COVER PAGE

Official Title: Suppression of HIV 1 RNA in People Living With HIV

NCT number: NCT02363387

Document Date of the Protocol: July 14, 2020

Date: July 14, 2020
Principal Investigator: Kenneth Silverman
Application Number: IRB00044740

JHM IRB - eForm A – Protocol

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1. Abstract

a. Provide no more than a one page research abstract briefly stating the problem, the research hypothesis, and the importance of the research.

Consistent use of antiretroviral medications by adults living with HIV can suppress plasma HIV-1 RNA (viral load) to undetectable levels and thereby improve survival rates and quality of life, and reduce HIV-related infections, health care costs, and transmission of HIV. Despite the potential benefits of antiretroviral therapy, adults living with HIV have not been reliably engaged in HIV care or sustained on antiretroviral medications. Few interventions have been shown effective in increasing adherence and suppressing viral loads to undetectable levels, and no treatments have produced long-term effects that sustain after the intervention is discontinued. Interventions that provide incentives to patients when they meet required therapeutic goals have been demonstrated extraordinarily effective in promoting therapeutic behavior change in diverse populations and they have shown promise in promoting adherence to antiretroviral medications and suppression of viral loads. However, only limited evaluations of these interventions have been conducted to promote adherence to antiretroviral medications and suppress viral loads, those evaluations have not employed optimal parameters of incentive interventions, and they have not produced levels of viral load suppression that are needed clinically. We propose to evaluate a novel incentive intervention to promote suppression of viral load in people living with HIV that will employ empirically-based parameters that have been proven critical to the effectiveness of incentive interventions. Participants (N = 200) from two medical clinics that serve adults living with HIV in Baltimore will be randomly assigned to an Incentive or a Usual Care Control group. Incentive group participants will receive incentives for maintaining suppressed and undetectable viral loads. The incentive program will employ high magnitude incentives, provide incentives for decreases in viral load early in treatment before a patient's viral load has reached undetectable levels, arrange frequent incentives early in treatment and reduce the frequency of incentives as participants achieve progressively longer periods of viral load suppression, arrange a schedule of escalating incentives for sustained suppression of viral load, and the intervention will be maintained for two years. Usual Care Control participants will only receive the standard HIV medical care offered in their clinic. Assessments will be conducted every 3 months throughout the two years of treatment and every 6 months throughout the year following treatment. The primary outcome measure will be the percentage of participants that have undetectable viral loads at the 3-month assessments conducted throughout the 2-year intervention period. Secondary measures will include adherence to HIV care and post-treatment outcomes. We will also assess moderators and mediators of the effects of the incentives on the suppression of viral load, and conduct cost-effectiveness and cost-benefit analyses. If the incentive intervention maintains suppressed viral load and is economically sound, it could be used to improve the health of adults living with HIV, reduce health care costs, and reduce HIV transmission in the community.

2. Objectives (include all primary and secondary objectives)

The project has the following primary and secondary objectives:

Primary Objective

Suppression of viral load. Assess the effectiveness of an empirically-based incentive intervention in maintaining undetectable HIV-1 RNA (viral loads) in people living with HIV.

Secondary Objectives

Adherence to HIV care. Assess the effectiveness of an empirically-based incentive intervention for viral load suppression in promoting biologically-verified adherence to antiretroviral medications, promoting maintenance of prescriptions for antiretroviral medications, and retaining patients in HIV medical care.

Post intervention effects. Assess the effectiveness of an empirically-based incentive intervention for viral load suppression in promoting effects after the intervention is discontinued.

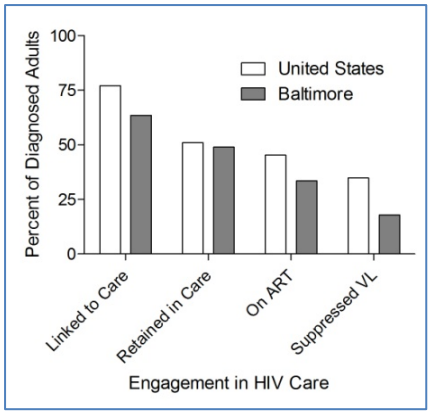
Moderators. Determine if drug dependence, alcohol dependence, depression, health literacy, and impulsivity moderate viral load suppression and response to the incentive intervention.

Mediators. Determine if ART adherence as assessed by qualitative HRMS blood tests of 15 antiretroviral medications mediates the effect of the incentive intervention on viral load suppression.

Economic Aims. Assess the costs, cost-effectiveness and cost-benefit of the incentive intervention.

3. Background (briefly describe pre-clinical and clinical data, current experience with procedures, drug or device, and any other relevant information to justify the research)

Consistent use of antiretroviral therapy (ART) by people living with HIV can suppress plasma HIV-1 RNA (viral load) and thereby increase survival rates and improve health (Leone et al., 2011; Montaner, Wood et al., 2010); reduce health care costs (Gebo et al., 2010); and reduce HIV transmission (Cohen et al., 2011; Das et al., 2010; Montaner, Lima et al., 2010). These benefits require that patients maintain nearly perfect adherence for their entire lives (Paterson et al., 2000; Vrijens et al., 2005). However, people living with HIV are not reliably sustained on ART. The adjacent figure shows that few adults diagnosed with HIV in the US (CDC, 2011) or Baltimore (MDHMH, 2011) are linked or retained in HIV care, inducted onto ART, and have their viral loads suppressed. To address this problem, NIMH and NIADI issued PA-14-126 to strengthen adherence to ART and requests "*Research using behavioral economic approaches to encourage or incentivize adherence and/or viral suppression*." We have assembled a multidisciplinary team of highly experienced investigators to apply the state-of-the-art science on incentives, HIV and ART to develop an incentive intervention to promote suppression of viral load in adults living with HIV. This intervention could promote long-term ART adherence, suppress viral loads, improve health, reduce medical costs, and prevent the transmission of HIV.



Interventions to Promote Adherence to Antiretroviral Therapy and Suppression of Viral Load

Reviews and meta-analyses suggest that some interventions increase ART adherence, but do not significantly affect viral load (Simoni et al., 2006; Mathes et al. 2013). The authors of one review concluded that "most adherence interventions have no effect (Mathes et al., 2013)." One of the more promising approaches was directly observed ART. Meta-analyses of directly observed ART showed conflicting results (Ford et al., 2009; Hart et al., 2010), but it is clear that its effects do not last after the intervention is discontinued. Research is desperately needed to develop interventions that can increase ART adherence and that can maintain life-long ART adherence and suppressed viral load.

