessments have been limited to those that contribute directly to the study objectives or that are necessary for reasons of safety or regulatory compliance.

10.1 Protocol Specific Measures

10.1.1 HCV Related Measures

HCV-Specific Outcomes.

Access to and Utilization of Medical Care (Self-Report) and Access to and Utilization of HCV Medical Care (Medical Record): We will ask participants about their prior experience with HCV testing, liver assessment and HCV treatment. These assessments will include information about the doctor and clinic where the services were provided to facilitate obtaining medical records. These questions will be repeated at the two follow-up visits to facilitate access to medical records for outcome determination. *Each step in the HCV care continuum will be based on these medical records and calculated by algorithm.* Any cases that are not clear from this algorithm will be adjudicated by an independent clinical committee blind to treatment assignment.

Potential Mediators and Moderators of HCV-Specific Outcomes.

HCV Knowledge Questionnaire: *HCV knowledge* will be assessed using a modified *Brief HCV Knowledge Scale* which has established reliability and validity (Balfour, Kowal, Corace, Tasca, Krysan, Cooper, et al., 2009). Some additional items have been added to assess known facts about HCV that have emerged since this scale's development.

HCV Self-Efficacy Questionnaire: *Self-efficacy* for taking HCV medications will be measured using the *HCV Treatment Self Efficacy Scale*, a 17-item scale by Bonner, Esserman, & Evon (2012), which has been shown to be valid and reliable with internal consistency (.92-.94 for the global score).

HCV Stigma Questionnaire: *HCV stigma* will be measured using *Fife's Experience of Illness Scale* (Fife, Wright, 2000) which has been shown to work well in HCV assessments (Golden, Conroy, O'Dwyer, Golden, Hardouin, 2006).

Facilitators and Barriers to Care Questionnaire: *Patient-Perceived Facilitators and Barriers to Care* (i.e., barriers to HCV clinical evaluation, care, treatment and HIV care) will be assessed using step-specific questions following from treatment and care self-report and with the Seek, Test, Treat and Retain for Vulnerable Populations Data harmonization Measure, Barriers to Care/Treatment (Kalichman, Catz, Ramachandran, 1999). Some additional items have been added to differentiate between barriers/facilitators to HCV vs. HIV care and treatment.

Community Cohesion Scale: *The Community Cohesion Subscale of the Collective Efficacy Scale* from the Project on Human Development in Chicago Neighborhoods will be used due to its validity and reliability as well as its association with multiple health outcomes (Burdette, Wadden, Whitaker, 2006; Cagney, Browning, Wallace, 2007).

Locator Information Form: Patient address, minimally at the block level including zip-code+4, will be collected at each assessment and Google-map verified. At baseline, participants will be asked if the address

they give is different than from when they started the CTN-0049 study and if so will be asked the address(es) at which they lived during that protocol. This will be used to calculate meso/macro measures hypothesized to impact movement along the HIV/HCV care continuum. These meso/macro measures include: *Concentrated Disadvantage* (Kawachi, Berkman, 2003; Massey, Denton, 1993; Sampson, Morenoff, Gannon-Rowley, 2002; Wilson, 1987), *Measure of Unmet need for drug and alcohol treatment* based on the geocoded data from the Substance Abuse and Mental Health Data Archive (SAMHDA). National Survey on Drug Use and Health, and *Racial/Ethnic residential segregation* (e.g., Massey, Denton, 1988).

10.1.2 HIV Related Measures

HIV-Specific Outcomes.

Clinical Lab Data (CLD) and Access to and Utilization of Medical Care (Medical Record): Blood samples will be collected at baseline and 6- and 12-month follow-up visits for assessment of *CD4* (T-helper cells) and *HIV-1 viral load*. Trained staff will be responsible for collecting biologic specimens. In the event that the baseline results are not available or that the follow-up specimens cannot be collected or their results are not available, medical record abstraction will be used and lab results will be recorded on the Access to and Utilization of Medical Care (Medical Record) form.

Access to and Utilization of Medical Care (Self-Report) and Access to and Utilization of HIV Medical Care (Medical Record): The forms will be used to assess both self-reported HIV care visits and medical record HIV care visits at baseline and at 6- and 12-month follow-up visits. Information regarding HIV providers and clinics will also be collected on these forms.

HIV Adherence Measures and ARV Medication Log: Since HIV viral suppression is most strongly influenced by optimal use of ART, evaluation of *adherence* to one's *ART regimen* is essential. Adherence will be assessed with a short self-report *HIV Adherence Measure* that incorporates a "preamble" acknowledging that patients typically find it difficult to take their HIV medicines exactly as prescribed, uses "normalizing" wording of the questions themselves such that missing doses is expected, and incorporates several recall periods (past weekend, past 7 days, past month) (Simoni, Kurth, Pearson, Pantalone, Merrill, and Frick, 2006). These questions are combined with section "I" of the ACTG (AIDS Clinic Trial Group) Adherence Questionnaire for measuring antiretroviral adherence (Chesney, Ickovics, Chambers, Gifford, Neidig, Zwickl, Wu et al., 2000). Section "I" of the ACTG questionnaire lists symptoms experienced by people with HIV and asks the participant how frequently they are bothered by such symptoms (Justice, Holmes, Gifford, et al., 2001).

Because self-reported use of specific antiretrovirals has limited reliability when compared with medical record review (Korthuis, Asch et al., 2002; Brouwer, Napravnik et al., 2011), the ARV Medication Log (Medical Record) will confirm ARV use with medical record review at baseline, the 6 and 12 month visits, or at any point when the participant mentions or the medical records indicate starting or stopping ARVs. The ARV Medication Log (Medical Record) will collect information regarding ARV prescriptions, including the clinician providing the prescription, the date the prescription was written, and whether there is evidence in the medical record the participant took the medication.

Potential Mediators and Moderators of HIV-specific Outcomes. There are important factors that are related to HIV medication adherence and HIV care which are crucial to fully understand both how the intervention did and did not work. Whereas we believe the interventions tested will be extremely effective relative to current practices, it is still expected that more than 50% of those receiving the interventions may fail to achieve an undetectable viral load. Measuring these factors in this protocol will allow the identification of ways to improve future implementation efforts.

HIV Medication Adherence Self-Efficacy: *HIV Medication Adherence Self-Efficacy* will be measured by the 12-item *HIV Treatment Adherence Self-Efficacy Scale* (Johnson, Neilands, Dilworth, Morin, Remien, Chesney, 2007). This scale has good overall reliability ($\alpha = .92$) and higher self-efficacy has been shown by Johnson et al., (2007), to be related to fewer emergency HIV care visits and fewer missed appointments, higher CD4 cell count and lower viral load. Medication Adherence Self-Efficacy at baseline is a potential moderator of intervention effects on viral suppression. Change in self-efficacy is a potential mediator of intervention effects on viral suppression.

Cognitive Screening: *HIV-Related Cognitive Problems* will be screened using the 3-task *International HIV Dementia Scale* (Sacktor, Wong, Nakasujja, Skolasky, Selnes, Musisi, et al., 2005). Participants with HIV-related cognitive problems are more likely to have difficulty with negotiating the HIV/HCV care systems, remembering appointments and health care instructions. HIV-related cognitive problems have been shown to be related to reduced HIV medication adherence (Barclay, Hinkin, Castellon, Mason, Reinhard, Marion, et al., 2007; Hinkin, Castellon, Durvasula, Hardy, Lam, Mason, et al., 2002) and are anticipated to moderate the viral suppression outcomes. Presence of neurocognitive impairment also may require modifications to HIV medication regimen to address HIV in the central nervous system.

Access to and Utilization of HIV Medical Care (Medical Record):

Renal function will be measured via medical record abstraction of serum creatinine and eGFR. Because impaired renal function precludes the use of one of the most potent and easily tolerated first line HIV drugs, Truvada (TDF/FTC), we will examine renal function as potential moderator of virologic suppression.

Liver function will be measured via medical record abstraction of liver function tests. Impaired liver function can affect choice of antiretroviral therapy and participants with significant liver dysfunction may not be able to tolerate ART. Therefore, we will examine liver function as a potential moderator of virologic suppression.

Potential Mediators and Moderators of both HCV and HIV Outcomes

Additional Demographics: *Housing instability* will be measured by two questions: “In the past 6 months, where did you live or sleep most of the time?” and “Indicate all the places you have lived in the last 6 months” (with multiple response categories). An ordering of unstable to stable will be created using the weights suggested by Milby, et al., (2005). Housing instability has shown relationships with substance use outcomes in cocaine users. Housing instability also has been associated with HIV medication adherence (Palepu, Milloy, Kerr, Zhang, Wood, 2011; Phillips, 2011). Adherence is the most proximal mediator of HIV viral suppression; therefore, participants who enter the study unstably housed may differ in their response to the intervention. This would lead to a moderating effect of housing instability. Similarly, moving along the HCV continuum is likely moderated by housing instability. Masson et al., (2013) found that individuals who were homeless were less likely to have an initial HCV evaluation than those with stable living arrangements and the authors suggested the more immediate need for food and shelter may trump the need for health care.

Household Food Insecurity: Food insecurity will be measured by the Household Food Insecurity Access Scale (HFIAS), (Coates, Swindale, Bilinsky, 2007). The estimated prevalence of food insecurity in HIV-infected populations remains well above general population estimates, even in well- resourced settings (Normen, Chan, Braitstein, Anema, Bondy, Montaner, et al., 2005; Vogenthaler, Hadley, Lewis, Rodriguez, Metsch, & del Rio et al., 2010; Weiser, Fernandes, Brandson, 2008). Food insecurity has been associated in HIV-infected individuals with substance use disorders, depressive symptoms, suboptimal adherence, lack of virologic suppression and mortality (Vogenthaler, et al., 2010; Weiser et al., 2008; Weiser, Fernandes, Brandson, Lima, Anema, Bangsberg, et al., 2009; Weiser, Frongillo, Ragland, Hogg, Riley,

& Bangsberg, 2009). Food insecurity also has been associated with postponing needed medications, increased emergency department use and increased hospitalizations (Kersey, Beran, McGovern, Biros, Lurie, 1999; Kushel, Gupta, Gee, Haas, 2006). An improved understanding of the role food insecurity plays in successful linkage to care, retention in HIV and HCV care and health outcomes is essential in meeting the needs of this vulnerable population. Food insecurity is an hypothesized moderator of the HIV viral suppression outcome as well as the engagement to care secondary outcome. We hypothesize similarly that food insecurity will moderate movement along HCV care continuum.

Physician-Patient Relationship with HIV Doctor and Health Care System and Physician-Patient Relationship with HCV Doctor and Health Care System: *The Physician-Patient Relationship* will be measured using a series of seven short scales (30 total items). Higher scores on these scales were shown by Schneider, et al., (Schneider, Kaplan, Greenfield, Li, Wilson, 2004) to be independently related to better HIV medication adherence. This team also showed that all the subscales have good reliability with HIV-infected participants. The alphas reported below are from Schneider, et al., (2004). The scales measure General Communication ($\alpha = .93$) and Provision of HIV-Specific information ($\alpha = .93$); (Wilson, Kaplan, 2000), Adherence Dialogue ($\alpha = .93$); (Schneider, et al., 2004), Egalitarian Decision-making Style ($\alpha = .86$); (Kaplan, Gandek, Greenfield, Rogers, Ware, 1995), Overall Satisfaction with care ($\alpha = .92$), Willingness to recommend this physician to others ($\alpha = .81$); (Davies, Ware, 1991), and Trust in Physician ($\alpha = .71$) (Safran, Kosinski, Tarlov, Rogers, Taira, Lieberman, et al., 1998). Again, because these factors are related to adherence and that the care facilitator will be facilitating participant's interactions with health care it is anticipated that they will also be mediators of the viral suppression outcome. In a cross-sectional study of 322 outpatients diagnosed with chronic hepatitis C, 41% reported communication problems with physicians who were involved in their care (Zickmund, Hillis, L., Barnett, Ippolito, LaBrecque, 2004). The more commonly reported problems were that they thought their physician had poor communication skills, they thought their physician was incompetent with regard to diagnosis and treatment of hepatitis C, and the patient had feelings of being misled, misdiagnosed or abandoned (Zickmund et al., 2004). Therefore, it might be expected that measures of the physician-patient relationship may be mediators of movement along the HCV care continuum. The subscales will be assessed with respect to the patient's HCV provider (if the provider is different from their HIV provider).

Health Literacy: *Health Literacy* will be measured by three items found to be effective at identifying persons with inadequate health literacy (Chew, Bradley, Boyko, 2004; Chew, Griffin, Partin, Noorbaloochi, Grill, Snyder, et al., 2008). Health literacy has been shown to be an important predictor of HIV medication adherence and health status (Kalichman, Rompa, 2000; Kalichman, Pope, White, Cherry, Amaral, Swetzes, et al., 2008). It is anticipated that health literacy will be a moderator of the viral suppression outcome as well as movement along the HCV care continuum.

Perceived Health Status: *Perceived health status* will be measured using the Short Form-12 (SF-12) Measure (Ware, Kosinski, Keller, 1996). The SF-12 can be converted to quality-adjusted health index to be utilized in cost-effectiveness analyses (Brazier, Roberts, Deverill, 2002). This quality-adjusted health index has been shown to have moderate to good associations with substance use outcome measures (Pyne, Tripathi, French, McCollister, Rapp, Booth, 2011). The SF-12 also has been shown to be reliable in HIV populations (Han, Pulling, Telke, Huppler Hullsiek, Terry Beirn, Community Programs for Clinical Research on AIDS, 2002) and related to HIV medication adherence with higher medication adherence being associated with greater gains in quality of life (Mannheimer, Matts, Telzak, Chesney, Child, Wu, et al., 2005).

Medical Mistrust: *The Group Based Medical Mistrust Scale* assesses the tendency to distrust mainstream health care professionals and health care systems. The measure consists of 12-items and responses will be on a Likert scale ranging from 1 (strongly agree) to 5 (strongly disagree) (Thompson, Vladimarsdottir, Winkel, Jandorf, Redd, 2004). Mistrust is known to be a critical factor in the decision to access health care (Freedman, 1998). Change in mistrust is a potential mediator of intervention effects

of viral suppression as well as movement along the HCV care continuum.

Access to Care: *Access to Care* will be measured using the 6-item *Access to Care Scale* which addresses the accessibility of reaching medical services (e.g., affordability, availability, and convenience of medical care) on a 5 point Likert scale ranging from 1 (strongly agree) to 5 (strongly disagree). Assessing the access to care among those who are poor, medically underserved and are infected with HIV may be useful in evaluating HIV virologic suppression (Cunningham, Hays, Williams, Beck, Dixon, Shapiro, 1995) as well as movement along the HCV care continuum.

