

NIDA CTN Protocol 0049

**Project HOPE -- Hospital Visit as Oppportunity for
Prevention and Engagement for HIV-Infected Drug
Users**

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Note: This document to only be used for the purpose of checking for 508 compliance before posting to NIDA Data Share.

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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
ART	Antiretroviral Therapy
AUDIT	Alcohol Use Disorders Identification Test
CAPI	Computer Assisted Personal Interview
CCC	Clinical Coordinating Center
CM	Contingency Management
CoC	Certificate of Confidentiality
CRF	Case Report Form
CTN	Clinical Trials Network
CTP	Community Treatment Program
DHHS	Department of Health and Human Services
DM	Data Monitoring
DSC	Data Statistics Center
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
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
OI	Opportunistic Infection
PI	Principal Investigator
PN	Patient Navigator
PN+CM	Patient Navigator plus Contingency Management
PT	Participant
PV	Protocol Violation
PVL	Plasma Viral Load
QA	Quality Assurance
RA	Research Assistant
RRTC	Regional Research and Training Center
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TAU	Treatment As Usual

2.0 STUDY SYNOPSIS AND SCHEMA

STUDY OBJECTIVES:

This study will evaluate the most effective strategy to achieve HIV virologic suppression among hospitalized HIV-infected substance users.

STUDY DESIGN:

This study is a three-group randomized, prospective trial. HIV-infected patients admitted for in-patient care who report having recently used opioids and/or stimulants and/or heavy alcohol in the past 12 months are eligible. Patients will be 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 participants will provide informed consent and will complete a baseline computer assisted personal interview or CAPI (focusing on drug use, mental health, demographics and socio-economic factors, HIV care and drug treatment history) and blood draws (for viral load and CD4 count). The two intervention groups will receive up to eight sessions/contacts during months 1 - 3, followed by up to three check-ins during months 4 - 6. Follow-up assessments consisting of CAPI, blood draws, urine collection and breath analysis in all groups will be conducted at approximately 6 and 12 months post-baseline. Medical records will be reviewed to document use of HIV care and drug treatment during the study period.

STUDY POPULATION:

All adult HIV-infected patients admitted for inpatient care will be screened for eligibility. A total of 800 individuals who report opioid and/or stimulant and/or heavy alcohol use will be randomized with approximately 73 (range of 20 - 175) from each of 11 participating sites throughout the United States.

ELIGIBILITY CRITERIA:

Site Eligibility Criteria: Participating sites will 1) be located in HIV epicenters (areas with high HIV prevalence), 2) have a high HIV inpatient census, 3) have a high prevalence of substance use among HIV inpatients, and 4) have prior experience in participating in research/clinical studies.

Participant Eligibility Criteria: Participating individuals will 1) be inpatients in a participating hospital and be HIV-infected, 2) be at least 18 years old, 3) meet one of the following: have an AIDS-defining illness during the current hospital admission **OR** have the most recent CD4 count and viral load performed within the past 6 months be <350 cells/uL AND >200 copies/mL **OR** have the most recent CD4 count and viral load performed within the past 12 months be ≤500 cells/uL AND >200 copies/mL or unknown¹ accompanied by the Site PI's discretion² that the patient a) is likely to currently have a viral load >200 copies/mL, b) is not currently successfully/correctly taking ART and c) needs to be on ART, 4) report (OR have evidence in the medical record of) any opioid and/or stimulant and/or heavy alcohol use within the past 12 months. Medical record evidence may consist of a) positive toxicology screen(s) for stimulants or heavy alcohol or b) clinician notes indicating heavy use of alcohol, use of

¹ If the VL is unverifiable through hospital medical records, efforts should be made to obtain VL information from the outpatient clinic(s) that are part of the medical center of the enrolling hospital. Ultimately, a patient with an unknown (unverifiable) VL may be enrolled in the study provided that all other inclusion criteria are met.

² The Site PI's discretion will be operationalized via a review of the patient's hospital system medical record for HIV viral load in the past 12 months and a current prescription for ART. If there is insufficient information in the medical record, the Site PI or other designated clinician will hold a brief conversation with the patient to determine if the patient a) is likely to currently have a viral load >200 copies/mL, b) is not currently taking ART or is not taking ART correctly/regularly and c) should be prescribed ART based on available clinical information.

stimulants or non-prescribed opioids or abuse of prescribed opioids, 5) have a Karnofsky performance scale index score of ≥ 60 , 6) provide informed consent, 7) provide locator information, 8) sign a HIPAA authorization form / medical record release form to facilitate medical record abstraction, 9) report living in the vicinity and being able to return for follow-up visits, 10) complete the baseline assessment, including blood draw, and 11) be able to communicate in English.

TREATMENTS:

Participants will be randomized to one of three groups: 1) Patient Navigator intervention, 2) Patient Navigator plus Contingency Management intervention, or 3) Treatment as Usual. The intervention content of these groups is briefly described below.

Patient Navigator (PN) Group: This intervention ideally begins at bedside in the hospital and motivates individuals to engage in care and initiate or maintain antiretroviral therapy. The intervention also emphasizes the importance of drug treatment in assisting drug users to link to HIV primary care and views this as a critical and necessary part of the treatment plan.

Patient Navigator plus Contingency Management (PN+CM) Group: This intervention will combine the above-described PN intervention with Contingency Management. Consistent with previous studies on contingency management, the interventionist (Patient Navigator) will offer incentives on a progressive (escalating) scale of reinforcement. Incentives will be provided for key behaviors including, but not limited to: attending HIV care and/or drug treatment appointments, and filling antiretroviral therapy medication prescriptions.

Treatment as Usual (TAU) Group: This group will receive no protocol directed intervention. They will get standard of care referral/engagement services of the particular hospital site.

SAFETY ASSESSMENT:

Adverse events (AE) and serious adverse events (SAE) related to the study intervention (biologic specimen collection) will be collected at the time of the visit. Psychological AEs and SAEs will be reported and monitored throughout the study. Assessment of suicidal risk will be conducted at baseline and both follow-up visits and collected on a study specific form. Medical events related to underlying HIV disease and substance use 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:

Virologic suppression at the 12-month follow-up is the primary outcome. All-cause mortality will be counted as virologic failures. There are three main secondary outcomes: 1) linkage to and retention in HIV primary care, 2) linkage to and retention in drug treatment, and 3) decreased hospitalizations. Additional secondary outcomes (including those related to cost and cost-effectiveness) are described in sections 12.3 and 12.4.

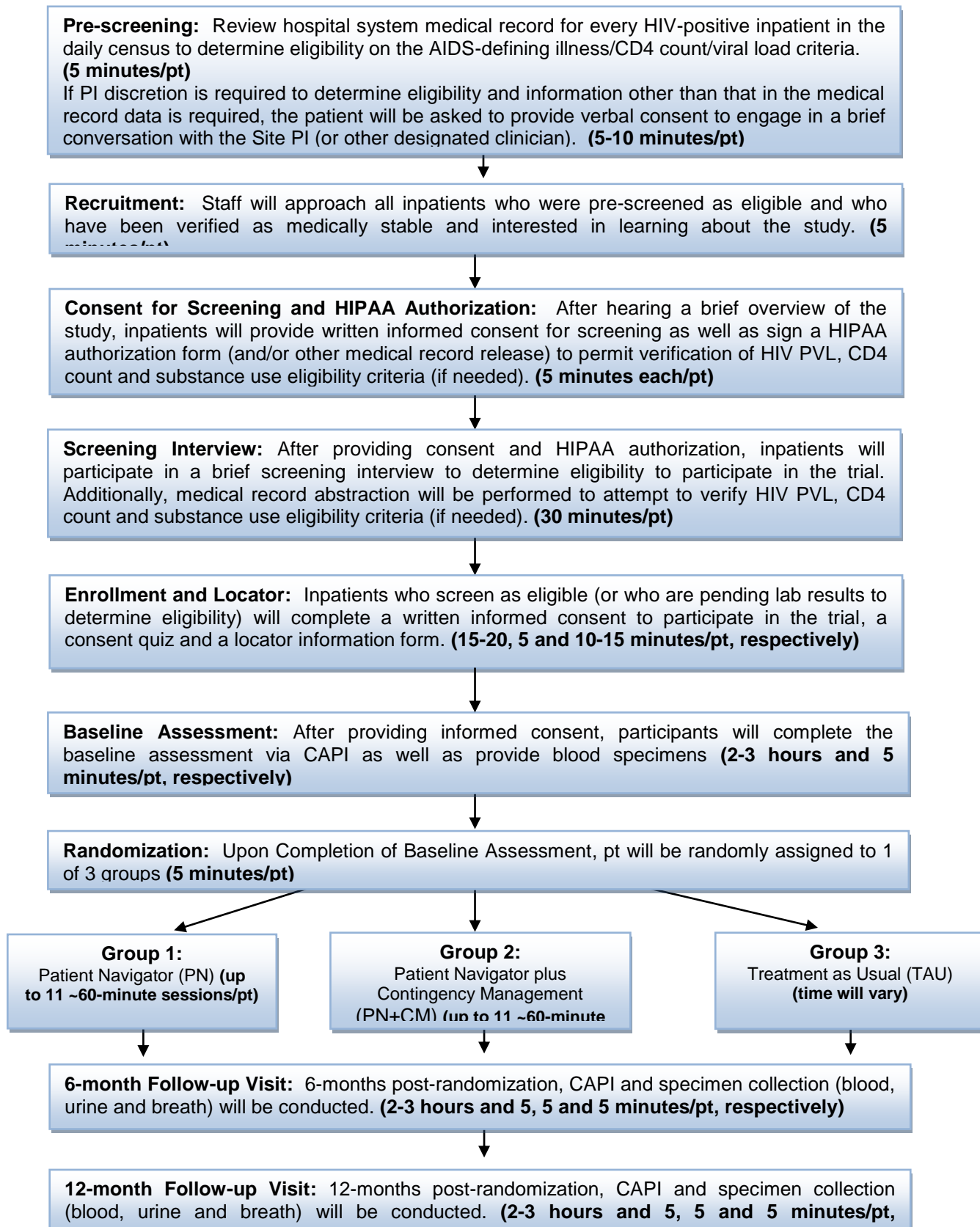
PRIMARY OUTCOME ANALYSIS:

The primary outcome variable, virologic suppression, will be measured as a binary variable: plasma HIV viral load (PVL) ≤ 200 copies/mL (yes) and PVL > 200 copies/mL or all cause mortality (no). It will be analyzed using GEE with a binomial link function. The incremental cost of the interventions will be assessed based on study records supplemented by site-level data collection (detailed further in section 12.3.3). Primary analyses will be performed under intent-to-treat (ITT) criteria.

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



4.0 INTRODUCTION

4.1 Background

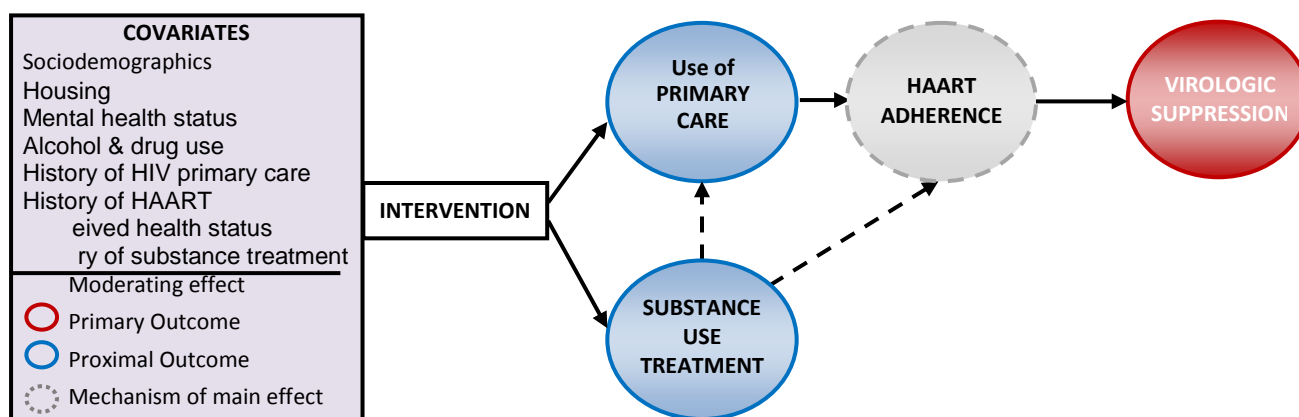
“Testing and Linkage to Care Plus (TLC+)” or “Seek, Test, Treat, and Retain” has recently emerged as a major part of the new national HIV/AIDS strategy in the United States (Obama administration unveils national HIV/AIDS strategy, 2010; Crowley & Kilmarx, 2009; Dieffenbach & Fauci, 2009; Folkers & Fauci, 2010; Granich, Gilks, Dye, De Cock, & Williams, 2009; Montaner et al., 2006; Volkow & Montaner, 2010). This strategy posits that awareness of HIV status through testing and linking persons to care to receive HIV medical care, including antiretroviral therapy (ART) as well as mental health, housing, substance use and other ancillary treatment services will improve both health outcomes at the individual level and reduce HIV transmission at the population level. To date, many of the efforts and discussion surrounding this new strategy have focused on testing and the identification of new cases of HIV. There is less attention focused on linkage to, engagement in, and retention in care. Specifically, little attention has focused on identifying HIV-infected individuals who are aware of their diagnosis and have never been in HIV care, are intermittent users of care, or have dropped out of care (Cheever, 2007; Giordano et al., 2007; Horstmann, Brown, Islam, Buck, & Agins, 2010; Mugavero et al., 2009; Christopoulos, Das, & Colfax, 2010).

Approximately one-third of HIV-infected persons either delay seeking care or do not seek care until their disease has progressed to require acute treatment (Althoff et al., 2010; Cheever, 2007; Fleming et al., 2002; Ulett et al., 2009). These patients may cycle through emergency rooms and hospital inpatient wards, and thus may fail to receive optimal HIV primary care, including ART and prevention interventions. Recent studies have shown that hospitalizations continue to occur at high rates among HIV-infected patients (Crum-Cianflone et al., 2010). The majority of these individuals are from communities of color that traditionally have been medically underserved; many of them also are either active or former substance users (Bell et al., 2010; Metsch et al., 2009). Because patients not treated with ART are more likely to have high viral loads and more infectious fluids, there is increased risk of transmission to their seronegative sex and drug using partners (Attia, Egger, Muller, Zwahlen, & Low, 2009; Donnell et al., 2010; Lingappa et al., 2010; Quinn et al., 2000).

The hospital setting is an ideal setting to implement a linkage to care intervention for HIV-infected drug users. First, the inpatient population includes individuals who cycle in and out of public hospitals, many of whom are likely to be users of illicit drugs and who frequently fail to follow up in HIV outpatient clinics (Bell et al., 2010; Floris-Moore et al., 2003; Metsch et al., 2009). HIV-infected drug users are more likely to be hospitalized (Fielden et al., 2008; Laine et al., 2001; Pulvirenti, Herrera, Venkataraman, & Ahmed, 2003; Sherer et al., 2002) and have longer hospital stays than non-users (Markson et al., 1994; Mor, Fleishman, Dresser, & Piette, 1992; Schoenbaum, Lo, & Floris-Moore, 2002; Seage, Hertz, Stone, & Epstein, 1993). Recent data from two inner-city hospitals in Miami and Atlanta demonstrate that HIV-infected drug users comprised over one-third of the HIV admissions and that crack cocaine use was associated with higher odds of patients never having seen an HIV primary care provider, not being on antiretroviral therapy, and engaging in unprotected vaginal or anal sex with an HIV-negative or unknown status partner (Bell et al., 2010; Metsch et al., 2009). These hospitalized HIV-infected drug users also had high rates of mental health problems, alcohol use, homelessness, and food insecurity (Anema, Vogenthaler, Frongillo, Kadiyala, & Weiser, 2009; Vogenthaler, Hadley, Lewis, Rodriguez, Metsch, & Del Rio, 2010; Vogenthaler, Hadley, Rodriguez et al., 2010). Second, the hospital stay may provide a “teachable moment” during which patients are not using drugs and may be more receptive to behavioral interventions (Aszalos, McDuff, Weintraub, Montoya, & Schwartz, 1999; Munafo, Rigotti, Lancaster, Stead, & Murphy, 2001; Saxon, Wells, Fleming, Jackson, & Calsyn, 1996). When patients are hospitalized for an HIV/AIDS-related medical problem, denial is likely to be challenged and diminished, making them potentially more open to facing their HIV diagnosis and the need to obtain medical treatment. Third, most hospitals are passively linked to HIV outpatient clinics,

drug treatment programs, and other prevention services. Therefore, hospitals provide an optimal place to begin interventions to enhance the likelihood that individuals will seek and obtain these services.

Conceptual Model: The Project HOPE study seeks to evaluate three strategies in order to find the most effective one to link and retain HIV-infected substance users recruited from the hospital setting to HIV primary care and substance use treatment. The primary outcome will be virologic suppression, the primary goal of antiretroviral therapy (Department of Health and Human Services, 2009). Virologic suppression reduces HIV associated morbidity, prolongs survival, restores and preserves immunologic function and decreases HIV transmission. As shown in the conceptual model below, use of HIV primary care and substance use treatment are proximal outcomes. Once linked to HIV primary care, most HIV-infected substance users should begin antiretroviral therapy and should be able to achieve virologic suppression if they continue care and adhere to



antiretroviral therapy (Cofrancesco et al., 2008; Hicks et al., 2007). In this model, substance use treatment is hypothesized as an important moderator. Previous research has shown that HIV-infected patients with a history of substance use treatment are more likely to use HIV primary care (Bell et al., 2010; Knowlton et al., 2006; Loughlin et al., 2005; Strathdee et al., 1998). The model also includes other covariates that may be related to use of HIV primary care or substance use treatment (see further discussion of outcomes and covariates in section 12).

Intervention: Brief interventions have successfully linked persons newly diagnosed with HIV to primary care and have also linked drug users to substance use treatment (Bradford, Coleman, & Cunningham, 2007b; Craw et al., 2008; Gardner et al., 2005; Sorensen et al., 2005). Two strategies shown to be successful in this linking are (1) patient navigation and (2) contingency management/ use of incentives.

Patient Navigation (PN): Although rooted in the field of oncology, patient navigation has been shown to be effective in helping patients with other chronic diseases by increasing patients' confidence and support networks and helping them to navigate through the complex and often fragmented systems of care (Bradford, Coleman, & Cunningham, 2007b; Broadhead et al., 2002; Lebowhl et al., 2010; Ramirez & Turner, 2010; Wells et al., 2008). This type of approach differs from other care coordination models such as case management in its orientation toward flexible problem solving to overcome barriers rather than the provision of a predefined set of services (Dohan & Schrag, 2005). Patient navigation has also been described as an emerging model of care coordination within HIV care; community health centers in the U.S. have begun to assess the added value of patient navigation as an enhanced model of outreach and care coordination for patients with HIV (Behforouz, Farmer, & Mukherjee, 2004; Bradford, Coleman, & Cunningham, 2007b). Investigating whether outreach program contacts increased the likelihood of engagement and retention in HIV primary care for hard-

to-reach patients, Cabral et al. (2007) concluded that 1) frequent contacts with HIV-infected, hard-to-reach, marginalized persons helped them to engage and remain in HIV primary care and 2) accompaniment to HIV primary care visits appeared to be most strongly associated with retention in care for the participants (Cabral et al., 2007).

Drs. Metsch and del Rio participated in the development and implementation of the CDC-funded multisite ARTAS (Antiretroviral Treatment Access Study) intervention, one of the few published randomized controlled trials that demonstrated the efficacy of a brief patient navigator 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., 2005). In this study a brief patient navigator intervention was compared with “passive referral” (standard-of-care) in linking recently diagnosed HIV-infected persons to medical care. Participants in the intervention arm received up to 5 sessions with a patient navigator over 90 days to facilitate linkage. Seventy-eight percent of patients in the intervention arm of the study visited an HIV clinician at least once within 6 months and at least twice within 12 months, compared to only 60% of patients in the standard-of-care arm. At 12 month follow up, 64% of participants in the intervention arm had linked to care compared to 49% in the control arm (RR(adj)=1.41; p=0.006). ARTAS II replicated these results and demonstrated the effectiveness of this linkage intervention by using actual clinic personnel (Craw et al., 2008).

Contingency Management/Use of Incentives: Contingency management is based on the principles of operant conditioning, in which behavior that is followed by positive consequences is more likely to be repeated (Carroll & Onken, 2005; Dutra et al., 2008) and will increase in frequency (Stitzer & Petry, 2006). Principles of contingency management as outlined by Petry et al., (2001) include frequent monitoring of the target behavior, provision of tangible, positive reinforcers where the target behavior occurs, and removal of the reinforcer/incentive when the target behavior does not occur.

Contingency management has historically been employed in substance abuse treatment settings to primarily reinforce drug abstinence (Higgins, Silverman, & Heil, 2008; Stitzer & Petry, 2006). Other targeted behaviors have included, but are not limited to: attending therapy sessions (Iguchi et al, 1996); (Iguchi, Belding, Morral, Lamb, & Husband, 1997; Jones, Haug, Silverman, Stitzer, & Svikis, 2001) and obtaining therapy goals (Iguchi et al., 1997). In the typical protocol, monetary rewards (cash or vouchers), clinic privileges, or chances to win prizes from a drawing are made contingent on negative toxicology screens, indicating abstinence from drug use (Dutra et al., 2008). This approach has shown consistent success with drug use disorders, ranging from opiate and cocaine dependence to nicotine dependence (Dutra et al., 2008). Contingency management has particularly strong, consistent, and robust empirical support across different types of drug use (Carroll & Onken, 2005). In meta-analyses, (Lussier, Heil, Mongeon, Badger, & Higgins, 2006); Prendergast, Podus, Finney, Greenwell, & Roll, 2006) CM interventions increased durations of abstinence, with estimated overall effect sizes across studies ranging from $d = 0.32$ to 0.42 . More recently, Petry et al., (2010) have demonstrated the effective use draws for prizes to contingently reward HIV-infected substance abusers for completing health related behaviors such as attending medical appointments, refilling medication prescriptions, and working out at the gym. Participants in the CM reward condition significantly lowered their HIV viral load compared to a 12 step facilitation control group.