The Use of Incentives in the Promotion of Health Behaviors

Research over the past 40 years on the use of behavioral economic incentives in the treatment of drug addiction and other health problems suggests that incentives could promote and sustain ART adherence.

Incentives to initiate drug abstinence and medication adherence. Interventions in which patients receive incentives for health behaviors have been effective in promoting abstinence from most commonly abused drugs and in promoting adherence to addiction medications, among other targets (Higgins, Silverman, & Heil, 2008). Reviews and meta-analyses suggest that contingency management

interventions may be the most effective psychosocial addiction treatments (Castells et al., 2009; Dutra et al., 2008; Knapp et al., 2007; Pilling et al., 2007). Voucher reinforcement, in which patients receive monetary vouchers exchangeable for goods and services for providing drug-free urine samples (Higgins et al., 1991), is one of the most effect treatments for drug addiction and can increase abstinence from a wide range of drugs (Lussier et al., 2006). Silverman (PI) and others (Castells et al., 2009) have conducted studies showing that voucher reinforcement can increase cocaine (Silverman et al., 1996a; Silverman et al., 1998) and opiate (Robles et al., 2002; Silverman et al., 1996b) abstinence in injection drug users in methadone treatment and that increasing the voucher values can initiate abstinence in refractory patients (Dallery et al., 2001; Silverman et al., 1999). Incentives have also been used effectively to promote adherence to a variety of medications and vaccines to treat or prevent tuberculosis, hepatitis, psychosis, and stroke (DeFulio and Silverman, 2012; Petry et al., 2012).

Incentives to maintain behavior change. As with other treatments, many patients relapse after incentives end. To address this, Silverman (PI) has employed incentives as a maintenance intervention. One study showed that voucher incentives could maintain cocaine abstinence for a year (Silverman et al., 2004) Silverman (PI) and colleagues also showed that contingent access to paid employment in the Therapeutic Workplace could promote and maintain drug abstinence and medication adherence over time (Silverman, 2004; Silverman et al., 2012) for between one (DeFulio et al., 2009) and three (Silverman et al. 2002) years.

Incentives for Adherence to Antiretroviral Therapy and Suppression of Viral Load

Incentives for MEMS caps openings. Binford et al. (2012) found three studies that evaluated the use of incentives to promote use of ART in which patients earned monetary incentives for opening medication bottles using the Medication Event Monitoring System (MEMS). The studies arranged incentives for 4 (Rigsby et al., 2000), 12 (Sorensen et al., 2007) and 16 (Rosen et al., 2007) weeks, and participants could earn about $7, $10 and $14 per day, respectively, for taking their medications. All studies showed that incentives increased ART adherence. One study (Rosen et al., 2007) showed that the incentive intervention significantly decreased mean viral load compared to a control group, but did not increase the percentage of patients with undetectable viral loads. As with other interventions, the effects were not maintained after the incentives were discontinued.

Incentives for suppression of viral load. Two studies provided incentives for suppressed viral loads. This procedure is similar to the procedures that we have used to promote abstinence from drug use in which patients receive incentives when the patient provides biological samples that confirm recent drug abstinence (Silverman et al., 2011). In one study (Javanbakht et al., 2006), participants earned $20 for monthly viral load assessments (or $1.10 per day) that either showed a 3-fold decrease in viral load or reached undetectable levels. Significantly more participants in the case management plus incentives group achieved a 1-log10 decrease in viral load at the 12-, 24- and 48-week time points compared to the standard care participants. However, case management plus incentives did not increase the percentage of participants with undetectable viral loads. The other study (Farber et al., 2013) compared the viral loads of patients during a pre-intervention year to an intervention year. During the intervention, participants could earn $100 every 3 months ($0.67 per day) for providing blood samples that either had undetectable viral loads or that had viral loads that decreased 1 log10 lower than their lowest viral load in the past year. Overall, the intervention did not affect the viral loads, but it did affect a subset of participants who had detectable viral loads during the pre-intervention year.

A Novel Incentive Intervention

Incentive interventions have been extraordinarily effective in promoting therapeutic behavior change in diverse populations and they have shown some promise in promoting ART adherence and suppressing viral loads. However, limited evaluations of these interventions have been conducted, those evaluations have not employed optimal parameters of incentive interventions, and they have not produced levels of viral load suppression that are needed clinically. *We propose to develop and evaluate a novel incentive intervention to promote suppression of viral load in adults living with HIV that will employ empirically-based parameters that have been proven critical to the effectiveness of incentive interventions*.

4. Study Procedures

a. Study design, including the sequence and timing of study procedures

(distinguish research procedures from those that are part of routine care).

COVID-19 Procedures

To reduce the risk of contracting or transmitting COVID-19, we will complete the remaining assessments without any in person contact. Interviews will be conducted over the phone and when possible we will obtain blood and urine sample results from each participant's clinic. If needed, we will mail a re-loadable credit card to participants.

Study Participants

Participants will be recruited from medical clinics in Baltimore that serve HIV-infected adults, from other programs that serve people living with HIV, and through word of mouth.

Recruiting Participants

We will employ six recruitment procedures. First, we will inform staff at medical clinics and programs that serve people living with HIV about the study and encourage them to refer potential participants to us. Second, we will post flyers and distribute business cards and information sheets with our toll-free number in each of these programs and in Baltimore publications (on the internet and paper). Copies of the proposed flyer, business card and information sheets are enclosed with this application. Third, we will visit programs and recruit for the study onsite at each program. Interested applications will contact our research staff directly. Fourth, as in our previous studies, participants will have the optional opportunity to earn incentives for referring people who are interested in the study. If a referral attends the initial screening appointment and completes the necessary assessments, the participant who referred the person will receive up to $20. If a referred person enrolls in the main study, the participant who referred the person will receive up to $40 for making the referral. Fifth, we will prepare stamped envelopes that providers can mail directly to their patients. Each envelop will include the letter approved by the IRB and an IRB-approved flyer. The letter will be put on the provider's letterhead, the letter will be signed by the provider, and the provider will address and mail the envelopes to their patients. The text of the letter is included section 13.7. Sixth, we will distribute IRB-approved flyers, information sheets and business cards to public events that are attended by people living with HIV (e.g., gay pride parade, AIDS walk, etc.).