Brief Symptom Inventory: *Mental Health* will be operationalized as psychological distress and be assessed by the 18-item *Brief Symptom Inventory* at baseline, 6 and 12 months (Recklitis, Parsons, Shih, Mertens, Robison, Zeltzer, 2006; Zabora, BrintzenhofeSzoc, Jacobsen, Curbow, Piantadosi, Hooker, et al., 2001). The BSI-18 provides specific scales for anxiety, depression, somatization as well as a global severity index. The global severity index will be used as our measure of psychological distress. In prior research of the protocol team, reliability of these scales ranged from .85 to .93. Depressive symptoms have been shown to be related to HIV medication adherence (Ammassari, Antinori, Aloisi, Trotta, Murri, Bartoli, et al., 2004; Safren, Hendriksen, Mayer, Mimiaga, Pickard, Otto, 2004) and are therefore hypothesized to be a potential moderator of HIV viral suppression. Utilization of mental health services will be assessed by self-report and confirmed with medical record abstraction. Likewise, individuals with mental health issues are more likely to have difficulties navigating from HCV testing to referral to treatment (reviewed in Bonner, Barritt, Fried, Evon, 2012) and therefore, mental health is a likely moderator of movement along the HCV care continuum.

Conflictual Social Interaction Scale: *Social support* will be measured at baseline, 6 and 12 months by the *Short Social Support Scale* consisting of five items (Fleishman, Sherbourne, Crystal, Collins, Marshall, Kelly, et al., 2000) and the *Conflictual Social Interaction Scale*, consisting of three items (Fleishman et al., 2000; Berry, Brown, Athey, et al., 2002). Social support is positively related to medication adherence (Gardenier, Andrews, Thomas, Bookhardt-Murray, Fitzpatrick, 2010; Johnson, Heckman, Hansen, Kochman, Sikkema, 2009) and retention in drug treatment (Buckman, Bates, Mortenstern, 2008; Johns, Baker, Webster, Lewin, 2009; Palmer, Murphy, Piselli, Ball, 2009). It has been suggested that a hepatitis C diagnosis is associated with a loss in social support (Blasiolo, Shinkunas, Labrecque, Arnold, Zickmund, 2006) and, thus, getting a diagnosis itself may be a barrier to care due to such losses. Because the care facilitator will provide support to the participants with respect to both engagement into medical care and into drug treatment, social support is a hypothesized mediator of HIV viral suppression, movement along the HCV continuum and drug use outcomes.

DAST-10, Alcohol Use Disorders Identification Test (modified AUDIT), CTN-ASI Lite v1.0: Drug/Alcohol Use and Substance Use: *Substance use* may be a mediator of HIV viral suppression and movement along the HCV continuum and is measured by the SUB, CTN-ASI-Lite, modified AUDIT and DAST-10 as described below.

Access to and Utilization of Medical Care (Medical Record): *HCV infection status* (i.e., absent, untreated, treated) will be evaluated as a potential moderator of HIV virologic suppression.

Access to and Utilization of Medical Care (Medical Record): *HIV infection status* (i.e., untreated or treated) will be evaluated as a potential moderator of HCV virologic suppression.

Substance Use Measures

DAST-10 and Alcohol Use Disorders Identification Test (modified AUDIT): *Drug use severity* may be a moderator of substance use treatment outcomes and will be assessed using the DAST-10 (Yudko, Lozhkina, Fouts, 2007). The DAST-10 has good psychometric properties and has moderate to

high levels of sensitivity and specificity for substance use disorder diagnoses (Maisto, Carey, Carey, Gordon, & Gleason, 2000; Yudko, et al., 2007). The modified AUDIT (Kitchens, 1994; Piccinelli, Tessari, Bortolomasi, Plasere, Semenzin, Garzotto, et al., 1997) will be used to assess alcohol use severity. These self-report measures will be collected at each visit.

Urine Drug and Urine Alcohol Screen: We also will measure *recent drug and alcohol use* by performing urine drug and alcohol (ethyl glucuronide metabolite) screens at baseline, 6 and 12 months follow-up visits. These biological variables will be examined separately from self-report, but can also be combined into an abstinence outcome with self-report.

Gain Risk Behaviors: We will include a minimum set of questions on *drug injection and sexual risk behaviors* that were used in the ARTAS study (Metsch, Pereyra, Messinger, Del Rio, Strathdee, Anderson-Mahoney, et al., 2008). Sexual risk items will be limited to just those necessary to determine number and riskiness of sexual partners/acts and condom use for vaginal and anal intercourse.

CTN-ASI Lite v1.0: Drug/Alcohol Use and Substance Use: *Drug Use* will be assessed by the *CTN-ASI-Lite v1.0* (drug/alcohol use module) and the drug use matrix (SUB) that was used in the NIDA CTN-0032 HIV testing study (Metsch, Mandler, Feaster, Gooden, Tross, Haynes, et al., 2010) at baseline and repeated at 6 and 12 months. Because the ASI only asks about drug use in the last 30 days and lifetime use, the SUB matrix will get information on each 6-month interval covering the entire follow-up period. The ASI includes limited questions on drug treatment utilization. These will be expanded to collect more extensive treatment history information to contextualize the results of the linkage to drug treatment hypotheses.

Fagerström Test for Nicotine Dependence: *The Fagerström Test for Nicotine Dependence* assesses the dependency of the participant on nicotine. This is a self-report scale consisting of 8 items and will be completed at Baseline and 12 months follow-up. This scale has been shown to have valid measurability of dependency on smoking and nicotine (Heatherton, Kozlowski, Frecker, Fagerström, 1991).

Readiness for Substance Use Treatment: Participants' attitudes toward and *Readiness for Substance Use Treatment* will be measured by a 4 item readiness scale (Longshore, Teruya, 2006) and a 4 item-negative attitudes scale (Conner, Longshore, Anglin, 2009) both of which have good reliability in prior studies and relationships with treatment retention. Readiness for drug treatment is hypothesized to be both a moderator (at baseline) and mediator (change) of the substance use outcome.

CTN-ASI Lite v1.0: Drug/Alcohol Use: Attendance at *Substance Use Treatment* will be assessed by self-report at baseline, 6 and 12 months.

Comorbid Conditions and Ancillary Measures

Participant Satisfaction: Several questions about the participant's relationships and *satisfaction with their Patient Navigator* will be asked at baseline of those participants in the PN and PN+CM groups from CTN-0049. Similar questions will be asked at the 6- and 12- month assessment of the CTN-0064 participants with respect to their *satisfaction with their HCV Care Facilitator*.

History of Abuse and Interpersonal Violence: *History of Abuse and Interpersonal Violence* will be measured by the *Interpersonal Violence Scale*, and questions regarding abuse history. The interpersonal violence screener consists of 5 items and was adapted from STaT (**S**lapped, **T**hreatened, or **T**hrow things), an instrument that was developed to succinctly screen for lifetime IPV in a clinical setting and was previously validated in urban emergency departments (Paranjape, Rask, Liebschutz, 2006; Paranjape, Liebschutz, 2003). Participants who reported IPV were asked to identify from a list the services they used after experiencing abuse (Paranjape, Heron, Kaslow, 2006).

Intervention Tracking. The care facilitators will maintain an electronic tracking system in which they will log contacts with each participant. The tracking system will include a categorization of the type and location of contacts and their duration. These measures will be collected on an ongoing basis throughout the 6-month intervention period.

Service Utilization Detail and Modified Illegal Activities and Access to and Utilization of Medical Care (Self Report and Medical Record): *Self-reported doctor's office and/or outpatient clinic visits and other service use* will be assessed at baseline and at 6- and 12-month follow-up visits with the *Service Utilization Adherence Measurement*. This measurement consists of 14 items and subscales according to the type of health care visit: Emergency room, Inpatient, Nursing home, Day Hospital, Clinic, Doctor's Office, Mental Health Care, Residential treatment for substance use, Outpatient Treatment for substance use, Self-help support group, Dental Care, Formal home care, or Case Management (HIV/AIDS Treatment Adherence, Health Outcomes and Cost Study Group, 2004). At the 2 follow-up visits, we will record health-seeking behavior in the previous 6 months. In addition, we will collect information (both through self-report and medical record abstraction) on emergency department and hospital visits in the past 6 months. This assessment of service use will be supplemented with substance treatment services, illegal activities (**Modified Illegal Activities**) and arrest information (Feaster, Mitrani, Burns, McCabe, Brincks, Rodriguez, et al., 2010) to be used in the cost analysis.

10.2 Demographics

Demographics to be collected at screening include age, gender, education, income, race/ethnicity and marital status.

10.3 Safety Assessments

Adverse Events, including Serious Adverse Events, and Protocol Deviations: Adverse Events, Serious Adverse Events, and Protocol Deviations will be assessed and documented as described in Section 15.9 of the protocol.

Concise Health Risk Tracking - Self Report (CHRT-SR) Suicidal Behavior > Evaluation (CHP): The *CHRT-SR* (Trivedi, Wisniewski et al., 2011) is a 16-item participant self-report assessment of suicidality and related thoughts and behaviors. The scale is designed to quickly and easily track suicidality in a manner consistent with the Columbia Classification Algorithm of Suicide Assessment (C-CASA) (Posner, et al., 2007). The CHRT-SR will be assessed at baseline, as well as the 6 and 12 month follow up visits. The CHRT-SR will assess high risk suicide ideation by a positive response (Agree or Strongly Agree) on any of the last three questions (thoughts of, thoughts of how and/or a specific plan to commit suicide) and prompt a clinician assessment for suicide risk before leaving the clinic. A participant's response indicating suicidal ideation would prompt a clinician or other mental health professional's assessment.

10.4 Assessments Timetable

Assessment	Visit		
	00	01	02
	Baseline	6 Month Follow Up	12 Month Follow Up
CAPI ASSESSMENTS			
Additional Demographics (ADM)	X		X
Community Cohesion Subscale (CCS)	X	X	X
Household Food Insecurity Access Scale (HFI)	X		
Health Literacy (HLT)	X		
Group Based Medical Mistrust Scale (MMT)	X	X	X
Access to Care Scale (ATC)	X	X	X
Barriers to Medical Care (BMC)	X	X	X
HCV Knowledge Scale (HKQ)	X	X	X
Fife's Experience of Illness Scale (EIS)	X	X	X
Physician-Patient Relationship with HIV Doctor and Health Care System (PPR)	X	X	X
Physician-Patient Relationship with HCV Doctor and Health Care System (PPH)	X	X	X
Access to and Utilization of Medical Care (self-report) (AUS)	X	X	X
HIV Adherence Measures (ADH)	X	X	X
HIV Treatment Adherence Self-Efficacy Scale (HTA)	X	X	X
HCV Treatment Self-Efficacy Questionnaire (HSE)	X	X	X
Facilitators and Barriers to Care (FBC)	X	X	X
Fagerstrom Test for Nicotine Dependence (FND)	X		X
Alcohol Use Disorders Identification Test - AUDIT (AUD)	X		
Alcohol Use Disorders Identification Test Modified - AUDIT (AUC)		X	X
Gain Risk Behaviors (GRB)	X		X
Substance Use (SUB)	X	X	X
International HIV Dementia Scale (IDS)	X		
Short Form-12 (SF-12) Measure (SFM)	X	X	X
Brief Symptom Inventory (BSI)	X	X	X
Concise Health Risk Tracking (CHRT) – Self Report (CHP)	X	X	X
DAST-10 (DST)	X	X	X
Readiness for Substance Use Treatment (RST)	X	X	X
CTN-ASI Lite v1.0: Drug/Alcohol Use (ASD)	X	X	X
Modified Illegal Activities (MIA)	X	X	X
Service Utilization Adherence Measurement (SUD)	X	X	X

Assessment	Visit		
	00	01	02
	Baseline	6 Month Follow Up	12 Month Follow Up
SUD Module A Emergency Room (SDA) (Self-Report and Medical Record)	To Be Completed for Each Visit/Stay if Endorsed on the Service Utilization Details (SUD) Form		
SUD Module B Inpatient Hospital (SDB) (Self-Report and Medical Record)			
SUD Module C Nursing Home (SDC) (Self-Report)			
SUD Module D Day Hospital (SDD) (Self-Report)			
SUD Module E Hospital Clinic (SDE) (Self-Report)			
SUD Module I Residential Treatment (SDI) (Self-Report)			
SUD Cost Information (SCI)	To Be Completed for the Most Recent Visit reported for SDE, SDI, and/or Q8b in the SUD form		
Conflictual Social Interaction Scale and Short Social Support Scale (CSI)	X	X	X
Interpersonal Violence Scale (IVS)	X		X
CLINICAL LABORATORY ASSESSMENTS			
Clinical Lab Data (CLD)	X	X	X
Urine Drug Screen (UDS)	X	X	X
Urine Ethyl Glucuronide (ETG)	X	X	X
STUDY MANAGEMENT TOOLS			
Screening Enrollment (ENR0064A)	To Be Completed at the Time of Screening Enrollment		
Randomization Enrollment (ENR0064B)	To Be Completed at the Time of Randomization		
Study Completion (STC)	To Be Completed Upon Completion of the Study		
Baseline Investigator Attestation (BIA)	To Be Completed at Time of Screen Failure or Upon Completion of Study Component 1		
Protocol Deviation (PDV)	To Be Completed for Each Protocol Deviation		
Protocol Deviation Review (PDR)	To Be Completed by the Protocol Specialist for Each Protocol Deviation		
Adverse Event (AD1)	To Be Completed for Each Reportable AE		
Serious Adverse Event Summary (AD2)	To Be Completed for Each Reportable SAE		
Serious Adverse Event Medical Reviewer (AD3)	To Be Completed by the Medical Monitor for Each Reportable SAE		
Death Form (DTH)	To Be Completed If Participant Dies		
GENERAL ASSESSMENTS			
Locator Information Form (LIF)	X	X	X
Access to and Utilization of HIV Medical Care (medical record) (AUM; AM2 supplemental form, as needed)	X	X	X

Assessment	Visit		
	00	01	02
	Baseline	6 Month Follow Up	12 Month Follow Up
Access to and Utilization of HCV Medical Care (medical record) (AUH)	X	X	X
Access to and Utilization of HCV Liver Care (medical record) (AUL)	X	X	X
ARV Medication Log (Self Report) (ARS)	To Be Completed by Participant if Taking Antiretroviral Medications		
ARV Medication Log (Medical Record) (ARV)	To Be Completed by Staff if Taking Antiretroviral Medications		
HCV Medication Log (Self Report) (HCS)	To Be Completed by Participant if Received or Filled HCV Medications		
HCV Medication Log (Medical Record) (HCM)	To Be Completed by Staff if Received or Filled HCV Medications		
Baseline HCV Results and Referral (HRR)	X		
Participant Satisfaction (INS)	X	X	X
Non-Participant Contact Log (NPC)	Completed by CF for Brief Contact with Individuals other than Participant (e.g., scheduling, rescheduling, and confirming appointments for participant)		
Additional Psychiatric Diagnoses (Medical Record) (APD)	X	X	X
HIV Abstracted Data (HAB)	To Be Completed at for non-randomized participants at Baseline when Baseline blood collection does not yield HIV viral load or CD4 results		

10.5 Care Facilitator Assessment

We will conduct a brief survey of care facilitators to garner basic information about their socio-demographic characteristics, level of experience with case management, beliefs and attitudes about care facilitation, HCV testing, clinical evaluation and treatment, and substance use treatment. Additionally, we will assess care facilitators' attitudes and beliefs about barriers that patients face in accessing HCV clinical evaluation and treatment, HIV care and treatment, and substance use treatment. We will collect this information to describe care facilitator characteristics (including attitudes and beliefs about the intervention strategies) which will be reported in the Component 2 (RCT) primary outcome manuscript to give the context of study implementation. In addition, a planned secondary analysis will examine whether there is significant variability in treatment effects at different sites and whether counselor characteristics and attitudes may be associated with these differences. Study investigators will identify care facilitators from the master study personnel contact sheet. The care facilitators will initially be contacted via email with a cover letter inviting them to complete the survey online. They may also be contacted by phone and invited to complete the survey online or by phone. Completion of the survey constitutes their consent; this will be described in the invitation cover letter. Care facilitators will be compensated for their time and effort dedicated to completing the survey.