Previous research on interventions for linking drug users to drug treatment suggests that incentives or vouchers are potent intervention strategies grounded in behavioral modification (Haug & Sorensen, 2006) and efficacious in promoting attendance and antiretroviral adherence for HIV-infected drug users (Petry, Martin, & Finocche, 2001b; Petry, Weinstock, Alessi, Lewis, & Dieckhaus, 2010; Rosen et al., 2007). These studies have shown that it is essential that incentives be provided in such a way that they yield verifiable outcomes. For example, if an incentive is going to be given for “drug abstinence,” then a urine test would be required to verify the outcome.

Combining Patient Navigation and Contingency Management: Chutuape, Katz, and Stitzer (2001) demonstrated that the patient navigator/staff escort approach combined with offering incentives (compared to standard referral and standard referral with incentive) was the more effective approach in transitioning substance users from inpatient to outpatient treatment. Sorensen et al., (2005) showed that the combined approach of case management and offering vouchers was efficacious in linking drug users to drug treatment.

4.2 Rationale for the 3-Group Design

This study will determine whether interventions of increasing intensity are more effective in reducing viral load. The most intensive arm adds an incentive component to the navigator paradigm to determine if a positive-reinforcement strategy confers additional benefit. Although previous research including research conducted by the lead investigators in the ARTAS study suggests the efficacy and effectiveness of PN for linking recently diagnosed HIV-infected individuals to HIV care, this strategy has not been tested systematically in a clinical trial with persons who have known their HIV status for some time and have not engaged in regular HIV care and these studies have not had virologic suppression as the primary outcome. Additionally, studies have shown that the PN strategy has been less effective for drug users who are not engaged in drug treatment (Gardner et al., 2005). Despite this, the HIV field is moving toward implementing PN as a standard practice to link HIV-infected persons who are either newly diagnosed or not engaged in care to outpatient care and ancillary services (Obama administration unveils national HIV/AIDS strategy, 2010; Bradford, Coleman, & Cunningham, 2007a; Christopoulos et al., 2010). Because CM strategies have demonstrated effectiveness in linking substance users to substance use treatment, a combined PN+CM intervention may be a particularly potent strategy for HIV-infected substance users. However, using incentives/contingency management is somewhat controversial for some HIV care providers and this proposed study would be able to evaluate what is the added benefit of this approach over and above the PN strategy. The proposed 3-group design will facilitate our measuring the effect of adding CM to PN on HIV virologic suppression and linkage to HIV primary care and substance use treatment among HIV-infected inpatients who report substance use. The inclusion of the TAU group, which receives as little interaction with study staff as possible at baseline, provides a control by which to measure the assessment effect and to compare the intervention strategies to standard practice at each of the participating hospitals. The PN and PN+CM groups will each be compared to TAU.

All three comparisons are of practical and theoretical interest, and each significant difference between groups, if found, would provide meaningful evidence of treatment effect, but with different implications for practice as described above. The main disadvantage to the 3-group design is the increase in complexity and cost. Although the increase in complexity is relatively small due to the simplicity of the TAU condition, costs are increased due to the larger sample size needed to maintain statistical power to test the three between-group contrasts without inflating type 1 error rate. The protocol development team believes that the increased potential for knowledge gained with the 3-group design more than compensates for the increase in complexity and cost.

4.3 Rationale for Cost-Effectiveness Study Component

President Obama's National HIV/AIDS strategy calls for scale-up of sustainable interventions that link and engage HIV-infected persons into care (Obama administration unveils national HIV/AIDS strategy, 2010). For any such intervention to be widely adapted, it must be cost-effective: that is, compared to standard of care, the net health benefits of the intervention must outweigh the expenditures necessary to implement and sustain it (Hornberger et al., 2007; Sansom et al., 2008; Walensky, Freedberg, Weinstein, & Paltiel, 2007; Weaver et al., 2009). For the proposed Project HOPE, determining the potential cost effectiveness of the intervention arms will have major implications for adaptation. In this era of increasingly limited resources and budget cuts, determining if new interventions are cost effective will help Federal, State, and local health departments justify or reject their scale-up. Showing

cost effectiveness may be especially important for interventions that use incentive-based behavioral modifications, where a proportion of intervention costs go directly to reward clients of the program. While cost-effectiveness of contingency management has been shown in substance use treatment, we are unaware of studies that have shown this modality to be cost effective in reducing HIV viral load (Olmstead & Petry, 2009; Sindelar, Elbel, & Petry, 2007; Sindelar, Olmstead, & Peirce, 2007). Thus, in HOPE we will determine the potential cost effectiveness of both the navigator and contingency components compared with standard of care, using our internationally recognized experts on cost effectiveness and HIV care, Drs. Jim Kahn and Elliot Marseille.

5.0 OBJECTIVES

5.1 Primary Objective

This study will evaluate the most effective strategy in achieving HIV virologic suppression among HIV-infected substance users recruited from the hospital setting who are randomly assigned to one of three treatment conditions: 1) Patient Navigator (PN); 2) Patient Navigator + Contingency Management (PN+CM); and 3) Treatment as Usual (TAU).

Primary Hypothesis: The rate of viral suppression (plasma HIV viral load of ≤ 200 copies/mL) relative to non-suppression or all-cause mortality in the 3 study groups will differ from each other at the 12 month follow-up.

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.

Sub-hypothesis 2. The rate of virologic suppression in the PN+CM group will be greater than that in the PN group.

Sub-hypothesis 3. The rate of virologic suppression in the PN group will be greater than that in the TAU group.

5.2 Secondary Objectives

1. To evaluate the effect of the experimental interventions on: HIV virological suppression and CD4 T-cell count changes at 6 months post-randomization; engagement in HIV primary care (defined as having attended two visits -- one within the first three months and one within four to six months -- post-randomization) and visit attendance; and rate of hospitalizations.
2. To evaluate the effect of the experimental interventions on: drug use frequency and severity; and drug use treatment engagement and session attendance.
3. To assess selected mechanisms of action of the intervention (i.e., mediators of intervention effect).
4. To assess potential characteristics associated with differential treatment effectiveness (i.e., moderators of intervention effect).
5. To evaluate the incremental cost and cost-effectiveness of the interventions.

6.0 STUDY DESIGN

6.1 Overview

The proposed study is a 3-arm randomized, prospective trial in which HIV-infected inpatients who report substance use at screening will be randomized in 1:1:1 ratio to PN vs. PN+CM vs. TAU. Randomization will occur after screening, informed consent, baseline assessment and collection of biological (blood) specimens. Participants assigned to the PN and PN+CM groups will meet (ideally at bedside if the participant is still hospitalized at the time of randomization) with the Patient Navigator interventionist and will complete up to 11 intervention sessions over the 6-month-long intervention period. Participants assigned to the TAU group will receive care as it is typically offered in the inpatient setting. Follow-up visits will be conducted at approximately 6 and 12 months post-randomization.

6.2 Duration of Study and Visit Schedule

Screening, enrollment, assessment, randomization and the initial intervention visit will (ideally) occur during the participant's stay at an inpatient facility. Recognizing that participants may be recruited at various stages of illness during their inpatient visit, however, this may not be possible. To allow maximum flexibility, we will require that the screening informed consent process and the collection of sufficient contact information to allow the patient to be reached after discharge occur while the patient is still in the hospital. The screening interview, completion of remaining required locator information and baseline activities (baseline computer assisted personal interview and specimen collection), randomization and initial intervention session can be completed after the patient has been discharged from the hospital, but should be done as soon as possible after obtaining screening consent and before the patient's first HIV primary care appointment. Specific windows will be detailed in a SOP. The intervention duration will be 6 months with sessions ideally occurring weekly during the first month, bi-weekly during months 2 and 3 and monthly during months 4- 6. 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.

7.0 STUDY POPULATION

7.1 Inclusion Criteria

Participating individuals must:

1. be admitted to a hospital and be HIV-infected at the time of recruitment
2. be at least 18 years old
3. meet one of the following:
 - a. have an AIDS-defining illness during the current hospital admission **OR**
 - b. have the most recent CD4 count AND viral load performed within the past 6 months be <350 cells/uL AND >200 copies/mL **OR**
 - c. have the most recent CD4 count AND viral load performed within the past 12 months be ≤500 cells/uL AND >200 copies/mL or unknown³ accompanied by the Site PI's discretion⁴ that the patient a) is likely to currently have a viral load >200 copies/mL, b) is not currently successfully/correctly taking ART and c) needs to be on ART
4. report (OR have evidence in the medical record of) any opioid and/or stimulant and/or heavy alcohol use within the past 12 months. Medical record evidence may consist of a) positive toxicology screen(s) for stimulants or heavy alcohol or b) clinician notes indicating heavy use of alcohol, use of stimulants or non-prescribed opioids or abuse of prescribed opioids,
5. have a Karnofsky performance scale index score of ≥60
6. provide informed consent
7. provide locator information
8. sign a HIPAA form / medical record release form to facilitate medical record abstraction
9. report living in the vicinity and being able to return for follow-up visits
10. complete the baseline assessment, including blood draw
11. be able to communicate in English

7.2 Exclusion Criteria

Individuals will be excluded from study participation if they:

1. do not meet any one or more of the above-described inclusion criteria
2. have significant cognitive or developmental impairment to the extent that they are unable to provide informed consent
3. are terminated via site PI decision with agreement from study LI.

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 in the study provided that they have local IRB approval to do so.

³ If the VL is unverifiable through hospital medical records, efforts should be made to obtain VL information from the outpatient clinic(s) that are part of the medical center of the enrolling hospital. Ultimately, a patient with an unknown (unverifiable) VL may be enrolled in the study provided that all other inclusion criteria are met.

⁴ The Site PI's discretion will be operationalized via a review of the patient's hospital system medical record for HIV viral load in the past 12 months and a current prescription for ART. If there is insufficient information in the medical record, the Site PI or other designated clinician will hold a brief conversation with the patient to determine if the patient a) is likely to currently have a viral load >200 copies/mL, b) is not currently taking ART or is not taking ART correctly/regularly and c) should be prescribed ART based on available clinical information.

7.3 Participant Recruitment

7.3.1 Pre-screening

To minimize patient and staff burden, sites may implement a pre-screening procedure with permission from their respective IRBs. This will involve sites securing local IRB permission via HIPAA waiver and/or other approval to perform a review of the hospital system medical record for every HIV-positive inpatient in the daily census. The purpose of the record review is to determine which patients would/would not meet the study's AIDS-defining illness/CD4 count/viral load inclusion criteria. Those patients who do not meet these inclusion criteria⁵ may not be approached about the study. Those patients who meet some of the CD4 count/viral load criteria, but require PI discretion to determine if their current viral load is likely to be detectable and that they are not on, but should be on ART may be asked to provide verbal consent to engage in a brief conversation with the Site PI (or other designated clinician) to allow the PI to make an appropriate assessment of eligibility on these criteria. The type of consent required will be determined by the local IRBs of jurisdiction. Those patients who do meet the inclusion criteria would be approached about the study according to the procedures outlined in section 7.3.2.

In addition to determining whether or not each HIV-positive patient meets the AIDS-defining illness/CD4 count/viral load inclusion criteria, staff would also abstract and record minimal demographic information for all pre-screened patients. The purpose of this is to adequately describe the sample of patients who were ineligible for the study or who declined to participate in the study prior to signing the screening consent form. Minimal demographic information to be abstracted as part of pre-screening, in addition to AIDS-defining illness, CD4 count and HIV viral load copies, includes: gender, age range, race, ethnicity and insurance status (yes/no). To avoid collecting data on duplicate patients, sites may obtain local IRB permission to at least temporarily record the patients' medical record numbers locally, at least until the patients are discharged from the hospital. The medical record numbers collected as part of pre-screening would not be stored in the national data capture system. If a patient who meets the AIDS-defining illness/CD4 count/viral load inclusion criteria ultimately provides written informed consent to take part in the screening interview to determine eligibility to enroll in the study, the patient's pre-screening data (described above) will be linked to his/her screening data via an assigned research identification number.

At the conclusion of the recruitment period, the participating hospitals will provide aggregate data on the total number of unduplicated HIV-positive patients admitted during the recruitment period as well as these patients' gender, race/ethnicity, and average, minimum and maximum length of stay in the hospital. This information combined with the above minimal descriptive information will enable the investigators to adequately describe the sampling frame for the study.

7.3.2 Recruitment

Based on our previous work with this population (Bell et al., 2010; Metsch et al., 2009), we conservatively estimate that our ratio of screened to enrolled individuals will be 3:1. Given this ratio and our expected rate of randomization of 1-2 participants per week, sites are expected to screen

⁵ Ideally, pre-screening, screening and baseline activities will occur in a linear fashion; however, this may not always be possible. For example, it is possible that pre-screening activities such as the verification of the patient's CD4 count may not be able to be performed prior to the patient's discharge due to the lab results being pending. For this reason, it may not be possible to determine eligibility on the pre-screening criteria while the patient is still in the hospital. Therefore, if the site has ample staff/time resources, study staff may proceed with approaching patients who have pending labs. If the patient is medically stable and interested in the study, study staff may proceed with screening consent, screening and subsequent baseline activities.

approximately 6 individuals per week. We will allow approximately 18 months for study recruitment to ensure that our goal of randomizing 800 participants across all 11 sites (approximately 20-175 per site) is met.

Members of the medical teams within each hospital (i.e., attending physicians, fellows, residents and nurse practitioners) who are involved in patient care and who know the patients' HIV-infected status will assess the medical stability⁶ of the patients. If the patient has expressed interest in potentially participating in research and is deemed medically stable, then a study staff member will meet with the patient at bedside to discuss the study. Strict ethical guidelines regarding professional conduct and confidentiality will be enforced for all study staff.

Enrolling patients at bedside and meeting the challenges inherent in the hospital setting including: acuity of the patients, the rapid pace of care, multiple care procedures (including some off-unit tests), and the presence of medical staff, all of which may cause delays and interruptions in interviews (Berkman, Leipzig, Greenberg, & Inouye, 2001) will be challenging. Nevertheless, as part of training, our interviewers will spend considerable time in the hospital setting interacting with staff, familiarizing themselves with the operations of the inpatient wards, and learning how to communicate and negotiate time and space with the hospital staff that is necessary to conduct the participant interviews. We will also rely on the experience of the Site PIs to address any potential problems that may arise during the project. Staff and sites with experience and expertise in conducting inpatient research studies will be chosen.

While we expect that some patients will be in single rooms, some will be in shared rooms separated from other patients with curtains. Therefore, during the brief, rapport-building discussion with the potential participant, the interviewer will determine the potential participant's comfort level in proceeding with the screening consent and screening interview for those who are in shared rooms. The interviewer will negotiate the location of the interview as necessary to protect confidentiality. If necessary, the participant will be given the option to conduct the interview in a nearby room or staff/patient lounge if it is unoccupied or to reschedule the interview at another time when no other patients are in the room. To ensure that participants are comfortable and that no confidentiality is violated in shared room situations, we will have readily available a "white noise machine" which is often used in clinicians' offices to drown out extraneous noises. If a patient feels ill during the interview, we will stop and reschedule the interview. In our prior experience conducting bedside interviews, we have found that patients often view them as a welcome distraction that breaks the monotony of their hospital stay and provides social interaction with people other than hospital staff.

7.4 Number of CTP Sites

Approximately 11 HIV inpatient services will participate as sites for the study.

7.5 CTP Characteristics

Participating hospitals should have the following characteristics:

- be located in cities that are HIV epicenters
- have a high HIV inpatient census
- have high prevalence of substance use among HIV inpatients
- have prior experience in participating in research/clinical studies

⁶ "Medical stability" refers to the treating clinician deeming the patient to be cognitively and medically able to tolerate the study's screening procedures.

7.6 Rationale for CTP Selection

We plan to select sites for participation that have an adequate number of substance-using HIV-infected patients admitted each year. A study site will be defined as a hospital or a small network of hospitals within a limited geographic area. In order to achieve target enrollment for this study, which is an average of 73 patients/site over the course of approximately 18 months, we expect that each participating site will need to see ≥ 200 unduplicated HIV-infected inpatients/year. This number is based on estimates of the percent of HIV-infected inpatients who will meet study eligibility criteria and percent of eligible patients who will consent to study enrollment.

In preparation for this study, our study team conducted a brief survey between October 2010 and January of 2011 of hospitals with a high HIV inpatient census in metropolitan service areas (MSAs) most heavily affected by HIV/AIDS. At this time, we have received completed surveys from 17 potential sites located in Boston, MA, New York City, NY, Baltimore, MD, Birmingham, AL, Miami, FL, Dallas, TX, Philadelphia and Pittsburgh, PA, Atlanta, GA, Oakland, CA, Los Angeles, CA, Chicago, IL and New Haven, CT.

The goals of the survey were to: 1) assess potential study sites' capacity to enroll and randomize an adequate number of study participants; 2) describe treatment as usual in regards to linkage to outpatient HIV care and substance use treatment from the inpatient setting at potential study sites; and 3) describe physicians' perceptions of barriers to linkage to HIV care and substance use treatment to help inform intervention design.

Due to our desire to include hospitals located within HIV epicenters, we asked the Principal Investigators and Coordinators of targeted CTN Nodes to distribute the survey to Infectious Diseases and HIV physicians who provide care at hospitals in within their node that are heavily affected by HIV. We have received results from 17 potential sites which collectively had approximately 13,196 unduplicated HIV-infected individuals admitted during a 12-month period. Annual admissions of HIV-infected individuals ranged from 190 to 2,555. Respondents estimated that between 22% - 80% of HIV-infected inpatients had a history of substance use (Table 1).

Table 1: Hospital Demographics and Volume

Hospital	# Beds	# HIV-infected discharges	# HIV-infected admits	HIV infected discharges/Bed	% with Substance Use
1	549	2555		4.7	50
2	1000		882	0.9	40
3	1146		470	0.4	22
4	1550	871	899	0.6	40
5	900	600		0.7	50
6	640	1300		2	60
7	1015	1302		1.3	28.4
8	224	600		2.7	55
9	235	190		0.8	38
10	600	562	562	0.9	75
11	450	400-500		1.0	30
12	639	600		0.9	60
13	616		600	1.0	30-40

Hospital	# Beds	# HIV-infected discharges	# HIV-infected admits	HIV infected discharges/Bed	% with Substance Use
14	464		709	1.5	30-50
15	660		418	0.6	25-30
16	1000	749		.75	80

As an initial assessment of treatment as usual (TAU) at our potential study sites, we gathered data on how hospitalized patients are linked to outpatient HIV care and substance use treatment. All sites have an on-site HIV clinic as well as other community HIV clinics to which patients are discharged. The patient navigator and research assistant may need to work with more than one outpatient HIV clinic at some sites. Of sites surveyed, most report having a “linkage team,” though it seems the primary method of linking HIV inpatients to outpatient HIV care is that “an outpatient appointment is set up during hospital stay.” Two sites reported that they have a patient navigator who facilitates linkage to care. At one of these two sites the program is coordinated from the outpatient not the inpatient setting. We found that ART is initiated in the hospital <50% of the time at all sites, and <25% of the time at 15/17 sites. The average wait time for an outpatient appointment is <4 weeks at 16/17 of the sites, but follow-up appointments are frequently missed. Few sites had a systemized approach to linkage to care services for substance use treatment. In most cases, hospitalized patients were given a written referral to a particular substance abuse program or set of programs, with few additional measures to assist with linkage to substance abuse treatment. A thorough assessment will be conducted of each site’s standard practice for linkage to HIV care and substance use treatment during the formal site selection process. During the course of the study, each hospital site will be monitored for any potential changes that might occur in standard practice around linkage to HIV and substance use care.

The physicians surveyed reported that patient-level factors, including substance use, mental illness and competing life priorities were the major barriers to linkage to outpatient HIV care. System-level factors, including distance to clinic, appointment availability, paperwork, system complexity, and lack of social work or case management services were infrequently reported as barriers. The primary barriers to initiation of ART were the patient not wanting to start treatment (7/17 sites) and clinicians having concerns about patient’s adherence (9/17 sites). Both patient-level factors, including mental illness (15/17 sites), lack of interest in treatment (13/17 sites) and other competing life priorities (13/17 sites), as well as system complexity (4/17 sites) were reported as barriers to linkage to substance use treatment.

8.0 OUTCOME MEASURES

8.1 Primary Outcome Measure

The primary outcome variable is binary: HIV viral suppression (≤ 200 copies/ml), as determined by blood draw⁷ (or medical record abstracted non-study lab result, as needed) at the 12 month follow-up versus presence of viral load > 200 or death (all-cause mortality). We are aware that, for patients on therapy, the goal of antiretroviral therapy is achieving a viral load “below the limit of detection of the assay” which currently is usually < 40 copies/ml. However, we have chosen to define “suppression” as ≤ 200 copies/ml to be consistent with the January 2011 Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents.

8.2 Secondary Outcome Measures

Secondary outcomes include those related to HIV and those related to substance use.

8.2.1 HIV Related Secondary Outcomes

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

- a) Viral suppression at 6 months (binary; laboratory assay)
- b) CD4 Cell count (continuous; laboratory assay)
- c) Engagement into HIV care (binary attendance of two visits – once within the first three months and one within four to six months – post-randomization; self-report/medical record abstraction)
- d) HIV care visit attendance (count; self-report/medical record abstraction)
- e) Medication Adherence (count; self-report/ Adherence Questionnaire)
- f) Hospitalizations (count; self-report/medical record abstraction)
- g) All cause mortality (binary)

8.2.2 Substance Use Related Secondary Outcomes

- a) Substance use frequency (count; self-report ASI and binary; urine/breath analysis)
- b) Substance Use Severity (continuous, DAST and AUDIT)
- c) Treatment engagement (binary attendance of two visits – once within the first three months and one within four to six months – post-randomization; self-report)
- d) Number of drug treatment sessions (Count; self-report)

⁷ In the event that any (baseline, 6-month or 12-month) blood specimen cannot be collected for any reason (e.g., vein is “dry”, participant is lost to follow-up, etc.) or the result of any collected blood specimen is not available (e.g., not enough specimen drawn, lab processing error, etc.), the study team may abstract and use a non-study viral load result for the purpose of evaluating the outcome.

8.2.3 Mediators and Moderators of Outcomes

- a) Viral Suppression Moderators: psychological distress (BSI), Housing instability, Food Insecurity Health literacy, HIV-related cognitive problems, renal and liver function status.
- b) Viral Suppression Mediators: Medication self-efficacy, Physician-Patient relationship, social support and substance use.
- c) CD4 Count Moderators: HCV status.
- d) Drug Use Moderators: Readiness for drug treatment.
- e) Drug Use Mediators: Readiness for drug treatment and social support.

