Insomnia in HIV: Studies I and II
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SCHEMA

OBJECTIVES

There are two primary objectives of this study. The first is to compare 10-week changes in Insomnia Severity Index (ISI) scores in HIV-infected adults with clinically relevant insomnia severity and who are already receiving virologically suppressive antiretroviral therapy (ART) and are then randomized to either treatment with the SHUTi cognitive behavioral therapy program or to Usual Care (UC). The second is to compare measures of frailty and cognitive function between HIV-infected, virologically suppressed adults with and without clinically relevant insomnia severity.

DESIGN

Our objectives will be met by performing two studies. The first is a 10-week, randomized, controlled, single-blinded, two-arm, parallel group, pilot trial at a single center and the second is a cross-sectional two-group comparative study.

Study I: A total of 40 persons with HIV may be screened and consented to identify the 32 participants to be enrolled and randomized into the pilot trial. We expect a screen failure rate of 20%. These participants will be ≥ 18 years old, have been receiving antiretroviral therapy with an HIV viral load < 75 copies/mL within three months of the Entry Visit, and have an ISI score ≥ 11 within three months of the Entry Visit. These participants will be randomized 1:1 (stratified by age <40 vs. ≥ 40 years) to either insomnia treatment with the SHUTi cognitive behavioral therapy program (N=16) or usual care (N=16).

Study II: The 32 participants with insomnia from Study I will then be compared to a similar group of 12 HIV-infected patients but with an ISI score < 11 within three months of the Entry Visit. Six will be <40 years old and the other six will be ≥ 40 years old). Approximately 15 persons with HIV may be screened and consented to identify this second group of 12 participants without insomnia. We expect a screen failure rate of 20%.

DURATION

Each individual participant in Study I will be followed for approximately 10 weeks. Those enrolled specifically into Study II will have a single one-day study visit.

POPULATION

All participants will be HIV-infected, 18 years of age or older, will have received stable ART for at least 3 months, will have a HIV viral load of less than 75 as per a measurement that was obtained as a part of standard clinical care, and have this load measured within 90 days of study entry. Participants will be recruited from the infectious diseases outpatient clinics of Eskenazi Health Hospital and the Indiana University Health Hospitals.

1.0 STUDY OBJECTIVES

1.1 Study I Primary Objective

1.1.1 To compare 10-week changes in ISI scores between those undergoing insomnia treatment using the SHUTi cognitive behavioral therapy program vs those receiving Usual Care (UC).

1.2 Study I Secondary Objectives

1.2.1 To compare 10-week changes in Pittsburgh Sleep Quality Index (PSQI) scores and brief sleep diaries between those undergoing insomnia treatment using the SHUTi cognitive behavioral therapy program vs those receiving Usual Care (UC).

1.2.2 To compare 10-week changes in PHQ-9, SF-36, and WHOQOL-HIV Brief scores between those undergoing insomnia treatment using the SHUTi cognitive behavioral therapy program vs those receiving Usual Care (UC).

1.3 Study II Primary Objectives

1.3.1 To compare FRAIL scale, Fried Index, and SPPB scores between those with ISI scores ≥ 11 and those with ISI < 11.

1.3.2 To compare CSRQ-25 and Digit Symbol Substitution Test (DSST) scores between those with ISI scores ≥ 11 and those with ISI < 11.

1.4 Study II Secondary Objectives

1.4.1 To correlate ISI scores with each of the following: PSQI, PHQ-9, SF-36, WHOQOL-HIV Brief, FRAIL scale, Fried Index, SPPB, CSRQ-25, and DSST.

2.0 HYPOTHESES, BACKGROUND, AND INTRODUCTION

2.1 Hypotheses

2.1.1 Treatment with SHUTi will reduce ISI, PSQI, PHQ-9, SF-36, and WHOQOL-HIV Brief scores at 10 weeks when compared to UC.

2.1.2 HIV-infected patients with ISI scores ≥ 11 will have higher FRAIL scale, Fried Index, and SPPB scores and lower CSRQ-25 and DSST scores compared to those with ISI scores < 11.

2.2 Background

Insufficient sleep is a highly prevalent and harmful health behavior that contributes to poor mental and physical health outcomes (1). Here, insufficient sleep is defined as the presence of insomnia – frequent and persistent difficulty in initiating or maintaining sleep causing functional impairment or distress (2-4). A 2006 Institute of Medicine report (5) stated that "the cumulative effects of sleep loss and sleep disorders represent an under-recognized public health problem and have been associated with a wide range of health consequences."

Therefore, promoting *sufficient sleep*, a positive health behavior, may alter the adverse mental and physical health aging trajectories of vulnerable adults.