10.6 HIV/HCV Provider Assessments

To more thoroughly document “treatment as usual” for HCV care at the participating sites and gain a comprehensive understanding of the local HCV evaluation/care/treatment and referral practices, including barriers and facilitators to HIV/HCV co-infected patients’ movement along the HCV care continuum, we will conduct a survey of all (approximately 200) HIV and HCV-treating providers within the participating study sites (ideally) prior to implementing the study intervention. Site administrators and local health department administrators (approximately 33) will also be surveyed for the purpose of gathering site-level data on HCV testing and referral practices, HCV treatment policies, insurance restrictions, etc. HCV-treating providers outside of the study sites who receive HCV treatment referrals from the study sites will also be invited to participate in the survey. This provider “pre-survey” will include questions on clinician demographics, patient-clinician relationship, attitudes and concerns about prescribing HCV treatment to HIV/HCV co-infected substance users, and clinician perceptions of barriers to HCV clinical evaluation, care and treatment. Study investigators will identify providers and administrators by obtaining a list of HIV and HCV providers and administrators from each participating Site PI. Study investigators may also search health department directories to identify health department administrators. When completing the survey, providers may identify other HIV and HCV- treating clinicians to whom they refer patients for care; these providers would be invited to participate in the survey as well. All providers/administrators will initially be contacted via email with a cover letter inviting them to complete the survey online. They may also be contacted by phone and invited to complete the survey online or by phone. Completion of the survey constitutes their consent; this will be described in the invitation cover letter. Providers/administrators will be compensated for their time and effort dedicated to completing the survey. To gauge changes in the local provision of HCV care/treatment and providers’ perceived barriers that may occur over the course of the study, we will conduct a follow-up “post-survey” at the end of the study’s 12-month follow-up period. This survey will be administered as outlined above and participating providers/administrators will be compensated for their time and effort dedicated to completing the survey.

11.0 CARE FACILITATION INTERVENTION

As outlined in section 2.0, the care facilitator will actively work with intervention participants to first motivate the participant to return for his/her HCV RNA result (confirmation of active HCV) and, subsequently, to engage in HCV care and to initiate HCV treatment, as applicable. The intervention emphasizes the importance of linking to and/or maintaining ongoing HIV primary care and views this as a critical and necessary part of the treatment plan. Likewise, the intervention emphasizes the importance of linkage to (and/or maintenance of) substance use treatment, as needed. Given the replicated success that ARTAS (Antiretroviral Treatment Access Study), in which Drs. Lisa Metsch and Carlos del Rio participated, has demonstrated with linking HIV-infected individuals to HIV primary care and the success of Drs. Carmen Masson and David Perlman's hepatitis care coordination intervention demonstrated with linking methadone maintenance patients to an HCV medical evaluation, the CTN- 0064 Care Facilitation Intervention (CFI) merges the key elements, some of which overlap, from these efficacious interventions to facilitate HIV/HCV co-infected substance users' progression along the HCV care continuum.

ARTAS's five principles of strengths-based case management include: 1) Encourage identification and the use of strengths, abilities and assets; 2) Recognize and support client control over goal setting and the search for needed resources; 3) Establish an effective working relationship; 4) View the community as a resource and identify sources of support; and 5) Conduct case management as an active, community-based activity. (Academy for Educational Development Center on AIDS & Community Health). The key elements of Ballew and Mink's case management (used in the hepatitis care coordination intervention) include: 1) Engagement; 2) Needs Assessment & Planning; 3) Accessing Resources; 4) Monitoring (clients' progress in care); and 5) Advocacy (Ballew, Mink, 1996). The CTN- 0064 CFI uses motivational interviewing (used in both previous interventions) to build an effective, working relationship with the participant, conduct a participant needs assessment, conduct a strengths assessment and encourage the participant to identify and use his/her strengths, abilities, and skills to move along the HCV care continuum (e.g., link them to HCV clinical evaluation, link them to HCV care, facilitate their obtaining and completing HCV treatment), link them to HIV care (as needed) and link them to substance use treatment (as needed). One of the critical intervention components is meeting each participant in the environment where the participant feels comfortable and accompanying the participant to key medical care visits (e.g., HCV clinical evaluation, HIV primary care and substance use treatment visits). The care facilitator actively coordinates and links the participant to available clinics and community resources through scheduling appointments, arranging transportation, and assisting the participant with completing any clinic registration (or other) paperwork that a clinic or service agency may require. Additionally, the care facilitator assists the participant in identifying and utilizing informal and formal sources of support to move along the HCV care continuum, including accessing and utilizing (as needed) HIV care and substance use treatment.

Over the six month intervention period, the intervention will include up to 12 care facilitator/participant face-to-face meetings which are about 30 minutes in duration. These meetings are ideally spread out to occur about every other week, but will be tailored around each participant's needs. If a participant has numerous needs that must be addressed quickly, then the care facilitator visits may occur weekly. Conversely, if a stable participant has been proactive in seeking and following through with care then monthly meetings may be more appropriate. On a case-by-case basis, (e.g., if a participant moves out of the area or is too ill to meet in person), the care facilitator may substitute face-to-face time with telephone time to address the intervention content and assist with identified concrete issues. These 12 face-to-face meetings will include the care facilitator accompanying the participant to at least the initial HCV, HIV, and substance use care appointments with the caveat that the participant may opt out and the accompaniment does not interfere with provider care. Brief, but frequent telephone, email and

text message communication is expected both between the care facilitator and care agencies/support services and between the care facilitator and the participant. These non-face-to-face contacts will be logged and tracked, but will not count as any of the 12 face-to-face intervention meetings.

The CFI manual will provide general guidance as well as specific suggested scripted sessions as part of the intervention tool box for the care facilitator's use. Scripted sessions will include the following: conducting a needs assessment, conducting a strengths assessment, preparing to meet the provider, debriefing a provider visit, supporting self-care efforts/addressing ambivalence, and concluding the intervention relationship. The participant's individual start point along the HCV care continuum (including utilization of HIV care and substance use treatment) and how quickly the participant proceeds through subsequent steps on the continuum will determine which type of meeting is most appropriate for the participant at a given point in time.

Because Component 2 will assess the effectiveness of the intervention (compared to Control) in moving HIV/HCV co-infected substance users forward along the HCV care continuum, randomized participants who test HCV RNA negative will count only toward the receipt of HCV RNA result step in the Component 2 primary outcome analysis. For this reason, participants randomized to the intervention group who test HCV RNA negative will receive intervention focused primarily on achieving this step; once they receive their HCV RNA results, the Care Facilitator will not provide further intervention other than referrals (as applicable) for additional HCV risk-reduction counseling and testing in the community as well as referrals for drug/alcohol treatment and other social services that are available in the community. Additionally, if the participant self-reports that s/he is not in HIV care, study personnel will make an HIV care appointment for the participant. Study personnel will make this attempt only during the study visit in which the participant learns that s/he is HCV RNA negative. If an appointment cannot be scheduled, study personnel will provide a written referral to the participant.

12.0 STATISTICAL ANALYSIS

12.1 Objectives of the Analysis

The primary objective of Component 1 is to examine the long-term primary outcome of the CTN-0049 study, HIV viral suppression.

The primary objective of Component 2 is to discover whether there is a difference in the number of steps individuals move forward along the HCV care continuum assessed 12 months post- randomization between the two study groups: 1) HCV Care Facilitation intervention or 2) Control. There is one primary hypothesis: the number of steps achieved along the HCV care continuum in the two study groups will be different. The error rate for this hypothesis is controlled to be no greater than .05.

12.2 Primary Outcomes

As previously outlined in section 8.1, the Component 1 primary outcome variable is binary: HIV viral suppression (≤ 200 copies/ml), as determined by blood draw (or medical record abstracted non-study lab result, as needed) at the baseline visit versus presence of viral load >200 copies/ml or death (all-cause mortality).

As previously outlined in section 8.2, the Component 2 primary outcome is a count variable: number of completed steps along the HCV care continuum by the 12 month follow-up. Participants' final step on the HCV care continuum will be assessed the last time they are observed in medical records within the 12-month of follow-up period. Participants who die will be counted as achieving however many steps in the HCV care continuum they completed prior to death.

12.3 Secondary Outcome Measures

HCV Related Secondary Outcome (Component 1)

Point prevalence of HCV among the CTN-0049 cohort (binary; CLD/medical record abstraction, AUH)

HCV Related Secondary Outcomes (Component 2)

The data associated with the HCV secondary outcomes include binary (Yes/No), count and continuously distributed data. In the following list of HCV secondary outcomes the expected distribution is in parenthesis:

1. Specific Steps on the HCV Care Continuum

- a. Receipt of HCV RNA result (binary; self-report, AUS, HRR; medical record abstraction, AUH)
- b. HCV evaluation (binary; self-report, AUS/medical record abstraction, AUH, AUL) with an indicator of any of the following through self-report/medical abstraction: liver function assessment by clinician (note that documents evaluation), liver biopsy, FibroScan, sero-marker with score (FIB-4, FibroSURE, APRI, FibroSpect II)

Note: The rates of completion of the following steps will be documented, however statistical testing of differences across condition on individual step completion will only be considered if the overall rate of completion exceeds 25%.

- c. HCV treatment offered (binary; self-report, AUS/medical record abstraction, AUH)
- d. HCV treatment initiation (binary; self-report, AUS/medical record abstraction, AUH, HCM)

- e. HCV treatment completion (binary; self-report, AUS/laboratory assay, CLD/medical record abstraction, AUH, HCM)
 - f. Sustained virologic response (binary; laboratory assay, CLD/medical record abstraction, AUH/self-report, AUS)
2. HCV-specific mortality (binary; medical record abstraction, DTH)

HIV Related Secondary Outcomes (Components 1 and 2)

1. HIV viral suppression (suppression binary defined as viral load \leq 200 copies/ml (yes) vs. viral load
2. > 200 copies/ml or all-cause mortality (no); viral load continuous; laboratory assay, CLD/medical record abstraction, AUM)
3. Initiated ART (binary; prescription bottle, ARS/medical record abstraction, ARV)
4. CD4 cell count (continuous; laboratory assay, CLD/medical record abstraction, AUM)
5. HIV care visit attendance (count; self-report, AUS/medical record abstraction, AUM)
6. Medication adherence (count, binary; self-report, ADH)
7. Inpatient hospitalizations (count; self-report, SUD, SDB/medical record abstraction, SUD, SDB)
8. All-cause mortality (binary; self-report/medical record abstraction/National Death Index, DTH)
9. HIV-related mortality (binary; medical record abstraction or National Death Index, DTH)

Substance Use Related Secondary Outcomes (Components 1 and 2)

1. Substance use frequency (count; self-report ASD and binary; self-report, SUB/; laboratory assay, ETG, UDS)
2. Substance use severity (continuous, DST, AUD, AUC)
3. Substance use treatment engagement (binary; self-report, ASD, ADM, SUD, SDI)
4. Number of alcohol and drug treatment sessions (count; self-report, SUD)

12.4 Tertiary Analyses: Mediators and Moderators of Outcomes

1. HIV Viral Suppression and HCV Care Continuum Moderators: psychological distress (continuous; BSI questionnaire), housing instability (categorical; ADM questionnaire), food insecurity (continuous; HFI questionnaire), health literacy (continuous; HLT questionnaire), medical mistrust (continuous; MMT questionnaire), perceived health status (continuous; SFM questionnaire), renal and liver function status (continuous; medical record abstraction, AUM).
2. HIV Viral Suppression and HCV Care Continuum Mediators: medication self-efficacy (continuous; separate questionnaires for HIV [HTA] and HCV [HSE]), physician-patient relationship (continuous; PPR, PPH questionnaires), access to care (continuous; ATC questionnaire), social support (continuous; STS questionnaire), substance use (binary; SUB and continuous; ASD questionnaire, DAST10 [DST], modified AUDIT [AUD, AUC]), psychological distress (continuous; BSI questionnaire), perceived health status (continuous; SFM questionnaire).
3. CD4 Count Moderators: HIV viral suppression status (binary; CLD, AUM), HIV viral load (continuous; CLD, AUM).
4. HCV Specific Mediators/Moderators: HCV knowledge (continuous; HKQ Questionnaire), HCV stigma (continuous; EIS Questionnaire), community cohesion (continuous; CCS questionnaire), measure of unmet need for drug/alcohol treatment (continuous; neighborhood level, LIF), concentrated disadvantage (continuous; neighborhood level, LIF), racial/ethnic residential segregation (continuous; neighborhood level, LIF).
5. HIV Specific Mediators/Moderators: HIV-related cognitive problems (continuous; IDS).

6. Drug Use Mediators/Moderators: Readiness for drug treatment (continuous; RST Questionnaire), social support (continuous; STS Questionnaire), measure of unmet need for drug/alcohol treatment (continuous; neighborhood level, LIF).

12.5 Overview of Analysis Plan

Primary Outcomes

As specified in the aims, the Component 1 primary hypothesis test will compare the proportions achieving HIV viral suppression at baseline across the three CTN-0049 study groups. The Component 2 primary hypothesis will compare the number of steps achieved along the HCV care continuum post randomization by the 12-month visit between the two study groups. Treatment comparisons will be performed under the Intent-to-Treat (ITT) criterion in the sense that participants will be analyzed in the arm to which they were randomized, regardless of subsequent events.

The primary outcome will be tested using a generalized linear model for count data. Due to participants having different numbers of steps they can complete for this outcome (see section 8.2), it is possible that this model will need to account for over-dispersion as well as excess zero responses. Therefore, a model search procedure will be employed to determine the appropriate distributional assumptions for this model. This procedure will be completed blind to treatment assignment. The following distributions will be considered: Poisson, Negative Binomial, zero-inflated Poisson, zero-inflated Negative Binomial and the Beta-binomial. The distribution with the best fit will be determined by using the Bayes Information Criterion (BIC; Schwarz, 1978). The model with the lowest BIC value will be used for testing treatment effect.

Randomization

Participants will be randomized in a 1:1 ratio to one of the two treatment groups. Randomization will be stratified by CTN-0049 treatment assignment and baseline self-reported engagement in HIV care (i.e., participant has attended an HIV primary care visit within the last 6 months [yes/no] and participant is currently taking ART [yes/no]; in care and on ART defined as “yes” on both conditions. The randomization procedure will be conducted in a centralized process through the Data and Statistics Center (DSC). Specifically, the DSC statistician will create stratum-specific randomization schedules for each site. The randomization schedules will be of a randomized-block nature to ensure relative equality of assignment across condition throughout the recruitment period and to prevent the potential for study personnel guessing the next assignment, which is heightened when a fixed block-size is used. Randomization for each participant is done over the Internet using the Enrollment Module in Advantage eClinical.

The DSC statistician will review the randomization data on a regular basis to ensure that the scheme is being implemented according to plan. If a participant drops out of the study at any point after randomization, the randomization slot will not be re-allocated to a new patient due to the intent-to-treat nature of the study.