9.0 STUDY PROCEDURES

9.1 Screening and Enrollment Procedures

9.1.1 Screening

As previously outlined in section 7.3.1, those patients who are pre-screened as eligible on the AIDS-defining illness/CD4 count and /viral load inclusion criteria (or whose CD4 count and/or viral load eligibility is pending verification) may be approached about the study according to the recruitment procedures outlined in section 7.3.2. Subsequently, if these patients are deemed to be medically stable and they are interested in taking part in the study, then those individuals willing to be screened to determine eligibility will provide written informed consent prior to participating in screening activities. Sites may need to obtain a signed HIPAA authorization form for medical records abstraction to verify that the patient meets the substance use eligibility criterion. Additionally, those sites that do not implement the pre-screening procedure outlined in section 7.3.1 will need to obtain a signed HIPAA authorization form for medical record abstraction to verify that patients meet the AIDS-defining illness/HIV viral load/CD4 eligibility criteria. After signing the consent form (and HIPAA authorization form, as applicable), participants will be offered copies of the form(s) to keep for their records. If possible, the screening interview will be done at bedside immediately after informed consent. Those who are not willing to be screened at that time will be asked if study staff may return at a later time that day or within the next few days to complete the screening interview. Ideally, the screening interview will take place at bedside prior to discharge; however, it is permissible for it to take place in the field post-discharge. The screening interview will elicit information about the potential participant's demographics, HIV care seeking behaviors, use of antiretroviral therapy and drug use. In addition, there will be questions related to health problems other than HIV and drug use that will be used to mask the eligibility criteria. The screening informed consent, HIPAA authorization (as applicable) and screening interview will take approximately 5, 5 and 30 minutes to complete, respectively.

9.1.2 Study Enrollment Procedures

Participants will complete the enrollment process prior to commencing baseline activities (e.g., blood specimen collection and CAPI). The enrollment process consists of providing written informed consent for study participation and passing the consent quiz.

9.2 Informed Consent Process

Study procedures and the potential risks and benefits of participating in the trial will be explained. We will also obtain permission to audio record intervention sessions for intervention fidelity monitoring purposes. Given the size of the study sample and 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 will also 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. After signing the consent form, participants will be offered a copy of the form to keep for their records. The process will take approximately 15-20 minutes.

9.3 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 and to locate participants who cannot be found. When completing this form, participants will be required to provide their names, addresses, and telephone numbers as well as contact information for at least one other person. Permission will also 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 10-15 minutes to complete.

9.4 HIPAA Authorization and Medical Record Release Forms

Participants will complete HIPAA Authorization and medical record release forms throughout the study (as applicable) to grant permission to study staff to review their HIV inpatient, HIV outpatient and substance use treatment clinic records. After an individual provides informed consent for screening and HIPAA authorization, we may review records back to 12 months before study screening to verify that the patient meets the study criteria. The purpose of medical records review is to document information needed to 1) evaluate primary and secondary outcomes (including ancillary study outcomes) and 2) verify completion of intervention target behaviors. Specifically, we will abstract medical record information to corroborate participants' self-report of information including, but not limited to the following: HIV viral load and CD4 count, utilization of HIV primary care, filling of HIV medication prescriptions, utilization of substance use treatment (if funding permits), length of original inpatient stay as well as subsequent hospitalizations. Other clinical information concerning renal function, liver function and Hepatitis C status will be abstracted to enable investigators to better characterize comorbidities of the study sample and to use as covariates in analyses. Other clinical information to be abstracted as part of the ancillary study, CTN0049 A-2, is outlined in Appendix B, section 20.0 of this protocol.

Records review/abstraction will occur throughout the study (as needed) and up to 18 months post-randomization.

9.5 Baseline Assessment

After the informed consent process is complete and a brief rapport-building discussion between the interviewer and participant has taken place, the research interviewer will prepare a new data record for the participant and the baseline assessment will be administered through a handheld CAPI. Multiple PIs have experience in the use of these handheld 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 assessment will include, but not be limited to questions on participant demographics, HIV care, medication adherence, substance use and co morbid conditions such as depression, etc. (see section 10 for a detailed description and timetable of measures) The baseline CAPI will take approximately 2-3 hours to complete.

9.6 Collection of Biologic Specimens

We will collect blood specimens⁸ at the baseline, 6-month and 12-month follow-up visits to evaluate the primary outcome, HIV virologic suppression, as well as to measure CD4 count, and complete blood count (CBC). We will also offer toxicology screening during each intervention visit within the PN and PN+CM groups to assess for recent drug and alcohol use to verify whether or not the participant has attained his/her behavioral target. If the participant accepts this screening, study personnel will collect urine and perform breath analysis. Additionally, we will collect urine and perform breath

⁸ 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 for the purpose of evaluating the HIV virologic suppression outcome and measuring CD4 count and CBC.

analysis for all 3 groups during the 6-month and 12-month follow-up visits to characterize substance use over time. CD4, viral load and toxicology results will be filed in the study record. Additionally, some participating sites may require that copies of some or all of these results be filed in participants' medical records.

9.7 Randomization

Participants will be randomized in a 1:1:1 fashion to one of the three treatment groups. Randomization will be stratified by site. The randomization procedure will be conducted in a centralized process through the Data and Statistical Center (DSC2). Specifically, randomization schedules will be created by the study statistician for each site. The randomization schedules will be of a randomized-block nature to ensure relative equality of assignment across condition across the recruitment period and to prevent the potential for study staff guessing the next assignment which is heightened when a fixed block-size is used. After the baseline assessment is successfully completed, a designated study staff member will perform the randomization. Randomization for each participant is done over the Internet using the Enrollment Module in AdvantageEDC.

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.

9.8 Treatment

9.8.1 Study Interventions

The three treatment conditions/study groups are: 1) Patient Navigator intervention (PN), 2) Patient Navigator plus Contingency Management (PN+CM) intervention and 3) Treatment as Usual (TAU). Details of the three arms are described in Section 11.

9.8.2 Discontinuation

All participants will be followed for the duration of the study (12 months) unless they withdraw consent, 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.

9.8.3 Follow-Up

Follow-up visits will be conducted at approximately 6 and 12 months post-randomization. Specific windows will be detailed in a SOP prior to study commencement. Follow-up visits will involve CAPIs, the collection of blood and urine, and performance of breath analysis. 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 primary outcome/biologic outcome data may be missing in these cases. To minimize missing specimens 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. In the event that study blood specimens cannot be drawn or processed or their results are not available, medical record abstracted lab results will be used.

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.

9.9 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 \$210 for completing the following non-intervention related activities: screening interview, baseline visit, 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 PN+CM groups may earn intervention incentives for completing intervention visits and associated target behaviors. These incentives are described in section 11.3.2.

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, feasibility of completing the baseline at bedside in the hospital, 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 HIV Related Measures

HIV-1 Viral Load, CD4 Count and Complete Blood Count. 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* testing. 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 abstracted lab results will be used.

HIV Care Visits. Self-reported HIV care 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 18 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). Use of primary HIV care services will be operationalized as at least one visit to an HIV primary care provider in the past six months. 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 abuse services, illegal activities and arrest information (Feaster, et al., 2010) to be used in the cost-effectiveness analysis.

Adherence to HIV medication regimen. Since HIV viral suppression is most strongly influenced by optimal use of HAART, evaluation of adherence to one's HAART regimen is essential. Self-reported adherence will be assessed with the ACTG (AIDS Clinic Trial Group) Adherence Questionnaire for measuring antiretroviral adherence (Reynolds et al., 2007). The ACTG questionnaire includes items measuring adherence to medications yesterday, 2, 3, and 4 days ago, adherence to schedule, instructions, during the last weekend and when any medication was last skipped. The questionnaire's responses are weighted to calculate an adherence level from 0-100.

Potential Mediators and Moderators of HIV Related 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.

Medication Adherence Self-Efficacy will be measured by the 12-item HIV Treatment Adherence Self-Efficacy Scale (Johnson et al., 2007). This scale has good overall reliability ($\alpha = .92$) and higher self-efficacy has been shown by Johnson et al., 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.

Physician-Patient Relationship. Aspects of this relationship will be measured using a series of seven short scales (30 total items). These higher scores on these scales were shown by Schneider, et al. (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. The scales measure *General Communication* ($\alpha = .93$) and *Provision of HIV-Specific information* ($\alpha = .93$); (Wilson & Kaplan, 2000), *Adherence Dialogue* ($\alpha = .93$); (Schneider, Kaplan, Greenfield, Li, & Wilson, 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 et al., 1998). Again, because these factors are related to adherence and that the patient navigator will be facilitating participant's interactions with health care it is anticipated that they will also be mediators of the viral suppression outcome.

Health Literacy will be measured by three items found to be effective at identifying persons with inadequate health literacy (L. D. Chew, Bradley, & Boyko, 2004; L. D. Chew et al., 2008). Health literacy has been shown to be an important predictor of HIV medication adherence and health status (Kalichman & Rompa, 2000; Kalichman et al., 2008). It is anticipated that health literacy will be a moderator of the viral suppression outcome.

HIV-Related Cognitive Problems will be screened using the 3-item International HIV Dementia Scale (Sacktor et al., 2005). Participants with HIV-related cognitive problems are more likely to have difficulty with negotiating the HIV care system, remembering appointments and health care instructions. HIV-related cognitive problems have been shown to be related to reduced HIV medication adherence (Barclay et al., 2007; Hinkin et al., 2002) and are therefore 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.

Perceived health status will be measured using a computer-assisted version of the SF-12 measure (Ware, Kosinski, & Keller, 1996). The SF-12 can be converted to quality-adjusted health index to be utilized in cost-utility analyses or cost-benefit 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 et al., 2010). The SF-12 also has been shown to be reliable in HIV populations (Han, Pulling, Telke, Huppler Hullsiek, & Terry Bein 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 et al., 2005). This measure will be primarily used in the cost-effectiveness analysis.

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 critical factor in the decision to access health care (Freedman, 1998). Change in mistrust is a potential mediator of intervention effects of viral suppression.

Access to Care Scale will be measured using a 6-item scale addressing the accessibility of reaching medical services 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 the human immunodeficiency virus may be useful in evaluating virologic suppression (Cunningham et al., 1995).

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.

As chronic Hepatitis C can also affect liver function and influence choice of ART if HCV treatment is being considered, HCV Ab status will be measured via medical record and evaluated as a potential moderator of virologic suppression.

10.1.2 Substance Use Measures

Screening Measures. Participants must have drug and/or alcohol involvement to be eligible. We will utilize a *single question drug use screen*: “How many times in the past year have you used an illegal drug or used a prescription medication for nonmedical reasons?” Scores that are ≥ 1 have 100% sensitivity and about 73.5% specificity for presence of a drug disorder (Smith, Schmidt, Allensworth-Davies, & Saitz, 2010). This will be followed by a *drug checklist* to assess which drugs are involved. Study inclusions include stimulants and/or opiates. To assess for alcohol problems we will use the *AUDIT-C* which contains the 3 consumption items of the AUDIT. A cut-off of 5 or more for men and 3 or more for women will be used (Frank et al., 2008).

Baseline and Follow-up Substance Use Measures. *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 AUDIT (Kitchens, 1994; Piccinelli et al., 1997) will be used to assess alcohol use severity (at baseline only the additional questions beyond the AUDIT-C done at screening will be assessed). We will also measure recent drug and alcohol use by performing urine drug screens and breath analysis at the 6-month and 12-month 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. Reduced substance use is hypothesized to be a mediator of HIV viral suppression.

We will include a minimum set of questions on drug injection and sexual risk behaviors that were used in the ARTAS study (Metsch 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.

Drug Use will be assessed by the ASI-Lite (drug/alcohol use module) at baseline and repeated at 6 and 12 months. Because the ASI only asks about drug use in the last 30 days, a short series of questions on drug use over the prior 6 months based on the drug use matrix that was used in the NIDA CTN 0032 HIV testing study (Metsch et al., 2010) will also be asked at baseline, 6 and 12 months to get information 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.

Fagerstrom 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 1991).

Readiness and Resistance to Drug Treatment. Participants' attitudes toward and readiness for drug 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.

Attendance at Substance Use Treatment will be assessed by self-report at baseline, 6 and 12 months.

10.1.3 Comorbid Conditions and Ancillary Measures

Hepatitis status will be assessed by medical record review. Hepatitis, particularly Hepatitis C complicates HIV care and HIV drug selection so it is an important control factor.

Mental Health will be assessed by the 18-item Brief Symptom inventory at baseline, 6 and 12 months (Recklitis et al., 2006; Zabora et al., 2001). The BSI-18 provides specific scales for anxiety, depression, somatization as well as a global severity index. 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 et al., 2004; Safren et al., 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.

Social support will be measured by at baseline, 6 and 12 months by the *Short Social Support Scale* consisting of five items (Fleishman et al., 2000), and the *Conflictual Social Interaction Scale*, three items (Fleishman et al., 2000; Berry 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). Because the patient navigator 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 both viral suppression and drug use outcomes.

Several questions about the participant's relationships and satisfaction with their Patient Navigator will be asked at 6 and 12 months of those participants in the PN and PN+CM groups.

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 (Slapped, Ithreatened, or Ithrow 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).

10.2 Demographics

Demographics to be collected at screening include age, gender, education, income, race/ethnicity and marital status. At baseline, the following additional measures will be included:

Housing instability will be measured by two questions: Where do you live most of the time? And Where have you lived in the last 6 months (with multiple response categories). An ordering of instable 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 has also 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.

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 et al., 2005; Vogenthaler, Hadley, Lewis, Rodriguez, Metsch, & del Rio et al., 2010; S. Weiser, Fernandes, & Brandson, 2008). Food insecurity has been associated in HIV-infected individuals with substance abuse, depressive symptoms, suboptimal adherence, lack of virologic suppression and mortality (Vogenthaler, Hadley, Rodriguez et al., 2010; S. Weiser et al., 2008; S. D. Weiser et al., 2009; S. D. Weiser, Frongillo et al., 2009). Food insecurity has also 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 care, and HIV-related 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.

Tracking System. The patient navigators 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. For the PN+CM group, the tracking system will also include a listing of all incentives earned, as well as the date on which they were earned and the reasons (target behaviors such as negative urine drug screens, HIV care appointment attendance, etc.) for the incentive. These measures will be collected on an ongoing basis throughout the 6-month intervention period.

10.3 Safety Assessments

10.3.1 Adverse Events, including Serious Adverse Events, and Protocol Violations

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

10.4 Assessments Timetable

Assessment Form	Visit			
	0	00	01	02
	Screening	Baseline	6 Month Follow Up	12 Month Follow Up
Demographics (DEM)	To Be Completed Prior to Screening Enrollment			
Screening Enrollment (ENR0049A)	To Be Completed at the Time of Screening Enrollment			
Randomization Enrollment (ENR0049B)	To Be Completed at the Time of Randomization/Screen Failure			
Additional Demographics (ADE)	X			X
Medical Mistrust (MMT)	X	X	X	X
Household Food Insecurity (HFS)		X	X	X
Hepatitis C Questions (HEP)	X			
Global Assessment of Functioning—Karnofsky (GAF)	X		X	X
Gain Risk Behaviors (GRB)	X	X	X	X
Substance Use (SUB)	X			
AUDIT (AUC)	X	X	X	X
Brief Symptom Inventory (BSI)		X	X	X
Cognitive Screening (COG)		X		X
Health Literacy (HLT)		X		
Perceived Health Status (PHS)		X	X	X
HIV Adherence Measures (ADH)		X	X	X
Medication Adherence Self-Efficacy (ADS)		X	X	X
Access to Care (ATC)		X	X	X
Physician-Patient Relationship (PPR)		X	X	X
Fagerstrom (FTA)		X	X	X
DAST-10 (DST)		X	X	X
Readiness for Substance Use Treatment (MTT)		X	X	X
CTN ASI: Drug/Alcohol Use (ASA)		X	X	X
Modified Illegal Activities (MIA)		X	X	X
Service Utilization Details (SUD)		X	X	X
Conflictual Social Interaction Scale (STS)		X	X	X
History of Abuse and Interpersonal Violence (MIV)		X	X	X
Concise Health Risk Tracking (suicide assessment) - Participant (CHR)		X	X	X
Clinical Lab Data (CLD)		X	X	X
Locator Form (LIF)		X	X	X
Initial Hospitalization Form (IHA)		X		

Assessment Form	Visit			
	0	00	01	02
	Screening	Baseline	6 Month Follow Up	12 Month Follow Up
Patient Navigator Satisfaction (PNS)			X	
Urine Drug Screen (UDS)			X	X
Alcohol Breathalyzer (ALB)			X	X
ARVs Med Log (ARV)	To Be Completed if Taking Antiretroviral Medications			
SUD Module A Emergency Room (SMA)	To Be Completed for Each Visit/Stay Endorsed on the Service Utilization Details (SUD) Form			
SUD Module B Inpatient Hospital (SDB)				
SUD Module C Nursing Home (SMC)				
SUD Module D Day Hospital (SDD)				
SUD Module E Hospital Clinic (SDE)				
SUD Module I Residential Treatment (SDI)				
SUD Cost Information (SCI)	To Be Completed for the Most Recent Visit reported on the SUD Form			
Protocol Violation (PVL)	To Be Completed for Each Protocol Violation			
Non-Intervention Tracking Form (NIT)	To Be Completed for Each Non-Intervention Contact with Participant			
Adverse Event Form (AD1)	To Be Completed for Each Reportable AE			
Serious Adverse Event Form (AD2)	To Be Completed for Each Reportable SAE			
SAE Medical Reviewer (AD3)	To Be Completed by the Medical Monitor for Each Reportable SAE			
Death Form (DTH)	To Be Completed If Participant Dies			
Study Termination Form (STT)	To Be Completed Upon Termination From the Study			

10.5 Interventionist/Counselor Assessments

We will conduct a brief survey of interventionists to garner basic information about interventionists' demographics, level of experience with patient navigation (and/or strengths-based case management), beliefs about patient navigation and contingency management, attitudes and beliefs about HIV care, treatment and substance use treatment, and beliefs about barriers that patients face in accessing and maintaining HIV care and substance use treatment. Because it is the interventionist's role in the study to provide both the PN and PN+CM interventions, the study team wants to be able to describe counselor characteristics (including attitudes and beliefs about the intervention strategies) which will be reported in the 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 related to these differences.

11.0 STUDY CONDITIONS

The three intervention conditions are : 1) Treatment as Usual (TAU); 2) Patient Navigation (PN) to link to and retain patients in HIV care and substance abuse treatment; and 3) Patient Navigation plus Contingency Management (PN+CM) to link to and retain patients in HIV care and substance abuse treatment. The PN and PN+CM interventions will be conducted by trained patient navigators who will attend a centralized, national intervention training and who will have ongoing supervision and quality assurance monitoring. TAU will be conducted by existing staff who normally provide linkage to care services.

11.1 Treatment as Usual (TAU) Group

Participants assigned to the TAU group will receive the standard treatment provided at each hospital for linking patients to HIV and substance use care. In the preliminary hospital survey that we conducted (see section 7.7), hospitals described current practices for linkage to care and substance abuse treatment. The primary method of linkage reported is that patients are scheduled with an outpatient HIV care appointment during hospitalization. According to the survey results, the scheduled care appointment dates range from less than one week to up to four weeks from hospital discharge. Hospitals reported the existence of designated staff responsible for scheduling an outpatient HIV appointment, which varied from hospital to hospital, and included social workers, case managers, interns, attending physicians, or infectious disease consultants. The majority of hospitals surveyed indicated that their standard practice for linking patients to substance use treatment is a written referral to a particular program or set of programs.

During the formal site selection process, a thorough assessment will be conducted of each site's standard practice for linkage to HIV care and substance use treatment. Throughout the course of the trial, hospital sites will be monitored for any potential changes that might occur in standard practice around linkage to HIV care and substance use treatment.

11.2 Patient Navigation (PN) Group

Drs. Metsch and del Rio participated in the development and implementation of the CDC-funded multisite ARTAS intervention, one of the few published randomized controlled trials that demonstrated the efficacy of a brief patient navigator 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 over a 12 month period (Gardner et al., 2005). The patient navigator approach includes five functions: 1) establishing an effective working relationship; 2) encouraging identification and use of strengths, abilities and assets; 3) supporting client control over goal setting and the search for needed resources; 4) viewing the community as a resource and identifying informal sources of support; and 5) conducting case management as an active community based activity. Other patient navigation programs demonstrating increases in the number of patient visits to HIV care clinics and decreases in HIV viral load at follow-up (Bradford, 2007) included the following key activities: 1) relationship building (between PN and patient); 2) appointment coordination; 3) appointment accompaniment; 4) service coordination; 5) health care and other referrals; 6) provision of concrete services; and 7) development and maintenance of linkages to other service organizations. For this study, our manualized PN intervention will be based on the above-described key activities and functions of the PN approach. Specifically, patient navigators will provide the following to all study participants randomized to the PN group:

1. Four initial meetings, ideally having the first one during hospitalization and three within the first three weeks of hospital discharge. The meetings will serve to:
 - Introduce patient navigation and establish rapport.
 - Discuss the participant's experience with HIV/AIDS.
 - Engage in an assessment of current barriers (including substance use) to participant's linkage to care and possible strategies for minimizing those barriers.
 - Engage in an assessment of participant's strengths, abilities, and skills for self-care and examine past and current success in self-care.
 - Identify individuals who might support the participant in linking to care and ways to solicit their assistance versus those who may prove to be a detriment to care linkage.
 - Provide encouragement for linkage to HIV care and substance use treatment.
 - Identify appropriate clinical care placement and facilitate treatment engagement.
 - Identify an appropriate treatment program and directly facilitate enrollment.
 - Receive a virtual tour of the HIV care clinic and possible substance use treatment clinic.
 - Receive a reminder of upcoming care appointment(s) and steps to be completed prior to care appointment (e.g., lab work).
 - Review and begin necessary paperwork for linkage to HIV care, substance use treatment, and access to other services such as for mental health.
 - Review participant's goals for initial care appointments and practice how the participant desires to communicate with providers what he/she wishes to convey.
 - Explore the possibility and potential benefits of the patient navigator (or outreach worker) accompanying the study participant to the care and/or substance treatment visit(s).

Hospitalized study participants may exhibit wide variations in severity of illness, cognitive ability, length of required hospitalization, completion of medical treatment (versus premature self-discharge against medical advice), and motivation to engage in HIV care. Therefore, delivery of intervention material during the course of the first four patient navigation visits may require flexibility in timing and location.