In the general population, insomnia has been linked to a higher risk for the development of several comorbid conditions, including cardiovascular disease (CVD) (6), frailty (7), cognitive impairment (8, 9), and depression (10). Plausible underlying mechanisms for the relationship between insomnia and cardiovascular disease include biological factors (systemic inflammation, altered coagulation, autonomic dysfunction), behavioral factors (smoking, excessive alcohol use, physical inactivity), and traditional CVD risk factors (obesity, diabetes, hypertension) (11). Insomnia may lead to frailty through its potential to lead to cardiovascular and cerebrovascular disease, impaired physical functioning, and reduced daytime physical and social stimulation (7). Insomnia may impair cognitive function by preventing normative CNS repair functions that occur during nocturnal sleep or by reducing daytime intellectually stimulating activities (9).

While it is not uncommon for insomnia to be conceptualized as a depressive symptom in clinical settings, current diagnostic manuals (e.g., DSM-5) assert that insomnia is not simply a symptom of other conditions and exists as a clinical problem warranting attention as an independent diagnosis – regardless of medical and psychiatric co-morbidities, including depression (12, 13). Moreover, research examining the directionality between insomnia and depression consistently finds that, insomnia increases the risk of future depression (14, 15) and less consistently finds that depression increases the risk of future insomnia (16-20). This suggests that insomnia manifests independently of depression and likely precedes, rather than follows, depression onset.

HIV infection is itself associated with an increased prevalence of insomnia (21), as well as increased risks for cardiovascular disease (22), frailty (21, 23), cognitive impairment (24), and depression (25). Thus, it is possible that the detrimental effects of insomnia on these comorbid complications may be particularly problematic in those with HIV. However, it is not known if treating insomnia would reduce the risk of developing these comorbid conditions in the HIV-infected population.

The American College of Physicians has stated that the preferred treatment for chronic insomnia in adults is not pharmacologic therapy but rather cognitive behavioral therapy for insomnia (CBT-I) due to its more significant results in terms of both efficacy and longevity of response (26). In addition, CBT-I is not associated with adverse effects that may complicate therapy with sleep medications (e.g. abuse potential, cognitive impairment, drug interactions with HIV antiretrovirals, accidents). However, providing CBT-I has proven difficult in environments where there are insufficiently trained providers. In addition, patients may not be able to attend dedicated sessions with a CBT-I therapist due to financial or time restraints. To address these issues, an evidence-based, cognitive-behavioral, online intervention for insomnia called Sleep Healthy Using The Internet (SHUTi) was developed by our colleague and consultant, Dr. Lee Ritterband. SHUTi is based on a well-established face-to-face CBT-I (27, 28) and incorporates sleep restriction, stimulus control, sleep hygiene, cognitive restructuring, and relapse prevention. A comparison of CBT-I to insomnia medications revealed that patients receiving CBT-I have similar short-term and better long-term outcomes (29). There is also a preference for and greater acceptance of CBT-I (30). Each SHUTi session has the same structure: the main content, a homework screen with options, and a summary of the main points. The Internet requirements are minimal (SHUTi can run on a dial-up connection). Although SHUTi has proven quite successful in treating insomnia in the general population, *this intervention has not been tested specifically in an HIV-infected population for whom there are unique characteristics and stressors that may influence the response to this intervention.* For example, the previous studies using SHUTi involved primarily white, educationally-advantaged persons as opposed to our local HIV patient population that is majority black and from lower socioeconomic status (SES) backgrounds with a chronic, stigmatizing disease.

2.3 Study Rationale

Our long-term goal is to use SHUTi as an intervention to treat insomnia in patients with HIV infection in order to improve long-term outcomes (including reducing the risk of cardiovascular disease, frailty, cognitive

functioning, and depression) and quality of life. Our group has extensive experience in cardiovascular disease prevention research (e.g. our currently NIH-funded R01 trial of internet-based CBT depression therapy in HIV to reduce inflammation and improve endothelial function), but we also want to develop research expertise in HIV-related frailty and cognitive impairment, as these are increasingly important outcomes (and areas of interest to the NIH) in the aging HIV population.