Covariates Including Site

The primary analysis will include a vector of dummy variables to control for site of recruitment. In addition, the two randomization stratification factors, 1) currently in HIV care and taking HIV ART, and 2) CTN-0049 randomized group, as well as initial steps made in the HCV cascade will be included as covariates.

Tests of the Specific Aims

Aim 1: To evaluate the effectiveness of HCV Care Facilitation intervention in achieving HCV treatment among substance using HIV/HCV co-infected individuals.

Primary Hypothesis: The number of steps achieved along the HCV care continuum after randomization will differ between the two study groups at the 12 month follow-up. Statistical significance will be assessed by use of a Wald test.

Tests of the Secondary Outcomes

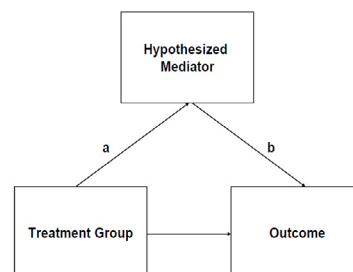
Each of the stated secondary outcomes listed in section 12.3 will be tested separately, using analogous comparisons as is planned for the primary hypothesis. The statistical methods used will also mirror the methods used for the primary hypothesis. Secondary outcomes that are binary will be tested using a logistic regression; secondary outcomes that involve either continuous or ordinal variables will utilize the appropriate distribution and link function. Note that the exact method of analysis will depend on the realized distribution of the particular outcome in this trial. For example, an expected count data variable may need to be modeled using a zero-inflated Poisson regression rather than a Poisson regression if there are too many zero observations to fit the standard Poisson. If there is over-dispersion, a negative binomial (or zero-inflated negative binomial) regression may be appropriate.

Note that the HIV Outcome variables measured at the CTN-0064 baseline assessment will be tested for differences by the randomized treatment group from CTN-0049. These analyses are the primary analyses of the CTN-0049 long-term outcomes (for those who consented to the 0064 study) described in Component 1. These outcomes also will be examined as secondary outcomes at the 6 and 12 month follow-up where the predictor of interest will be the randomized treatment assignment within CTN-0064. Note that death from any cause will be considered equivalent to non-suppression for the purpose of calculating the proportion achieving HIV viral suppression. We will, however, explore differences in the HIV viral suppression and other outcomes when deaths are categorized with respect to likelihood of being HIV-related. There may be times when our investigative team does not reach consensus about whether a death is HIV-related or HCV-related. Such cases will be referred to an independent committee for adjudication. Additionally, as resources permit, cause of death may be ascertained via searching the National Death Index.

The hypothesized moderator variables (section 12.4 above) will be addressed. Models will be estimated with main effects for these variables, a main effect for randomization group and an interaction between the particular variable and randomized group on the primary outcomes.

Mediation

Mediation will be tested using structural equation modeling with Mplus 7.3. These models estimate the effect of the intervention on the potential mediator (path a, e.g., the effect of intervention on Physician-Patient relationship) and the effect of the mediator on the outcome or next proximal intermediate outcome (path b, e.g., the effect of Physician-Patient relationship on HCV treatment completion). Longer mediation pathways also can be tested (e.g., $a*b*c$). There is significant mediation if the product of these two paths ($a*b$) is greater than zero. Statistical significance will be assessed using bias-corrected bootstrap confidence intervals on the product terms (Fritz, Mackinnon, 2007). This test is the most powerful test of mediation (Mackinnon, Lockwood, Williams, 2004) and can test multiple mediating pathways within a single structural model.



Ancillary Analyses

All intervention sessions will be audio-taped for quality assurance with the permission of the participant. Approximately 10% of the intervention sessions will be randomly selected and rated for fidelity to the two conditions. A smaller subset, about 15% of the 10% will be rated by two raters. The double rated cases will be used to calculate a kappa statistic to assess the inter-rater reliability of the fidelity instrument. Means and/or frequencies of ratings will be reported in the Component 2 primary outcome manuscript and the final report to describe intervention fidelity.

Cost Analysis

The cost analysis will be conducted from the societal perspective, including 1) incremental costs to deliver the intervention, 2) participant time and travel costs, and 3) net incremental health care costs or savings incurred as a result of the intervention. In secondary analyses we will consider criminal activity economic costs. To determine staff and participant time delivering and receiving the intervention, we will utilize intervention tracking form data that include start time and stop times. The self-reported session times will be independently validated when the study team fidelity raters review audio tapes representing approximately 10% of all sessions. We will adapt data collection tools that were developed for CTN-0032: *HIV Rapid Testing and Counseling in Drug Abuse Treatment Programs in the U.S.* to identify and measure the resources used for training and quality assurance/fidelity assessment from study administrative records. During site visits and telephone interviews, we will use structured interview guides to collect data on site-level resources incurred for start-up activities, staff time that occurs outside of the intervention sessions but is directly related to the intervention, and overhead. We will use national average wage and fringe benefit rates to value personnel time. The advantage of using national labor rates is that they provide a benchmark that can be adjusted uniformly to reflect different settings where the interventions might be implemented (Gold, Siegel, Russell, Weinstein, 1996). We will determine start-up costs, variable costs, and total costs for the intervention (including overhead) by multiplying unit costs by the number of resource units consumed, and then calculate a cost per participant by study arm. Health care costs incurred in each arm will be calculated by comparing self-reported health care utilization collected in the Service Utilization Details (SUD) form, supplemented by chart review data, and applying standardized costs to each service delivered. Participant time and travel costs will also be determined from the SUD forms, supplemented by interviews with study staff. Criminal activity will be assessed by self-report on the Modified Illegal Activities (MIA) form and economic cost will be assigned to each illegal activity using values provided in the literature (McCollister, French, Fang, 2010).

Mean costs will be estimated by the nonparametric method of Zhao and Tian (Zhao, Tian, 2001) to account for censoring and results will be reported as mean values and standard deviations. Differences between arms will be compared using non-parametric methods (e.g., Wilcoxon tests to compare medians and non-parametric bootstrap to compare means) due to the skewness frequently observed in cost data. We will also perform sensitivity analyses on costing assumptions that can vary by site location (e.g., wage rates) or client/patient volume (e.g., overhead). Results of the cost analysis and the self-reported quality-of-life data collected on the Perceived Health Status (SFM) form will provide valuable input data for future cost-effectiveness modeling studies.

12.6 Missing Data and Dropouts

We will make efforts to maintain all participants in our assessment protocol regardless of their participation or non-participation in the intervention component of the protocol. Historically we have had excellent retention rates. Our Component 2 primary outcome, movement along the HCV care continuum, will be calculated on all available medical records data on an individual participant within the 12 months post randomization. Participants who die will be counted as achieving the number of steps in the HCV continuum completed

prior to death. In secondary analyses, we will examine results excluding participants who did not have a 12 month assessment or any medical records within our window periods for the 12 month assessment. There may also be missing data for secondary analyses. In these cases, we will pursue multiple imputation under the assumption of missing at random (MAR), if the amount of missing data significantly degrades the power to uncover effects. Under the MAR assumption, the multiple imputations procedure can be used to fill in the data without artificially compressing the variance associated with the imputed data (Schafer, 1997). If nonrandom missingness is of concern (Missing not at Random, MNAR), this problem will be addressed either with the MNAR control statement of SAS PROC MIXED, or by applying pattern-mixture, propensity score or related models so that the effect of bias can be assessed in sensitivity analyses.

12.7 Interim Analysis

Because recruitment for this study is from an existing cohort, enrollment for the CTN-0064 clinical trial should occur in a relatively short time. Therefore, all trial procedures should be completed nearly concurrently for participants, and there is no planned interim analysis for either efficacy or futility. Further, there is no scenario for which sample size re-estimation will be necessary. In addition, safety interim looks will be performed (without formal statistical testing) at the regular DSMB meetings or at unscheduled times per the DSMB's request.

12.8 Power and Sample Size

Power calculations were based on a simulation of several scenarios with 500 iterations per scenario. For each iteration, the number of steps moved along the HCV care continuum was evaluated for the Care Facilitation intervention and Control groups and compared via a Poisson regression parameter estimate. Because the data will be counts, the Poisson is an appropriate statistical model for the data distribution. A generalized linear model with Poisson distribution and log link was run on each set of simulated data (SAS, PROC GENMOD); the significance of the estimator for group membership from the regression for log of the number of steps was recorded for each run and was coded as 0/1 corresponding to significance at $\alpha=0.05$ (0=n.s., 1=sig). Power was estimated from the proportion of times, across the 500 simulations for a set of parameters, treatment group was significant. This was performed for four different sample sizes. Masson et al., (2013) found a 28% risk difference between their intervention group (those receiving hepatitis care coordination) and a control group in obtaining an HCV evaluation in six months (equivalent to a one step move in our described HCV care continuum). The base rate in their study (the control group) was 37.2%, i.e., 37.2% of the control group obtained an HCV evaluation, or equivalently, each person on average has the probability of 0.372 to make one step. Therefore, we used a base mean of the Poisson distribution for the control group of 0.4 which implies approximately 67% of the sample makes no movement along the continuum. The odds ratio for the two groups in the Masson et al., (2013) study, for obtaining an HCV evaluation, was 4.10. We estimated power for a number of rate ratios, more conservative than 4.10. The rate ratio for Poisson-distributed data can be determined by the ratio of the mean rates among groups, in this case treatment/control (λ_T / λ_C). We used the following rate ratios (simulations A-E, Table 3): 2.375, 2.25, 2.125, 2.00, and 1.875 ($\lambda_C = 0.4$ and IT ranging from 0.95-0.75). Therefore, data was simulated for the two groups, based on a mean rate set by each group's value for λ . Greater than 80% power is achieved for all sample sizes greater than 125 people (62.5 per group) for rate ratios above 2.00 and for sample sizes over 100 for ratios greater than 2.13 (Figure 1). To examine the sensitivity of the simulation to the assumption of $\lambda=.4$ for the control group we set the control at $\lambda=.4$, .45 and .5 and held the treatment λ at .9 (rate ratios of 2.25, 2.00 and 1.85) in Figure 2 (Simulations B, F & G from Table 3).

Although we will enroll as many participants who are eligible in the cohort and consent to participate, this power analysis shows that we have over 80% power for as few as 125 participants total with our expected effect-sizes. It is important to enroll all that consent to provide as much precision of our

estimates of the impact of the intervention on the individual steps of the HCV care continuum. For example with $n=270$ we should have 80% power to uncover an .11 to .15 percentage absolute difference in any step of the HCV cascade achieved as the base-rate for that particular step in the control group varies from .05 to .20.

Table 3: Estimated Probabilities of Number of Steps Using Poisson Distribution with Different λ .

Simulation Parameters			Estimated Mean Probabilities of obtaining exactly __steps in HCV Continuum								
Sim	Group	I	0	1	2	3	4	5	6	7	8
A	C	0.40	0.670	0.268	0.054	0.007	0.001				
	T	0.95	0.387	0.367	0.175	0.055	0.013	0.003			
B	C	0.40	0.670	0.268	0.054	0.007	0.001				
	T	0.90	0.407	0.366	0.165	0.049	0.011	0.002			
C	C	0.40	0.670	0.268	0.054	0.007	0.001				
	T	0.85	0.427	0.363	0.154	0.044	0.009	0.002			
D	C	0.40	0.670	0.268	0.054	0.007	0.001				
	T	0.80	0.449	0.360	0.144	0.038	0.008	0.001			
E	C	0.40	0.670	0.268	0.054	0.007	0.001				
	T	0.75	0.472	0.354	0.133	0.033	0.006	0.001			
F	C	0.45	0.638	0.287	0.065	0.010	0.001				
	T	0.90	0.407	0.366	0.165	0.049	0.011	0.002			
G	C	0.50	0.607	0.303	0.076	0.013	0.002				
	T	0.90	0.407	0.366	0.165	0.049	0.011	0.002			

Note: Blank cells have essentially zero probability.

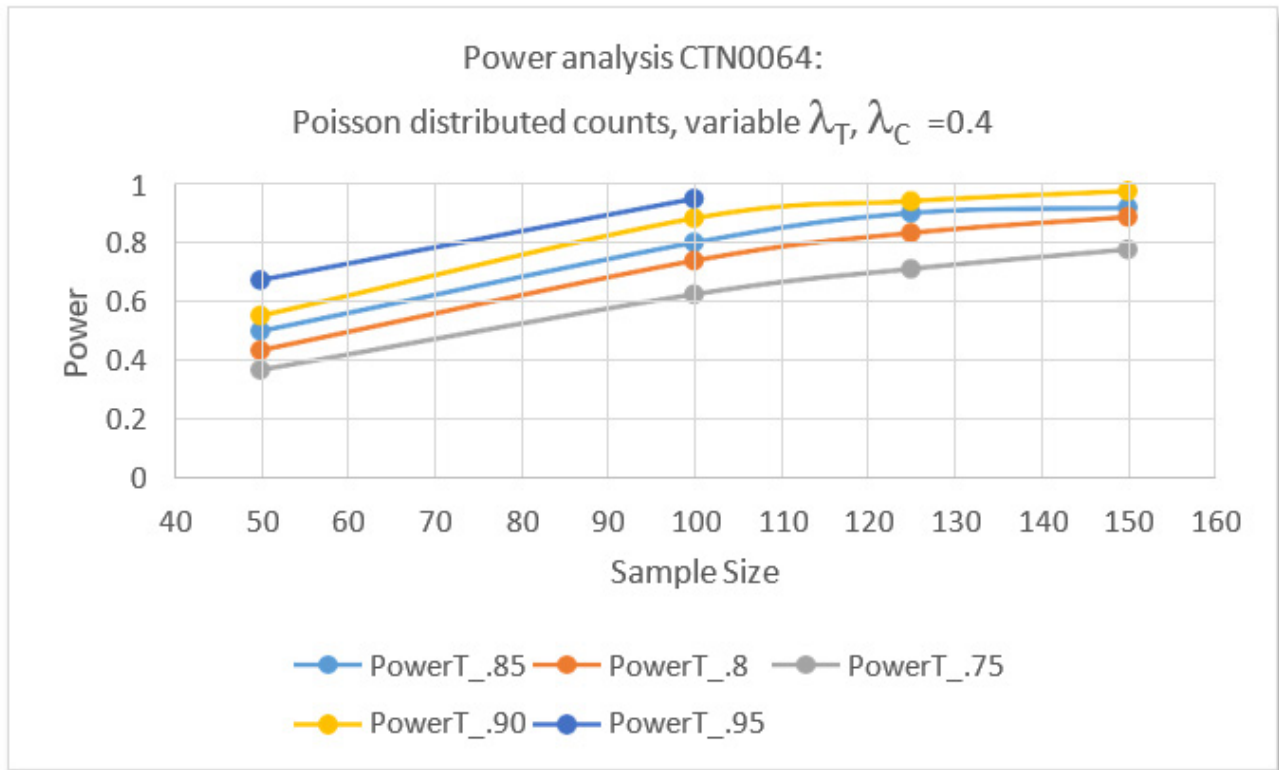


Figure 1. Estimated power from simulation with Control Rate=.4.