Responses from our preliminary hospital survey (see section 7.7) indicate that HIV-infected hospitalized patients are routinely scheduled for an initial HIV care appointment between 1 and 4 weeks post hospital discharge. The PHAST (Positive Health Access to Service and Treatment) team at San Francisco General Hospital (not a hospital under consideration for the HOPE study) uses a patient navigation-like approach to link hospitalized HIV-infected patients to outpatient HIV care. According to the PHAST team (personal communication, 10-16-10) up to fifty percent (50%) of post-hospital care appointments are routinely missed. Therefore, maintaining frequent and close contact with study participants post hospital discharge is crucial.

2. After the initial four meetings, patient navigators will meet with PN group participants ideally twice monthly during months 2 and 3 and once monthly during months 4 - 6 to:
 - Provide support for completing any or all steps for accessing care and reinforce successful strategies to maintain care.
 - Discuss outcomes of meetings with care providers and next steps.
 - Discuss and plan for medication pick up.
 - Strategize around treatment adherence.

- Provide reminders for upcoming care appointments.
- Discuss who will be supportive of participant in accessing care.
- Discuss access for other needed services.
- Assist in the completion of additional paperwork.
- Accompanying patients to medical or substance use treatment appointments.

If care visits were not completed:

- Assess reasons for missed visit(s).
- Discuss ways to overcome barriers to HIV and substance use treatment.
- Provide encouragement for linkage to HIV care and substance use treatment.
- Review participant's strengths, abilities, and skills for self-care and examine past and current success in self-care with the goal of discussing how these successes with self-care can be transferred to attending HIV care visits.
- Provide reminders for upcoming care appointments.
- Revisit who will be supportive of participant in accessing care for HIV and/or substance use.
- Discuss access for other needed services (mental health, housing, etc.).
- Assist in the completion of any additional paperwork.
- Review participant's goals for initial care appointments and practice how the participant desires to communicate with providers what he/she wishes to convey.
- Explore the possibility and potential benefits of the patient navigator (or outreach worker) accompanying the study participant to the care and/or substance treatment visit.

We recognize that many of the HOPE study participants will be disenfranchised, marginally housed, actively using substances, suffering from mental illness, and experiencing chaotic lives. As a result, participants may miss appointments and may sometimes be out of communication with study staff. With the assistance of outreach workers, patient navigators will conduct field work in an effort to maintain contact with participants. This will require outreach and visits to service agencies, care facilities, free kitchens, homeless shelters, homeless encampments and likely homeless hangouts. To be effective in maintaining contact, relocating and reconnecting with participants, patient navigators will access the participant locator forms completed at baseline which will include detailed information about: 1) where the participant lives or, if homeless, where the participant tends to sleep at night including outdoor locations, shelters, friends' homes; 2) where the participant spends time during the day such as outdoor locations, service organizations, indoor public spaces such as libraries; 3) at least one contact (friend, family member, case manager) who should be able to locate the participant in the event that direct contact cannot be made. Additionally, patient navigators will be expected to maintain good working relationships with staff at care and support clinics/agencies so that patient navigators and agency staff have open communication about participant contact.

11.3 Patient Navigator Plus Contingency Management (PN+CM) Group

Study participants randomized to this group will receive the patient navigation (PN) intervention as outlined above combined with contingency management (CM). Contingency management is an efficacious intervention that improves outcomes in substance abuse treatment (Dutra et al., 2008; Lussier et al., 2006; M. Stitzer & Petry, 2006), attendance rates in a variety of settings (Haukoos, Witt, Coil, & Lewis, 2005; Petry, Martin, & Finocche, 2001a; Sigmon & Stitzer, 2005), and medication

adherence (Preston et al., 1999; Seal et al., 2003; M. L. Stitzer, Polk, Bowles, & Kosten, 2010) including adherence to HIV medications (Rigsby et al., 2000; Sorensen et al., 2007). Using the principles of contingency management, this combined intervention will incorporate viral load suppression as a target of reinforcement as well as several other behaviors (HIV clinical care, medication adherence, cessation or reduction of substance use) that are hypothesized to be moderators or mediators of the primary outcome.

For participants randomly assigned to the PN+CM study group, patient navigators will: 1) effectively communicate the incentive plan to the participant, 2) track each of the seven target behaviors that may earn participant incentives, 3) verify occurrence of the target behaviors, 4) deliver incentives according to the protocol, and 5) maintain a record of incentives delivered. PNs will use a computer-based tracking program to facilitate this work.

11.3.1 Rationale for Selection of Target Behaviors

Participants are asked to perform multiple behaviors that are in their own best interests for promoting health and recovery. The incentive plan is designed to enhance motivation in all targeted areas of performance engagement in healthy moderating or mediating behaviors (HIV care, medication adherence, drug use cessation or reduction) that are hypothesized as essential to achieve the primary outcome of viral load suppression. Thus, incentives are available for seven different target behaviors and one outcome, as discussed below. Incentives for each behavior operate independently of incentives for all the other behaviors. Conceptualizing the CM plan in this manner (rather than having reinforcement for any given behavior depending on performance of one or more other behaviors) will allow investigators to separately examine target behaviors of PN and PN+CM groups to see which behaviors have been effectively influenced by contingent incentives and which have not. Study participants may choose to earn all available incentives by complying with all target behaviors, earn some incentives by complying with any combination of target behaviors or earn no incentives at all. Further, each incentive schedule is tailored to the expected frequency and spacing of intervention visits. Several target behaviors, including HIV care and substance abuse treatment visits, have flexible starting and stopping times within the 6-month intervention period since the time at which a participant might initiate engagement in the target behavior will vary across participants. For most of the target behaviors an escalating schedule of incentive payments will be used. The incentive amounts available increase over time in order to take advantage of early enthusiasm and to counteract waning interest and drop-out at later time points. Except for substance use toxicology screening, re-sets (the incentive amount is “re-set” to the starting amount on the schedule when the target behavior is not achieved as scheduled) will not be used. Although some studies have suggested “re-sets” are valuable (Roll, Higgins, & Badger, 1996) the protocol development team decided against utilizing re-sets for most behaviors to lessen the complexity of the incentive program for study participants and for the PNs who will be responsible for managing the incentive program. A more complete description of the incentive plan for each of the seven target behaviors and the one outcome is given below.

11.3.2 Incentive Plan for Targeted Behaviors

1. Attend meetings with Patient Navigators

Eleven meetings with the PN are scheduled during the 6-month intervention. The first will ideally take place in the hospital setting and the remainder at scheduled appointment sites. However, if a participant is re-hospitalized during the course of the 6-month intervention period, 1-2 intervention sessions may take place within the hospital depending on the length of the hospitalization or as needed. These meetings are scheduled with declining frequency over the 6-month intervention time-frame, on the assumption that more contact and support will be needed at the beginning compared to the end of the intervention. As indicated above, no re-set of incentive amount is planned; if an appointment is missed, the participant is incentivized at the same value as the last incentivized

appointment. The next available incentive value would be disbursed at the next visit. A total of up to \$220 may be earned for attending all PN visits.

2. Complete precursor paperwork

Initiating HIV clinical care or substance use treatment often requires completing agency, insurance, and other types of paperwork which will vary across locales and between participants. A total of up to \$80 is available to reinforce each participant for completing/submitting paper work.

3. Enroll and attend scheduled visits at an HIV care clinic

One primary goal of the project is to help HIV-infected drug users initiate or re-engage in HIV clinical care and ART. Up to four visits will be incentivized during the 6-month tracking period. HIV care and incentive earnings can begin at any time during the protocol; payments escalate over time for attending successive visits without re-set for missed appointments. A total of up to \$180 can be earned for HIV care visits that are verified via medical record abstraction.

4. Enroll and attend visits at a substance abuse treatment program

Incentives are available for making and keeping the first four appointments at a substance abuse treatment program which may include intake, assessment and initial counseling appointments. Providing incentives for the first four treatment appointments is designed to facilitate initial engagement. Available incentive payments escalate over successive appointments with no re-set or time frame specified for distribution. A total of up to \$90 can be earned for this initial engagement in substance abuse treatment.

5. Submit drug-negative specimens

Prior research supports a strong link between active drug use and poor HIV outcomes (Arnsten et al., 2002; Celentano & Lucas, 2007; Lucas et al., 2006) and suggests that stopping drug use may set the stage for improved HIV treatment adherence. Research also supports the ability of abstinence incentives to initiate and sustain periods of abstinence, as referenced above. Study participants have the option of earning incentives for submission of urine samples for toxicology screening that are negative for opiates, stimulants (cocaine, methamphetamine) and submitting to a breath analysis to screen for alcohol. To supplement and enhance the impact of substance use treatment, the negative urine/breath incentive schedule operates independently of the PN visit incentive and independently of all other target behaviors including substance abuse treatment participation. Participants may start earning abstinence incentives at the initial hospital visit or at any point thereafter. For those who wish to participate, the PN will collect and test biological samples at each visit and disburse reinforcers according to the protocol. In order to promote sustained abstinence, negative sample incentives are available on an escalating schedule with a re-set for positive or missing samples. One advantage of this approach is that it allows participants, who feel they can lessen their substance use without formal treatment, to earn incentives for evidence of non-substance use without being in substance abuse treatment. A total of up to \$220 could be earned for submission of negative urine/breath samples.

6. Laboratory visit to have blood drawn

Incentives are available for participants to provide blood specimens so primary care providers can measure and monitor viral load during the intervention. Participants will be incentivized for having blood drawn during two separate lab visits. A total of \$50 can be earned for provision of blood specimens.

7. HIV medication pick up

Study participants will be provided incentives for collecting their HIV medication prescriptions approximately on a monthly basis. Incentive payments escalate over time with no reset for missed HIV prescription collection. A total of \$170 can be earned for HIV medication pick up.

11.3.3 Incentive Plan for Primary Outcome

Achieve viral load suppression

Two bonus payments will be offered to participants for achieving the primary health outcome of viral load suppression (defined as ≤ 200 copies/mL). The first bonus can be earned approximately 8-16 weeks post-randomization and after starting HIV medications. It is not certain that all participants, even those who are taking their HIV medications as prescribed, will achieve full suppression by 8-16 weeks post-randomization. Thus, in addition to full suppression, a viral load reduction criterion has been formulated for awarding the first bonus payment (a two log drop in baseline viral load). The second bonus can only be earned at the 6-month study follow-up time point if the participant achieves full suppression or remains fully suppressed (defined as ≤ 200 copies/mL). We will also discuss medication adherence with patients and discuss how the best indicator that they are being adherent is to have an undetectable viral load. Participants may earn up to \$150 for achieving viral load suppression.

11.4 Patient Navigators Delivering Both Interventions

Patient navigators will be trained and will deliver both PN and PN+CM interventions. We recognize that using distinct patient navigators may possibly protect the discreteness of each condition. This option was rejected, however, as it may introduce a larger problem of interventionist effects. Najavits, Crits-Christoph and Dierberger (2000) provide an excellent review of this literature. The following quote highlights the potency of interventionist effects: "Ironically, however, clinicians typically account for more variance in patient outcomes than do differences between active treatments or patient baseline characteristics, a result which holds both in the substance abuse disorder field and psychotherapy research in general." By using the same interventionists to conduct both interventions, we will: (1) reduce the possibility of confounding intervention with interventionist effect; (2) deliver training in two interventions rather than one to all patient navigators; and thus (3) provide thorough coverage of both treatment conditions throughout the course of the trial, including during times of interventionist vacation, illness, or other leave of absence.

Several procedures will be in place to maintain quality control of the interventions: 1) in house intervention sessions will be audio recorded and a percentage of those will be randomly selected for intervention fidelity review; 2) interventionists will use an electronic participant tracking system and an electronic incentive tracking system which will be monitored by study coordinators, QA monitors and lead team members; and 3) participants will complete a fidelity questionnaire at each follow-up assessment to determine if they have been exposed to elements of both interventions.

12.0 STATISTICAL ANALYSIS

12.1 Objectives of the Analysis

The single primary objective of this trial is to discover whether there is a difference in the proportion achieving HIV viral suppression amongst the three study groups: (1) Patient Navigator, (2) Patient Navigator plus Contingency Management and (3) Treatment as Usual. There are three primary hypotheses, $\text{arm1} = \text{arm2}$, $\text{arm1} = \text{arm3}$, and $\text{arm2} = \text{arm3}$. The family-wise error rate for these hypotheses is controlled to be no greater than .05

12.2 Primary Outcome

As previously outlined in section 8.1, the primary outcome variable is binary: presence of HIV viral suppression (≤ 200 copies/ml) at the 12 month follow-up versus presence of viral load > 200 or death (all-cause mortality). Viral suppression is defined as a viral load ≤ 200 copies/ml rather than achieving a viral load “below the limit of detection of the assay” which, in this day, is usually < 50 copies/ml to avoid “blips” and episodes of low level viremia that are not uncommon, even among patients on stable antiretroviral therapy.

12.3 Secondary Outcome Measures

Secondary outcomes are divided into those related to HIV and those related to substance use. Note that the date of randomization is the time point from which all outcomes will be measured.

12.3.1 HIV Related Secondary Outcomes

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

- a) Repeat primary analysis with the addition of a treatment interaction with viral suppression status at baseline (binary)
- b) Viral suppression at 12 months or HIV-related deaths (binary, note that non-HIV related deaths would be classified as missing in this analysis)
- c) Viral suppression at 6 months (binary)
- d) CD4 Cell count (continuous at 6 and 12 months)
- e) Engagement into care (visit constancy, a repeated binary at 3-month intervals)
- f) HIV care visit attendance (count)
- g) Medication Adherence (count)
- h) Hospitalizations (count)
- i) All cause mortality (binary)

12.3.2 Substance Use Related Secondary Outcomes

- a) Substance use frequency (count and binary)
- b) Substance Use Severity (continuous)

- c) Self-reported treatment engagement (binary)
- d) Self-reported number of drug treatment sessions (Count)

12.3.3 Mediators and Moderators of Outcomes

- a) Viral Suppression Moderators: psychological distress (BSI), Housing instability, Food Insecurity Health literacy, HIV-related cognitive problems renal function and liver function.
- b) Viral Suppression Mediators: Medication self-efficacy, Physician-Patient relationship social support and substance use.
- c) CD4 Count Moderators: HCV status.
- d) Drug Use Moderators: Readiness for drug treatment.
- e) Drug Use Mediators: Readiness for drug treatment and social support.

12.4 Cost and Cost-Effectiveness Secondary Outcomes

Significance: In this era of constrained resources, it is particularly important that public dollars are managed wisely and that program managers are able to provide evidence-based support for their funding decisions. Cost-effectiveness analysis in public health is an analytic technique that quantifies the health benefits obtained from spending on selected activities compared with other possible uses of the funds. It can aid decision-makers to increase the value obtained from available resources, and can provide a transparent rationale for decisions.

Study design: We will conduct an incremental unit cost and cost effectiveness evaluation using standard micro-costing techniques, (Muenning, 2002) combined in a deterministic model with estimates of the long-term health and cost consequences of the three intervention strategies employed in the trial. Two unit cost and cost-effectiveness comparisons will be completed, the incremental cost and benefits of *PN* vs. *TAU*; and *PN+CM* vs. *PN*. We will conduct one-way, two-way and multi-way sensitivity analyses using Monte Carlo simulations for estimating the confidence intervals associated with the base-case incremental cost-effectiveness ratios. Cost-effectiveness will be assessed from the health care system analytic perspective. Future costs and benefits will be discounted over a 20-year horizon at 3% per annum, and all costs will be adjusted to 2010 dollars. We will report results two ways, both including and excluding the benefits of transmission prevention and their associated future savings in HIV /AIDS treatment costs.

Program cost estimation: The incremental cost of the interventions will be assessed using a uniform cost data collection protocol for gathering expenditure data at each of the 11 study sites. We will work in close consultation with staff at each site to complete this protocol for the 12-months of post-randomization services we plan to study. Expenditures will be classified in one of four categories; (i) personnel (including fringe benefits); (ii) recurring supplies and services; (iii) capital and equipment; and (iv) facility space (as appropriate). The costs of each program activity will be identified through interviews with administrative, finance and human resources officers, supplemented by direct observation in a limited number of formal time and motion studies. The costing approach will emphasize resources utilized, rather than out-of-pocket costs. For example, where expenditures do not fully reflect the opportunity cost of the resources used (e.g., donations or transfer payments), we will adjust the valuations accordingly. Costs for capital items (if any) will be amortized on a straight-line basis over their expected useful life, and assuming no salvage value. Facility space required by the interventions, (if any), will be valued at the market rental rate. Following assignment of expenditures to these four broad categories, we will further allocate each expenditure item across three activity areas, (i) service delivery; (ii) staff training directly related to service delivery; (iii) indirect

costs consisting of intervention overhead and administration. The latter will be allocated to the programs in proportion to the full-time equivalent staff (FTEs) that study intervention service providers constitute of all service provider FTEs at the study sites (Marseille et al., 2011). We expect that the preponderance of intervention costs will be personnel time. The appropriate approach to measuring the opportunity cost of that time will depend upon the way services are organized at the 11 study sites. For example, if dedicated staff is hired specifically for these interventions, costs can be obtained directly from compensation data. In the more likely case that counselors and other direct service providers have multiple responsibilities, the time dedicated to these interventions can be obtained via interviews supplemented by direct “time and motion” observations.

Estimating unit intervention costs: Program outputs will be obtained from the analyses described under “Study Design”. Outputs include the numbers of patients receiving *PN* and *PN+CM* and the number of patient-hours of services received. Unit costs are defined as program costs divided by each of these outputs, respectively. To supplement this information, we will also collect information on patient-level contact hours, to quantify and examine the importance of participant and interventionist-level factors related to variation in unit-cost. To the extent possible, these data will be obtained through extraction of the various types of service-hours received as recorded in existing patient logs. As necessary these data will be supplemented by interviews with administrative staff. For activity items that may not be available from existing records, we will ask providers to complete a computer-based record of activities that record the time spent and services provided to a sample of clients. We will also calculate unit costs based on outputs more proximal to the final outcomes of interest, i.e., suppression of viral load and reduction in substance use. These include health-seeking behaviors such as self-reported HIV care visits, and attendance at substance use treatment. At this level of the analysis, we will not attempt a joint product cost allocation.

Estimating health and cost-of-care outcomes: The primary health outcomes are suppression of viral load and reduced substance use, and we will express the final cost-effectiveness ratio as cost per patient with newly-suppressed viral load. This calculation fulfills our primary objective of comparing the cost-effectiveness of *PN* with *PN+CM*. However, a broader metric is needed, if the cost-effectiveness of these interventions is to be compared with other HIV or non-HIV public health options. The potential benefits of the intervention include (1) improved prognosis (slower disease progression) of the index patient; and (2) reduced HIV transmission to their sex and drug-using partners. Both benefits can be captured by their contributions to additional Quality-Adjusted Life-Years (QALYs) (Gold, 1996). The benefits of improved prognosis will be estimated from the published literature on disease progression by initial CD4 and viral-load strata. Incidence of AIDS-defining conditions, other medical events and their associated care costs will be based on values reported in the published literature from validated disease transition state models, especially the Cost-effectiveness of Preventing AIDS Complications (CEPAC) model (Linac et al., 2009; Paltiel et al., 2006; Rydzak et al., 2010; B.R. Schackman et al., 2006; Walensky et al., 2006; Walensky et al., 2007). All costs and QALYs are incremental; that is, the additional cost and benefit for each intervention over the cost and benefits of its less expensive comparator (*PN* vs. TAU; and *PN+CM* vs. *PN*). Calculations of the reductions in transmission will be based on HIV transmission probability estimates using simple Bernoulli models to estimate the risk of transmission via sexual contact and needle sharing (Kahn, 1998; Pinkerton & Abramson, 1998). CD4 strata-specific utility weights will be based on published studies (Mrus et al., 2006; B. R. Schackman et al., 2002; Stavem, Froland, & Hellum, 2005). The model will be tested for technical accuracy and predictive ability before it is used with program data.

Intervention cost + additional ART cost - averted future medical costs

QALYs for index Pt. + QALYs for partners

The cost-effectiveness ratio will thus consist of intervention costs adjusted for increased ART costs in responders, and the averted future medical costs. This net cost result will be divided by the QALYs attributed to improved outcome for index clients and the averted morbidity and mortality due to reduced HIV transmission risk.

Estimating broader social costs and benefits. In addition to conducting traditional cost-effectiveness analysis that examines net program and medical costs as compared with changes in health outcome, we will also conduct cost-benefit analyses that take into account the broader social costs related to averted jail and illegal activity, work-related gains in income, and averted social welfare costs. Changes in individuals' employment income and averted social welfare costs will be estimated based on self-reported employment status data at baseline and 12-months follow-up. We will measure changes in illegal activities such as robbery and burglary through the administration of a self-report instrument on arrest, incarceration and potentially criminal activity (Cartier, 2006). By comparing the average number of jail or prison-days served (*PN* vs. *TAU*; and *PN+CM* vs. *PN*); and applying a literature-derived range of estimates to the cost per jail-day, we will estimate the potential program-attributable savings in jail time. Via the self-report arrest and crime information, we can obtain lower-bound estimates of the saved crime-related societal cost generated by the interventions. For example, based on self-report, a 2008 study of the cost-effectiveness of substance abuse treatment found that robbery declined by 85%, from 0.83 per client/year to 0.12 per client/year following substance abuse treatment, whereas a reduction in robberies per client of only 5% would meet societal willingness-to-pay criteria (Basu, 2008). As discussed by Olmstead and Petry (Olmstead, 2009), both the link between drug use and crime, and the social costs of various types of crime are well established. As a supplementary approach, estimates of the likely reductions in crime incidence associated with additional abstinence can be obtained by interviews with service providers and correctional officers and through review of the existing literature. By adopting conservative values of reduced crime incidence based on the incremental days of abstinence generated by the interventions we can derive a second rough but serviceable estimate of the reduced crime-related social costs.

Limitations: Modeling efforts in HIV disease are always limited by the use of retrospective data linking surrogate markers and clinical events. Particularly in an era of ART and the "seek, test and treat" prevention agenda, rapid changes in local practice guidelines and patterns can introduce time-dependent variation into the epidemiologic data on which HIV models must depend. We plan to minimize the effects of data variation by using more than one data source, and by extensive use of sensitivity analysis with a Monte Carlo approach to examine the effect of variations in parameters and distributional assumptions on model predictions. Precision of the estimates of reduced crime and its attendant social cost is limited by the nature of the available data. Existing methods tend to underestimate the likely benefit (Olmstead, 2009). However, the proposed approach will produce a more accurate final cost-effectiveness estimate than if we simply omitted these dimensions due to the imperfection of available data and methods.