There are several R01-level NIH funding mechanisms focused on cardiovascular disease, frailty, cognitive impairment, and depression in HIV (PA-16-427, PAR-17-321). We believe that treating insomnia in HIV is a unique method by which to improve all of these endpoints. But to be competitive for these funding opportunities, we will first need to develop preliminary data showing that SHUTi can be effective both in our hands and in our target population. Of note, we already have preliminary cross-sectional data demonstrating an inverse relationship between more severe insomnia symptoms using the PSQI scale and lower endothelial function (as measured by flow-mediated dilation of the brachial artery in Dr. Gupta's CTSI Vascular Imaging Core) in HIV-infected patients on virologically-suppressive antiretroviral therapy (ART). *However, we need to develop additional preliminary data in a similar group of HIV-infected patients that relate insomnia measures to frailty and cognitive impairment, as these are new areas of research for our group.* If we can demonstrate that insomnia is negatively related to frailty and cognitive impairment in HIV and that SHUTi improves sleep outcomes in this population, then we can more readily justify randomized trials of SHUTi to improve these measures in HIV and thus be more competitive for extramural funding.

3.0 STUDY DESIGN

3.1 Overview

Our objectives will be met by performing two studies. The first is a 10-week, randomized, controlled, single-blinded, two-arm, parallel group, pilot trial at a single center and the second is a cross-sectional two-group comparative study.

Study I: A total of 40 persons with HIV may be screened and consented to identify the 32 participants to be enrolled and randomized into the pilot trial. These participants will be ≥ 18 years old, have been receiving antiretroviral therapy for at least three months with an HIV viral load < 75 copies/mL, and have an ISI score ≥ 11. These participants will be randomized 1:1 (stratified by age <40 vs. ≥ 40 years) to either insomnia treatment with the SHUTi cognitive behavioral therapy program (N=16) or usual care (N=16).

Study II: The 32 participants with insomnia from Study 1 will then be compared to a similar group of 12 HIV-infected patients but with an ISI score < 11. Six will be <40 years old and the other six will be ≥ 40 years old). Approximately 15 persons with HIV may be screened to identify this second group of 12 participants without insomnia.

3.2 Eligibility Assessment

We will screen for insomnia using two methods. First, we currently screen for insomnia in the Eskenazi HIV clinics using the Insomnia Severity Index (ISI). As such, we will use these results to determine eligibility of these patients for either Study I or Study II. Patients will be asked in the clinic by our screeners if they wish to be contacted by our study personnel for study participation. If so, these patients will be referred to the study team. The patients' medical records will be reviewed so to determine their true eligibility. If found eligible for either Study I or Study II, then will then be contacted to schedule their Entry Visit. Second, we will do phone screening for insomnia using the ISI questionnaire for patients who either self-refer to Study I or who are referred by their HIV provider for Study I but who have not undergone in-person ISI screening in the clinics.

3.3 Study I Randomization

For those patients eligible for the pilot trial in Study I, they will be randomized at their Entry Visit. Randomization will be stratified by age (<40 years and ≥ 40 years). The randomization sequence will be placed in opaque envelopes that will only be opened and witnessed at the Entry Visit.

3.4 Entry Visit for both Study I and Study II

The Entry Visit will occur within 60 days of the routine clinic or phone ISI screening and HIV-1 RNA (viral load) testing that prompted referral to this study. This visit will occur at the Infectious Diseases Research Clinic located at the Fifth Third Office Building on the Eskenazi Hospital campus. After written, informed consent is provided by the participant, a random study code number will be assigned to the participant to ensure confidentiality. This study code number will be used for result reporting and data recording.

At this visit, medical records and current medications will be reviewed. Height, weight, and vital signs will be measured. All participants (both Study I and Study II) will complete the following surveys: ISI, PSQI, Generalized Anxiety Disorder-7 (GAD-7), PANAS (PANAS PA), SF-36, WHOQOL-HIV BREF, and CSRQ-25. All participants will begin the baseline sleep diary entries the night of the Entry Visit, which will be collected verbally over the phone 3 days later. In addition, information on alcohol use, tobacco use, and substance use will be solicited. These questionnaires will be administered in private with availability of the study team to assist only when asked by the participant. The participant may refuse to complete any of the questionnaires.

The participant will then perform the Digit Symbol Substitution Test, the FRAIL Index, and the Fried Index studies.

After these procedures are completed, participants in Study I will be randomized to either the SHUTi intervention or to Usual Care. For participants in Study II, study participation will be considered completed with no further follow-up.

Of note, study participants do not need to be fasting or refrain from smoking for any study visits in this protocol.

Participants who exhibit elevated depressive symptoms (PHQ-9 ≥ 10) at the final study visit will be urged to follow-up with their primary HIV provider and/or clinical social worker regarding their depression. In addition, the study team will notify the primary HIV provider that his/her patient has completed participation in our trial and still has clinically elevated depressive symptoms. A list of local mental health service providers and clinics will be given to the patients' primary HIV providers or social workers.