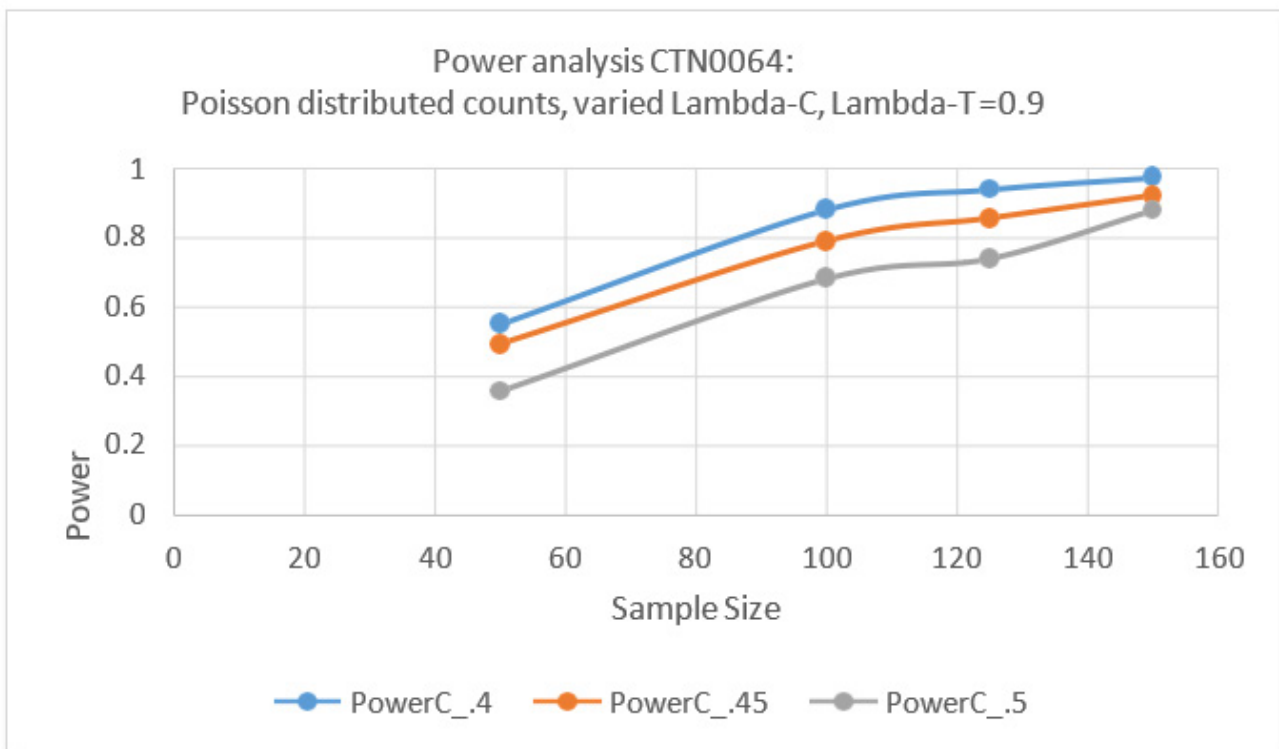


Figure 2. Impact of Varying Rate of Control

13.0 TRAINING

Training in study-specific assessments will be provided as specified in a comprehensive training plan that will be developed by the Lead and Co-Lead Nodes, the CCC, the DSC, and other participating nodes. All non-intervention training is expected to be delivered via conference call, webinar and self-study. Most of the intervention training will occur via in-person training sessions. Research assistants (and all other study personnel) will receive GCP training through the web-based system currently in use. The CTN-0064 Training Plan will provide a detailed description of training, supervision, and fidelity monitoring procedures.

13.1 Training, Supervision, and Fidelity Monitoring Procedures for Study Interventions

Selection of Interventionists/Care Facilitators

One care facilitator per site participating in Component 2 will be hired with a backup care facilitator to be designated from existing study staff. The lead team will provide a sample job posting for care facilitators. Ideally, care facilitators selected will be applicants who have: 1) experience in case management; 2) familiarity with HCV, HIV/AIDS, substance use, and mental health illness; 3) knowledge of local resources for HCV clinical evaluation and treatment, HIV care, substance use treatment, mental health services, housing and benefits; and 4) a high comfort level in venturing out into the field not only to build and maintain rapport with care or treatment agency staff, but also to locate study participants not following through with care or who are lost to follow-up. Attention will be paid to hiring care facilitators who represent the diversity that will be found in each site's substance using, HCV/HIV co-infected, population. The lead team will provide consultation as needed to nodes and hospital sites during the selection process.

Selection of Expert Trainers

The lead team is a varied group of investigators with depth and breadth of experience in HCV and HIV treatment, substance use treatment, patient navigation, case management, care coordination, intervention training and supervision, and quality assurance monitoring. As needed, the lead team will also seek out consultants in designing and implementing the training. A training work group will be established and will be responsible for ensuring that the appropriate training is provided by the experienced lead team members.

Training of Care Facilitators

The training of care facilitators will occur in three phases: 1) pre-national training; 2) national training; and 3) post-national training. Pre-national training will occur through the use of conference calls, webinars, written materials and self-study and will help prepare care facilitators for the national training and trial launch.

The pre-national training will provide instruction on the overall CTN-0064 study, the importance of meeting staff at the HCV and HIV clinics and substance abuse treatment facilities to, creating an extensive local resource list for study participants, making personal connections with key staff at all care agencies, and visiting and meeting staff at free kitchens, homeless shelters and mental health agencies.

The national training will occur in one location, will include all care facilitators and back-up care facilitators and will provide didactic and experiential (role-play) training based on the Care Facilitation intervention manual. The training will include a discussion of care facilitator roles, responsibilities, and boundaries; detailed overviews of each treatment group; appropriate communication techniques such as asking open-ended questions, paraphrasing, summarizing, and rolling with resistance; role-plays of various

participant/care facilitator meetings with receipt of immediate feedback; Post-national training will occur via conference calls, webinars, and/or written materials with the purpose of providing additional support and guidance on intervention delivery and to assist care facilitators in preparing for trial launch.

13.2 Treatment Fidelity (Evaluation of Treatment Integrity)

Supervision of Staff Conducting the Control and Care Facilitation Conditions

HCV pre- and post-test information/counseling is provided in both conditions/groups. HCV pre- and post-test information/counseling sessions in both groups and the intervention sessions in the Care Facilitation group will be audio recorded. A percentage of digitally recorded sessions will be randomly selected, reviewed and scored by the intervention team. Feedback from reviewed HCV pre- and post-test information/counseling sessions will be provided to the interventionist. The Intervention Director will conduct regularly scheduled conference calls to discuss difficulties and successes in providing HCV pre- and post-test information/counseling and in delivering the Care Facilitation sessions; to facilitate learning from and supporting each other; and to facilitate receiving support and feedback from the Intervention Director. Interventionists will be invited to seek additional consultation with the Intervention Director via phone or email as intervention issues arise. Lastly, local interventionist supervision will be available through the existing hierarchy of the CTN nodes.

Quality Control of the Care Facilitation Intervention

Quality control of the Care Facilitation intervention will be maintained through several methods: 1) a percentage of digitally recorded sessions will be randomly selected, reviewed and scored by the intervention team; 2) as much of the contact care facilitators may have with study participants may occur off site and out in the field where digitally recording sessions will not be appropriate, study coordinators may randomly choose a day to shadow the care facilitator out in the field, provide any necessary feedback; and 3) study coordinators, QA monitors and lead study team members will routinely review patient tracking spreadsheet to ensure that care facilitators are engaging with study participants accordingly.

14.0 CONCOMITANT INTERVENTION

Prior enrolling in CTN-0064, participants may have pre-existing relationships with case managers, social workers, or clinicians for the purposes of securing housing, benefits, food, HCV care, HIV care, substance use and mental health treatment. Renewed or continued contact with any such professional or paraprofessional staff may include discussion of HCV and HCV treatment, HIV care and treatment and substance use treatment. During the study, participants in either group may also be exposed to HCV testing, evaluation, treatment, HIV treatment or substance use treatment media campaigns and/or outreach. Regardless of study group, impeding any such contacts would be both unethical and infeasible. To account for non-study related professional or paraprofessional contacts, participants will be asked about such exposures during follow-up assessments.

15.0 REPORTING AND MONITORING

15.1 Statement of Compliance

This trial will be conducted in compliance with the appropriate protocol, current Good Clinical Practice (GCP), the principles of the Declaration of Helsinki, and all other applicable regulatory requirements. Participating sites must obtain written approval of the study protocol, consent form, other supporting documents, and any advertising for participant recruitment from their local institutional review board (IRB) in order to participate in the study. Prior to study initiation, the protocol and the informed consent documents will be reviewed and approved by an appropriate Ethics Review Committee (ERC) or IRB. Any amendments to the protocol or consent materials must be approved before they are implemented. Annual progress reports and local Serious Adverse Event (SAE) reports will be submitted to each IRB, according to its usual procedures.

15.2 Regulatory Files

The regulatory files should contain all required regulatory documents, study-specific documents, and all important communications. Regulatory files will be checked at each participating site for the regulatory documents compliance prior to study initiation, throughout the study, as well as at the study closure.

15.3 Informed Consent

The informed consent process is a means of providing study information to each prospective participant and allows for an informed decision about participation in the study. The informed consent form will include all of the required elements of informed consent. Each study site must have the study informed consent approved by their IRB(s). A copy of the IRB-approved consent, along with the IRB study approval, must be sent to the Clinical Coordinating Center (CCC) and the Lead Node (LN) prior to the site initiation visit and with each subsequent consent revision. Every study participant is required to sign a valid, IRB-approved current version of the study informed consent form prior to the initiation of any study related procedures. The site must maintain the original signed informed consent for every participant in a locked, secure location that is in compliance with their IRB and institutional policies and that is accessible to the study monitors. Every study participant should be given a copy of the signed consent form.

Prior to informed consent, research staff will explain the study to the potential participant and provide a copy of the consent to read. If the participant is interested in participating in the study, a staff member will review each section of the informed consent form in detail and answer any questions the participant may pose. The participant will consent by signing and dating the consent document. The person obtaining consent and a witness, if required by the local IRB(s), will also sign and date the consent document. It is strongly recommended that another research staff member review the consent after it is signed to ensure that the consent is properly executed and complete. Staff members delegated by the PI to obtain informed consent must be listed on the Staff Signature Log and must be approved by the IRB, if required. All persons obtaining consent must have completed appropriate training.

The informed consent form must be updated or revised whenever important new safety information is available, or whenever the protocol is amended in a way that may affect participants' participation in the trial. A copy of the informed consent will be given to a prospective participant to review during the consent process and to keep for reference. The participant will be informed that their participation is voluntary and they may withdraw from the study at any time, for any reason without penalty. Individuals who refuse to participate or who withdraw from the study will be treated without prejudice. Study sites

will be responsible for maintaining signed consent forms as source documents for quality assurance review and regulatory compliance.

15.4 Health Insurance Portability and Accountability Act (HIPAA)

Study sites may be required by their institutions to obtain authorization from participants for use of protected health information. Sites will be responsible for communicating with their IRBs or Privacy Boards and obtaining the appropriate approvals or waivers to be in regulatory compliance. Releases of participant identifying information that are permitted by the HIPAA regulations, but which are prohibited by other applicable federal regulations and/or state/Commonwealth law and regulation, are prohibited.

15.5 Investigator Assurances

Each community treatment program site must file (or have previously filed) a Federal Wide Assurance (FWA) with the DHHS Office for Human Research Protection setting forth the commitment of the organization to establish appropriate policies and procedures for the protection of human research subjects, with documentation sent to NIDA or its designee. Research covered by these regulations cannot proceed in any manner prior to NIDA receipt of certification that the research has been reviewed and approved by the IRB provided for in the assurance (45 CFR 46.103(b) and (f)). Prior to initiating the study, the principal investigator at each study site will sign a protocol signature page, providing assurances that the study will be performed according to the standards stipulated therein.

15.6 Financial Disclosure

All investigators will comply with the requirements of 42 CFR Part 50, Subpart F to ensure that the design, conduct, and reporting of the research will not be biased by any conflicting financial interest. Everyone with decision-making responsibilities regarding the protocol will confirm to the sponsor annually that they have met their institutional financial disclosure requirements.

15.7 Clinical Monitoring

Investigators will host periodic visits by NIDA contract monitors who will examine whether study procedures are conducted appropriately and that study data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulations. These monitors will audit, at mutually agreed upon times, regulatory documents, case report forms (CRFs), informed consent forms and corresponding source documents for each participant. Monitors will have the opportunity and ability to review any study-associated document or file.

NIDA-contracted monitors will assess whether submitted data are accurate and in agreement with source documentation and will also review regulatory/essential documents such as correspondence with the IRB. Areas of particular concern will be participant informed consent forms, protocol adherence, reported safety events and corresponding assessments, and principal investigator oversight and involvement in the trial. Reports will be prepared following the visit and forwarded to the site principal investigator, the lead investigator and NIDA CCTN.

Qualified node personnel (Node QA monitors) will provide site management for each site during the trial. Node QA staff will audit source documentation, including informed consent forms and HIPAA forms. This will take place as specified by the local protocol team, node PI or lead team and will occur as often as needed to help prevent, detect, and correct problems at the study sites. Node QA personnel will verify that study procedures are properly followed and that site personnel are trained and able to conduct the protocol appropriately. If the node personnel's review of study documentation indicates that additional training of site study personnel is needed, node QA personnel will undertake or arrange for that training.

Details of the contract, node QA and data monitoring are found in the study QA monitoring plan.

15.8 Study Documentation

Study documentation includes all case report forms, workbooks, source documents, monitoring logs and appointment schedules, sponsor-investigator correspondence, and signed protocol and amendments, Ethics Review Committee or Institutional Review Committee correspondence and approved consent form and signed participant consent forms.

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study. Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

15.9 Safety Monitoring

Data and Safety Monitoring Board (DSMB)

An independent CTN DSMB will examine accumulating data to assure protection of participants' safety while the study's scientific goals are being met. The CTN DSMB is responsible for conducting periodic reviews of accumulating safety and efficacy data. It will determine whether there is support for continuation of the trial, or evidence that study procedures should be changed, or if the trial should be halted, for reasons relating to the safety of the study participants, the efficacy of the treatment under study, or inadequate trial performance (e.g., poor recruitment).

Protocol Deviations Reporting and Management

Any departures from procedures or requirements outlined in the protocol will be classified as protocol deviations. A protocol deviation is an action (or inaction) that alone may or may not affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. In some cases, a protocol deviation may compromise participant safety, participant rights, inclusion/exclusion criteria or the integrity of study data and is cause for corrective action to resolve the departure and to prevent re-occurrence. Protocol deviations will be monitored at each site for (1) significance, (2) frequency, and (3) impact on the study objectives, to ensure that site performance does not compromise the integrity of the trial. The decision about whether a deviation from the protocol will be designated as minor or major will be made by the Clinical Coordinating Center (CCC) in conjunction with the protocol's Lead Investigator(s). The consequences will be specified and participating sites will be informed.

All protocol deviations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Deviation CRF. The CCC, DSC and the Lead Investigator must be contacted immediately if an unqualified or ineligible participant is randomized into the study. Additionally, each site is responsible for reviewing their local IRB's definition of a protocol deviation or violation and understanding which events need to be reported to the IRB. Sites must recognize that the CTN and IRB definition of a reportable event may differ and act accordingly in following all reporting requirements for both entities.