12.5 Overview of Analysis Plan

12.5.1 Primary Outcomes

As specified in the aims, the primary hypothesis test will compare the proportions achieving HIV viral suppression at 12 months across the three study groups. Death from any cause will be considered equivalent to non-suppression for the purposes of calculating this proportion. We will, however, explore differences in outcome when deaths are categorized with respect to likelihood of being HIV and/or drug use related. All 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. However, participants who are lost to follow-up before 6 months will not contribute to the primary analysis. A Generalized Estimating Equations (GEE) model will be

employed (Zeger & Liang, 1986) with a binomial distribution and logit link as implemented in SAS. The GEE model will include both 6-month and 12-month HIV viral suppression status. However, the primary test of the hypothesis will be based on contrasts involving the 12-month proportions only. This model gains statistical power by pooling the error term across the two follow-up times and is closer to an ITT approach than would be the analysis of 12-month events only. It does not impute data that are missing at month 12. Any potential correlation between patients within a site will be controlled by estimating a fixed effect for site in this model.

A simple closed-testing procedure (Westfall, Tobias, Rom, Wolfinger, & Hochberg, 1999) will be used to control family-wide type I error at 0.05 while still allowing all three pairwise comparisons between arms. Specifically, let $P(123)$ be the (two-sided) p-value of the contrast testing equality among all three arms, while $P(12)$, $P(13)$, and $P(23)$ are the (two-sided) p-values for arms 1&2, 1&3, and 2&3, respectively. Then, let the adjusted p-value for the (1,2) comparison be

$$P^*(12) = \max[P(123), P(12)]$$

and similarly for the other pairwise comparisons. Tests of pairwise equality will be performed by comparing $P^*(12)$, $P^*(13)$, and $P^*(23)$ to the 0.05 level of significance.

12.5.2 Covariates including Site

Randomization should ensure that the distributions of characteristics across our 3 groups are similar at baseline. Thus, the analysis is straightforward, and the primary analysis of association of the particular contrasts of group on the particular outcome will not need to control for covariates, with the exception of an indicator of baseline CD4 count (greater than 350 cells/uL), an indicator of detectable viral load at baseline, and site of recruitment. Site will be included as a covariate because there is the possibility that participants within a site will be more alike than will be participants from different sites. If ignored, this would violate an assumption of the simple model that all observed participants are independent of each other. Inclusion of site as a covariate will correct the model for any dependence in observations within a site, and baseline viral load and CD4 count may prove important predictors. As noted, randomization should control for all other participant level covariates. Nevertheless, to assess the effects of and control for any unintended impact of group differentials across the range of covariates, in a second sensitivity analysis, the simple analysis listed above will be extended to additionally control for, age at baseline, race and ethnicity, gender, and primary type of drug use (injection drug use vs. non-injection drug use, opiate vs. non-opiate, stimulant vs. non-stimulant) and baseline viral load. The significance levels for any of these covariates will be reported, but will not affect the conclusions of the primary analysis. As listed below, the effects of these variables on viral suppression will be explored more fully in the secondary aims. We will also assess the interaction of each of these covariates with treatment group as they affect the primary outcomes. If statistically significant, the results of these analyses will not affect the p-value of the primary analyses, but may affect our interpretation. However, the results will be reported in the secondary analyses sections (see section 12.4.4).

12.5.3 Tests of the Specific Aims

Aim 1: To evaluate the effectiveness of Patient Navigator and Contingency management in achieving suppression of HIV viral load among substance using hospitalized HIV-infected individuals with initially unsuppressed HIV viral load.

Primary Hypotheses: The proportion achieving viral suppression (plasma HIV viral load of ≤ 200 copies/mL) relative to non-suppression or any-cause mortality in the 3 study groups will differ from each other at the 12 month follow-up. Specifically:

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

Sub-hypothesis 2. The proportion achieving virologic suppression in the PN+CM group will be greater than that in the PN group.

Sub-hypothesis 3. The proportion achieving virologic suppression in the PN group will be greater than that in the TAU group.

Using a logistic GEE model, a type III contrast of the overall group membership will be estimated in a model controlling for whether viral load was suppressed at baseline and for whether CD4 cell count at baseline was greater than 350 cells/uL. Following the closed testing procedure, if this overall group test is significant at $p < 0.05$, then the three pairwise-comparisons will also be tested. Equivalently, the adjusted level of significance (adjusted p-value) used for each particular pairwise contrast will be the maximum of the simple calculated p-value of the observed overall test and the simple calculated p-value of each pairwise test.

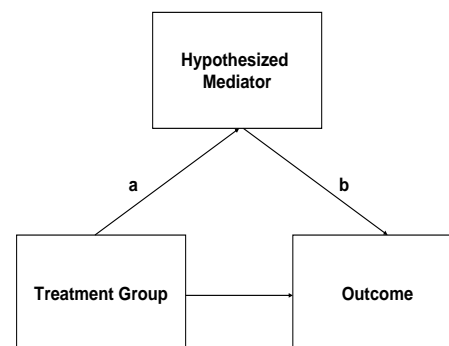
In the primary outcome analysis, missing data caused by a death from any cause will be considered a failure and therefore not meeting virologic suppression. Missing data associated with drop out or any other cause will not be imputed in the primary analyses. We will explore differences in outcome when deaths are categorized with respect to likelihood of being HIV and/or drug use related.

12.5.4 Tests of the Secondary Outcomes

Each of the stated secondary outcomes listed in Section 12.3 will be tested separately, using the closed testing procedures described for the primary outcome to control family-wide type I error. The statistical methods used will also mirror the methods used for the primary hypothesis. Those secondary outcomes that are binary will be tested as described for the primary hypothesis using a logistic regression; whereas those 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. The hypothesized moderator variables (for viral suppression: psychological distress, housing instability, food insecurity, health literacy, HIV-related cognitive function, renal function and liver function; and CD4 count. Drug Use moderator: readiness for treatment and HCV status) will be addressed in the same way that the covariates for the planned sensitivity analysis of the primary outcomes (site, age at baseline, race and ethnicity, gender, and primary type of drug use [IV vs. non-IV, opiate vs. non-opiate, and stimulant vs. non-stimulant], baseline level of viral load) 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. For these analyses, the overall Type I error will not be controlled, rather, the reader of any resulting journal article will be alerted to the fact that these analyses were the result of *post-hoc* exploratory analyses, and that any statistically significant results may have resulted from a Type I error, and require replication.

12.5.5 Mediation

Mediation will be tested using structural equation modeling with Mplus 6.1. These models estimate the effect of the intervention on the potential mediator (path a, e.g., the effect of intervention on *information*) and the effect of the mediator on the outcome or next proximal intermediate outcome (path b, e.g., the effect of *information* on *motivation*). Longer mediation pathways can also 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.¹⁶⁸ This test is by far the most powerful test of mediation¹⁶⁴ and can test multiple mediating pathways within a single structural model.



12.5.6 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 three intervention 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. On the full sample of rated intervention sessions, a simple ANOVA will be used to compare the 3 conditions on the ratings of various behaviors performed during the intervention. Depending on the realized distribution of the ratings, a non-parametric test, the Kruskal-Wallis test, may be substituted for the ANOVA procedure. These means and the associated test-statistics will be reported in the primary outcome manuscript and the final report to describe intervention fidelity.

12.6 Missing Data and Dropouts

Missing data are a ubiquitous problem in substance use research, primarily due to dropping out and refusal. Missing data can lead to biased estimates and reduction of power, affecting the generalizability of the study. We will make every effort to minimize the amount of missing data and in the primary analyses we will include only participants with available data at 6 or 12 months, although study participants who have died will be considered a failure and not meeting virologic suppression. In all cases missingness patterns will be identified and analyses will be conducted to determine if there is differential non-death attrition by treatment arm, and if missingness is related to any of the covariates. In the case that covariates predict missingness, the data are called "Missing at Random," (MAR) (Little & Rubin, 1987). GEE analyses are only appropriate if data are "Missing Completely at Random," which means that no covariates predict the occurrence of missing data. 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). Therefore, if observed covariates predict the existence of missing data, multiple imputation will be used in a secondary analysis of the primary outcome to assess the effects of missingness on the reported results. If nonrandom missingness is of concern (Missing not at Random, MNAR), this problem will be addressed 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

If recruitment goes as planned, which originally was to enroll 800 participants over a 10 month period (80 participants/month), no interim efficacy or futility analyses will be done, as recruitment will be completed before any participants will have reached 12 months of follow-up, the period at which the primary outcome is measured. However, if the recruitment period becomes protracted to a point where, over a 26-month period, the number enrolled is 23.5 participants per month or slower (i.e. about 600 participants or fewer at 26 months), we will perform efficacy and futility analyses for DSMB and NIDA review. For these analyses, a two-sided, symmetric O'Brien-Fleming (1979) type boundary using the flexible Lan-DeMets (1983) procedure will be implemented for group sequential testing for efficacy, and a conditional power analysis (Jennison & Turnbull, 2000) will be implemented for futility. The threshold of 23.5 participants per month over 26 months was selected because this corresponds to an approximate point in time when 288 participants (approximately 40% of the targeted sample size after accounting for 10% attrition) will be available for 12-month outcome analysis, and approximately 600 of the targeted participants will have been enrolled (achieving 75% of the targeted sample size). Therefore, if a conclusion is reached based on efficacy or futility to stop the trial early, approximately 200 participants would not need to be enrolled into the trial. If the recruitment rate is higher than 23.5 participants per month at 26 months, i.e., if recruitment is expected to take less than 34 months, no interim analyses will be performed. 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

Power calculations were based on a simulation of several scenarios, with 5000 iterations per scenario. In each iteration, 266 virally unsuppressed participants were recruited to each of three treatment groups, after which death and dropout rates, and rates of suppression before and after 6 months, were imposed so as to result in proportions of simulated participants dead, lost, suppressed, and unsuppressed at both 6 and 12 months as indicated below. These rates characterized the scenario. (Note that the rates dictate the probabilities of joint occurrences of outcomes at 6 and 12 months, but it is possible for more than one set of rates to produce the same set of 6-month and 12-month margins.)

Once these data were simulated, they were subjected to a Generalized Estimating Equation (GEE) analysis in which dropouts were ignored and dead participants were combined with unsuppressed participants. More specifically, the GEE regressed state (suppressed versus unsuppressed or dead) on time (6 months, 12 months), treatment group (Patient Navigator = PN, Contingency Management + Patient Navigator = CM, Treatment as usual = TAU) site (1-10) and the time by treatment group interaction using a binomial link. The outcome of interest was the proportion suppressed (versus unsuppressed or dead) in each arm at 12 months, but the analysis incorporated 6-month data so that the 6-month/12-month correlation could in part offset loss to follow-up between 6 and 12 months. Contrasts were used to obtain p-values for the hypotheses CM=PN=TAU, CM=PN, CM=TAU, and PN=TAU with respect to the outcome of interest.

These p-values were combined together using the closed-testing methodology explained in Section 12.4.1. Note was taken of which of the pairwise hypotheses were rejected ($\alpha = 0.05$, two-tailed), and which accepted according to the Closed testing algorithm in each iteration. Finally, the power for the tests of the various hypotheses was estimated as the proportion of the 5000 iterations in which each hypothesis was rejected.

The scenarios were defined by the following parametric values, which varied from treatment group to treatment group:

- M6 = target suppressed proportion at 6 months (assuming no death or dropout)
- M12 = target suppressed proportion at 12 months (assuming no death or dropout)
- S = Probability that a participant will be suppressed at 12 months, given he was suppressed at 6 months
- U = Probability that a participant will be unsuppressed at 12 months, given that he was unsuppressed at 6 months
- E = quarterly probability of death for a suppressed participant
- F = quarterly probability of death for an unsuppressed participant
- G = quarterly dropout probability for a suppressed participant
- H = quarterly dropout probability for an unsuppressed participant

Four scenarios (A-D) were investigated, with parametric values given by the table below:

Scenario	Group	M6	M12	S	U	E	F	G	H
A	TAU	0.18	0.16	0.95	0.99	0.02	0.05	0.04	0.04
A	PN	0.375	0.26	0.85	0.99	0.02	0.05	0.04	0.04
A	CM	0.55	0.4	0.85	0.98	0.02	0.05	0.04	0.04
B	TAU	0.175	0.16	0.98	0.99	0.015	0.03	0.03	0.03
B	PN	0.33	0.24	0.94	0.98	0.015	0.03	0.03	0.03
B	CM	0.49	0.44	0.96	0.98	0.015	0.03	0.03	0.03
C	TAU	0.175	0.16	0.98	0.99	0.02	0.05	0.04	0.04
C	PN	0.33	0.24	0.94	0.98	0.02	0.05	0.04	0.04
C	CM	0.49	0.44	0.96	0.98	0.02	0.05	0.04	0.04
D	TAU	0.18	0.16	0.95	0.99	0.015	0.03	0.03	0.03
D	PN	0.375	0.26	0.85	0.99	0.015	0.03	0.03	0.03
D	CM	0.55	0.4	0.85	0.98	0.015	0.03	0.03	0.03

The numerical values of the parameters selected in scenarios A-D were chosen to match prior experience of the investigators and data from the literature. Out of care HIV-infected individuals who are admitted to the hospital will have very low rates of viral suppression, in the range of 10-15%. From clinical discussions amongst the research team it was decided that a 10% to 12% increase (i.e., moving from 15% to 25% or 15% to 27%) is a minimally clinically meaningful change. We therefore aimed power determination at uncovering around a 12% pair-wise difference between intervention conditions. From an ongoing study of Metsch and del Rio, a 12-15% death rate seemed to be likely in this cohort. Finally, since all participants are heavy drug and/or alcohol users it is appropriate to account for 10-15% attrition (in addition to the deaths) in these calculations even though, the research team has a history of achieving high rates of follow-up.

Power results are given in the following table, along with the parametric value of M12 and simulated resulting proportions of death, attrition, and suppression ignoring dropouts. Across each of the 4 scenarios, there is 87% power or greater to reject any of the 3 pair-wise comparisons under the assumptions set forth and a sample size of 266 study participants per treatment group.

Scenario	12-Month Statistics (percent)														
	Observed Attrition			Observed Death			Target Suppression(M12)			Realized Suppression			Power		
	TAU	PN	CM	TAU	PN	CM	TAU	PN	CM	TAU	PN	CM	TAU vs PN	PN vs CM	TAU vs CM
A	14	14	14	16	15	14	16	26	40	16	29	42	93	87	100
B	11	11	11	10	10	9	16	24	44	17	30	44	94	92	100
C	14	14	14	16	15	14	16	24	44	16	28	42	93	89	100
D	11	11	11	10	10	9	16	26	40	16	30	44	94	89	100

* Realized Suppression Outcome = suppressed / (suppressed + unsuppressed + dead)

13.0 TRAINING

Training in study-specific assessments will be provided as specified in a comprehensive training plan that will be developed by EMMES, the Lead and Co-Lead Nodes, and other participating nodes. The trainings will include modules targeting interventionists and other research staff, conducted via web, telephone, and 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 0049 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

13.1.1 Training Timeline

As currently projected, a one-time centralized, national training of patient navigators will occur within 8 months of the DSMB approving the final protocol. All navigators from all sites will be required to attend the entire training. The national training is scheduled for 4 days and patient navigators will be trained on most other study activities as well as on the intervention. Post-national training will occur within weeks of the national training and will continue as needed up to trial launch. Pre- and post-national training is further described in section 13.1.4.

13.1.2 Selection of Interventionists/Patient Navigators

At least two patient navigators per hospital site will be hired. Working with input from the RRTC and hospital staff, the lead team will provide a sample job posting for patient navigators. Ideally, patient navigators selected will be applicants who have: 1) experience in patient navigation or case management; 2) familiarity with HIV/AIDS, substance use behaviors, and mental health illness; 3) knowledge of local resources for 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 patient navigators who represent the diversity that will be found in each site's substance using, HIV-infected, and not-in-care population. The lead team will provide consultation to nodes and hospital sites during the selection process.

13.1.3 Selection of Expert Trainers

The lead team is a varied group of investigators with depth and breadth of experience in HIV treatment, substance use treatment, patient navigation, contingency management, 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.

13.1.4 Training of Patient Navigators

The training of patient Navigators 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 patient navigators for the national training and trial launch.

The pre-national training will provide instruction, discussing the importance of meeting key hospital staff and presenting the HOPE study, creating an extensive local resource list for study participants, making personal connections with key staff at all care agencies, creating virtual (digital) tours of HIV

primary care and substance use treatment agencies, and visiting and meeting staff at free kitchens, homeless shelters and homeless encampments, and mental health agencies.

The national training will occur in one location, will include all patient navigators and will provide didactic and experiential (role-play) training based on the patient navigator intervention manual. The training will include a discussion of patient navigator roles, responsibilities, and boundaries; detailed overviews of each treatment arm; appropriate communication techniques such as asking open-ended questions, paraphrasing, summarizing, and rolling with resistance; role-plays of various participant/patient navigator meetings with receipt of immediate feedback; and review and practice of the participant tracking database and the incentive tracking database.

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 patient navigators in preparing for trial launch.

13.1.5 Training of Outreach Workers

Similar to the training of patient navigators, outreach workers will be trained in three phases: 1) pre-national training, 2) national training; and 3) post-national training. Methods for training outreach workers will include written manuals, conference calls, and other written materials. Outreach workers will be included in a number of the patient navigation trainings, including training in conducting field work, appropriate communication techniques with study participants, providing or facilitating transportation for study participants to get them to HIV care and substance use treatment appointments, corroborating appointments kept by study participants for confirmation that participants in the PN+CM group should receive their incentive(s).

13.2 Treatment Fidelity (Evaluation of Treatment Integrity)

13.2.1 Supervision of Patient Navigators

A percentage of digitally recorded sessions will be randomly selected, reviewed and scored by the intervention team. Feedback from reviewed sessions will be provided to the individual patient navigators. The Intervention Director will conduct regularly scheduled patient navigator conference calls to facilitate PNs discussing difficulties and successes in delivering the interventions, learning from and supporting each other, and receiving support and feedback from the Intervention Director. Patient navigators will be invited to seek additional consultation with the Intervention Director via phone or email as intervention issues arise. Lastly, local patient navigator supervision will be available through the existing hierarchy of the CTN nodes.

13.2.2 Quality Control of Interventions Administered

Quality control of the patient navigation interventions 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) much of the contact patient navigators may have with study participants may occur off site and out in the field where digitally recording sessions will not be appropriate, study coordinators will randomly chose a day per month to shadow the patient navigator (or outreach worker) out in the field and fill out an assessment form and provide necessary feedback; 3) study coordinators will on a monthly basis make contact with HIV care and substance use clinics to update records on study participants, thus verifying patient navigator database and care clinic records; 4) study coordinators, QA monitors and lead study team members will routinely review the patient tracking database and the incentive database to help ensure that patient navigators are engaging with study subjects accordingly; 5) when out in the field patient navigators and outreach workers will complete a map of the various destinations visited in their effort to locate and reengage with patients

from both the PN and PN+CM groups. Quality control of the TAU condition will consist of monitoring hospital standard practice by asking the key hospital staff to complete a questionnaire on their TAU at several time points: trial launch, trial midway point, and trial completion.

14.0 CONCOMITANT INTERVENTION

Prior to hospitalization, participants randomized to any of the three treatments may have pre-existing relationships with case managers, social workers, or clinicians for the purposes of securing housing, benefits, food, HIV care, substance use and mental health treatment. Renewed or continued contact with any such professional or paraprofessional staff may include discussion of HIV care and substance use treatment. During study participation participants in any treatment arm may also be exposed to HIV treatment or substance use treatment media campaigns and/or outreach. Regardless of treatment arm, impeding any such contacts would be both unethical and unfeasible. To account for non-study related professional or paraprofessional contacts, subjects will be asked about such exposures during follow-up assessments. No concomitant interventions are prohibited during the study.

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 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. 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 researcher will review each section of the informed consent form in detail and answer any questions the participant may have. 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. Persons 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 (CTP) 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 ensure all study procedures are conducted 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), and corresponding source documents for each participant.

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 staff will verify that study procedures are properly followed and that site staffs are trained and able to conduct the protocol appropriately. If the node staff's review of study documentation indicates that additional training of study personnel is needed, node QA staff 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, data correction 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

15.9.1 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).

15.9.2 Protocol Violations Reporting and Management

A protocol deviation is any departure from procedures and requirements outlined in the protocol. Protocol departures may occur on two levels, deviation versus violation. The difference between a protocol deviation and violation has to do with the seriousness of the event and the corrective action required. A protocol deviation is considered an action (or inaction) that by itself is not likely to affect the scientific soundness of the investigation or seriously affect the safety, rights, or welfare of a study participant. Protocol violations are departures that may compromise the participant safety, participant rights, inclusion/exclusion criteria or study data and could be cause for corrective actions if not rectified or prevented from re-occurrence. Protocol violations will be monitored at each site for (1) significance, (2) frequency, and (3) potential effect on the study objectives, to ensure that site performance does not compromise the integrity of the trial. The decision about whether a departure from the protocol will be designated as a protocol deviation or a protocol violation will be made by the protocol's Lead Investigator in conjunction with the CCC. The consequences will be specified and participating sites should be informed.

All protocol violations will be recorded in the Electronic Data Capture (EDC) system via the Protocol Violation Log. Additionally, each site is responsible for tracking and reporting to their IRB as required. Protocol deviations will be noted by participating sites and reported to their IRBs as required. The CCC and the Data and Statistics Center and the Lead Investigator must be contacted immediately if an unqualified/ ineligible participant is randomized into the study.

15.9.3 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.

15.9.4 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.

15.9.4.1 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.

15.9.4.2 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, substance use treatment or admission for substance detoxification, hospitalizations for medical and psychological reasons and deaths will be captured on study specific forms and not duplicate reported as an adverse or serious adverse event. 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. Adverse events will be reported from the time of specimen collection through the remainder of that visit to capture events directly related to collection of blood samples.

Serious Adverse Events

Serious adverse events will be reported from the time of specimen collection through the remainder of that visit to capture events directly related to collection of blood samples.

Requirements for reporting other SAEs to local IRBs will be determined and complied with by each site. They would 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. AdvantageEDC, 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 CTP will be specified by the DSC and outlined in the AdvantageEDC 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 CTPs, 5) monitor any preliminary analysis data cleaning activities as needed, and 6) rigorously monitor final study data cleaning.