3.4 SHUTi Treatment Sessions and Usual Care

3.4.1 SHUTi

SHUTi (www.myshuti.com) is an evidence-based, cognitive-behavioral, online intervention for insomnia developed by our colleague and consultant, Dr. Lee Ritterband (31). It is based on a well-established face-to-face CBT-I (27, 28). SHUTi consists of six, 40-minute, weekly sessions during which the intervention components of stimulus control, sleep restriction, sleep hygiene, cognitive restructuring, and relapse prevention are delivered. Each SHUTi session has the same structure: the main content, a homework screen with options, and a summary of the main points. The internet requirements are minimal, as SHUTi can run on a dial-up connection. The SHUTi program is currently being used in both research and clinical settings.

To minimize treatment barriers, attrition, and subject burden, the SHUTi treatment sessions will occur in private at Dr. Stewart's laboratory, the Infectious Diseases Research Clinic at Eskenazi Health Hospital, or a

location selected by the patient where s/he can access a computer with internet, such as the patient's home, the patient's work, a family member's/friend's home, or a public library. The location will be chosen by the participant. To help maintain privacy, patients will be provided with ear bud headphones if they plan to complete SHUTi sessions at remote locations and do not already own a pair of headphones that they would rather use. We will also tell patients that, if they choose to complete SHUTi session where others are present, these other people (e.g., family member or friend) may realize that they are completing a treatment for insomnia. It will be up to each patient to decide if the available remote locations provide sufficient privacy. Up to 6 sessions will be performed between the Entry Visit and the Week 10 Visit. No physiologic or biologic assessments will be performed during these sessions. The participants need not be fasting for these sessions.

At each in-person SHUTi session, a research assistant trained in the use of this intervention will first collect homework and will start the appropriate session on a computer. The patient will then work through the session alone at his/her own pace. At the end of the session, the research assistant will give the patient the printed homework assignment and will schedule the next session.

Remote SHUTi sessions will be scheduled just like in-person sessions. Patients who select the remote treatment option will complete the first SHUTi session in person, at which time they will be given a SHUTi binder with printouts of all future homeworks. To begin each remote SHUTi session, an assistant will call the patient to instruct the patient to put last week's homework in the SHUTi binder, to address any technical issues, and to ensure that the patient has launched the correct SHUTi session for that day. The patient will then work alone through the SHUTi session at his/her own pace, with the assistant monitoring progress remotely on the secure SHUTi website set up for this trial. To end the session, the assistant will call the patient back to address any questions and ensure that the patient has identified the correct printed homework in the SHUTi binder.

Information is collected by the SHUTi program while it is being used by participants, which the program requires to tailor interventions to each participant's particular sleep problem. Of note, participants in our trial will not enter any identifying information into the SHUTi program. Instead, they will only enter information related to their current sleep problem (sleep diary, insomnia symptoms, and treatment goals) and will only be identified by a unique study ID number and a password provided by our team. Thus, the data entered into SHUTi will remain anonymous. The key linking participant names with their SHUTi login information will be kept in a separate secure and locked file cabinet. All data collected through SHUTi will be saved on password-protected computers and secure severs.

3.4.2 Usual Care

Patients randomized to the Usual Care group will be encouraged to follow-up with their primary care or HIV provider. There will be no formal interaction with the participants between the Entry Visit and the Week 10 Visit. However, the participants will be encouraged to contact the study team for any changes in their condition. There will be no restrictions on the care that can be received, although we will assess changes in care during the trial.

3.5 Week 10 Visit for Study I

The participant will come back to the Infectious Diseases Research Clinic for the Week 10 Study Visit. This visit will be scheduled between 63 and 84 days after the Entry Visit. The participant does not need to be fasting nor refrain from smoking at this study visit.

Weight and vital signs will be measured again. Participants will complete again the following surveys: ISI, PSQI, GAD-7, PANAS, SF-36, WHOQOL-HIV BREF, and CSRQ-25. Participants will begin the follow-up sleep diary entries the night of the 10 Week Visit, which will be collected verbally over the phone 3 days later. Questionnaires asking about personal alcohol, tobacco, and substance use will also be administered. These questionnaires will be administered in private with availability of the study team to assist only when asked by the participant. The participant may refuse to complete any of the questionnaires.

The frailty and cognitive function tests performed at the Entry Visit will not be repeated at the Week 10 Visit.

Participants who exhibit elevated depressive symptoms (PHQ-9 ≥ 10) at this final study visit will be urged to follow-up with their primary HIV provider and/or clinical social worker regarding their depression. In addition, the study team will notify the primary HIV provider that his/her patient has completed participation in our trial and still has clinically elevated depressive symptoms. A list of local mental health service providers and clinics will be given to the patients' primary HIV providers or social workers.