Brief Screening and Study Consent

In the initial contact with an applicant, a brief screening interview will be conducted to inform interested persons about the study and to confirm that the person might qualify for the study. This interview may take place over the phone or in person when an applicant initially inquires about the study. Prior to asking any questions, the interviewees will be told that they do not have to answer any of the questions and can stop the interview at any time. In cases where the brief screening interview is conducted in-person (i.e., at an inpatient treatment program or at the Therapeutic Workplace), the interview will take place in a private area to ensure confidentiality. If the results of the brief screening interview suggest that the applicant might be eligible, the applicant will be invited to sign the study consent form to be screened more fully for study eligibility. Results of the brief screening interviews will be entered into a database, but no identifying information will be entered in this database. A person's name, phone number and address will only be written on the brief screening interview form if the person is invited to participate in an Initial Screening Interview. This contact information will be used to help schedule the interview and to allow us to reschedule the interview as needed. If a person decides not to participate in the Initial Screening Interview, his/her brief screening interview will be shredded. Hard copies of the brief screening interview forms will only be saved for participants who signed the Initial Screening Consent form**.**

Initial Screening Interview

Initial screenings will occur at the collaborating program or at our research unit to determine eligibility for the study and collect baseline data on the study population. The participant will be asked to sign a consent form to allow his/her medical clinic to release medical records to determine study eligibility, to characterize medications used, and to characterize the population. The Initial Screening Interview will take place in a private area to ensure confidentiality. Participants will be paid for completing the screening interview. Patients who meet criteria for inclusion in the study will be invited to participate in the main randomized controlled study.

During the research interviews, participants will be asked to complete a contact information sheet. The contact information sheet will include the participant's contact information as well as the contact information of family members or other individuals we may contact by phone or in writing in order to locate the participant for future research interviews. Participants who do not qualify for the study will be referred to services that they need or want. We have used similar recruitment procedures in prior studies (e.g.,

Donlin et al., 2008; Silverman et al., 2007). See the Letters of Support section for letters from the Medical Directors of these clinics.

Standard HIV Medical Care

Upon enrollment, participants will be taught about the benefits of HIV medical care, ART adherence and the need to maintain nearly perfect adherence. Participants will be able to earn incentives for engaging in this education. Participants will be able to earn up to about $100 for completing the program. Some or all of the training may be given through a computer-based training program. We may also evaluate the effectiveness of the education program by giving participants tests before and after participants complete parts or all of the training program. We may re-administer the test at the end of the intervention to measure retention.

If a participant is not currently receiving HIV medical care, the participant will be referred to an HIV medical care clinic. Participants will typically receive their HIV medical care at the Comprehensive Care Practice or the Chase Brexton Health Services clinic.

Experimental Design

Participants (N = 200) who complete the HIV Medical Care Education program will be randomly assigned to a Usual Care Control group or the Incentive group. A computerized urn randomization procedure (Wei & Lachin, 1988) will be used to balance groups on five baseline characteristics that may influence outcome: (1) opiate or cocaine positive urine sample at intake to the study (Y/N); (2) Self-reported use alcohol to intoxication on 20 or more days in the past 30 on the ASI (Y/N); (3) health literacy as assessed on the TOFHLA (score ≤ the rolling median, Y/N); (4) impulsivity as assessed by delay discounting (k value from the raw discounting data for each participant, which is an index of impulsivity (≤ the rolling median of k, Y/N); and (5) depression as assessed by the Beck Depression Inventory (score ≤ the rolling median, Y/N). Participants will be stratified by DSM V cocaine, opiate and alcohol dependence, health literacy, and depression at intake because drug use (Mimiaga et al., 2013), health literacy (Kalichman et al., 2008), and depression (Murphy et al. 2013) has each been associated with poor ART adherence. Participants will be stratified based on measures of impulsivity because high levels of impulsivity have been associated with poor health decision making and adverse health behaviors (Axon et al. 2009; Bickel et al. 2014; Bradford et al., 2010). Participants will be taught the details of their group with written instructions and quizzes. Participants will earn up to about $15 for answering questions on the quiz.

Incentive Group

The Incentive group will receive the novel empirically-based incentive intervention to promote long term suppression of HIV-1 RNA (viral load) being evaluated in this study. The incentive intervention will employ features and parameters that have been shown critically important to promote therapeutic behavior change in drug users and other populations (Higgins et al., 2008; Lussier et al., 2006; Silverman et al., 2011). Participants will be taught the details of the incentive program with written instructions and quizzes.

A Prescription for ART. When a participant gets assigned to the Incentive group, he/she will be asked if he/she has a current prescription for ART and if he/she has at least a 2-day supply of medication. As described below, blood draws and the incentive program described below will not begin until the participant has a active ART prescription and has at least a 2-day supply of medication.

Feedback of the viral load tests. Participants will provide blood samples according to the schedule described below. Each sample will be tested for HIV-1 RNA (viral load) by a CLIA-certified outside laboratory. We should obtain the results of the viral load test within 1 week of the collection. Each participant will be instructed to call the Incentive Program staff to obtain the results of the viral load testing 1 week after the blood sample was collected. Incentives will be provided when the participant calls the Incentive Program staff for the results of viral load testing. If the viral load results are obtained by the time the participant calls in for the next blood draw (see below), the results will be provided to the participant at that time. With the patient's consent, the results will be forwarded to the patient's physician.

Providing incentives for decreased viral load. Throughout the intervention, participants will be able to earn up to $10 per day for providing blood samples that have undetectable viral loads (i.e., <200 copies/mL) or viral loads that have decreased by 0.15 log per week since the last viral load assessed. This amount of decrease is based on research of the decay dynamics of viral load in response to ART. Dr. Robert Siliciano, a co-investigator on this grant application, is a world renowned expert on decay dynamics of viral load in response to ART. Research by Dr. Siliciano and others (Maldarelli et al., 2007; Perelson et

al. 1997; Sedaghat et al. 2008) shows that HIV-1 viremia decays in three stages in response to ART. HIV-1 viremia decays rapidly in the initial stage, with a half-life of as little as one day. That stage is relatively brief and lasts only a matter of days. In the second stage, HIV-1 viremia decays at a slower rate, with a half-life of about two weeks. The third stage occurs after viral load has fallen below the level detection by clinical assays, and is thus not relevant to the incentive intervention. Our criterion for incentives assumes: 1) patients will typically be in the second stage until their viral load reaches the undetectable threshold, and 2) HIV-1 viremia will always decay at a rate equal to or greater than the second stage (i.e., with a half-life of 2 weeks or shorter). We expect that viral load should decrease by at least 0.15 log per week until it is undetectable if the patient is taking ART consistently.

To ensure that we provide incentives when it appears that participants are adhering to their antiretroviral medications, when a participant's viral load falls at or below 1,000 copies/mL, the participant will earn the scheduled incentive when their viral load decreases by any amount. We may make further adjustments to the criteria for earning incentives based on our experience with this intervention in an effort to ensure that we provide incentives when it appears that participants are adhering to their antiretroviral medications.