16.4 Data Collection

The data collection process consists of direct data entry at the study sites into AdvantageEDC. In the event that AdvantageEDC is not available, the DSC will provide the sites with a final set of guided source documents and completion instructions. Data entry into AdvantageEDC 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 AdvantageEDC system in accordance with the AdvantageEDC User's Guide. Only authorized individuals shall have access to eCRFs.

16.6 Data Editing

Completed data will be entered into AdvantageEDC. If incomplete or inaccurate data are found, a query will be generated to the sites for a response. Sites will resolve data inconsistencies and errors and enter all corrections and changes into AdvantageEDC.

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 CTP staff includes provisions for training on assessments, eCRF completion guidelines, data management procedures, and the use of AdvantageEDC.

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, 8 months will be allowed for trial preparation prior to commencing randomization. Trial preparation will include site selection activities, 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 endorsing sites. We intend to implement the study in a single wave; however, sites may launch on a rolling basis of 2-3 sites per week. Target enrollment is expected to take approximately 18 months, with follow-up continuing for approximately 14 months post recruitment. 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 $8 + 18 + 14 + 2 = 42$ months after DSMB approval of the final protocol.

18.0 REFERENCES

- Althoff, K. N., Gange, S. J., Klein, M. B., Brooks, J. T., Hogg, R. S., Bosch, R. J., et al. (2010). Late presentation for human immunodeficiency virus care in the United States and Canada. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 50(11), 1512-1520.
- Ammassari, A., Antinori, A., Aloisi, M. S., Trotta, M. P., Murri, R., Bartoli, L., et al. (2004). Depressive symptoms, neurocognitive impairment, and adherence to highly active antiretroviral therapy among HIV-infected persons. *Psychosomatics*, 45(5), 394-402.
- Anema, A., Vogenthaler, N. S., Frongillo, E. A., Kadiyala, S., & Weiser, S. D. (2009). Food insecurity and HIV/AIDS: Current knowledge, gaps, and research priorities. *Curr HIV/AIDS Rep.*, 6(4), 224-231.
- Arnsten, J. H., Demas, P. A., Grant, R. W., Gourevitch, M. N., Farzadegan, H., Howard, A. A., et al. (2002). Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *Journal of General Internal Medicine*, 17(5), 377-381.
- Aszalos, R., McDuff, D. R., Weintraub, E., Montoya, I., & Schwartz, R. (1999). Engaging hospitalized heroin-dependent patients into substance abuse treatment. *Journal of Substance Abuse Treatment*, 17(1-2), 149-158.
- Attia, S., Egger, M., Muller, M., Zwahlen, M., & Low, N. (2009). Sexual transmission of HIV according to viral load and antiretroviral therapy: Systematic review and meta-analysis. *AIDS*, 23(11), 1397-1404.
- Barclay, T. R., Hinkin, C. H., Castellon, S. A., Mason, K. I., Reinhard, M. J., Marion, S. D., et al. (2007). Age-associated predictors of medication adherence in HIV-positive adults: Health beliefs, self-efficacy, and neurocognitive status. *Health Psychology: Official Journal of the Division of Health Psychology, American Psychological Association*, 26(1), 40-49.
- Basu, A., Paltiel, A.D., and Pollack, H. A. (2008). Social costs of robbery and the cost-effectiveness of substance abuse treatment. *Health economics*: 17(8): 927-46.
- Behforouz, H. L., Farmer, P. E., & Mukherjee, J. S. (2004). From directly observed therapy to accompagnateurs: Enhancing AIDS treatment outcomes in Haiti and in Boston. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 38 Suppl 5, S429-36.
- Bell, C., Metsch, L. R., Vogenthaler, N., Cardenas, G., Rodriguez, A., Locascio, V., et al. (2010). Never in care: Characteristics of HIV-infected crack cocaine users in 2 US cities who have never been to outpatient HIV care. *Journal of Acquired Immune Deficiency Syndromes*, 54(4), 376-380.
- Berkman, C. S., Leipzig, R. M., Greenberg, S. A., & Inouye, S. K. (2001). Methodologic issues in conducting research on hospitalized older people. *Journal of the American Geriatrics Society*, 49(2), 172-8.
- Berry S.H., Brown J.A., Athey L.A., et al. (2002). *HCSUS patient questionnaires*. Santa Monica, CA: RAND Health Corporation. (Accessed December 13, 2012, at <http://www.rand.org/health/hcsus/quest.html>.)

- Blaney, N. T., Goodkin, K., Feaster, D., Morgan, R., Millon, C., Szapocznik, J., et al. (1997). A psychosocial model of distress over time in early HIV-1 infection: The role of life stressors, social support and coping. *Psychology & Health*, 12(5), 633.
- Booth, R. E., Kwiatkowski, C., Iguchi, M. Y., Pinto, F., & John, D. (1998). Facilitating treatment entry among out-of-treatment injection drug users. *Public Health Reports*, 113(1), 116-128.
- Bradford, J. B. (2007). The promise of outreach for engaging and retaining out-of-care persons in HIV medical care. *AIDS Patient Care and STDs*, 21 Suppl 1, S85-91.
- Bradford, J. B., Coleman, S., & Cunningham, W. (2007a). HIV system navigation: An emerging model to improve HIV care access. *AIDS Patient Care and STDs*, 21 Suppl 1, S49-58.
- Brazier, J., Roberts, J., & Deverill, M. (2002). The estimation of a preference-based measure of health from the SF-36. *Journal of Health Economics*, 21(2), 271-292.
- Broadhead, R. S., Heckathorn, D. D., Altice, F. L., van Hulst, Y., Carbone, M., Friedland, G. H., et al. (2002). Increasing drug users' adherence to HIV treatment: Results of a peer-driven intervention feasibility study. *Social Science & Medicine* (1982), 55(2), 235-246.
- Cabral, H. J., Tobias, C., Rajabiun, S., Sohler, N., Cunningham, C., Wong, M., et al. (2007). Outreach program contacts: Do they increase the likelihood of engagement and retention in HIV primary care for hard-to-reach patients? *AIDS Patient Care and STDs*, 21 Suppl 1, S59-67.
- Carroll, K. M., & Onken, L. S. (2005). Behavioral therapies for drug abuse. *The American Journal of Psychiatry*, 162(8), 1452-1460.
- Cartier, J., Farabee, D., Prendergast, M. L. (2006). Methamphetamine Use, Self-Reported Violent Crime, and Recidivism Among Offenders in California Who Abuse Substances. *Journal of Interpersonal Violence*: 21: 435.
- Celentano, D. D., & Lucas, G. (2007). Optimizing treatment outcomes in HIV-infected patients with substance abuse issues. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 45 Suppl 4, S318-23.
- Cheever, L. W. (2007). Engaging HIV-infected patients in care: Their lives depend on it. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 44(11), 1500-1502.
- Chew, L. D., Bradley, K. A., & Boyko, E. J. (2004). Brief questions to identify patients with inadequate health literacy. *Fam.Med.*, 36(8), 588-594.
- Chew, L. D., Griffin, J. M., Partin, M. R., Noorbaloochi, S., Grill, J. P., Snyder, A., et al. (2008). Validation of screening questions for limited health literacy in a large VA outpatient population. *Journal of General Internal Medicine*, 23(5), 561-566.
- Christopoulos, K., Das, M., & Colfax, G. (2011). Linkage and retention in HIV care among men who have sex with men in the united states. *Clinical Infectious Diseases*, 15, 52; Suppl 2: S214-22.
- Chutuape, M. A., Katz, E. C., & Stitzer, M. L. (2001). Methods for enhancing transition of substance dependent patients from inpatient to outpatient treatment. *Drug and Alcohol Dependence*, 61(2), 137-143.

- Coates, J., Swindale, A., & Bilinsky, P. (2007). *Household food insecurity access scale (HFIAS) for measurement of household food access: Indicator guide*. Washington D.C.: Food and Nutrition Technical Assistance Project, Academy for Educational Development.
- Cofrancesco, J., Jr, Scherzer, R., Tien, P. C., Gibert, C. L., Southwell, H., Sidney, S., et al. (2008). Illicit drug use and HIV treatment outcomes in a US cohort. *AIDS*, 22(3), 357-365.
- Conner, B. T., Longshore, D., & Anglin, M. D. (2009). Modeling attitude towards drug treatment: The role of internal motivation, external pressure, and dramatic relief. *The Journal of Behavioral Health Services & Research*, 36(2), 150-158.
- Craw, J. A., Gardner, L. I., Marks, G., Rapp, R. C., Bosshart, J., Duffus, W. A., et al. (2008). Brief strengths-based case management promotes entry into HIV medical care: Results of the antiretroviral treatment access study-II. *Journal of Acquired Immune Deficiency Syndromes*, 47(5), 597-606.
- Crowley, J., & Kilmarx, P. (2009). How might the results of this conversation benefit the development of the NHAS and the CDC strategic plan for HIV prevention? *Think Tank on the Development of a U.S. HIV Test & Treat Strategy*, Washington, D.C.
- Crum-Cianflone, N., Grandits, G., Echols, S., Ganesan, A., Landrum, M., Weintrob, A., et al. (2010). Trends and causes of hospitalizations among HIV-infected persons during the late HAART era: What is the impact of CD4 counts and HAART use? *Journal of Acquired Immune Deficiency Syndromes*, 54(3): 248-257.
- Cunningham WE, Hays RD, Williams KW, et al. (1995) Access to medical care and health-related quality of life for low-income persons with symptomatic human immunodeficiency virus. *Med Care*, Jul;33(7):739-54
- Cutrona, C. E., & Russell, D. (1987). *Advances in personal relationships*. (1st ed., pp. 37-67). Greenwich, CN: JAI Press.
- Davies, A., & Ware, J. (1991). *GHAA's consumer satisfaction survey and user's manual* (2nd ed.). Washington, DC: Group Health Association of America.
- Department of Health and Human Services. (2009). *Panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. Retrieved October 22, 2010, from <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>.
- DiClemente, C. C., & Prochaska, J. O. (1982). Self-change and therapy change of smoking behavior: A comparison of processes of change in cessation and maintenance. *Addictive Behaviors*, 7(2), 133-42.
- Dieffenbach, C. W., & Fauci, A. S. (2009). Universal voluntary testing and treatment for prevention of HIV transmission. *JAMA : The Journal of the American Medical Association*, 301(22), 2380-2382.
- Dohan, D., & Schrag, D. (2005). Using navigators to improve care of underserved patients: Current practices and approaches. *Cancer*, 104(4), 848-855.
- Donnell, D., Baeten, J. M., Kiarie, J., Thomas, K. K., Stevens, W., Cohen, C. R., et al. (2010). Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: A prospective cohort analysis. *Lancet*, 375(9731), 2092-2098.

- Dutra, L., Stathopoulou, G., Basden, S. L., Leyro, T. M., Powers, M. B., & Otto, M. W. (2008). A meta-analytic review of psychosocial interventions for substance use disorders. *The American Journal of Psychiatry*, 165(2), 179-187.
- Feaster, D. J., Mitrani, V. B., Burns, M. J., McCabe, B. E., Brincks, A. M., Rodriguez, A. E., et al. (2010). A randomized controlled trial of structural ecosystems therapy for HIV medication adherence and substance abuse relapse prevention. *Drug and Alcohol Dependence*, 111(3), 227-234.
- Fielden, S. J., Rusch, M. L., Levy, A. R., Yip, B., Wood, E., Harrigan, R. P., et al. (2008). Predicting hospitalization among HIV-infected antiretroviral naive patients starting HAART: Determining clinical markers and exploring social pathways. *AIDS Care*, 20(3), 297-303.
- Fisher, J. D., & Fisher, W. A. (1992). Changing AIDS-risk behavior. *Psychological Bulletin*, 111(3), 455-474.
- Fisher, J. D., Fisher, W. A., Cornman, D. H., Amico, R. K., Bryan, A., & Friedland, G. H. (2006). Clinician-delivered intervention during routine clinical care reduces unprotected sexual behavior among HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes*, 41(1), 44-52.
- Fleming, P. L., Byers, R. H., Sweeney, P. A., Daniels, D., Karon, J. M., & Janssen, R. S. (2002). HIV prevalence in the United States, 2000 [Abstract]. 5(11) 1.
- Fleishman JA, Sherbourne CD, Crystal S, et al. Coping, conflictual social interactions, social support, and mood among HIV-infected persons. HCSUS Consortium. *Am J Community Psychol*. 2000 Aug; 28(4):421-53
- Floris-Moore, M., Lo, Y., Klein, R. S., Budner, N., Gourevitch, M. N., Moskaleva, G., et al. (2003). Gender and hospitalization patterns among HIV-infected drug users before and after the availability of highly active antiretroviral therapy. *Journal of Acquired Immune Deficiency Syndromes*, 34(3), 331-337.
- Folkers, G. K., & Fauci, A. S. (2010). Controlling and ultimately ending the HIV/AIDS pandemic: A feasible goal. *JAMA : The Journal of the American Medical Association*, 304(3), 350-351.
- Frank, D., DeBenedetti, A. F., Volk, R. J., Williams, E. C., Kivlahan, D. R., & Bradley, K. A. (2008). Effectiveness of the AUDIT-C as a screening test for alcohol misuse in three race/ethnic groups. *Journal of General Internal Medicine*, 23(6), 781-787.
- Freedman TG. "Why don't they come to pike street and ask us"? Black American women's health concerns. *Soc Sci Med* 1998;47: 941-7.
- Gardenier, D., Andrews, C. M., Thomas, D. C., Bookhardt-Murray, L. J., & Fitzpatrick, J. J. (2010). Social support and adherence: Differences among clients in an AIDS day health care program. *The Journal of the Association of Nurses in AIDS Care: JANAC*, 21(1), 75-85.
- Gardner, L. I., Metsch, L. R., Anderson-Mahoney, P., Loughlin, A. M., del Rio, C., Strathdee, S., et al. (2005). Efficacy of a brief case management intervention to link recently diagnosed HIV-infected persons to care. *AIDS*, 19(4), 423-431.
- Giordano, T. P., Gifford, A. L., White, A. C., Jr, Suarez-Almazor, M. E., Rabeneck, L., Hartman, C., et al. (2007). Retention in care: A challenge to survival with HIV infection. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 44(11), 1493-1499.

- Gold, M. (1996). *Cost-Effectiveness in Health and Medicine*. New York: Oxford University Press; 1996.
- Granich, R. M., Gilks, C. F., Dye, C., De Cock, K. M., & Williams, B. G. (2009). Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: A mathematical model. *Lancet*, 373(9657), 48-57.
- Han, C., Pulling, C. C., Telke, S. E., Huppler Hullsiek, K., & Terry Beirn Community Programs for Clinical Research on AIDS. (2002). Assessing the utility of five domains in SF-12 health status questionnaire in an AIDS clinical trial. *AIDS*, 16(3), 431-439.
- Haug, N. A., & Sorensen, J. L. (2006). Contingency management interventions for HIV-related behaviors. *Current HIV/AIDS Reports*, 3(4), 154-159.
- Haukoos, J. S., Witt, M. D., Coil, C. J., & Lewis, R. J. (2005). The effect of financial incentives on adherence with outpatient human immunodeficiency virus testing referrals from the emergency department. *Academic Emergency Medicine : Official Journal of the Society for Academic Emergency Medicine*, 12(7), 617-621.
- Heatherton T.F., Kozlowski L.T., Frecker R.C., & Fagerstrom K.O. (1991). The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom tolerance questionnaire. *British Journal of Addiction*, 86(9), 1119-27.
- Hicks, P. L., Mulvey, K. P., Chander, G., Fleishman, J. A., Josephs, J. S., Korthuis, P. T., et al. (2007). The impact of illicit drug use and substance abuse treatment on adherence to HAART. *AIDS Care*, 19(9), 1134-1140.
- Higgins, S. T., Silverman, K., & Heil, S. H. (2008). *Contingency management in substance abuse treatment*. New York: Guilford.
- Hinkin, C. H., Castellon, S. A., Durvasula, R. S., Hardy, D. J., Lam, M. N., Mason, K. I., et al. (2002). Medication adherence among HIV+ adults: Effects of cognitive dysfunction and regimen complexity. *Neurology*, 59(12), 1944-1950.
- HIV/AIDS Treatment Adherence, Health Outcomes and Cost Study Group. *AIDS Care*. Vol. 16, Iss. sup1, 2004.
- Hornberger, J., Holodniy, M., Robertus, K., Winnike, M., Gibson, E., & Verhulst, E. (2007). A systematic review of cost-utility analyses in HIV/AIDS: Implications for public policy. *Medical Decision Making: An International Journal of the Society for Medical Decision Making*, 27(6), 789-821.
- Horstmann, E., Brown, J., Islam, F., Buck, J., & Agins, B. D. (2010). Retaining HIV-infected patients in care: Where are we? Where do we go from here? *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 50(5), 752-761.
- Iguchi, M. Y., et al. (1996). Contingent reinforcement of group participation versus abstinence in a methadone maintenance program. *Experimental and Clinical Psychopharmacology*, 4(3), 315-321.
- Iguchi, M. Y., Belding, M. A., Morral, A. R., Lamb, R. J., & Husband, S. D. (1997). Reinforcing operants other than abstinence in drug abuse treatment: An effective alternative for reducing drug use. *Journal of Consulting and Clinical Psychology*, 65(3), 421-428.
- Jennison, C., & Turnbull, B. W. (2000). *Group sequential methods with applications to clinical trials*. Boca Raton and London: Chapman and Hall/CRC.

- Johnson, C. J., Heckman, T. G., Hansen, N. B., Kochman, A., & Sikkema, K. J. (2009). Adherence to antiretroviral medication in older adults living with HIV/AIDS: A comparison of alternative models. *AIDS Care*, 21(5), 541-551.
- Johnson, M. O., Neilands, T. B., Dilworth, S. E., Morin, S. F., Remien, R. H., & Chesney, M. A. (2007). The role of self-efficacy in HIV treatment adherence: Validation of the HIV treatment adherence self-efficacy scale (HIV-ASES). *Journal of Behavioral Medicine*, 30(5), 359-370.
- Jones, H. E., Haug, N., Silverman, K., Stitzer, M., & Svikis, D. (2001). The effectiveness of incentives in enhancing treatment attendance and drug abstinence in methadone-maintained pregnant women. *Drug and Alcohol Dependence*, 61(3), 297-306.
- Kahn, J. G. (1998). Economic evaluation of primary HIV prevention in intravenous drug users. In D. R. Holtgrave (Ed.), *Handbook of economic evaluation of HIV prevention programs* (pp. 45-62). New York: Plenum Press.
- Kalichman, S. C., Pope, H., White, D., Cherry, C., Amaral, C. M., Swetzes, C., et al. (2008). Association between health literacy and HIV treatment adherence: Further evidence from objectively measured medication adherence. *Journal of the International Association of Physicians in AIDS Care (Chicago, Ill.: 2002)*, 7(6), 317-323.
- Kalichman, S. C., & Rompa, D. (2000). Functional health literacy is associated with health status and health-related knowledge in people living with HIV-AIDS. *Journal of Acquired Immune Deficiency Syndromes*, 25(4), 337-344.
- Kaplan, S. H., Gandek, B., Greenfield, S., Rogers, W., & Ware, J. E. (1995). Patient and visit characteristics related to physicians' participatory decision-making style. Results from the medical outcomes study. *Medical Care*, 33(12), 1176-1187.
- Kersey, M. A., Beran, M. S., McGovern, P. G., Biros, M. H., & Lurie, N. (1999). The prevalence and effects of hunger in an emergency department patient population. *Academic Emergency Medicine: Official Journal of the Society for Academic Emergency Medicine*, 6(11), 1109-1114.
- Kitchens, J. M. (1994). Does this patient have an alcohol problem? *JAMA : The Journal of the American Medical Association*, 272(22), 1782-1787.
- Knowlton, A., Arnsten, J., Eldred, L., Wilkinson, J., Gourevitch, M., Shade, S., et al. (2006). Individual, interpersonal, and structural correlates of effective HAART use among urban active injection drug users. *Journal of Acquired Immune Deficiency Syndromes*, 41(4), 486-492.
- Kushel, M. B., Gupta, R., Gee, L., & Haas, J. S. (2006). Housing instability and food insecurity as barriers to health care among low-income Americans. *Journal of General Internal Medicine*, 21(1), 71-77.
- Laine, C., Hauck, W. W., Gourevitch, M. N., Rothman, J., Cohen, A., & Turner, B. J. (2001). Regular outpatient medical and drug abuse care and subsequent hospitalization of persons who use illicit drugs. *JAMA: The Journal of the American Medical Association*, 285(18), 2355-2362.
- Lebwohl, B., Neugut, A. I., Stavsky, E., Villegas, S., Meli, C., Rodriguez, O., et al. (2010). Effect of a patient navigator program on the volume and quality of colonoscopy. *Journal of Clinical Gastroenterology*,
- Linaz, B. P., Losina, E., Rockwell, A., Walensky, R. P., Cranston, K., & Freedberg, K. A. (2009). Improving outcomes in state AIDS drug assistance programs. *Journal of Acquired Immune Deficiency Syndromes*, 51(5), 513-521.