3.6 Study Duration and Participant Retention

The maximum study period for each Study I participant will be preferably 10 weeks but at most 12 weeks (if the participant requires extra time to schedule the Week 24 visit). In order to promote retention in the study, the participant participants will be financially compensated at each visit.

4.0 SELECTION AND ENROLLMENT CRITERIA FOR BOTH STUDY I AND STUDY II

4.1 Inclusion Criteria

4.1.1 HIV-1 infection, documented by both: (1) any licensed rapid HIV test or HIV enzyme test kit at any time prior to study entry and (2) by at least one detectable HIV-1 antigen or at least one detectable plasma HIV-1 RNA viral load.

4.1.2 Age equal to or greater than 18 years.

4.1.3 Ongoing receipt of stable antiretroviral therapy of any kind for at least 3 months prior to the Entry Visit.

4.1.4 HIV-1 RNA level < 75 copies/mL obtained during routine clinical care within 90 days of the Entry Visit.

NOTE: There are no CD4 cell count eligibility criteria for this trial.

4.1.5 ISI score ≥ 11 for Study I and ISI score < 11 for Study II

4.2 Exclusion Criteria

4.2.1 Inability to complete written, informed consent.

4.2.2 Incarceration at the time of any study visit.

4.2.3 Active suicidality, as determined by the patient's HIV provider or social worker following a positive response (1, 2, or 3) to PHQ-9 Item #9 and a positive response (yes) to one or more of the three questions (for Question #3, the previous attempt must be within the past 10 years) on the Patient Suicidality Form (see Appendix).

4.2.4 Diagnosed vascular disease (documented history of angina pectoris, coronary disease, peripheral vascular disease, cerebrovascular disease, aortic aneurysm, or otherwise known atherosclerotic disease).

4.2.5 History of congestive heart failure, even if currently compensated.

4.2.6 Diagnosed disease or process, besides HIV infection, associated with increased systemic inflammation (including, but not limited to, systemic lupus erythematosis, inflammatory bowel diseases, other collagen vascular diseases).

Note: Hepatitis B or C co-infections are NOT exclusionary

4.2.7 Known or suspected malignancy requiring systemic treatment within 180 days of the Entry Visit.

NOTE: Localized treatment for skin cancers is not exclusionary.

4.2.8 Therapy for serious medical illnesses within 14 days prior to screening.

Note: Therapy for serious medical illnesses that overlaps with a main study visit will result in postponement of that study visit until the course of therapy is completed; postponement outside of the allowed study visit timeframe will result in study discontinuation.

4.2.9 Pregnancy or breastfeeding during the course of the study.

4.2.10 Receipt of investigational agents, cytotoxic chemotherapy, systemic glucocorticoids (of any dose), or anabolic steroids at the Entry Visit.

Note: Physiologic testosterone replacement therapy or topical steroids is not exclusionary. Inhaled/nasal steroids are not exclusionary as long as the participant is not also receiving HIV protease inhibitors.

4.2.11 Active drug use or dependence that, in the opinion of the investigator, would interfere with adherence to study requirements.

4.2.12 History of schizophrenia, bipolar disorder, or dementia.

NOTE: Depression is not exclusionary as long as the severity of depression does not impede ability to perform the required study procedures.

4.2.13 Musculoskeletal or neurologic disorders that impede ability to perform the required study procedures.

4.2.14 History of sleep apnea or restless leg syndrome.

If participants are excluded due to the above criteria, they may be approached again in the future or have their study visit rescheduled within the allowable timeframe if these criteria are no longer applicable.

5.0 STUDY TREATMENT

5.1 SHUTi

To minimize treatment barriers, attrition, and subject burden, the SHUTi treatment sessions will occur in private at Dr. Stewart's laboratory, the ICRC, the Infectious Diseases Research Clinic at Eskenazi Health Hospital, or a remote location selected by the patient where s/he can access a computer with internet, such as the patient's home, the patient's work, a family member's/friend's home, or a public library. The location will be chosen by the participant. Patients will be provided with ear bud headphones if they plan to use them at remote locations and do not already own a pair of headphones that they would rather use. Up to 6 sessions will be performed between the Entry Visit and the Week 10 Visit. No physiologic or biologic assessments will be performed during these sessions. The participants need not be fasting for these sessions.

At each in-person SHUTi session, a psychology research assistant trained in the use of this intervention will first collect homework and will start the appropriate session on a computer. The patient will then work through the session alone at his/her own pace. At the end of the session, the research assistant will give the patient the printed homework assignment and will schedule the next session.