Although standard clinical assays have limits of detection of 50 copies/mL, we selected <200 copies/mL as the definition of undetectable viral load for the following reasons: Many patients on ART have occasional "blips" in which the level of plasma virus becomes detectable and then returns to below the limit of detection without intervention. It is now clear that all patients on ART have trace levels of viremia, typically on the order of 1 copy/mL (Palmer et al. 2008). This may reflect release of virus from stable reservoirs. Detailed studies of blips have shown that the virus present during blips is drug sensitive and occasional blips of <200 copies/mL are not considered clinically significant (Nettles et al. 2005). Importantly, patients' viral load should become detectable within about 2 weeks of stopping or interrupting ART (Davey et al., 1999).

Random schedule of testing with progressive decrease in frequency of testing. To ensure that Incentive participants do not wait to take their antiretroviral medications consistently in the month before a viral load test, viral load blood tests will be scheduled at random times throughout the 2-year intervention evaluation period. At each viral load blood test, if the participant provides a blood sample that meets the criteria for earning an incentive (e.g., an undetectable viral load or a decrease in viral load of 0.15 log per week since the last blood sample provided), the participant will earn an incentive equal to $10 per day for all the days since the last blood test. For example, if two weeks had passed since the last viral load test, the participant would earn $140 for providing a blood sample with an undetectable viral load ($10 per day X 14 days = $140). Initially, the viral load blood tests will occur once every week. Once the participant provides blood samples with sufficiently decreased or undetectable viral loads on 4 consecutive weekly blood tests, the inter-test interval will be increased to once every 2 weeks, on average. Once the participant provides blood samples with sufficiently decreased or undetectable viral loads on 2 consecutive blood tests, the inter-test interval will be increased to once every 4 weeks, on average. Once the participant provides blood samples with sufficiently decreased or undetectable viral loads on 2 consecutive blood tests at that inter-test interval, the inter-test interval will be increased to 8 weeks, on average. Once the participant provides blood samples with sufficiently decreased or undetectable viral loads on 2 consecutive blood tests at that inter-test interval, the inter-test interval will be increased to 12 weeks, on average. The inter-test interval will remain at 12 weeks for the remainder of the 2-year intervention evaluation period, which is equivalent to the standard inter-test interval for viral load testing under standard care (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2013). Each participant will call the Incentive Program every Monday to determine if they are scheduled to provide a blood sample that week. To ensure that participants call every week, participants will be paid $5 for each weekly call. If a blood sample is scheduled for that week, the participant will schedule a time for the collection within that week (Monday-Friday).

Reset in the incentive magnitude and increase in testing frequency for missed or detectable viral loads. If a participant ever misses a scheduled blood sample collection or provides a blood test that does not meet the criteria for earning an incentive, the participant will not receive an incentive and both the schedule of viral load testing and the magnitude of incentives will change. The schedule will switch to the most frequent testing schedule that was employed at the beginning of treatment. The value of the incentive will be decreased from $10 per day to $3 per day for the next blood sample that meets the criteria for an incentive. Once the participant earns an incentive at the $3 per day rate, the incentive will increase to $6 per day. Once the participant earns an incentive at the $6 per day rate, the incentive will increase to $10

per day.

Presenting ART prescription bottle to start the incentive program. When a participant starts the incentive program and calls the Incentive Program on the first Monday in the program, the participant will be told to bring his/her prescription bottle containing his/her ART medication to the research unit when they come to provide a blood sample. The participant will be paid for the first week ($70) if the participant brings his/her ART prescription bottle and if the bottle contains at least a 2-day supply of medication. Blood draws and the incentive program will not begin until the participant brings in an ART prescription bottle containing at least a 2-day supply of medication.

The web-based computerized program. Similar to our prior incentive programs, we will use a web-based computer program to manage the incentive program. The web-based program will schedule all blood sample collections, allow recording of the viral load tests, provide graphical feedback, and calculate the amounts that participants will earn for each blood sample that meets the required level of viral load. The program will be web-based, which will allow us to use the same program for both HIV medical clinics. The use of this web-based computerized program will facilitate the implementation of the incentive program and reduce the complication and burden on staff of implementing the incentive program.

Reloadable credit card. At the start of each participant's enrollment, each participant will be given a reloadable credit card. When the participant calls to get the results of a given viral load test, the Incentive staff will tell the participant the results. If the participant met the criterion for the incentive, the Incentive staff will tell the participant the amount of the incentive earned and add the incentive amount to the participant's reloadable credit card. This procedure will ensure that participants monitor the results of their viral load testing and know when, why and how much is added to their credit card. That card can then be used as a regular credit card to make purchases at most businesses. We currently use this reloadable credit card system in our Therapeutic Workplace incentive program, and it has proved very efficient and highly acceptable to participants.

Usual Care Control Group

Usual Care Control Only participants will receive the standard HIV medical care described above offered in their medical clinic. Participants in this group will not receive added viral load testing, feedback or incentives, beyond the viral load testing conducted as a routine part of their medical care.

Assessments

For all participants, assessments will be conducted at intake to determine eligibility and characterize participants. Outcome assessments will be conducted at intake, every 3 months throughout the 2-year intervention evaluation and every 6 months of the 1-year follow-up period. Except for the computerized delay discounting task, the assessments will be administered using the Qualtrics web-based software (http://qualtrics.com/) to administer and record responses for the questionnaires administered under this protocol. When necessary (e.g., if the web server is not operational), a printed version of the questions will be used.

Intake Only Assessment Instruments. At intake we will administer: 1) BDI to screen for depression (Beck et al. 1993). 2) Test of Functional Health Literacy in Adults (TOFHLA) to measure health literacy (Parker et al., 1995). 3) A computer delay discounting task to assess impulsivity (Johnson and Bickel, 2002). In this task, on each trial the participant makes a choice between a smaller immediate reward option (e.g., $5 now) and a larger $10 reward delivered after a given delay (e.g., 1 week). The magnitude of the smaller immediate reward is adjusted across trials to determine an indifference point, or the amount of immediate money equal to the delayed $10. Once an indifference point is detected, the task moves to the next of four delays (1 day, 1 week, 1 month, 6 months); 4) The Addiction Severity Index; 5) The Wide Range Achievement Test.