Confidentiality

Confidentiality will be maintained in accordance with all applicable federal regulations and/or state/Commonwealth law and regulations. By signing the protocol signature page the investigator affirms that information furnished to the investigator by NIDA will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committee; affiliated institution; and employees only under an appropriate understanding of confidentiality with such board

or committee, affiliated institution and employees. The lead investigator will obtain a federal Certificate of Confidentiality (CoC), protecting participants against disclosure of sensitive information (e.g., drug use), and will distribute it to all sites when received. The NIH office that issues the CoC will be advised of changes in the CoC application information. Participating CTP sites will be notified if CoC revision is necessary. Participant records will be held confidential by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data.

Adverse Events (AEs)

The Lead Investigator (LI) may appoint a Study Clinician (MD, NP or PA) for this study, who will review or provide consultation for each Serious Adverse Event (SAE) as needed. These reviews will include an assessment of the possible relatedness of the event to the study intervention or other study procedures. The Study Clinician will also provide advice for decisions to exclude, refer, or withdraw participants as required. In addition, NIDA will assign a Medical Monitor to this protocol to independently review the safety data, present it to the DSMB for periodic review, and provide PIs a Safety Letter when necessary. The Medical Monitor will determine which safety events require expedited reporting to NIDA, the DSMB and regulatory authorities. This will include events that are serious, related and unexpected. The study staff will be trained to monitor for and report adverse events and Serious Adverse Events. As there is no medication intervention, pregnancy will not be followed within the context of this study.

Each of the research sites have established practices for managing medical and psychiatric emergencies, and the study staff will continue to utilize these procedures. Treatment providers at each CTP will be responsible for monitoring participants for possible clinical deterioration or other problems, and for implementing appropriate courses of action.

15.9.1 Definitions of Adverse Event and Serious Adverse Event

Standard definitions for adverse events and serious adverse events, their identification, characterization regarding severity and causal relationship to study interventions, and processing are included in Appendix A.

15.9.2 Reportable Adverse Events and Serious Adverse Events

As this population will have significant ongoing health and substance use issues, events related to complications of HIV, HCV, substance use treatment or admission for substance detoxification, hospitalizations for medical, surgical and psychological reasons and deaths will be captured on study specific forms and will not be duplicate reported as an adverse or serious adverse event on the AE/SAE form set. These data will be presented to the DSMB at the regular meetings.

Adverse Events

The only study intervention associated with risk for participants is the collection of blood samples. As a result, only adverse events directly related to collection of blood samples will be reported. Adverse events will be captured from the time of specimen collection through the remainder of that visit.

Serious Adverse Events

Only serious adverse events directly related to collection of blood samples will be reported. Serious adverse events will be captured from the time of specimen collection through the remainder of that visit. Requirements for reporting other SAEs to local IRBs will be determined and complied with by each site. They should be reported to local IRBs per local IRB guidelines.

16.0 DATA MANAGEMENT AND PROCEDURES

16.1 Design and Development

This protocol will utilize a centralized Data and Statistics Center (DSC). The DSC will be responsible for development of the electronic case report forms (eCRFs), development and validation of the clinical study database, ensuring data integrity, and training site and participating node staff on applicable data management procedures. Advantage eClinical, a web-based distributed data entry system, will be implemented. This system will be developed to ensure that guidelines and regulations surrounding the use of computerized systems used in clinical trials are upheld. The remainder of this section provides an overview of the data management plan associated with this protocol.

16.2 Site Responsibilities

The data management responsibilities of each individual site will be specified by the DSC and outlined in the Advantage eClinical User's Guide.

16.3 Data Center Responsibilities

The DSC will 1) develop a data management plan and will conduct data management activities in accordance with that plan, 2) provide final guided source documents and eCRFs for the collection of all data required by the study, 3) develop data dictionaries for each eCRF that will comprehensively define each data element, 4) conduct ongoing data monitoring activities on study data from all participating sites, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

16.4 Data Collection

Data will be collected at the study sites on source documents and entered by the site into eCRFs in Advantage eClinical, or will be collected via direct entry into the eCRF. In the event that Advantage eClinical is not available, the DSC will provide the sites with a final set of guided source documents and completion instructions. Data entry into Advantage eClinical should be completed according to the instructions provided and project specific training. The investigator is responsible for maintaining accurate, complete and up-to-date records, and for ensuring the completion of the eCRFs for each research participant.

16.5 Data Acquisition and Entry

Completed forms and electronic data will be entered into the Advantage eClinical system in accordance with the Advantage eClinical User's Guide. Only authorized individuals shall have access to eCRFs.

16.6 Data Monitoring, Cleaning and Editing

eCRFs will be monitored for completeness and accuracy throughout the study. Dynamic reports listing missing values and forms are available to sites at all times in Advantage eClinical. These reports will be monitored regularly by the DSC. In addition, the DSC will identify inconsistencies within eCRFs and between eCRFs and post queries in Advantage eClinical on a scheduled basis. Sites will resolve data inconsistencies and errors by entering all corrections and changes directly into Advantage eClinical.

As described above, the CCC will conduct regular visits to sites during which audits comparing source documents to the data entered on the eCRF will be performed. Any discrepancies identified between the source document and the eCRF will be corrected by the site.

Trial progress and data status reports, which provide information on recruitment, availability of primary outcomes, treatment exposure, attendance at long term follow-up visits, regulatory status, and data quality, will be generated daily and posted to a secure website. These reports are available to the site, the corresponding RRTC, the lead investigator, the coordinating centers, and NIDA CCTN, to monitor the sites' progress on the study.

16.7 Data Lock and Transfer

Data will be transmitted by the DSC to the NIDA central data repository as requested by NIDA. The DSC will conduct final data quality assurance checks and "lock" the study database from further modification. The final analysis dataset will be returned to NIDA, as requested, for storage and archive.

16.8 Data Training

The training plan for site staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of Advantage eClinical.

16.9 Data QA

To address the issue of data entry quality, the DSC will follow a standard data monitoring plan. An acceptable quality level prior to study lock or closeout will be established as a part of the data management plan. Data quality summaries will be made available during the course of the protocol.

17.0 STUDY TIMELINE

After receiving DSMB approval of the full/final protocol, approximately 3-5 months of trial preparation activities will elapse prior to commencing randomization. Trial preparation will include obtaining IRB approval, applying for a Certificate of Confidentiality, developing the data collection systems, developing the manual of operating procedures, conducting all staff training, and sites' securing CLIA Certificates of Waiver (as needed), and endorsing sites. If feasible, the study may be implemented in a single wave; however, sites may launch on a rolling basis of 2-3 sites per week. Recruitment is expected to take approximately 4-5 months, with follow-up continuing for approximately 12 months post completion of the recruitment phase. Two months will be allowed for data lock after the end of the follow-up period. Therefore, data lock is projected to occur at approximately 21-24 months after DSMB approval of the final protocol.

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19.0 APPENDICES

- 19.1 **Appendix A** - Adverse Event Reporting Definitions and Procedures
- 19.2 **Appendix B** - Data and Safety Monitoring Plan
- 19.3 **Appendix C** - Ancillary Study, CTN-0064-A-1, Determination of Cause of Death Among HIV-Infected Substance Users Enrolled in Project HOPE: A 4-year Follow-Up

19.1 APPENDIX A: Adverse Event Reporting Definitions and Procedures

Each participating site's Principal Investigator is responsible for study oversight, including ensuring human research subject protection by designating appropriately qualified and trained study personnel to assess, report, and monitor adverse events.

For the purposes of this study only adverse events and serious adverse events directly related to biological specimen collection will be captured. The collection of these safety events will begin at the time of specimen collection and continue through the remainder of that study visit.

Definition of Adverse Events and Serious Adverse Events

An adverse event (AE) is any untoward medical occurrence in humans, whether or not considered study drug/intervention related which occurs during the conduct of a clinical trial. Any change from baseline in clinical status, ECGs, lab results, x-rays, physical examinations, etc., that is considered clinically significant by the study medical clinician are considered AEs.

Suspected adverse reaction is any adverse event for which there is a reasonable possibility that the study drug/intervention caused the adverse event. A reasonable possibility implies that there is evidence that the study drug/intervention caused the event.

Adverse reaction is any adverse event caused by the study drug/intervention.

An adverse event, suspected adverse reaction, or adverse reaction is considered "serious" (i.e., a serious adverse event, serious suspected adverse reaction or serious adverse reaction) if, in the view of either the study medical clinician or sponsor, it:

1. Results in death: A death occurring during the study or which comes to the attention of the study staff during the protocol-defined follow-up period, whether or not considered caused by the study drug/intervention, must be reported.
2. Is life-threatening: Life-threatening means that the study participant was, in the opinion of the medical clinician or sponsor, at immediate risk of death from the reaction as it occurred and required immediate intervention.
3. Requires inpatient hospitalization or prolongation of existing hospitalization.
4. Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5. Is a congenital abnormality or birth defect.
6. Important medical event that may not result in one of the above outcomes, but may jeopardize the health of the study participant or require medical or surgical intervention to prevent one of the outcomes listed in the above definition of serious event.

Definition of Expectedness

Any adverse event is considered "unexpected" if it is not listed in the investigator brochure or the package insert or is not listed at the specificity or severity that has been observed. If neither is available then the protocol and consent are used to determine an unexpected adverse event.

Pregnancy

As there is no medication intervention, pregnancy will not be followed within the context of this study.

Medical and Psychiatric History

A thorough medical and psychiatric history during the baseline phase should record any chronic, acute, or intermittent preexisting or current illnesses, diseases, symptoms, or laboratory signs of the participant, to avoid reporting pre-existing conditions as new AEs and to assist in the assessment of worsening in intensity or severity of these conditions that would indicate an AE. Stable chronic conditions, such as arthritis, which are present prior to clinical trial entry and do not worsen are not considered AEs.

Site's Role in Eliciting and Reporting Adverse Events

Appropriately qualified and trained personnel will elicit participant reporting of AEs and SAEs at each study visit designated to collect AEs. Adverse events (medical and/or psychiatric) assessment will initiate with participant consent and follow-up will continue through 30 days post last study visit. Study personnel will obtain as much information as possible about the reported AE/SAE to complete the AE/SAE forms and will consult as warranted.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events). Local sites are responsible for reporting SAEs to their IRB, per their IRB's guidelines.

Sites are required to enter reportable AEs and SAEs in the Advantage eClinical system. The AE form is used to capture reportable AEs (as defined in the protocol). Additional information may need to be gathered to evaluate SAEs and to complete the appropriate CRFs and the summary. This process may include obtaining hospital discharge reports, medical records, autopsy records or any other type records or information necessary to provide a complete and clear picture of the serious event and events preceding and following the event. If the SAE is not resolved or stable at the time of the initial report or if new information becomes available after the initial report, follow-up information must be submitted as soon as possible.

Reportable adverse events will be followed until resolution, stabilization or study end. Any serious adverse reactions will be followed until resolution or stabilization even beyond the end of the study.

Site's Role in Assessing Severity and Causality of Adverse Events

Appropriately qualified and trained study personnel will conduct an initial assessment of seriousness, severity, and causality when eliciting participant reporting of adverse events. A study medical clinician will review reportable AEs for seriousness, severity, and causality on at least a weekly basis.

Guidelines for Assessing Severity

The severity of an adverse event refers to the intensity of the event.

Grade 1	Mild	Transient or mild discomfort (typically < 48 hours), no or minimal medical intervention/therapy required, hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms, e.g., aspirin for simple headache, acetaminophen for post-surgical pain)
Grade 2	Moderate	Mild to moderate limitation in activity some assistance may be needed; no or minimal intervention/therapy required, hospitalization possible.
Grade 3	Severe	Marked limitation in activity, some assistance usually required; medical intervention/ therapy required hospitalization possible.

Guidelines for Determining Causality

The study medical clinician will use the following question when assessing causality of an adverse event to study drug/intervention where an affirmative answer designates the event as a suspected adverse reaction:

Is there a reasonable possibility that the study drug/intervention caused the event?

Site's Role in Monitoring Adverse Events

Local quality assurance monitors will review study sites and respective study data on a regular basis and will promptly advise sites to report any previously unreported safety issues and ensure that the reportable safety-related events are being followed to resolution and reported appropriately. Staff education, re-training or appropriate corrective action plan will be implemented at the participating site when unreported or unidentified reportable AEs or serious events are discovered, to ensure future identification and timely reporting by the site.

Sponsor's Role in Safety Management Procedures of AEs/SAEs

A NIDA-assigned Medical Monitor/Safety Monitor is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the Medical Monitor, Safety Monitor, Lead Investigator, and designees. All SAEs will be reviewed by the Medical Monitor/Safety Monitor in Advantage eClinical and, if needed, additional information will be requested. The Medical Monitor/Safety Monitor will also report events to the sponsor and the DSMB. The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the NIDA assigned Medical Monitor/Safety Monitor may also request additional and updated information. Details regarding specific adverse events, their treatment and resolution, will be summarized by the Medical Monitor in writing for review by the sponsor and DSMB. Subsequent review by the Medical Monitor, DSMB, FDA and ethics review committee or IRB, the sponsor, or relevant local regulatory authorities may also suspend further trial treatment at a site. The study sponsor, DSMB and FDA retain the authority to suspend additional enrollment and treatments for the entire study as applicable.