Remote SHUTi sessions will scheduled, just like in-person sessions. Patients who select the remote treatment option will be given a SHUTi binder with printouts of all future homeworks at the time of randomization at the Entry Visit. To begin each remote SHUTi session, an assistant will call the patient to instruct the patient to put last week's homework in the SHUTi binder, to address any technical issues, and to ensure that the patient has launched the correct SHUTi session for that day. The patient will then work alone through the SHUTi session at his/her own pace, with the assistant monitoring progress remotely on the secure SHUTi website set up for this trial. To end the session, the assistant will call the patient back to address any questions and ensure that the patient has identified the correct printed homework in the SHUTi binder.

5.2 Prohibited Medications

- Investigational agents
- Cytotoxic chemotherapy
- Systemic glucocorticoids (topical steroids are allowed; inhaled/nasal steroids are allowed only if the participant is not also receiving HIV protease inhibitors)
- Anabolic steroids (physiologic testosterone replacement therapy is not exclusionary)

6.0 CLINICAL EVALUATIONS

6.1 Schedule of Events

Evaluation	Entry Visit for both Study I and Study II (within 90 days of last clinic-based ISI screening and HIV-1 RNA level assessment)	Weekly SHUTi Sessions for the intervention group in Study I (6 sessions in total)	Week 10 Visit for Study I (for both groups; 63-84 days after Entry Visit)
Informed Consent	X		
Documentation of HIV Status	X		
Medical/Psychiatric History	X		
Medication/Supplement Use History	X		
Diagnoses	X		X
Updated Psychiatric Treatment History			X
Updated Medications			X
Updated Diagnoses			X
Height	X		
Weight	X		X
Vital Signs	X		X
Laboratories obtained through routine clinical care	X		
Questionnaires: ISI, PSQI, PHQ-9, SF-36, WHOQOL-HIV, CSRQ-25, GAD-7, PANAS	X		X
Sleep History and Beliefs Survey (PRE-Treatment)	X		
Sleep History and Beliefs Survey (Post-Treatment)			X
Sleep Diary*	X*		X*
Alcohol, tobacco, substance use questionnaires	X		X
FRAIL Scale (frailty assessment)	X		
Fried Index (frailty assessment)	X		
SPPB Physical Functioning Assessment	X		
DSST Dementia Assessment	X		
Randomization for Study I participants	X		
SHUTi Intervention		X	

*The study team will call the participant 3 days after the Entry Visit to verbally collect the participants first sleep diary. The study team will again call the participant 3 days after the Week 10 Visit to collect the second sleep diary.

6.2 Definitions for Schedule of Events – Special Instructions and Definitions of Evaluations

6.2.1 Documentation of HIV-1 Infection

HIV-1 infection documentation must be present in the source documentation at the Entry Visit. HIV-1 infection, documented by both: (1) any licensed rapid HIV test or HIV enzyme test kit at any time prior to study entry and (2) by at least one detectable HIV-1 antigen or at least one detectable plasma HIV-1 RNA viral load.

6.2.2 Medical/Psychiatric History

A medical/psychiatric history must be present in the source documents. Record the following on CRFs at either the Screening Visit:

- Birthdate
- Sex
- Patient's self-report of ethnicity (Hispanic vs. Non-Hispanic) and race (White, Black, Asian, Native American, Pacific Islander)
- Initial date of HIV infection documentation
- Route of HIV infection (heterosexual contact, same sex contact, injection drug use, blood transfusion)
- Diagnoses (all medical and psychiatric)

6.2.3 Medication/Supplement Use and Psychiatric Treatment History

A medication history must be present in source documents. The following information will be recorded on the CRFs at the Screening Visit:

- Start dates of current antiretroviral treatments
- Start dates of current insomnia and antidepressant treatments
- Any other prescription medications within 30 days of Entry Visit
- Any supplements (non-prescription) used within 30 days of Entry Visit
- Previous psychiatric cognitive behavioral therapy treatments within one year of screening

6.2.4 Diagnoses/Updated Diagnoses

All confirmed and probable new diagnoses will be recorded on the CRFs, including current status at the time of the study visit.

6.2.5 Updated Medications

All new and/or discontinued prescription medications (including insomnia and antidepressant medications) taken since the Entry Visit will be recorded on CRFs with start and stop dates.

6.2.6 Clinical Assessments

6.2.6.1 Height

Height will be recorded on CRFs at the Entry Visit

6.2.6.2 Weight

Weight will be recorded on CRFs at both Entry and the Week 10 Visit.