Intake, 3-Month and 6-month Follow-up Assessments. We may conduct these assessments at all time points: 1) HIV-1 RNA (viral load) in blood by Maryland DHMH Laboratories. 2) The presence or absence of 15 ART medications in blood (Marzinke et al., 2014). 3) We may assess blood samples that we collect for the quantitative levels of antiretroviral medications or their metabolites to determine if participants are maintaining the presumed therapeutic blood levels of the antiretroviral medications. The assessments of quantitative blood levels of antiretroviral medications could provide more information than the qualitative tests. For example, a participant could test positive for an antiretroviral medication on the qualitative test by taking the medication occasionally, but not take the antiretroviral medication often enough to maintain therapeutic blood levels of the medications. 4) blood tests of CD4 counts; 5) urine tests of drugs of abuse. 6) A

visual analog scale (VAS) to assess ART adherence in which participants mark a 100 mm line to indicate their percent adherence to their antiretroviral medications over the previous 4 weeks (Buscher et al., 2011; Walsh et al., 2002). Responses on this VAS have been associated with pill taking with MEMS (Buscher et al., 2011; Walsh et al., 2002), pill count (Walsh et al., 2002), and pharmacy records (Buscher et al., 2011). 7) Assess whether each participant refilled their ART prescription for each month, the pharmacy that filled each prescription, and the medication. 8) Pharmacy records will be obtained (with participant permission) to confirm self-reported data. 9) Participants will be asked how many primary HIV care visits they had in the past 3 months using procedures and definitions used in a prior multisite study (Purcell et al., 2007). Medical records will be obtained with permission to confirm self-reports. 10) The *Modified Economic Form 90 AIR/ED* will be created for this study based on the Economic Form 90 AIR/ED (Bray et al., 2007; Miller and Del Boca, 1994; Scheurich et al., 2005; Tonigan et al., 1997) to collect patient data on all health care utilization within the past 180 days. 10) A Modified SASCAP (Zarkin, Dunlap et al. 2004) will be used to estimate the costs associated with services in the study conditions. The SASCAP (www.rti.org/sascap) assesses activity-level resource use and cost data for intervention staff, consultants, and non-labor resources (e.g., building space) used in the provision of intervention services. The SASCAP method reliably estimates the costs of intervention activities and the cost per participant. Zarkin and Dunlap have applied this micro-costing approach (Zarkin et al., 2003, 2005, 2008, 2010; Dunlap et al., 2010). 11) A multiple-choice test evaluating the HIV Education Course.

b. Study duration and number of study visits required of research participants.

Participants in the incentive group will receive the incentive intervention for two years. For all participants, assessments will be conducted at intake to determine eligibility and characterize participants. Outcome assessments will be conducted at intake, every 3 months throughout the 2-year intervention evaluation and every 6 months of the 1-year follow-up period.

c. Blinding, including justification for blinding or not blinding the trial, if applicable.

Participants will not be blinded as to their study condition because participants in the incentive intervention cannot be blind to that intervention.

d. Justification of why participants will not receive routine care or will have current therapy stopped.

All participants will receive the best HIV medical and appropriate referrals to other care that is available in their respective HIV medical clinics. Participation in this study will not limit their access to the highest quality medical care that is available in their medical clinics.

e. Justification for inclusion of a placebo or non-treatment group.

There is not a placebo or non-treatment group in this study.

f. Definition of treatment failure or participant removal criteria.

Participants will be removed from the study if they threaten the safety of the research staff or other research participants.

g. Description of what happens to participants receiving therapy when study ends or if a participant's participation in the study ends prematurely.

Participants will continue to receive HIV medical care as long as that care is available in the medical clinic that they attend.

5. Inclusion/Exclusion Criteria

Applicants will be accepted if they: a) are ≥18 yrs old; b) have been diagnosed with HIV for at least 12 weeks; c) have a detectable viral load (>200 copies/mL); and d) are not currently receiving HIV medical care or have been in HIV medical care for at least 12 weeks. Applicants will be ineligible if they a) report current suicidal or homicidal ideation; or b) have a severe psychiatric disorder.

6. Drugs/ Substances/ Devices

a. The rationale for choosing the drug and dose or for choosing the device to be used.

NA

b. Justification and safety information if FDA approved drugs will be administered for non-FDA approved indications or if doses or routes of administration or participant populations are changed.

NA

c. Justification and safety information if non-FDA approved drugs without an IND will be administered.

NA

7. Study Statistics

We will compare the Incentive and Usual Care Control groups on primary, secondary and economic measures. To preserve statistical power and minimize the likelihood of false conclusions, we identified one primary biological outcome measure and a limited number of secondary and economic measures. Each measure is associated with a *Specific Aim*.

a. Primary outcome variable.

Specific Aim. Assess the effectiveness of an empirically-based incentive intervention in maintaining undetectable viral loads in people living with HIV. We will assess the percentage of blood samples that have undetectable viral loads (i.e., <200 copies/mL) at the eight 3-month assessments conducted throughout the 2-year intervention evaluation period (Y/N at each assessment).

a. Secondary outcome variables.

We expect that the incentive intervention could affect measures that are not directly targeted by the intervention. Since patients must adhere to ART and stay in HIV care to achieve undetectable levels of viral load, we expect that the incentive intervention will increase consistent adherence to ART, maintenance of prescriptions for ART, and retention in HIV medical care. It may also produce post-intervention effects.

Specific Aim. Assess the effectiveness of an empirically-based incentive intervention for decreased or undetectable viral loads in promoting biologically-verified adherence to antiretroviral medications. We will assess whether the participant maintained consistent ART adherence by conducting qualitative high-resolution mass spectrometry (HRMS) blood tests of 15 antiretroviral medications. Participants will be considered adherent if they test positive for all of their prescribed medications (Y/N at each 3-month assessment).

Specific Aim. Assess the effectiveness of an empirically-based incentive intervention for decreased or undetectable viral loads in promoting self-reported adherence to antiretroviral medications. We will assess whether the participant reports maintaining consistent ART adherence by reporting taking >90% of all scheduled doses in the past 30 days (Y/N at each 3-month assessment based on responses on a visual analog scale to assess adherence to antiretroviral medications, see below).

Specific Aim. Assess the effectiveness of an empirically-based incentive intervention for decreased or undetectable viral loads in maintaining prescriptions for antiretroviral medications. We will assess the percentage of months that the participant refilled a prescription for antiretroviral medications throughout the 2-year intervention evaluation period (Y/N for each month prior to each 3-month assessment based on timeline follow-back self-report and confirmed by pharmacy records).

Specific Aim. Assess the effectiveness of the incentive intervention for decreased or undetectable viral loads in promoting retention in HIV medical care. We will assess whether the participant attended at least 2 medical visits per year (Mugavaro et al. 2012; Y/N each year based on self-report and medical records).