- Lingappa, J. R., Hughes, J. P., Wang, R. S., Baeten, J. M., Celum, C., Gray, G. E., et al. (2010). Estimating the impact of plasma HIV-1 RNA reductions on heterosexual HIV-1 transmission risk. *PloS One*, 5(9), e12598.
- Little, R. J., & Rubin, D. B. (1987). *Statistical analysis with missing data* 1987. New York: Wiley.
- Longshore, D., & Teruya, C. (2006). Treatment motivation in drug users: A theory-based analysis. *Drug and Alcohol Dependence*, 81(2), 179-188.
- Loughlin, A. M., Calderon, P., Strathdee, S. A., Gardner, L., Metsch, L. R., Mahoney, P., et al. (2005). A longitudinal analysis of the role of drug treatment as a facilitator of entry into HIV medical care. *2005 National HIV Prevention Conference*, Atlanta, GA.
- Lucas, G. M., Griswold, M., Gebo, K. A., Keruly, J., Chaisson, R. E., & Moore, R. D. (2006). Illicit drug use and HIV-1 disease progression: A longitudinal study in the era of highly active antiretroviral therapy. *American Journal of Epidemiology*, 163(5), 412-420.
- Lussier, J. P., Heil, S. H., Mongeon, J. A., Badger, G. J., & Higgins, S. T. (2006). A meta-analysis of voucher-based reinforcement therapy for substance use disorders. *Addiction (Abingdon, England)*, 101(2), 192-203.
- Maisto, S. A., Carey, M. P., Carey, K. B., Gordon, C. M., & Gleason, J. R. (2000). Use of the AUDIT and the DAST-10 to identify alcohol and drug use disorders among adults with a severe and persistent mental illness. *Psychological Assessment*, 12(2), 186-192.
- Mannheimer, S. B., Matts, J., Telzak, E., Chesney, M., Child, C., Wu, A. W., et al. (2005). Quality of life in HIV-infected individuals receiving antiretroviral therapy is related to adherence. *AIDS Care*, 17(1), 10-22.
- Markson, L. E., McKee, L., Mauskopf, J., Houchens, R., Fanning, T. R., & Turner, B. J. (1994). Patterns of Medicaid expenditures after AIDS diagnosis. *Health Care Financing Review*, 15(4), 43-59.
- Marseille, E., Shade, S., Myers, J., Dawson, C., Koester, K., Maiorana, A., et al. (2011). The cost-effectiveness of HIV prevention interventions for HIV-infected patients seen in clinical settings. *JAIDS*, 56(3), e87-94.
- Metsch L., Pereyra M, Messinger S, et al. (2008). HIV transmission risk behaviors among HIV-infected persons who are successfully linked to care. *Clin Infect Dis*. 47(4):577-584.
- Metsch, L., Cardenas, G., Sullivan, T., Gooden, L., Rodriguez, A., Bell, C., et al. (2008). HIV sexual transmission behavior among HIV-infected hospitalized crack cocaine users in the United States. *XVII International AIDS Conference*, Mexico City, Mexico.
- Metsch, L., Mandler, R., Feaster, D., Gooden, L., Tross, S., Haynes, L., et al. (2010). Never HIV tested: Results of screening data from 12 drug treatment programs in the CTN 0032 HIV rapid testing and counseling study. *College on Problems of Drug Dependence Seventy-Second Annual Scientific Meeting*, Scottsdale, AZ.
- Metsch, L. R., Bell, C., Pereyra, M., Cardenas, G., Sullivan, T., Rodriguez, A., et al. (2009). Hospitalized HIV-infected patients in the era of highly active antiretroviral therapy. *American Journal of Public Health*, 99(6), 1045-1049.

- Milby, J. B., Wallace, D., Ward, C. L., Schumacher, J. E., & Michael, M. (2005). Towards a more sensitive assessment of homelessness: The homelessness severity Scale. *Journal of Social Distress and Homelessness*, 14(3 & 4), 151-169.
- Montaner, J. S., Hogg, R., Wood, E., Kerr, T., Tyndall, M., Levy, A. R., et al. (2006). The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet*, 368(9534), 531-536.
- Mor, V., Fleishman, J. A., Dresser, M., & Piette, J. (1992). Variation in health service use among HIV-infected patients. *Medical Care*, 30(1), 17-29.
- Mrus, J. M., Schackman, B. R., Wu, A. W., Freedberg, K. A., Tsevat, J., Yi, M. S., et al. (2006). Variations in self-rated health among patients with HIV infection. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, 15(3), 503-514.
- Muenning, P. (2002). Designing and conducting cost-effectiveness analyses in medicine and health care. San Francisco: Jossey-Bass.
- Mugavero, M. J., Lin, H. Y., Willig, J. H., Westfall, A. O., Ulett, K. B., Routman, J. S., et al. (2009). Missed visits and mortality among patients establishing initial outpatient HIV treatment. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 48(2), 248-256.
- Munafo, M., Rigotti, N., Lancaster, T., Stead, L., & Murphy, M. (2001). Interventions for smoking cessation in hospitalized patients: A systematic review. *Thorax*, 56(8), 656-663.
- Najavits, L. M., Crits-Christoph, P., & Dierberger, A. (2000). Clinicians' impact on the quality of substance use disorder treatment. *Substance use & Misuse*, 35(12-14), 2161-2190.
- Normen, L., Chan, K., Braitstein, P., Anema, A., Bondy, G., Montaner, J. S., et al. (2005). Food insecurity and hunger are prevalent among HIV-positive individuals in British Columbia, Canada. *The Journal of Nutrition*, 135(4), 820-825.
- Olmstead, T. A., & Petry, N. M. (2009). The cost-effectiveness of prize-based and voucher-based contingency management in a population of cocaine- or opioid-dependent outpatients. *Drug and Alcohol Dependence*, 102(1-3), 108-115.
- Paltiel, A. D., Walensky, R. P., Schackman, B. R., Seage, G. R., 3rd, Mercincavage, L. M., Weinstein, M. C., et al. (2006). Expanded HIV screening in the United States: Effect on clinical outcomes, HIV transmission, and costs. *Annals of Internal Medicine*, 145(11), 797-806.
- Palepu, A., Milloy, M. J., Kerr, T., Zhang, R., & Wood, E. (2011). Homelessness and adherence to antiretroviral therapy among a cohort of HIV-infected injection drug users. *Journal of Urban Health: Bulletin of the New York Academy of Medicine*, 88(3), 545-555.
- Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011; 1-166. Available at <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed [January 17, 2011]
- Paranjape A, Heron S, Kaslow NJ. Utilization of services by abused, low-income African-American women. *J Gen Intern Med*. Feb 2006;21(2):189-192.

- Paranjape A, Liebschutz J. STaT: a three-question screen for intimate partner violence. *J Womens Health (Larchmt)*. Apr 2003;12(3):233-239.
- Paranjape A, Rask K, Liebschutz J. Utility of STaT for the identification of recent intimate partner violence. *J Natl Med Assoc*. Oct 2006;98(10):1663-1669.
- Petry, N. M., Martin, B., & Finocche, C. (2001a). Contingency management in group treatment: A demonstration project in an HIV drop-in center. *Journal of Substance Abuse Treatment*, 21(2), 89-96.
- Petry, N. M., Martin, B., & Finocche, C. (2001b). Contingency management in group treatment: A demonstration project in an HIV drop-in center. *Journal of Substance Abuse Treatment*, 21(2), 89-96.
- Petry, N. M., Weinstock, J., Alessi, S. M., Lewis, M. W., & Dieckhaus, K. (2010). Group-based randomized trial of contingencies for health and abstinence in HIV patients. *Journal of Consulting and Clinical Psychology*, 78(1), 89-97.
- Phillips, J. C. (2011). Antiretroviral therapy adherence: Testing a social context model among black men who use illicit drugs. *The Journal of the Association of Nurses in AIDS Care: JANAC*, 22(2), 100-127.
- Piccinelli, M., Tessari, E., Bortolomasi, M., Piasere, O., Semenzin, M., Garzotto, N., et al. (1997). Efficacy of the alcohol use disorders identification test as a screening tool for hazardous alcohol intake and related disorders in primary care: A validity study. *BMJ (Clinical Research Ed.)*, 314(7078), 420-424.
- Pinkerton, S. D., & Abramson, P. R. (1998). The bernoulli-process model of HIV transmission: Applications and implications. In D. R. Holtgrave (Ed.), *Handbook of economic evaluation of HIV prevention programs* (pp. 13-33). New York: Plenum Press.
- Policy. Obama administration unveils national HIV/AIDS strategy.(2010). *AIDS Policy & Law*, 25(10), 1, 4.
- Prendergast, M., Podus, D., Finney, J., Greenwell, L., & Roll, J. (2006). Contingency management for treatment of substance use disorders: A meta-analysis. *Addiction (Abingdon, England)*, 101(11), 1546-1560.
- Preston, K. L., Silverman, K., Umbricht, A., DeJesus, A., Montoya, I. D., & Schuster, C. R. (1999). Improvement in naltrexone treatment compliance with contingency management. *Drug and Alcohol Dependence*, 54(2), 127-135.
- Prochaska, J. O., DiClemente, C. C., & Norcross, J. C. (1992). In search of how people change. Applications to addictive behaviors. *The American Psychologist*, 47(9), 1102-1114.
- Pulvirenti, J., Herrera, P., Venkataraman, P., & Ahmed, N. (2003). Pneumocystis carinii pneumonia in HIV-infected patients in the HAART era. *AIDS Patient Care and STDs*, 17(6), 261-265.
- Pyne, J. M., Tripathi, S., French, M., McCollister, K., Rapp, R., & Booth, B. M. (2010). Longitudinal association of preference-weighted health-related quality of life measures and substance use disorder outcomes. *Addiction*,
- Quinn, T. C., Wawer, M. J., Sewankambo, N., Serwadda, D., Li, C., Wabwire-Mangen, F., et al. (2000). Viral load and heterosexual transmission of human immunodeficiency virus type 1. Rakia project study group. *The New England Journal of Medicine*, 342(13), 921-929.

- Ramirez, A. G., & Turner, B. J. (2010). The role of peer patients in chronic disease management. *Annals of Internal Medicine*, 153(8), 544-545.
- Recklitis, C. J., Parsons, S. K., Shih, M. C., Mertens, A., Robison, L. L., & Zeltzer, L. (2006). Factor structure of the brief symptom inventory--18 in adult survivors of childhood cancer: Results from the childhood cancer survivor study. *Psychological Assessment*, 18(1), 22-32.
- Reynolds, N. R., Sun, J., Nagaraja, H. N., Gifford, A. L., Wu, A. W., & Chesney, M. A. (2007). Optimizing measurement of self-reported adherence with the ACTG adherence questionnaire: A cross-protocol analysis. *Journal of Acquired Immune Deficiency Syndromes* (1999), 46(4), 402-409.
- Rigsby, M. O., Rosen, M. I., Beauvais, J. E., Cramer, J. A., Rainey, P. M., O'Malley, S. S., et al. (2000). Cue-dose training with monetary reinforcement: Pilot study of an antiretroviral adherence intervention. *Journal of General Internal Medicine*, 15(12), 841-847.
- Roll, J. M., Higgins, S. T., & Badger, G. J. (1996). An experimental comparison of three different schedules of reinforcement of drug abstinence using cigarette smoking as an exemplar. *Journal of Applied Behavior Analysis*, 29(4), 495-504; quiz 504-5.
- Rosen, M. I., Dieckhaus, K., McMahon, T. J., Valdes, B., Petry, N. M., Cramer, J., et al. (2007). Improved adherence with contingency management. *AIDS Patient Care and STDs*, 21(1), 30-40.
- Rydzak, C. E., Cotich, K. L., Sax, P. E., Hsu, H. E., Wang, B., Losina, E., et al. (2010). Assessing the performance of a computer-based policy model of HIV and AIDS. *PloS One*, 5(9), e12647.
- Sacktor, N. C., Wong, M., Nakasujja, N., Skolasky, R. L., Selnes, O. A., Musisi, S., et al. (2005). The international HIV dementia scale: A new rapid screening test for HIV dementia. *AIDS (London, England)*, 19(13), 1367-1374.
- Safran, D. G., Kosinski, M., Tarlov, A. R., Rogers, W. H., Taira, D. H., Lieberman, N., et al. (1998). The primary care assessment survey: Tests of data quality and measurement performance. *Medical Care*, 36(5), 728-739.
- Safren, S. A., Hendriksen, E. S., Mayer, K. H., Mimiaga, M. J., Pickard, R., & Otto, M. W. (2004). Cognitive-behavioral therapy for HIV medication adherence and depression. *Cognitive and Behavioral Practice*, 11, 415-423.
- Sansom, S. L., Anthony, M. N., Garland, W. H., Squires, K. E., Witt, M. D., Kovacs Andrea, A., et al. (2008). The costs of HIV antiretroviral therapy adherence programs and impact on health care utilization. *AIDS Patient Care and STDs*, 22(2), 131-138.
- Saxon, A. J., Wells, E. A., Fleming, C., Jackson, T. R., & Calsyn, D. A. (1996). Pre-treatment characteristics, program philosophy and level of ancillary services as predictors of methadone maintenance treatment outcome. *Addiction (Abingdon, England)*, 91(8), 1197-1209.
- Schackman, B. R., Gebo, K. A., Walensky, R. P., Losina, E., Muccio, T., Sax, P. E., Weinstein, M. C., et al. (2006). The lifetime cost of current HIV care in the United States. *Med.Care*, 44, 990-997.
- Schackman, B. R., Goldie, S. J., Freedberg, K. A., Losina, E., Brazier, J., & Weinstein, M. C. (2002). Comparison of health state utilities using community and patient preference weights derived from a survey of patients with HIV/AIDS. *Medical Decision Making: An International Journal of the Society for Medical Decision Making*, 22(1), 27-38.
- Schafer, J. L. (1997). *Analysis of incomplete multivariate data*. London: Chapman and Hall.

- Schneider, J., Kaplan, S. H., Greenfield, S., Li, W., & Wilson, I. B. (2004). Better physician-patient relationships are associated with higher reported adherence to antiretroviral therapy in patients with HIV infection. *Journal of General Internal Medicine*, 19(11), 1096-1103.
- Schoenbaum, E. E., Lo, Y., & Floris-Moore, M. (2002). Predictors of hospitalization for HIV-positive women and men drug users, 1996-2000. *Public Health Reports*, 117 Suppl 1, S60-6.
- Seage, G. R., 3rd, Hertz, T., Stone, V. E., & Epstein, A. M. (1993). The effects of intravenous drug use and gender on the cost of hospitalization for patients with AIDS. *Journal of Acquired Immune Deficiency Syndromes*, 6(7), 831-839.
- Seal, K. H., Kral, A. H., Lorvick, J., McNees, A., Gee, L., & Edlin, B. R. (2003). A randomized controlled trial of monetary incentives vs. outreach to enhance adherence to the hepatitis B vaccine series among injection drug users. *Drug and Alcohol Dependence*, 71(2), 127-131.
- Sherer, R., Stieglitz, K., Narra, J., Jasek, J., Green, L., Moore, B., et al. (2002). HIV multidisciplinary teams work: Support services improve access to and retention in HIV primary care. *AIDS Care*, 14 Suppl 1, S31-44.
- Sigmon, S. C., & Stitzer, M. L. (2005). Use of a low-cost incentive intervention to improve counseling attendance among methadone-maintained patients. *Journal of Substance Abuse Treatment*, 29(4), 253-258.
- Sindelar, J., Elbel, B., & Petry, N. M. (2007). What do we get for our money? Cost-effectiveness of adding contingency management. *Addiction (Abingdon, England)*, 102(2), 309-316.
- Sindelar, J. L., Olmstead, T. A., & Peirce, J. M. (2007). Cost-effectiveness of prize-based contingency management in methadone maintenance treatment programs. *Addiction (Abingdon, England)*, 102(9), 1463-1471.
- Smith, P. C., Schmidt, S. M., Allensworth-Davies, D., & Saitz, R. (2010). A single-question screening test for drug use in primary care. *Archives of Internal Medicine*, 170(13), 1155-1160.
- Sorensen, J. L., Haug, N. A., Delucchi, K. L., Gruber, V., Kletter, E., Batki, S. L., et al. (2007). Voucher reinforcement improves medication adherence in HIV-positive methadone patients: A randomized trial. *Drug and Alcohol Dependence*, 88(1), 54-63.
- Sorensen, J. L., Masson, C. L., Delucchi, K., Sporer, K., Barnett, P. G., Mitsuishi, F., et al. (2005). Randomized trial of drug abuse treatment-linkage strategies. *Journal of Consulting and Clinical Psychology*, 73(6), 1026-1035.
- Stavem, K., Froland, S. S., & Hellum, K. B. (2005). Comparison of preference-based utilities of the 15D, EQ-5D and SF-6D in patients with HIV/AIDS. *Quality of Life Research: An International Journal of Quality of Life Aspects of Treatment, Care and Rehabilitation*, 14(4), 971-980.
- Stitzer, M., & Petry, N. (2006). Contingency management for treatment of substance abuse. *Annual Review of Clinical Psychology*, 2, 411-434.
- Stitzer, M. L., Polk, T., Bowles, S., & Kosten, T. (2010). Drug users' adherence to a 6-month vaccination protocol: Effects of motivational incentives. *Drug and Alcohol Dependence*, 107(1), 76-79.
- Strathdee, S. A., Palepu, A., Cornelisse, P. G., Yip, B., O'Shaughnessy, M. V., Montaner, J. S., et al. (1998). Barriers to use of free antiretroviral therapy in injection drug users. *JAMA: The Journal of the American Medical Association*, 280(6), 547-549.

- Thompson, H.S., Vladimarsdottir, H.B., Winkel, G., Jandorf, L., & Redd, W. (2004). The group-based medical mistrust scale: psychometric properties and association with breast cancer screening. *Preventive Medicine*, 38, 209-218.
- Ulett, K. B., Willig, J. H., Lin, H. Y., Routman, J. S., Abrams, S., Allison, J., et al. (2009). The therapeutic implications of timely linkage and early retention in HIV care. *AIDS Patient Care and STDs*, 23(1), 41-49.
- Vogenthaler, N. S., Hadley, C., Lewis, S. J., Rodriguez, A. E., Metsch, L. R., & Del Rio, C. (2010). Food insufficiency among HIV-infected crack-cocaine users in Atlanta and Miami. *Public Health Nutrition*, , 1-7.
- Vogenthaler, N. S., Hadley, C., Lewis, S. J., Rodriguez, A. E., Metsch, L. R., & del Rio, C. (2010). Food insufficiency among HIV-infected crack-cocaine users in Atlanta and Miami. *Public Health Nutrition*, 13(9), 1478-1484.
- Vogenthaler, N. S., Hadley, C., Rodriguez, A. E., Valverde, E. E., Del Rio, C., & Metsch, L. R. (2011). Depressive symptoms and food insufficiency among HIV-infected crack users in Atlanta and Miami. *AIDS and Behavior*, 15(7), 1520-1526.
- Volkow, N. D., & Montaner, J. (2010). Enhanced HIV testing, treatment, and support for HIV-infected substance users. *JAMA: The Journal of the American Medical Association*, 303(14), 1423-1424.
- Walensky, R. P., Freedberg, K. A., Weinstein, M. C., & Paltiel, A. D. (2007). Cost-effectiveness of HIV testing and treatment in the United States. *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America*, 45 Suppl 4, S248-54.
- Walensky, R. P., Paltiel, A. D., Losina, E., Mercincavage, L. M., Schackman, B. R., Sax, P. E., et al. (2006). The survival benefits of AIDS treatment in the United States. *The Journal of Infectious Diseases*, 194(1), 11-19.
- Ware, J., Jr, Kosinski, M., & Keller, S. D. (1996). A 12-item short-form health survey: Construction of scales and preliminary tests of reliability and validity. *Medical Care*, 34(3), 220-233.
- Weaver, M. R., Conover, C. J., Proescholdbell, R. J., Arno, P. S., Ang, A., Uldall, K. K., et al. (2009). Cost-effectiveness analysis of integrated care for people with HIV, chronic mental illness and substance abuse disorders. *The Journal of Mental Health Policy and Economics*, 12(1), 33-46.
- Weiser, S., Fernandes, K., & Brandson, E. (2008). The impact of food insecurity and body mass index on mortality among HIV-infected individuals first initiating HAART. *XVII International AIDS Conference on AIDS*, Mexico City, Mexico.
- Weiser, S. D., Fernandes, K. A., Brandson, E. K., Lima, V. D., Anema, A., Bangsberg, D. R., et al. (2009). The association between food insecurity and mortality among HIV-infected individuals on HAART. *Journal of Acquired Immune Deficiency Syndromes (1999)*, 52(3), 342-349.
- Weiser, S. D., Frongillo, E. A., Ragland, K., Hogg, R. S., Riley, E. D., & Bangsberg, D. R. (2009). Food insecurity is associated with incomplete HIV RNA suppression among homeless and marginally housed HIV-infected individuals in San Francisco. *Journal of General Internal Medicine*, 24(1), 14-20.
- Wells, K. J., Battaglia, T. A., Dudley, D. J., Garcia, R., Greene, A., Calhoun, E., et al. (2008). Patient navigation: State of the art or is it science? *Cancer*, 113(8), 1999-2010.

- Westfall, P. H., Tobias, R. D., Rom, D., Wolfinger, R. D., & Hochberg, Y. (1999). *Multiple comparisons and multiple tests using the SAS system*. NC: SAS Institute.
- Wilson, I. B., & Kaplan, S. (2000). Physician-patient communication in HIV disease: The importance of patient, physician, and visit characteristics. *Journal of Acquired Immune Deficiency Syndromes*, 25(5), 417-425.
- Yudko, E., Lozhkina, O., & Fouts, A. (2007). A comprehensive review of the psychometric properties of the drug abuse screening test. *Journal of Substance Abuse Treatment*, 32(2), 189-198.
- Zabora, J., BrintzenhofeSzoc, K., Jacobsen, P., Curbow, B., Piantadosi, S., Hooker, C., et al. (2001). A new psychosocial screening instrument for use with cancer patients. *Psychosomatics*, 42(3), 241-246.
- Zeger, S. L., & Liang, K. Y. (1986). Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*, 42(1), 121-130.

19.0 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.