6.2.6.3 Resting Blood Pressure

Blood pressure measurements will be recorded on the CRFs at Entry and the Week 10 Visit. Blood pressure measurements should be performed on the same arm throughout the study. The participant should first sit quietly for five minutes. With the elbow and forearm resting comfortably on a flat table, the blood pressure should then be measured. After two minutes, repeat blood pressure measurement in the same arm. After another two minutes, repeat blood pressure measurements again. Therefore, three blood pressure measurements are to be documented in the CRFs.

6.2.6.4 Resting Heart rate

Resting heart rate measurements will be recorded on the CRFs at the Entry Visit and Week 10 Visit. This may be done prior to the first blood pressure measurement. The participant should first sit quietly for five minutes prior to measurement of heart rate.

6.2.6.5 Laboratories obtained through routine clinical care

No laboratories will be obtained as part of this study. Rather, the most recent laboratories obtained as part of clinical care will be abstracted and recorded on CRFs. These include most recently obtained CD4 cell count (absolute count and percentage), HIV-1 RNA level, hepatitis C antibody status (positive, negative), hemoglobin, glucose, albumin, creatinine, and estimated GFR (per CKD-EPI equation). The most recent HIV-1 RNA level must have been obtained within 90 days prior to the Entry Visit.

6.2.6.6 Questionnaires

The ISI, PSQI, PHQ-9, SF-36, WHOQOL-HIV, PANAS, GAD-7, CSRQ-25, alcohol, tobacco, and substance use questionnaires (see Appendices) will be completed using online versions at both Study Visits in a quiet, private environment and assisted as needed by a trained member of the study team.

6.2.6.7 Sleep History and Belief Surveys

More detailed histories of the participants' sleep histories and their beliefs about their sleep habits will be obtained using these Surveys. The PRE-Treatment Survey will be used for participants in both Studies I and II; the POST-Treatment Survey will be used only for those enrolled into Study I at the Week 10 Visit.

6.2.6.8 Sleep Diary

A 3-night SHUTi self-reported sleep record diary will be used to provide descriptive information regarding sleep patterns, sleep latency, sleep duration, and sleep disturbances. One diary will be provided at the Entry Visit for all participants in both Study I and Study II and completed for the next 3 days/nights. The study team will call the patient and verbally receive the sleep diary results. For those in Study I, a second diary will be completed for the 3 days/nights after the Week 10 Visit. The study team will again the patient and verbally receive the sleep diary results.

6.2.6.9 Fatigue, Resistance, Ambulation, Illnesses, & Loss of Weight (FRAIL) Scale

The FRAIL Scale is a screening test to assess frailty that predicts development of disability, decline in health functioning, and overall mortality (32). Frail scale scores range from 0–5 (i.e., 1 point for each component; 0=best to 5=worst) and represent frail (3–5), pre-frail (1–2), and robust (0) health status. The components and scoring of the FRAIL scale are as follows:

- Fatigue: "How much of the time during the past 4 weeks did you feel tired?" 1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time. Responses of "1" or "2" are scored as 1 and all others as 0.
- Resistance: "By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?" 1 = Yes, 0 = No.
- Ambulation: By yourself and not using aids, do you have any difficulty walking several hundred yards?" 1 = Yes, 0 = No.
- Illnesses: For 11 illnesses, participants are asked, "Did a doctor ever tell you that you have [illness]?" 1 = Yes, 0 = No. The total illnesses (0–11) are recoded as 0–4 = 0 and 5–11 = 1. The illnesses include hypertension, diabetes, cancer (other than a minor skin cancer), chronic lung disease, heart attack, congestive heart failure, angina, asthma, arthritis, stroke, and kidney disease.
- Loss of weight: "How much do you weigh with your clothes on but without shoes? [current weight]" "One year ago in (MO, YR), how much did you weigh without your shoes and with your clothes on? [weight 1 year ago]" Percent weight change is computed as: [[weight 1 year ago - current weight]/weight 1 year ago]] * 100. Percent change > 5 (representing a 5% loss of weight) is scored as 1 and < 5 as 0.

The FRAIL scale will be assessed only at the Entry Visit.

6.2.5.10 Fried Index

The Fried Index is a measure of frailty (33). It is composed of 5 criteria:

- Self-reported unintentional weight loss of ≥ 10 pounds or 5% in the prior year (should be verified with medical records if possible)
- Reduced grip strength (<23 lbs. for women, <32 lbs. for men as measured in the dominant hand using a dynamometer; this is averaged over 3 assessments)
- Self-reported exhaustion (person states they are exhausted 3 or more days per week; exhaustion is feeling "everything I do is an effort" or "sometimes I just cannot get going")
- Reduced gait speed (>0.8 m/sec over 4 meters; this is averaged over 2 assessments)
- Self-reported low physical activity (being "limited a lot" in vigorous activities from the SF-36 form)

One point is given to each positive criterion with zero points indicating no frailty, 1-2 points indicating pre-frailty, and 3-5 points indicating frailty.