Specific Aim. Assess the effectiveness of an empirically-based incentive intervention in promoting undetectable levels of viral loads, maintenance of antiretroviral prescriptions, consistent adherence to antiretroviral therapy, and retention in HIV care after the incentive intervention is discontinued. We will assess measures described above but at the two 6-month assessments during the year after the intervention ends.

Moderator Analysis Measures

Specific Aim. Determine if drug (cocaine or opiate) dependence, alcohol dependence, depression, health literacy, and impulsivity assessed at intake moderate viral load suppression and response to the incentive intervention. A dichotomous value (Y/N) for cocaine, opiate and alcohol dependence will be used as assessed by the CIDI. The total score on the TOFHLA will be used to assess health literacy. The total score on the Beck Depression Inventory will be used to assess depression. Log transformed k for each participant on the delay discounting task will be used to assess impulsivity.

Mediator Analysis Measures

Specific Aim. *Determine if antiretroviral medication adherence as assessed by qualitative HRMS blood tests of 15 antiretroviral medications mediates the effect of the incentive intervention on viral load suppression*. We will assess mediating effects of medication adherence as assessed by qualitative blood testing on viral load using the method of Baron and Kenny (1986) as described below.

Economic Outcome Measures

Specific Aim. Assess the costs of HIV medical care for Usual Care and Incentive groups. We will assess the total cost per participant of both study interventions including cost of the incentive program (see below). We expect that Incentive group costs will be higher relative to the Usual Care due to the incentive program and because we expect that the Incentive participants will have greater treatment engagement.

Specific Aim. Assess the cost-effectiveness of the empirically-based incentive intervention for undetectable viral loads. We will assess incremental cost-effectiveness ratio (ICER) by dividing the difference in costs of two interventions by the difference in effects of the two interventions during the 2-year intervention evaluation period on viral load suppression (see below). The ICER can be interpreted as dollars spent per unit of desired outcomes gained. The Incentive Intervention should yield a better ICER.

Specific Aim. Assess the cost-benefit of empirically-based incentive intervention for undetectable viral loads. We will perform a Cost-Benefit Analysis (CBA) to examine the monetized benefits relative to costs for the Usual Care Control and Incentive intervention conditions. The economic outcomes are health care utilization during the 2-year intervention evaluation period (see below). We expect that the Incentive Intervention will yield greater economic benefits relative to its costs than the Usual Care Control.

Measures assessed repeatedly over time will be analyzed with a longitudinal logistic regression model. Within-person correlated outcomes will be handled using generalized estimating equations (GEE; Zeger, Liang, & Albert, 1988). Measures assessed once will be analyzed using logistic regression. The magnitude of effects will be expressed using odds ratios with 95% CI. Intent-to-treat analyses will be adjusted for covariates used for stratification (Pocock et al., 2002). Two-sided tests with p-values <.05 will be considered significant.

b. Statistical plan including sample size justification and interim data analysis.

STATISTICAL ANALYSES

Measures assessed repeatedly over time will be analyzed with a longitudinal logistic regression model. Within-person correlated outcomes will be handled using generalized estimating equations (GEE; Zeger, Liang, & Albert, 1988). Measures assessed once will be analyzed using logistic regression. The magnitude of effects will be expressed using odds ratios with 95% CI. Intent-to-treat analyses will be adjusted for covariates used for stratification (Pocock et al., 2002). Two-sided tests with p-values <.05 will be considered significant.

Primary outcome analyses. We will fit a longitudinal logistic regression model logit $(Y_{ij}) = \beta_0 + \beta_1 tx + \beta_{2\text{-}6}x_{2\text{-}6} + \varepsilon_{ij}$, where Y_{ij} is the presence of a detectable viral load for the ith person at the jth timepoint (8 visits over two years of treatment), β_1 is the covariate of interest representing the expected decrease in log odds of a detectable viral load as a function of assignment to the treatment group, and $\beta_{2\text{-}6}$ are the coefficients for the 5 randomization covariates. Additional models with time and time by treatment interactions will be fit secondarily to assess time trends in treatment effect.

Secondary outcome analyses. We will fit analogous longitudinal logistic regression models for HRMS-verified ART adherence, self-reported adherence, prescription maintenance, and attendence at HIV medical care visits. We will assess post-treatment effects by fitting analogous models for each outcome, but using only data from the two post-treatment visits.

Moderator analyses. For the primary outcome, we will fit models with interactions between treatment and each of the 5 randomization covariates (drug dependence, alcohol dependence, TOFHLA total score, delay discounting, and Beck Depression score) to assess whether treatment effect varies as a function of the putative moderator. For example, for CIDI drug dependence, we would fit the model $\text{logit}(Y_{ij}) = \beta_0 + \beta_1 tx + \beta_{2\text{-}6}x_{2\text{-}6} + \beta_7 tx*\text{drug dependence} + \varepsilon ij$, where β_1 would represent the treatment effect (expressed as a difference in log odds of a detectable viral load between treatment and control groups) among individuals without drug dependence, and β_7 would represent the *difference* in treatment effect between individuals with and without drug dependence. All moderator analyses will be considered exploratory and will not be corrected for multiple comparisons. These variables will be examined as potential moderators because drug use (Mimiaga et al., 2013), health literacy (Kalichman et al., 2008),

and depression (Murphy et al. 2013) has each been associated with poor adherence to antiretroviral medications. Impulsivity will be assessed as a potential moderator because high levels of impulsivity have been associated with poor health decision making and adverse health behaviors (Axon et al., 2009; Bickel et al. 2014; Bradford et al., 2010).

Mediation analysis. We will assess potential mediating effects of medication adherence as assessed by qualitative blood testing on viral load using the method of Baron and Kenny (1986). Specifically, this involves estimation of (1) the effect of treatment assignment (incentives) on undetectable viral load without controlling for medication adherence, (2) the direct effect of incentives on medication adherence, and if these two steps yield clinically and statistically significant effects, 3) the effect of incentives on viral load after controlling for medication adherence (logit $(Y_{ij}) = \beta_0 + \beta_1 tx + \beta_{2\text{-}6} x_{2\text{-}6} + \beta_7 \text{adherence} + \varepsilon ij$). If medication adherence does mediate the effect of the incentives on presence of a detectable viral load, in this final model we would expect the effect of treatment (β_1) to be attenuated relative to the step 1 model, and for adherence (β_7) to be a clinically and statistically significant predictor of presence of a detectable viral load.

Missing data. We expect to collect ≥80% of 3-month assessments (see below). Our primary approach will be to impute all missing values as the adverse outcome (e.g., detectable viral load). Model parameter estimates from this approach will be compared to a method without imputation. If these methods yield differing results, conclusions will need to be tentative. To investigate sensitivity to missing values, participants with and without missing values will be compared by covariates and treatment assignment.