Regulatory Reporting for a non-IND study

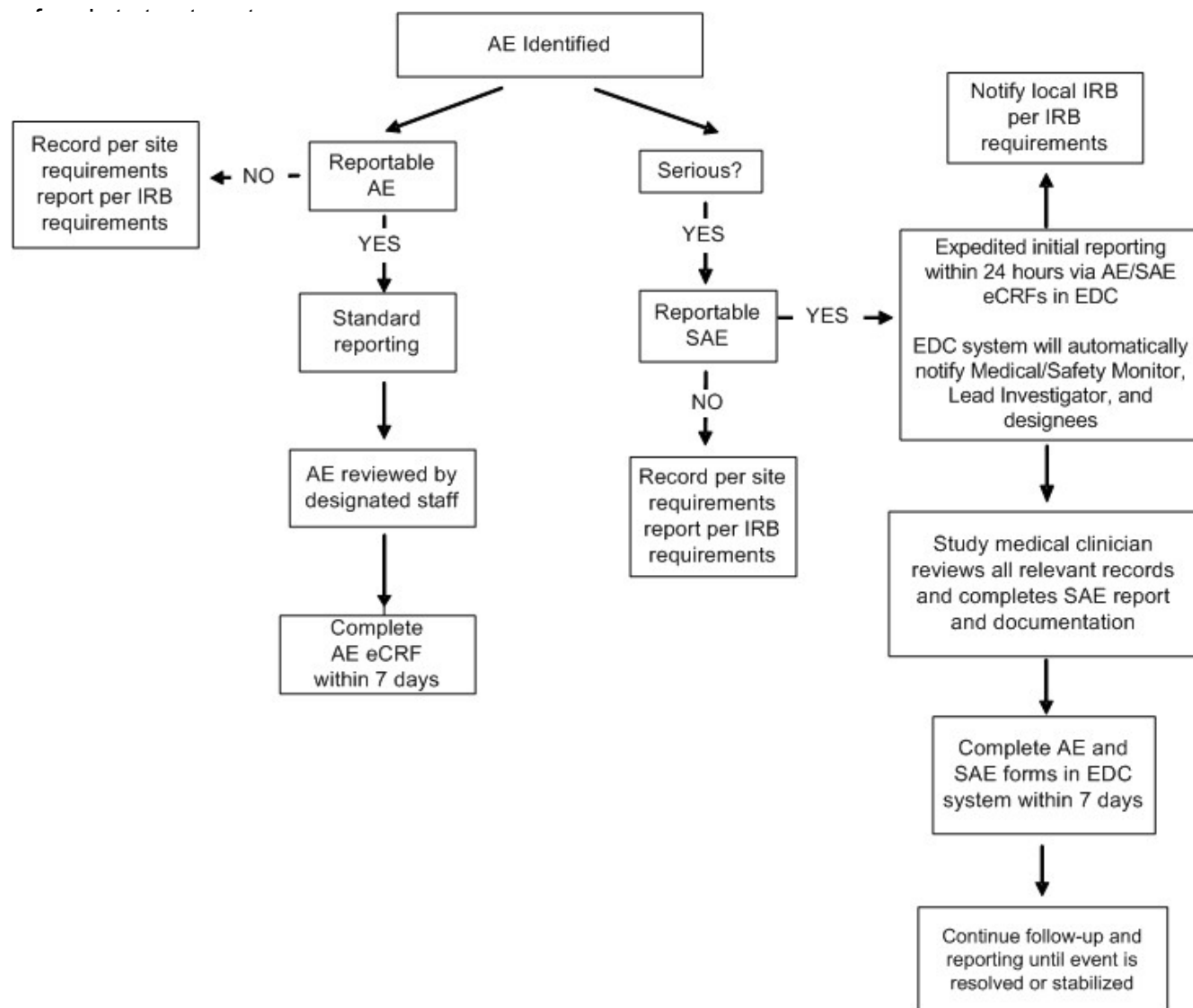
If an SAE meets the expedited reporting criteria (serious and unexpected suspected adverse reactions) the Medical Monitor on behalf of the sponsor will submit a volunteer MedWatch report to the FDA. The Medical Monitor will prepare an expedited report (MedWatch Form 3500 or similar) for the FDA and other regulatory authorities.

Reporting to the Data and Safety Monitoring Board

The DSMB will receive listing of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs.

Participant Withdrawal

The study medical clinician must apply his/her clinical judgment to determine whether or not an adverse event is of sufficient severity to require that the participant be withdrawn from further study medication administration/study intervention. The study medical clinician should consult with the site Principal Investigator, the lead investigator and/or Medical Monitor as needed. If necessary, a study medical clinician may suspend any trial treatments and institute the necessary medical therapy to protect a participant from any immediate danger. A participant may also voluntarily withdraw from treatment due to what he/she perceives as an intolerable adverse event or for any other reason. If voluntary withdrawal is requested, the participant will be asked to complete an end-of-medication visit to assure safety and to document end-of-medication outcomes and will be given recommendations for medical care and/or



19.2 APPENDIX B: Data and Safety Monitoring Plan

Brief Study Overview

The prevalence of hepatitis C virus (HCV) among HIV-infected individuals is estimated to be 15-fold higher than HCV prevalence rates in the general U.S. population and HCV in the presence of HIV is associated with increased morbidity and mortality. The most common risk factor for HCV is (past or present) injection drug use (IDU); intranasal drug use is also a risk factor. Despite high HCV prevalence, advances in HCV testing technologies, and emphasis on testing, diagnosis, and linkage to HCV care/treatment, uptake of HCV therapy in the era of new HCV treatment is low. Using the existing CTN-0049 cohort as a research platform, the proposed RCT will assess the effectiveness of an efficacious linkage to care intervention for HIV/HCV co-infected substance users. Linkage to care will be operationalized as receipt of clinical evaluation/treatment for HCV infection. Secondary objectives will be to assess: 1) success at each step in the cascade, 2) engagement in substance use treatment 3) engagement in HIV care, 4) HIV viral suppression as well as 5) to examine other long-run outcomes of the CTN 0049 cohort.

Oversight of Clinical Responsibilities

Site Principal Investigator

Each participating site's Principal Investigator (PI) is responsible for study oversight, including ensuring human research participant protection by designating appropriately qualified, trained research staff and medical clinicians to assess, report, and monitor adverse events.

Regarding safety and in accordance with FDA reporting requirements, all Adverse Events (AEs) occurring during the course of the clinical trial will be collected, documented, and reported by the investigator or sub-investigators according to the Protocol. The assessment of Adverse Events (medical and/or psychiatric) will commence at the time of participant consent and will continue through 30 days post last active treatment visit.

The occurrence of AEs and Serious Adverse Events (SAEs) will be assessed at each clinic visit during the study. Serious adverse events will be followed until resolved or considered stable, with reporting to the CCC Safety Monitor/Medical Monitor through the follow-up period.

Standard reporting, within 7 days of the site becoming aware of the event, is required for reportable AEs. Expedited reporting (within 24 hours of their occurrence and/or site's knowledge of the event) is required for reportable SAEs (including death and life-threatening events).

Medical Monitor/Safety Monitor

The NIDA CCTN Clinical Coordinating Center (CCC) Safety Monitor/Medical Monitor is responsible for reviewing all adverse events and serious adverse events reported. All SAEs will be reviewed at the time they are reported in the EDC. The Medical Monitor will also indicate concurrence or not with the details of the report provided by the site PI. Where further information is needed the Safety monitor/Medical monitor will discuss the event with the site. Reviews of SAEs will be conducted in the Advantage eClinical data system and will be a part of the safety database. All AEs are reviewed on a weekly basis to observe trends or unusual events.

Reports will be generated and presented for Data and Safety Monitoring Board (DSMB) meetings. The DSMB will receive listings of AEs and summary reports of all SAEs at a frequency requested by the DSMB, but at least annually. Furthermore, the DSMB will be informed of expedited reports of SAEs

Data and Safety Monitoring Board (DSMB)

The NIDA CTN DSMB affiliated with this trial will be responsible for conducting periodic reviews of accumulating safety, trial performance, and outcome data. The DSMB will make recommendations to NIDA CCTN as to whether there is sufficient support for continuation of the trial, evidence that study procedures should be changed, or evidence that the trial (or a specific site) should be halted for reasons relating to safety of the study participants or inadequate trial performance (e.g., poor recruitment).

Following each DSMB meeting, the NIDA CCTN will communicate the outcomes of the meeting, based on DSMB recommendations, in writing to the study Lead Investigator. This communication detailing study safety information will be submitted to participating IRBs.

Quality Assurance (QA) Monitoring

Monitoring of the study site will be conducted on a regular basis using a combination of NIDA CCTN CCC contract monitors and the RRTC site managers/monitors. Investigators will host periodic visits for the NIDA CCTN CCC contract monitors and RRTC site managers/monitors. The purpose of these visits is to assess compliance with GCP requirements and to document the integrity of the trial progress. Areas of particular concern will be the review of inclusion/exclusion criteria, participant informed consent forms, protocol adherence, safety monitoring, IRB reviews and approvals, regulatory documents, participant records, study drug accountability, and PI supervision and involvement in the trial. The monitors will interact with the site staff to identify issues and re-train the site as needed to enhance research quality.

QA Site Visit Reports will be prepared by the NIDA CCC contract monitors following each site visit. These reports will be generated and forwarded to the site PI, the study Lead Investigator and NIDA CCTN.

Management of Risks to Participants

Confidentiality

Confidentiality of participant records will be secured by the use of study codes for identifying participants on CRFs, secure storage of any documents that have participant identifiers, and secure computing procedures for entering and transferring electronic data. No identifying information will be disclosed in reports, publications or presentations.

Information Meeting Reporting Requirements

The consent form will specifically state the types of information that are required to be reported and the fact that the information will be reported as required. These include suspected or known sexual or physical abuse of a child or elders, or threatened violence to self and/or others.

Participant Protection

The study clinician will evaluate all pertinent screening and baseline assessments prior to participant randomization to ensure that the participant is eligible and safe to enter the study. Adverse events (AEs) will be assessed and documented at each clinic visit. Individuals who experience an AE that compromises safe participation will be discontinued from further medication administration/intervention and provided referrals for other treatment or to specialized care. Study personnel will request that the participant complete an end-of medication visit to assure safety and to document end-of-medication outcomes.

To maintain participant confidentiality throughout the conduct of the trial, most assessments, CRFs, reports and other records will be coded using alphanumeric identifiers only. All study data will be stored in a secure location with limited access. Only research staff will have access to the study records. Other parties with access to study data, such as local or central institutional review boards, will be specified to the participants, per HIPAA regulations.

Participant information will not be released without their written permission, except as necessary for monitoring. The Lead Investigator (LI) will apply for a certificate of confidentiality that will cover all sites participating in the study. By participating in this protocol, the local site investigator agrees that within local regulatory restrictions and ethical considerations, any regulatory agency may consult and/or copy study documents to verify study data.

By participating in this protocol, the local site investigator affirms that information furnished to the investigator by the Lead Investigator will be maintained in confidence and such information will be divulged to the IRB, Ethical Review Committee, or similar expert committees, affiliated institutions, and employees only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees.

Special Populations to Consider

The use of CAPI (computer assisted personal interview) will facilitate enrollment and completion of assessments with low-literacy and illiterate participants as all assessments/questionnaires (and answers) will be read to participants and recorded by study staff. According to CFR regulations, studies involving prisoners require special considerations and approvals. Unless a participating site has both IRB and OHRP approval to work with prisoners, research staff must cease all intervention and interaction with a participant and his/her contacts and may no longer obtain private identifiable information about the participant.

Pregnancy

It should be noted that pregnancy is not an exclusion criterion. Therefore, sites may enroll pregnant women and/or follow-up with already enrolled women who become pregnant after enrollment in the study provided that they have local IRB approval to do so. As there is no medication intervention, pregnancy will not be followed within the context of this study.

Study Specific Risks

- **Blood drawing (venipuncture) risks:** Drawing blood may cause temporary discomfort from the needle stick and/or bruising. Rarely, infection or the formation of a small clot or swelling to the vein and surrounding area may occur. All measures will be taken to minimize this risk by strict adherence to proper procedures for drawing blood.
- **HCV testing risks:** Being tested for HCV may cause anxiety regardless of the test results. A reactive rapid HCV antibody test means that the participant has been infected with the HCV virus. A positive HCV RNA test means that the participant has active HCV that should be evaluated and treated. If either test is negative, there is still the chance that the participant could later become infected with the HCV virus and test positive at some time in the future, even if his/her body has cleared the infection once. Also, there is always the chance that the test results could be wrong.
- **Other risks:** There are no known psychological risks associated with the interview questionnaires, procedures, or counseling in this study. It is possible that discussion of sensitive topics such as HCV, HIV or substance use may cause emotional discomfort in some participants. There may also be risks of emotional distress, inconvenience and possible loss of privacy and confidentiality associated with

taking part in a research study. There may be risks that are unknown.

19.3 APPENDIX C: Ancillary Study, CTN-0064-A-1, Determination of Cause of Death Among HIV-Infected Substance Users Enrolled in Project HOPE: A 4-year Follow-Up

19.3.1 Overview

19.3.1.1 Significance

In the past 30 years, an HIV diagnosis has been transformed from a lethal disease to a chronic disease; those with HIV infection have a life expectancy similar to those with other chronic diseases (Lohse N, Hansen AB, Pedersen G, et al., 2007). Reduction in HIV mortality has been attributed to engagement in the HIV care continuum as a person infected with HIV is quickly identified and diagnosed, linked to HIV care, treated with antiretroviral therapy (ART), continues engagement in HIV care, and achieves HIV viral suppression, which leads to an increase in CD4 cell count (Mugavero MJ, Amico KR, Horn T, Thompson MA, 2013) and virtually eliminates the possibility of HIV transmission. However, many HIV-infected substance users have not benefited from these advances in HIV treatment and many fail to engage in the HIV care continuum at various steps along the cascade; if engaged many still suffer from excess mortality (Suarez-Garcia I, Sobrino-Vegas P, Dalmau D, et al., 2016; Degenhardt L, Bucello C, Mathers B, et al., 2011). The most critical endpoint of HIV care is reduction in mortality. Studies continue to demonstrate excess risk of death in the substance using HIV population based on the standardized mortality ratio (SMR), the ratio of mortality of a study cohort with respect to the general population, which indicates excess mortality in the sample (Degenhardt L, Bucello C, Mathers B, et al., 2011). A literature review of dependent opioid users found an SMR of

14.66 (95% CI: 12.82, 16.50). The study also examined pooled crude mortality ratio (CMR), which is the number of deaths against person-years of follow-up. For death due to AIDS, SU (overdose, suicide, trauma), and non-HIV disease-related mortality, they found 3 times higher mortality among opioid or injection drug users (IDUs) infected with HIV compared to those who were not HIV-infected (Degenhardt L, Bucello C, Mathers B, et al., 2011). Furthermore, the SMR of 73.7 (95%CI 46.4-116.9) was found in IDUs who failed to suppress HIV viral replication and had CD4 cell counts <50 cells/ μ L at 6 months after receipt of ART (Antiretroviral Therapy Cohort C, Zwahlen M, Harris R, et al., 2009). Studies examining cause-specific mortality in IDUs with HIV have indicated different causes for mortality. Several studies among HIV IDUs have found excess mortality due to HCV (May MT, Justice AC, Birnie K, et al., 2015; Chen TY, Ding EL, Seage III GR, Kim AY, 2009). Yet, other studies have found un-intentional deaths increased significantly among IDUs in the post-ART era (Smit C, Gekus R, Walker S, et al., 2006). And still others have found AIDS related deaths to be the leading cause of death among HIV infected IDUs (34.6%) as well as those who acquired HIV through sexual transmission (52.9%). Thus, the data reflect a variety of causes of death among IDUs, but little is known about cause of death in non-injection substance users (NISUs). NISUs are at risk for HCV (Scheinmann R, Hagan H, Lelutiu-Weinberger C, et al., 2007) often associated with high risk sexual behavior (Daskalopoulou M, Rodger A, Thornton A, et al., 2014). It remains unknown if substance users who are often not engaged in care are at increased risk for death from HIV co-morbidities, HCV-related complications, other non-AIDS illnesses, or from SU. Thus, considerable gaps remain in our knowledge of cause-specific mortality in HIV-positive substance users, especially NISUs, and in our knowledge of the impact of treatment (HIV, HCV, SU) engagement on overall and cause specific mortality. Understanding the leading causes of death in these populations, and the impact of the care continuum engagement on mortality rates, can help focus resources to improve life expectancy.