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 screening 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 medical 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. Medical 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 AdvantageEDC system. The AE form is used to capture reportable AEs (as defined in the protocol). Additional information may need to be gathered to evaluate serious adverse events 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 medical 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 (< 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 is responsible for reviewing all serious adverse event reports. All reported SAEs will generate an e-mail notification to the Medical Monitor, Lead Investigator, and designees. All SAEs will be reviewed by the Medical Monitor in AdvantageEDC and, if needed, additional information will be requested. The medical monitor will also report events to the sponsor and the Data and Safety Monitoring Board (DSMB). The DSMB will receive summary reports of all adverse events annually, at a minimum. The DSMB or the NIDA assigned Medical 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 an IND study

All serious and unexpected suspected adverse reactions are reported by the medical monitor on behalf of the sponsor to the FDA in writing within 15 calendar days of notification. Suspected adverse reactions that are unexpected and meet the criteria for death or immediately life-threatening also require notification of the FDA as soon as possible but no later than 7 calendar days of notification of the event, with a follow-up written report within 15 calendar days of notification of the event. The medical monitor will prepare an expedited report (MedWatch Form 3500A or similar) for the FDA and

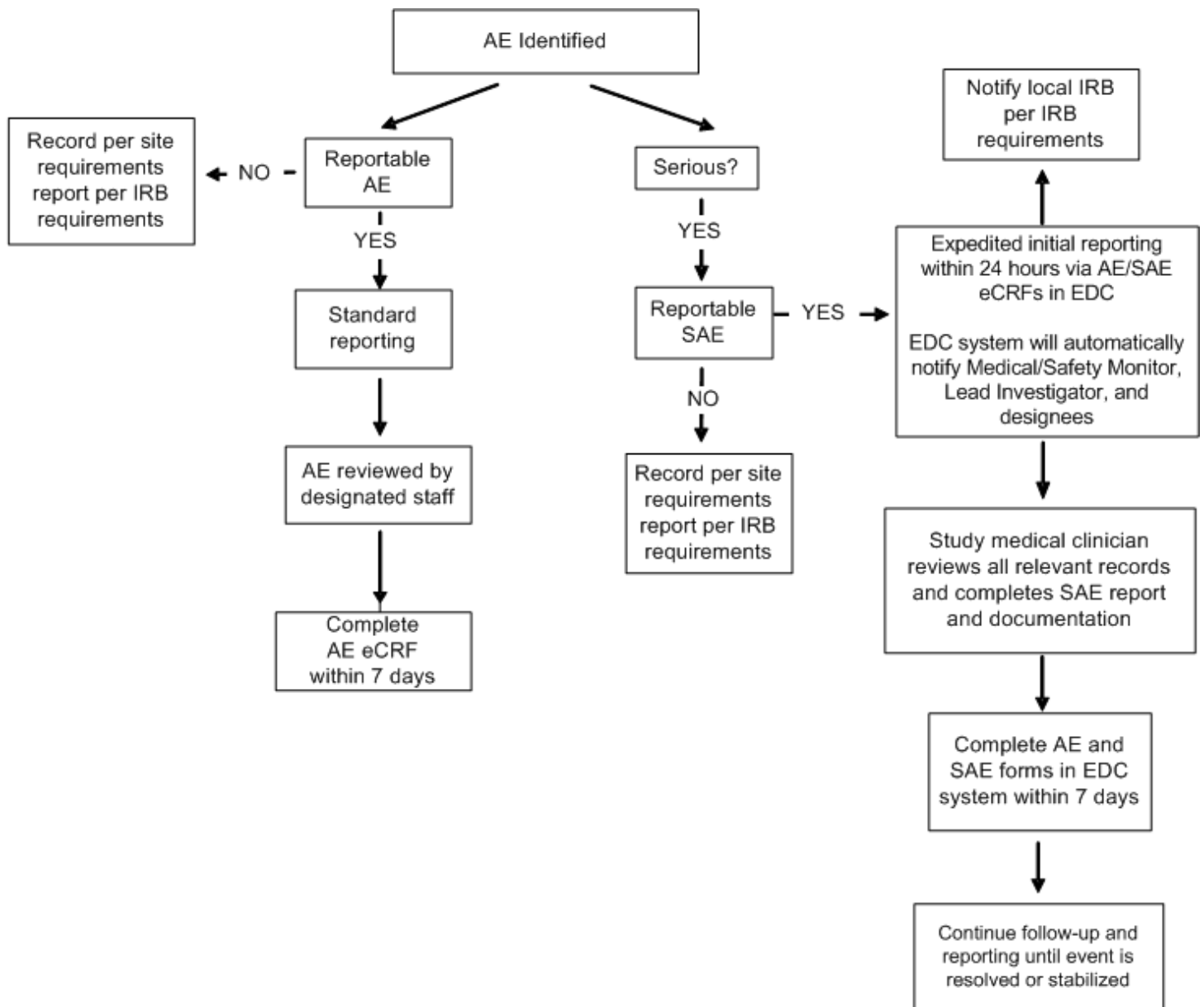
other regulatory authorities and copies will be distributed to all sites. Expedited reports will be placed in the site regulatory files upon receipt. A copy of all expedited reports will be forwarded to the site's local IRB, as required.

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. 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 referrals to treatment, as necessary.



20.0 APPENDIX B

Ancillary Study, CTN0049 A-2, Utilization of the Electronic Medical Record to Assess and Predict 30-day Readmission Risk Among HIV-infected Inpatients Enrolled in CTN0049

20.1 Overview

20.1.1 Significance

While inpatient admissions related to advanced AIDS and opportunistic infections have declined significantly in the post-HAART era, the rate of inpatient admission among HIV-infected individuals remains relatively high (Berry, Fleishman et al. 2012; Crum-Cianflone, Grandits et al. 2010; Gebo, Diener-West et al. 2001) with a slow rate of decline. (Fleishman and Hellinger 2003) High rates of hospitalization among HIV-infected individuals are in part due to complications from chronic end-organ disease, (Buchacz, Baker et al. 2008) but are also due to providing inpatient care for a particularly vulnerable subset of the HIV-infected population including African Americans, (Oramasionwu, Hunter et al. 2009; Fleishman and Hellinger 2003; Gebo, Diener-West et al. 2001) injection drug users, (Buchacz, Baker et al. 2008; Fielden, Rusch et al. 2008; Himelhoch, Chander et al. 2007; Fleishman and Hellinger 2003; Gebo, Diener-West et al. 2001; Tashima, Hogan et al. 2001) those with mental illness, (Himelhoch, Chander et al. 2007; Betz, Gebo et al. 2005) those not receiving HAART (Crum-Cianflone, Grandits et al. 2010; Floris-Moore, Lo et al. 2003) and those who have low CD4 counts. (Buchacz, Baker et al. 2008; Tashima, Hogan et al. 2001)

Several studies have sought to characterize individual clinical and social factors that may increase the risk of readmission among HIV-infected patients. Among those who had been admitted with pneumonia, patients who left against medical advice, who lived in the poorest urban neighborhoods, who had been hospitalized in the past 6 months, who did not have a companion at discharge or who reported crack cocaine use were at highest risk for readmission (Palepu, Sun et al. 2003; Grant, Charlebois et al. 1999) Another study found that taking HAART significantly reduced a patient's risk for readmission. (Nosyk, Sun et al. 2006) These studies, although limited by relatively small sample sizes, highlight the complex medical and social challenges that HIV-infected patients face and which may lead to readmission.

20.1.2 Innovation

At Parkland Hospital (one of the 11 sites participating in CTN 0049), a large safety net hospital in Dallas, Texas, we developed a real-time EMR-based prediction model for readmissions among HIV-infected patients. We identified 2,476 index admissions, representing 1509 unique individuals who were admitted between March 2006 and November 2008. Of these admissions, 25% were readmitted and 3% died within 30 days of discharge. These rates are comparable to congestive heart failure readmissions, (Amarasingham, Moore et al. 2010; Hernandez, Greiner et al. 2010; Krumholz, Parent et al. 1997) and higher than readmission rates for other illnesses such as myocardial infarction and pneumonia. (Krumholz, Lin et al. 2011; Lindenauer, Normand et al. 2011) Our prediction model is composed of factors accessible from the EMR within the first 48 hours of admission and includes clinical factors (e.g. laboratory values, medical history) and non-clinical factors (e.g. insurance, health care utilization, address changes). This model performed well (C statistic of 0.73, 95% CI 0.70 - 0.75) in predicting the 30-day risk of readmission among HIV patients (Nijhawan et al., JAIDS, 2012, in press).

An automated prediction tool could be invaluable in directing and implementing interventions aimed at high-risk individuals at the point of care. Validation of our readmission prediction model in a broad population, such as the participants from multiple sites in the CTN0049 study, will allow for assessment and refinement of the prediction model. It is possible that the interventions in the CTN 0049 trial will, in addition to improving HIV viral loads, decrease rates of readmission among study participants. Although the interventions last for a total of 6 months and we are examining 30-day readmission rates, the intensive intervention schedule immediately after discharge from the hospital (with weekly visits for the first month), has the potential to impact readmissions in this critical 30-day time period. Patient navigation has been shown to improve linkage to care and retention in care for HIV patients, (Craw, Gardner et al. 2008; Gardner, Metsch et al. 2005) and improved outpatient engagement in care may decrease the rate of HIV readmissions. A validated, refined readmission prediction model could be employed to identify those inpatients who would derive the greatest benefit from future interventions.

20.2 Specific Aims and Hypotheses

1. Validate the Electronic Medical Record (EMR)-derived prediction model for hospital readmissions within CTN0049 by comparing predicted 30-day readmission risk with actual 30-day readmission rates among the three different study arms.

Hypothesis: The 'treatment as usual' (TAU) arm will have 30-day readmission rates comparable to what the model predicts. The Patient Navigation (PN) and Patient Navigation + Contingency Management (PN +CM) arms will have readmission rates that are significantly lower than predicted by the model and lower readmission rates than the TAU arm.

2. Refine the EMR-derived prediction model for hospital readmissions based on additional variables collected in the CTN0049 trial.

Hypothesis: Additional variables collected in the trial may improve the performance of the readmission prediction model, such as measures of medication adherence, social support and access to care.

20.3 Approach

20.3.1 Methods

20.3.1.1 Study population

All participants enrolling in the CTN0049 trial are eligible to participate in this ancillary substudy as long as the specific study site is willing to collect the additional data required (see below).

20.3.1.2 Exposures and their measurement

The multivariate prediction model for 30-day Readmission risk among HIV-infected patients is presented in Table 1 (Nijhawan et al., JAIDS, 2012, in press). The majority of these variables, or very similar variables, are already being collected in CTN0049, as noted in the left columns in Table 1.

Table 1: Multivariate Predictive Model of 30-day Readmission				
Collected in CTN0049?	Where?	Variable	Odds Ratio (95% CI)	P
		Clinical		
Yes	Study lab	CD4 <= 92	1.30 (1.04 - 1.63)	0.022
Yes	abstracted	Creatinine <= 0.55	1.87 (1.15 - 3.04)	0.012
Yes	abstracted	Creatinine > 1.77	1.57 (1.11 - 2.22)	0.011
No	--	HCO3 <= 18	1.37 (1.01 - 1.88)	0.049
Yes	abstracted	ALT / AST > 35	1.27 (1.02 - 1.59)	0.032
Yes	Study lab	HCT <= 28.3 or > 48.8	1.85 (1.45 - 2.36)	< 0.001
No	--	Percent lymphocytes <= 33	1.45 (1.01 - 2.10)	0.045
No	--	PaO ₂ (57 – 113)	0.66 (0.48 - 0.90)	0.009
No	--	Anion Gap > 12 or missing	1.54 (1.17 - 2.02)	0.002
No	--	History of AIDS defining illness	1.32 (1.02 - 1.69)	0.032
		Non-clinical		
Yes	ACASI	Medicaid Payor Status	1.60 (1.27 - 2.02)	< 0.001
Yes	ACASI -- calculate distance from hospital using locator form address	Distance > 13 miles from hospital	1.77 (1.21 - 2.59)	0.004
Yes	ACASI	Number prior inpatient admits 6 mo	1.34 (1.20 - 1.49)	< 0.001
Yes	ACASI	Number prior ED visits 1 yr	1.04 (1.01 - 1.07)	0.006
Yes	ACASI	Homeless	2.09 (1.30 - 3.37)	0.002

As outlined in the above table, additional data that will need to be collected beyond what is currently planned in CTN 0049 includes the following:

1. History of an AIDS defining illness? (yes/no) (specific diagnoses to be provided to sites)
2. If PaO₂ was done w/in 48 hours of admit, were results between 57-113? (yes/no)
3. Additional laboratory values needed: Sodium (Na), Chloride (Cl), Bicarbonate (CO₂), percent lymphocytes.

Specific variables to be collected are outlined in Table 2 below.

Table 2: Additional Variables Collected in CTN0049 A-2		
Items (<i>All to be abstracted from medical records</i>)	Response Type	Response Options
Does the patient have a diagnosis of an AIDS defining illness* listed in the past (no date limit) medical history or problem list?	Categorical	No Yes
PaO ₂	Free text field, only numbers allowed	(xxx) mm Hg
Sodium (Na)	Free text field, only numbers allowed	(xxx) mEq/L (serum)
Chloride (Cl)	Free text field, only numbers allowed	(xxx) mmol/L (serum)
Bicarbonate (HCO ₃)	Free text field, only numbers allowed	(xx) mmol/L (serum)
Absolute lymphocyte count	Free text field, only numbers allowed	(x.xx) x10 ⁹ /L
<u>OR</u>		
WBC <u>and</u> % lymphocytes [because absolute lymphocyte count = WBC x % lymphocytes]	Free text field, only numbers allowed	WBC: (xx.x) x 10 ⁹ /L Lymphocytes: (xxx) %

20.3.1.3 Outcomes

The main outcome of interest is readmission to the hospital within 30 days of discharge. As all participants will be enrolled in the study from the inpatient setting, the initial enrollment admission will be considered the “index admission”.

20.3.1.4 Data Analysis

Predicted risk for 30-day readmission will be calculated for all participants in this CTN0049 substudy. As this is a randomized controlled trial, the overall risk for readmission should be comparable in each study arm prior to the intervention. Actual rates of readmission will be calculated by dividing the total number of 30-day readmissions per study arm divided by the number of participants at risk for readmission within that arm. These rates will be compared to the pre-intervention predicted risk using several different approaches, including the Hosmer-Lemeshow χ^2 goodness of fit test and a direct comparison between the pre- and post-intervention readmission risks/rates using a student's T-test.

If the goodness of fit test in the treatment as usual arm does not show that the model performs well in predicting readmissions, additional variables, based on their ease of collection from the electronic medical record (so as to be able to be used in future real-time EMR-based models) and their relationship with readmissions, will be tested in the model to evaluate for improved performance. Further analyses may then be conducted with the refined readmission prediction model.

20.3.1.5 Estimated Timeline:

0-10 months:	Collect data to calculate baseline readmission risk for all subjects participating in substudy
11-24 months:	Collect data on readmissions
24-30 months:	Complete analyses, prepare manuscript

20.4 Public Health Impact

Readmission and reimbursement for readmission have become critical issues in a time of economic crisis and rising health care costs. In a 2009 article published in the New England Journal of Medicine, Jencks et al. found that almost one-fifth (19.5%) of Medicare beneficiaries were readmitted within 30 days of discharge (Jencks, Williams et al. 2009) and that the cost to Medicare for unplanned re-hospitalizations in 2004 was estimated to be \$17.4 billion. Data from six states in 2004 indicate that a single HIV admission costs over \$15,000, with an average length of stay of 8.4 days.(Hellinger 2007; Hellinger 2004) A reduction in readmissions among patients infected with HIV has the potential to both improve patient outcomes and decrease hospital costs.

20.5 Suitability/Feasibility/Sustainability for the CTN

All participants enrolling in the CTN0049 trial will be eligible to participate in the substudy as long as the specific study site is willing to collect the additional data required. Since all of the research sites are using some form of electronic medical record this data collection should not require much additional medical record abstraction. (see *Exposures and their measurement above*).

20.6 References for Ancillary Study, CTN0049 A-2

- Berry, S.A., Fleishman, J.A., Moore, R.D., Gebo, K.A. (2012). "Trends in Reasons for Hospitalization in a Multisite United States Cohort of Persons Living with HIV 2001-2008." *J Acquir Immune Defic Syndr* **59**(4): 368-375.
- Krumholz, H.M., Lin, Z., Drye, E.E., Desai, M.M., Han, L.F., Rapp, M.T., Mattera, J.A., Normand, S.L. (2011). "An Administrative Claims Measure Suitable for Profiling Hospital Performance Based on 30-Day All-Cause Readmission Rates among Patients with Acute Myocardial Infarction." *Circulation. Cardiovascular Quality and Outcomes* **4**(2): 243-252.
- Lindenauer, P.K., Normand, S.L., Drye, E.E., Lin, Z., Goodrich, K., Desai, M.M., Bratzler, D.W., O'Donnell, W.J., Metersky, M.L., Krumholz, H.M. (2011). "Development, Validation, and Results of a Measure of 30-Day Readmission Following Hospitalization for Pneumonia." *Journal of Hospital Medicine : An Official Publication of the Society of Hospital Medicine* **6**(3): 142-150.
- Amarasingham, R., Moore, B.J., Tabak, Y.P., Drazner, M.H., Clark, C.A., Zhang, S., Reed, W.G., Swanson, T.S., Ma, Y., Halm, E.A. (2010). "An Automated Model to Identify Heart Failure Patients at Risk for 30-Day Readmission or Death Using Electronic Medical Record Data." *Medical Care* **48**(11): 981-988.
- Crum-Cianflone, N.F., Grandits, G., Echols, S., Ganesan, A., Landrum, M., Weintrob, A., Barthel, R., Agan, B., Infectious Disease Clinical Research Program. (2010). "Trends and Causes of Hospitalizations among HIV-Infected Persons During the Late HAART Era: What Is the Impact of CD4 Counts and HAART Use?" *Journal of Acquired Immune Deficiency Syndromes (1999)* **54**(3): 248-257.
- Hernandez, A.F., Greiner, M.A., Fonarow, G.C., Hammill, B.G., Heidenreich, P.A., Yancy, C.W., Peterson, E.D., Curtis, L.H. (2010). "Relationship between Early Physician Follow-up and 30-Day Readmission among Medicare Beneficiaries Hospitalized for Heart Failure." *JAMA* **303**(17): 1716-1722.
- Jencks, S.F., Williams, M.V., Coleman, E.A. (2009). "Rehospitalizations among Patients in the Medicare Fee-for-Service Program." *The New England Journal of Medicine* **360**(14): 1418-1428.
- Oramasionwu, C.U., Hunter, J.M., Skinner, J., Ryan, L., Lawson, K.A., Brown, C.M., Makos, B.R., Frei, C.R. (2009). "Black Race as a Predictor of Poor Health Outcomes among a National Cohort of Hiv/Aids Patients Admitted to US Hospitals: A Cohort Study." *BMC Infectious Diseases* **9**(Journal Article): 127.
- Buchacz, K., Baker, R.K., Moorman, A.C., Richardson, J.T., Wood, K.C., Holmberg, S.D., Brooks, J.T., Investigators, HIV Outpatient Study Investigators. (2008). "Rates of Hospitalizations and Associated Diagnoses in a Large Multisite Cohort of HIV Patients in the United States, 1994-2005." *AIDS (London, England)* **22**(11): 1345-1354.
- Craw, J.A., Gardner, L.I., Marks, G., Rapp, R.C., Bosshart, J., Duffus, W.A., Rossman, A., Coughlin, S.L., Gruber, D., Safford, L.A., Overton, J., Schmitt, K. (2008). "Brief Strengths-Based Case Management Promotes Entry into HIV Medical Care: Results of the Antiretroviral Treatment Access Study-II." *J Acquir Immune Defic Syndr* **47**(5): 597-606.
- Fielden, S.J., Rusch, M.L., Levy, A.R., Yip, B., Wood, E., Harrigan, R.P., Goldstone, I., Guillemi, S., Montaner, J.S., Hogg, R.S. (2008). "Predicting Hospitalization among HIV-Infected Antiretroviral Naive Patients Starting HAART: Determining Clinical Markers and Exploring Social Pathways." *AIDS Care* **20**(3): 297-303.

- Hellinger, F.J. (2007). "The Changing Pattern of Hospital Care for Persons Living with HIV: 2000 through 2004." *Journal of Acquired Immune Deficiency Syndromes (1999)* **45**(2): 239-246.
- Himelhoch, S., Chander, G., Fleishman, J.A., Hellinger, J., Gaist, P., Gebo, K.A. (2007). "Access to HAART and Utilization of Inpatient Medical Hospital Services among HIV-Infected Patients with Co-Occurring Serious Mental Illness and Injection Drug Use." *General hospital psychiatry* **29**(6): 518-525.
- Nosyk, B., Sun, H., Li, X., Palepu, A., Anis, A.H. (2006). "Highly Active Antiretroviral Therapy and Hospital Readmission: Comparison of a Matched Cohort." *BMC Infectious Diseases* **6**(Journal Article): 146.
- Betz, M.E., Gebo, K.A., Barber, E., Sklar, P., Fleishman, J.A., Reilly, E.D., Christopher Mathews, W., Network, H.I.V.R. (2005). "Patterns of Diagnoses in Hospital Admissions in a Multistate Cohort of Hiv-Positive Adults in 2001." *Medical care* **43**(9 Suppl): III3-14.
- Gardner, L.I., Metsch, L.R., Anderson-Mahoney, P., Loughlin, A.M., del Rio, C., Strathdee, S., Sansom, S.L., Siegal, H.A., Greenberg, A.E., Holmberg, S.D., Antiretroviral Treatment and Access Study Study Group. (2005). "Efficacy of a Brief Case Management Intervention to Link Recently Diagnosed HIV-Infected Persons to Care." *AIDS (London, England)* **19**(4): 423-431.
- Hellinger, F.J. (2004). "HIV Patients in the HCUP Database: A Study of Hospital Utilization and Costs." *Inquiry : A Journal of Medical Care Organization, Provision and Financing* **41**(1): 95-105.
- Fleishman, J.A., Hellinger, F.H. (2003). "Recent Trends in HIV-Related Inpatient Admissions 1996-2000: A 7-State Study." *Journal of Acquired Immune Deficiency Syndromes (1999)* **34**(1): 102-110.
- Floris-Moore, M., Lo, Y., Klein, R.S., Budner, N., Gourevitch, M.N., Moskaleva, G., Schoenbaum, E.E. (2003). "Gender and Hospitalization Patterns among HIV-Infected Drug Users before and after the Availability of Highly Active Antiretroviral Therapy." *Journal of Acquired Immune Deficiency Syndromes (1999)* **34**(3): 331-337.
- Palepu, A., Sun, H., Kuyper, L., Schechter, M.T., O'Shaughnessy, M.V., Anis, A.H. (2003). "Predictors of Early Hospital Readmission in HIV-Infected Patients with Pneumonia." *Journal of General Internal Medicine* **18**(4): 242-247.
- Gebo, K.A., Diener-West, M., Moore, R.D. (2001). "Hospitalization Rates in an Urban Cohort after the Introduction of Highly Active Antiretroviral Therapy." *Journal of Acquired Immune Deficiency Syndromes (1999)* **27**(2): 143-152.
- Tashima, K.T., Hogan, J.W., Gardner, L.I., Korkontzelou, C., Schoenbaum, E.E., Schuman, P., Rompalo, A., Carpenter, C.C. (2001). "A Longitudinal Analysis of Hospitalization and Emergency Department Use among Human Immunodeficiency Virus-Infected Women Reporting Protease Inhibitor Use." *Clin Infect Dis* **33**(12): 2055-2060.
- Grant, R.W., Charlebois, E.D., Wachter, R.M. (1999). "Risk Factors for Early Hospital Readmission in Patients with Aids and Pneumonia." *Journal of General Internal Medicine* **14**(9): 531-536.
- Krumholz, H.M., Parent, E.M., Tu, N., Vaccarino, V., Wang, Y., Radford, M.J., Hennen, J. (1997). "Readmission after Hospitalization for Congestive Heart Failure among Medicare Beneficiaries." *Archives of Internal Medicine* **157**(1): 99-104.