ECONOMIC ANALYSES

We will use the provider perspective using a modified SASCAP and the research team's financial records. Intervention activities will be captured with the modified Economic Form 90 AIR/ED.

Cost Analysis. We will derive cost estimates following an activity-based approach (Drummond et al., 2005; Gold et al., 1996; Zarkin, Dunlap et al., 2004; Zarkin et al. 2005 Zarkin, Dunlap, et al., 2008; Dunlap et al., 2010).The total cost per participant of each intervention (HIV health care costs and incentive/feedback program costs) will be the sum of the costs of (1) staff labor, (2) incentive payments; (3) medication; (4) building space, and (5) other supplies or materials. The labor costs of each activity are equal to the product of the amount of time spent by each person on the activity and their hourly wage. We will multiply the unit cost of other intervention resources with the quantity used per activity. The total intervention cost for each participant is the cost per activity multiplied by the number of activities received by the participant. The mean across patients in a given intervention condition yields the intervention's mean per participant cost.

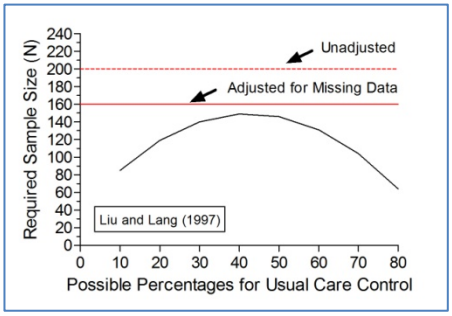
Cost-Effectiveness (CEA). Our CEA methodology follows a standard economic approach (Drummond et al., 2005; Dunlap, Zarkin, et al., 2010; Siegel et al., 1996; Zarkin et al., 1996, 1997, 2008). The primary cost-effectiveness outcomes will be the percentage of participants with undetected viral loads at 24 months (end of intervention) and at 36 months (post-intervention). The incremental cost-effectiveness ratio (ICER) is calculated by dividing the difference in costs of two alternatives by the difference in their effects of the two alternatives. The estimated ICER can be interpreted as dollars spent per unit of desired outcomes gained (e.g., $900 per percentage point increase in participants with undetected viral loads). To gauge the sampling uncertainty of the ICERs, we will calculate confidence intervals via nonparametric bootstrap methods (Indurkhya et al., 2001; Briggs et al., 2006). We will estimate cost-effectiveness acceptability curves (CEACs) using nonparametric bootstrap methods (Dunlap et al., 2008, 2010; Fenwick et al., 2001, 2006). The CEACs incorporate the inherent variability of the cost and effectiveness estimates and show the probability that a treatment is cost-effective as a function of the policy maker's intrinsic valuation or willingness to pay for the clinical outcome.

Cost-Benefit (CBA). We will examine the monetized health care benefits relative to costs for the two intervention conditions. Because previous studies have shown that health care costs can be much higher in individuals with higher viral loads (e.g., Chen et al., 2006; Gebo et al., 2010), primarily due to higher non-antiretroviral medications and hospitalizations, we will focus on assessing and monetizing the potential differences in health care utilization during the 2-year intervention period for the incentive condition group relative to the usual care group. Health care utilization will be collected using the modified Economic Form 90 AIR/ED. Unit costs used in monetizing these economic outcomes will be drawn from literature and public data.

Sensitivity Analysis. We will conduct sensitivity analyses to assess whether the economic results are affected by changes in model parameters, such as assumptions made in estimating costs. We will perform one-way sensitivity analyses and examine the effect of changing one of the model parameters holding all other parameters constant, as well as *n*-way sensitivity analyses in which *n* parameters of the model are varied jointly.

POWER ANALYSIS

The primary outcome measure of undetectable viral loads will be analyzed with a longitudinal logistic regression model using GEE (Diggle & Diggle, 2002). We used Liu and Liang (1997) to determine the total N required to detect a difference between groups with 80% power. The adjacent figure shows the total number of participants (N) required to detect a difference of 15% between the Usual Care Control and the Incentive Group at the eight 3-month assessments during the intervention evaluation period. The figure shows different percentages for the Usual Care Control group because that value affects the sample size required. 15% is smaller than the effects produced in all prior studies of voucher reinforcement of cocaine or opiate abstinence or medication adherence and smaller than all effects produced by the Therapeutic Workplace and smaller than the incentive effects in promoting drug abstinence, medication adherence and other health behaviors as shown in three different meta-analyses (Petry et al., 2012; Prendergast et al. 2006; Lussier et al., 2006). The horizontal red lines show the number of participants planned based on the number of participants enrolled and randomized to the two groups without (top dashed line) and after adjusting for the anticipated rates of missing data (20% missing, bottom solid red line). Based on this analysis, we need to enroll and randomize 200 participants (horizontal dashed line) to ensure that we have sufficient sample sizes after adjusting for the rates of missing data. After adjusting for missing data (20% missing), this would yield a sample size of 160 participants (200 participants x 0.80 collected samples = 160 participants). The adjusted sample size of 160 participants (solid red line) is a little more than the maximum number of participants that would required.



c. Early stopping rules.

The protocol can be stopped based on recommendations of the Scientific Advisory Committee overseeing this study. We will ask the Scientific Advisory Committee to recommend that the trial be stopped if a review of the adverse events suggests to any of the investigators that the number of related and unexpected adverse events is unacceptably high. The Scientific Advisory Committee will be allowed to request statistical analyses to compare the groups on the rates of different adverse events or to have the adverse event data summarized in other ways that they deem appropriate.

Risks

a. Medical risks, listing all procedures, their major and minor risks and expected frequency.

There is essentially no risk above those of normal daily living associated with the incentives, or with the data collection procedures used in these studies.

Blood samples will be collected from participants in the Incentive group. Those participants will provide a maximum of 1 blood sample per week. The samples will be tested for viral load and will involve collecting up to 10 cc of blood per sample. Participants in both groups will provide blood samples every 3 months for the primary and secondary outcome measures. Each of those samples (25 cc in total) will be tested for viral load (10 cc), for the presence of antiretroviral medications (5 cc), and for CD4 Counts (10 cc). Taking blood may cause some discomfort, bleeding or bruising where the needle enters the body, and in rare cases, it may result in fainting. There is a small risk of infection. When possible, we will use data available in each participant's medical records to get recent viral load and CD4 counts measures instead of collecting blood samples at each assessment time point.

b. Steps taken to minimize the risks.