Treatment of SUDS and HIV improves survival (Nosyk B, Min JE, Evans E, et al., 2015). Opioid substitution therapy (OST) can reduce mortality by decreasing accidental deaths, trauma, and suicide (Caplehorn

JR, Dalton MS, Cluff MC, Petrenas AM, 1994; Degenhardt L, Randall D, Hall W, Law M, Butler T, Burns L., 2009). A recent population-based study in British Columbia examined OST and ART initiation and found them to be protective against HIV-related deaths, drug-related deaths, and deaths due to other causes (Nosyk B, Min JE, Evans E, et al., 2015). However, this study focused only on IDUs starting ART. A Spanish study compared HIV-infected IDUs to un-infected IDUs and found survival similar after 1997, likely due to the availability of ART (Muga R, Langohr K, Tor J, et al., 2007). Although these studies imply that treatment of HIV can improve survival, there still remains a gap in knowledge about improvement in survival among NISUs and if other co-morbidities are leading to death in this population.

CTN-0049 and CTN-0064 provide the infrastructure for this Ancillary Study. CTN-0049 recruited patients from 11 hospitals in regions in the U.S. considered to be epicenters for HIV-infection, and enrolled 801 HIV-infected hospitalized patients. CTN-0049 participants are a vulnerable population who were enrolled during their index hospitalization, many of whom were not engaged in HIV care, often had AIDS, and were substance users. Participant median CD4 count at baseline was 110 cells/ μ L and HIV viral load was 52,448 copies/mL. IDU, either current or past, was reported in 32.5% of participants. Approximately one-third of participants were also co-infected with HCV likely transmitted through IDU or high risk sexual behavior associated with substance use. CTN-0064 is a follow-up to CTN-0049 in which all participants who agreed to be contacted for future research (97% of the 801 randomized participants agreed to be followed up after CTN-0049) and who were not documented as deceased in the CTN-0049 database (hereafter referred to as “CTN-0049 cohort”) are invited back for an interview, blood and urine collection and tested for HCV. Those who are HCV antibody positive are randomized to 6 months of care facilitation versus treatment as usual to determine if care facilitation can assist HCV/HIV co-infected participants in moving forward through the HCV care continuum. CTN-0064 serves as the platform for this ancillary study.

19.3.1.2 *Innovation*

This ancillary study is a unique opportunity to examine all cause and cause-specific mortality and to compare those who survived to those who did not. This cohort is one of the largest multi-center HIV substance using cohorts enrolled in a clinical trial and thus provides a unique opportunity to understand cause-specific mortality from diverse geographical distribution among a vulnerable population. During CTN-0049 (from randomization of 801 participants through 12 month follow-up assessments, outcome data were available on 96.6% of participants), 90 subjects (11%) died. Of these 36.7% were IDU and 63.3% were NISU. CTN-0064 is currently enrolling CTN-0049 cohort individuals as participants and as of November 15, 2016, 112 new deaths, (16% of the targeted enrollment of 687 participants), have been reported among the CTN-0049 cohort since their last CTN- 0049 visit. Although we recognize that linkage to HIV and SU treatment is important to improve clinical outcomes (Gardner LI, Marks G, Strathdee SA, et al., 2016), we now have an opportunity to examine cause-specific mortality in this population, ultimately allowing resources to be focused in high priority areas which can improve survival. The follow-up data from CTN-0049/0064 is an opportunity to learn what the leading cause of death is among HIV-infected SUs with or without HCV. Treatment now exists for hepatitis C (Afdhal N, Reddy KR, Nelson DR, et al., 2014; Afdhal N, Zeuzem S, Kwo P, et al., 2014; Feld JJ, Kowdley KV, Coakley E, et al., 2014; Nelson DR, Cooper JN, Lalezari JP, et al., 2015; Poordad F, Hezode C, Trinh R, et al., 2014; Sulkowski M, Hezode C, Gerstoft J, et al., 2015; Sulkowski MS, Gardiner DF, Rodriguez-Torres M, et al., 2014) which is highly effective. There is effective biomedical treatment for HIV, opioid use and alcohol use disorders, and the future holds promising new treatment such as long-acting injectable antiretroviral treatment for HIV (Margolis DA, Brinson CC, Smith GH, et al., 2015). Thus, we are poised with a unique opportunity to utilize mortality data collected from CTN-0049/0064 to understand cause of mortality, risk factors for mortality, and to use these data to develop a prediction tool to guide individual provider-level and system-level resource allocation to improve life expectancy.

19.3.2 Specific Aims and Hypotheses

Specific AIM 1: (a) To determine if the primary and secondary causes of death among CTN-0049 (Project HOPE) participants who have died, either during CTN-0049, the follow-up period after CTN-0049, or during CTN-0064 (hereafter referred to as “CTN-0049/0064 cohort”), were due to AIDS (i.e., opportunistic infections or malignancies), liver disease (decompensated liver disease, liver cancer), substance use (SU) (i.e., unintentional deaths due to overdose, accidents, suicide, trauma), or non-AIDS comorbidities (i.e., non-AIDS malignancies or cardiovascular disease). (b) To determine if differences in primary and secondary causes of death exist among those with hepatitis C (HCV)-HIV- co-infection compared to those with HIV alone. Specific Aim 1 will be accomplished by abstracting medical records of clinic visits, hospitalizations, emergency department (ED) visits, HIV-related, HCV-related and other lab results, additional diagnoses and co-morbidities, death certificates, and National Death Index. Section 164.512 of the Privacy Rule also establishes specific PHI uses and disclosures that a covered entity is permitted to make for research without an Authorization, a waiver or an alteration of Authorization, or a data use agreement. These limited activities are the use or disclosure of PHI preparatory to research and the use or disclosure of PHI pertaining to decedents for research. The hypotheses are that there is a higher mortality among CTN-0049/0064 cohort participants with HCV, and that this higher mortality is due to liver disease complications when compared to AIDS, SU, or other non-AIDS related co-morbidities.

Specific AIM 2: To determine the risk factors for all-cause mortality based on baseline CTN-0049/0064 cohort data and follow-up health services data. We will examine co-morbidities, engagement in HIV care continuum, and other risk factors such as ED visits, and hospitalizations. Co-morbidities to be examined as risk factors include HCV, SU including type of drug, method of use (injection vs. non-injection), pattern of use (daily versus episodic), addiction treatment, mental health such as depression or anxiety, homelessness, and smoking (current or past). Engagement in the HIV care continuum will be measured by clinic visits, HIV viral suppression, and CD4 count. A similar analysis using cause-specific death, evaluated through Specific AIM1, will be done. The hypothesis to be tested is that those with HCV, HIV, other co-morbidities, or those with current active SU with alcohol, injection drugs or non-injection substance use (NISU) (including cocaine, amphetamines, and non-prescription opioids) are at higher risk of death compared to those who have received or are receiving treatment for substance misuse and substance use disorders (SUDS), HIV, or HCV.

Specific AIM 3: Develop an HIV-specific mortality index to help clinicians and public health officials determine who is at highest risk for mortality in three years. This mortality index will be based on weighted assessments of risk factors derived from Specific AIM 2 and random forest plots to identify specific predictors of death to construct a mortality index. We hypothesize that based on data generated from Specific AIM 2, a number of predictors can be combined in order to develop an HIV-specific mortality index that can be used to predict 3-year mortality. This exploratory aim will then require validation in other datasets.

19.3.3 Approach

19.3.3.1 Methods/Methodology

All participants who died during CTN-0049 (n=90) had a death case report form (CRF) completed by a clinical investigator. Although clinicians were not versed on the WHO guidelines (Guidelines for HIV Mortality Measurement, Geneva, 2014), the death CRF followed the WHO guidance and included primary and secondary causes of death with instructions for the clinician to not enter terminal event as the primary cause, but instead determine the underlying disease that led to the death and to write a narrative on the circumstances leading to death. The death CRF used for CTN-0049 is being used for the CTN-0064 study. For deaths occurring after CTN-0049, the site PI/ research clinician and research

staff will be trained on WHO guidelines to determine primary and secondary cause of death. The site clinician will assist research staff in completing the death CRF, based on WHO guidelines, and signing the completed death CRF indicating agreement with listed causes of death. Data will be abstracted from known clinic and hospital(s) to help determine circumstances leading to death. For participants who were not engaged in HIV care and for whom no information from hospital records can be obtained, the primary source of information on death will be from death certificates and from a National Death Index search. Data, for those who enroll in CTN-0064 and die during follow-up will also be abstracted in a similar fashion. In addition, we will have a rich data set of information on demographics (including race/ethnicity and geospatial variables based on address of residence), mental health, substance use and treatment, clinical engagement as measured by CD4 count and HIV viral load, clinic visits and hospitalizations. Thus, this ancillary study will utilize data collected during CTN-0049 and already being collected during CTN-0064; it will also use existing CTN-0064 CRFs to collect data on the cohort individuals who died prior to CTN-0064 enrollment (not collected during CTN-0049). Data for those who died post CTN-0049 and did not enroll into CTN-0064 will be collected by Lead Node and/or Node staff. Data will be entered into a site specific Death Form in Advantage eClinical.

In order to harmonize data collected in CTN-0049 with new data, a Mortality Review and Adjudication Committee, composed of clinicians/clinical researchers with experience in HIV and/or HCV, trained on the WHO methodology of determining cause of death, will review the narrative and the primary and secondary causes of death of the initial CTN-0049 deaths. We will have two committee members review the death forms completed by the sites and either agree or establish a new primary and secondary causes of death. Both reviewers should reach consensus through discussion about the causes of death. If they are unable to reach consensus, then a third reviewer will be asked to evaluate the case. The committee will also review death CRFs completed by sites for those deaths occurring after CTN-0049 to ensure consistency in reporting across the study.

19.3.3.2 Study Population

The study population consists of decedents, CTN-0049/0064 cohort participants who have died since enrolling in either study. Additionally, the NDI search will include decedents as well as all cohort participants who were lost to follow-up, i.e., those who were never located for enrollment into CTN- 0064 and those who enrolled in CTN-0064 yet did not return for follow-up visits.

19.3.3.3 Measures

As outlined in the Specific Aims and Hypotheses section 19.3.2, measures will include clinic visits, hospitalizations, emergency department (ED) visits, HIV-related, HCV-related and other lab results, additional diagnoses and co-morbidities, and causes of death. Sources of measurement include medical records, death certificates, and National Death Index. These data will be captured using already existing CRFs as listed in the Assessments Timetable in section 10.4 of the parent/platform CTN-0064 protocol including the Death CRF, the “general assessments” (medical record), and service utilization emergency department and inpatient hospital modules (medical record). Additional co- morbidities (e.g., homelessness) as self-reported and/or abstracted in the CTN-0049 and/or CTN-0064 data sets will be included in the analyses.

19.3.3.4 Outcomes

The main outcomes of interest are primary and secondary causes of mortality and risk factors for mortality.

19.3.3.5 Data Analysis

Specific Aim 1: Cause-specific mortality. We will assess if primary causes of deaths were due to AIDS, liver disease, non-AIDS, or SU (overdose, trauma, accidents, suicide). A similar analysis for secondary causes of death will be performed. Additionally, we will examine primary and secondary causes of death among those with HIV alone compared to those co-infected with HIV/HCV and IDU compared to NISU.

Specific Aim 2: Risk factors for mortality. Using the CTN-0049/0064 baseline data and health services utilization data, we will employ Cox-proportional hazards to examine risk factors for death. Covariates will include elements from the HIV care continuum at the time of death such as HIV viral suppression, CD4 cell count, attendance at HIV clinic visits; HIV co-morbidities such as HCV infection (and degree of HCV care continuum engagement as measured in CTN 0064), malignancies, cardiac disease, active substance use, SUDS treatment, mental illness, and other risk factors for mortality such as hospitalizations and ED visits as well as demographic variables including race/ethnicity, gender and geospatial variables. We will also examine cause-specific deaths using the same methodology.

Specific Aim 3: Mortality Index to predict 3-year mortality. Using the weighted assessment of risk factors for mortality as a guide we will derive a mortality prediction model using random forests for survival models. Random forests (RF) have excellent predictive properties and are known to create predictive models which are replicable in future studies. RF has been successfully applied in many scientific problems (Bureau A, Dupuis J, Falls K, et al., 2005; Chen X, Wang L, Ishwaran H., 2010; Hsieh E, Gorodeski EZ, Blackstone EH, Ishwaran H, Lauer MS, 2011; Rice TW, Rusch VW, Ishwaran H, Blackstone EH, 2010; Rizk NP, Ishwaran H, Rice TW, et al., 2010; Wu B, Abbott T, Fishman D, et al., 2003; Svetnik V, Liaw A, Tong C, Culberson JC, Sheridan RP, Feuston BP, 2003). The resulting prediction will then be processed through a cluster analysis of RF procedure to identify the specific predictors associated with differential stages (or levels) of risk of death. From these predictors, we will develop an index to predict 3-year mortality.

As much of the above analyses will occur as resources permit.

19.3.3.6 Study Design

This is a retrospective medical record abstraction and review of NDI data and/or death certificates of CTN-0049/0064 participants who have died. We will perform medical record abstraction, search the National Death Index (NDI) and/or obtain death certificates for all participants who have died in the CTN-0049/0064 cohort. We recognize that death certificates can be incorrect (Guidelines for HIV Mortality Measurement, Geneva, 2014). Therefore, we will use WHO's established guidelines to determine primary and secondary causes of death.

19.3.3.7 Expected Sample Size

The proportion of deaths during CTN-0049 was 11% over approximately 2 years and as of 11/28/16, a total of 113 additional individuals have died since participating in CTN-0049 and before enrolling in CTN-0064 (amounting to approximately 14% of the 801 enrolled in CTN-0049 having died in approximately 2 years after that study). Based on the aforementioned deaths, we estimate a death rate of 6.25% per year. Therefore, we estimate that another 50 deaths may occur among those enrolled in the CTN-

0064 study by the end of the study, resulting in approximately 250 deaths: 90 during the course of the CTN-0049 study and approximately 160 occurring since participation in CTN- 0049 (roughly 115 prior to CTN-0064 enrollment and 45 after enrollment). Even with the current 203 known deaths (90 during CTN-0049 and 113 prior to CTN-0064 enrollment), we will have sufficient sample size to perform the risk analysis and prediction model.

19.3.3.8 *Estimated Timeframe*

The medical record abstraction for decedents will occur concurrently with ongoing study activities. The initial NDI application process will commence in approximately March 2017 for the purpose of securing NDI data for 2016 and prior years. NDI data sets are typically available in 2 waves: a preliminary data set is available approximately 3 months after a given calendar year and a final data set is available 10- 11 months after a given calendar year. Therefore, the 2017 NDI death data will be requested at the end of 2017 and the preliminary data available in March 2018 when the trial is closing down.

19.3.4 Public Health Impact

Both HIV and substance use carry significant public health burdens and a high risk for mortality. Although HIV treatment improves clinical outcomes, if other comorbidities are leading to death, then additional focus and priority needs to be placed on treatment for these comorbidities. This ancillary study is well aligned with the new NIH HIV high priority topics as it focuses on (1) research in health disparities among substance users to understand the underlying causes of the excess mortality (2) research in HIV-associated co-morbidities to understand which co-morbidities may be leading to excess mortality among substance users (3) research in HIV treatment, retention, and engagement among substance users to determine if excess mortality in this population is due to failure in achieving steps along the HIV and HCV care continuum.

19.3.5 Suitability/Feasibility/Sustainability for the CTN

Since all of the research sites are already performing medical record abstraction (and primarily electronic abstraction) for living participants, performing abstraction for these decedents to record the mortality, co-morbidity and health service data should not require much additional medical record abstraction.

19.3.6 References for Ancillary Study

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