To protect confidentiality, all research participants are identified by participant identification codes (Participant IDs) consisting of their initials and sequentially-assigned participant numbers on most forms and data files, and not by their names. Picture ID cards are maintained by staff in a locked container, and kept in a locked, secured area when not in use. All research data are stored in locked areas accessible only to research staff and are not left unattended. Documents with confidential information are shredded before being discarded. Confidential information is never given to anyone outside of the research program without the explicit written permission of the research participant. Only selected designated staff members are approved to give confidential information out after obtaining explicit written permission from the

participant. All research staff are trained in these procedures. We collect only general information about participant activities, legal and illegal. We do not collect information about specific illegal acts. To further protect confidentiality, we will obtain a confidentiality certificate from NIH to protect data collected in this study.

c. Plan for reporting unanticipated problems or study deviations.

Unanticipated problems or study deviations will be reported based on the guidelines of the Johns Hopkins University School of Medicine IRB.

d. Legal risks such as the risks that would be associated with breach of confidentiality.

There are risks that the confidential information we collect could be revealed to people not involved in the research such as a friend, relative, or an outside organization. This could be embarrassing to the participant if the participant wanted to keep participation in the study secret. The legal risks are limited because we collect only general information about participant activities, legal and illegal. We do not collect information about specific illegal acts. Thus, the risks associated with the assessments are not greater than the risks associated with routine psychological examinations or tests.

e. Financial risks to the participants.

There are no financial risks above those of normal daily living. Each participant is responsible for ensuring that the earnings are reported properly to relevant government or private agencies and for determining whether or not the earnings will affect any benefits they might receive from those agencies.

8. Benefits

a. Description of the probable benefits for the participant and for society.

Participants in the incentive group will receive incentives for maintaining undetectable viral loads. The incentive payments could substantially increase adherence to antiretroviral medications and thereby increase the percentage of patients that achieve undetectable viral loads. That could improve the long-term health of participants.

This novel incentive intervention being developed in this project could be an effective and economically sound means of promoting long-term adherence to antiretroviral medications and suppression of viral load in adults living with HIV. If the intervention is effective and economically sound, it could be used widely to promote suppression of viral load in adults living with HIV. The intervention could benefit those HIV-infected individuals by improving their long-term health. Importantly, if the incentive intervention is effective in suppressing viral load, it could dramatically reduce the transmission of HIV to others in the community.

9. Payment and Remuneration

a. Detail compensation for participants including possible total compensation, proposed bonus, and any proposed reductions or penalties for not completing the protocol.

At the start of each participant's enrollment in the study, each participant will be given a reloadable credit card. All payments will be made by adding the amount earned to the participant's reloadable credit card.

Incentives for taking and completing an education program on HIV medical care. Upon enrollment, participants will be taught about the benefits of HIV medical care, ART adherence and the need to maintain nearly perfect adherence. Participants will be able to earn up to about $100 for engaging in this education.

Incentives for viral suppression in the Incentive Group. The Incentive group will receive the novel empirically-based incentive intervention to promote long term suppression of HIV-1 RNA (viral load) being evaluated in this study. Throughout the intervention, participants will be able to earn up to $10 per day for providing blood samples that have undetectable viral loads (i.e., <200 copies/mL) or viral loads that have decreased by 0.15 log per week since the last viral load assessed..

Blood draws and the incentive program will not begin until the participant brings in an ART prescription bottle containing at least a 2-day supply of medication. The participant will be paid for the first

week ($70) if the participant brings his/her ART prescription bottle and if the bottle contains at least a 2-day supply of medication.

To ensure that Incentive participants do not wait to take their antiretroviral medications consistently in the month before a viral load test, viral load blood tests will be scheduled at random times throughout the 2-year intervention evaluation period. At each viral load blood test, if the participant provides a blood sample that meets the criteria for earning an incentive (i.e., an undetectable viral load or a decrease in viral load of 0.15 log per week since the last blood sample provided), the participant will earn an incentive equal to $10 per day for all the days since the last blood test. For example, if two weeks had passed since the last viral load test, the participant would earn $140 for providing a blood sample with an undetectable viral load ($10 per day X 14 days = $140). Initially, the viral load blood tests will occur once every week. The frequency of blood tests will be gradually decreased over time as described above until the average inter-test interval is 12 weeks. Each participant will call the Incentive Program every Monday to determine if they are scheduled to provide a blood sample that week. To ensure that participants call every week, participants will be paid $5 for each weekly call. If a blood sample is scheduled for that week, the participant will schedule a time for the collection within that week (Monday-Friday).

If a participant ever misses a scheduled blood sample collection or provides a blood test that does not meet the criteria for earning an incentive, the participant will not receive an incentive and both the schedule of viral load testing and the magnitude of incentives will change. The schedule will switch to the most frequent testing schedule that was employed at the beginning of treatment. The value of the incentive will be decreased from $10 per day to $3 per day for the next blood sample that meets the criteria for an incentive. Once the participant earns an incentive at the $3 per day rate, the incentive will increase to $6 per day. Once the participant earns an incentive at the $6 per day rate, the incentive will increase to $10 per day. Overall, participants will be able to earn up to $7,300 over the two years for maintaining suppressed viral load.

At the start of each participant's enrollment, each participant will be given a reloadable credit card. When the participant calls to get the results of a given viral load test, the Incentive staff will tell the participant the results. If the participant met the criterion for the incentive, the Incentive staff will tell the participant the amount of the incentive earned and add the incentive amount to the participant's reloadable credit card. This procedure will ensure that participants monitor the results of their viral load testing and know when, why and how much is added to their credit card. That card can then be used as a regular credit card to make purchases at most businesses. We currently use this reloadable credit card system in our Therapeutic Workplace incentive program, and it has proved very efficient and highly acceptable to participants.

Incentives for completing routine assessment s for both groups. Assessments will be conducted at intake to determine eligibility and characterize participants. Outcome assessments will be conducted at intake, every 3 months throughout the 2-year intervention evaluation and every 6 months of the 1-year follow-up period. Participants will be paid $30 for the intake assessment and $100 for each follow-up assessment. Participants will be paid $150 for a follow-up assessment if the participant has to go to two separate locations to complete the assessment.

Participant referral fees. As in our previous studies, participants will have the optional opportunity to earn incentives for referring people who are interested in the study. If a referral attends the initial screening appointment and completes the necessary assessments, the participant who referred the person will receive up to $20. If a referred person enrolls in the main study, the participant who referred the person will receive up to $40 for making the referral.

10. Costs

a. Detail costs of study procedure(s) or drug (s) or substance(s) to participants and identify who will pay for them.

There will be no costs to participants for any services or treatment provided in this study.