The Fried Index will be assessed only at the Entry Visit.

6.2.5.11 Short Physical Performance Battery (SPPB)

The SPPB assesses physical functioning and includes standing balance (3 stances), walking speed, and sit-to-stand test time. Each task is rated from zero (indicating inability to complete the task) to four points (indicating best performance) based on established criteria (33), and results from the 3 tasks are summed. Standing balance is measured by a hierarchical performance scale based on side-by-side stance, "semi-tandem" stance (heel to 1st MTP joint), and full tandem (heel to toe), with each stance being held up to for ten seconds. Walking speed is measured in m/sec based on the faster of two 4-m walks at usual pace. Sit-to-stand test time is assessed by the time required to perform five uninterrupted repetitions of sit-to-stand using a firm chair and without use of the arms. An SPPB score of less than 9 is highly predictive for subsequent disability and is considered low function, 9–11 points moderate function, and 12 points (no deficits) high function. A standardized scoring sheet (see Appendices) will be used for this assessment.

The SPPB will only be assessed at the Entry Visit.

6.2.5.12 Digit Symbol Substitution Test (DSST)

The DSST is a sensitive measure of dementia. The DDST requires that the participant fill in a series of symbols correctly coded within 90 seconds. The higher the score, the better the performance. This test requires a pencil with eraser, stop watch, DSS task sheet, and scoring template (see Appendices). The test will be administered in a quiet environment at a desk or table.

The DSST will only be administered at the Entry Visit.

7.0 ADVERSE EVENT MANAGEMENT

Although not an inherent risk of the study intervention or study procedures, participants for this study may have depression as determined through completion of the PHQ-9 questionnaire. As such, these participants may have suicidal ideation at screening or develop suicidal ideation during the course of the study. We have already put into place a protection protocol for just this event in our ongoing studies in HIV-infected and HIV-uninfected depressed patients (please see Appendix at end of this protocol). If a participant reports having thoughts of being better off dead or of hurting him/herself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation), the visit will be immediately stopped, and the research assistant will interview the participant to complete the Patient Suicidality Form (see Appendix). If the participant answers "no" to all three suicide questions or if the patient answers "yes" only to Question 3 (previous attempt) and the most recent attempt was ≥ 10 years ago, the visit will proceed as normal, and the completed Patient Suicidality Form will be given to the principal investigator.

If the participant answers "yes" to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), the research assistant will immediately contact the principal investigators. Dr. Stewart (a clinical psychologist) and Dr. Gupta (a physician) will review the case as soon as possible, but no later than the same day, to determine the appropriate course of action (e.g., immediately contact the patient's primary care provider, primary HIV provider, clinical social worker, or care coordinator, consult with clinicians at Midtown Community Mental Health Center, and/or escort the patient to the Crisis Intervention Unit at Eskenazi Health). Additional authorities, including the police, may be contacted if immediate harm is of concern. Participants may be withdrawn from the study.

A direct correspondence by phone call and letter (both an email and a hard copy version), will also be sent to the potential participant's primary provider notifying him/her of the situation (see below).

If an enrolled participant reports having thoughts of being better off dead or of hurting him/herself during any telephone calls (e.g., a scheduling call or a call to the study team initiated by the participant), the exact same procedures as outlined above will immediately be initiated. Please see the Appendix for the full Suicide Management Plan.

Since it is unknown if depression therapy (or lack thereof) results in somatic adverse events in antiretroviral-treated HIV-infected patients, we will also carefully document Grade 3 or 4 level toxicities defined using the Division of AIDS Table for Grading Adult Adverse Experiences. Clinical management decisions and decisions to discontinue participants from the trial will be made by the principal investigator(s) in conjunction with the participant's primary caregiver; care plans and outcomes must be included in the source documentation.

All serious adverse events (SAEs) will be documented on CRFs with unexpected SAEs forwarded to the IUPUI IRB within 10 working days of the event and the remainder to be documented on the annual continuing review.

8.0 CRITERIA FOR STUDY DISCONTINUATION

- Request by the participant to withdraw
- Request of the primary care provider if s/he believes the study is no longer in the best interest of the participant
- If the participant is found to be pregnant or begins breastfeeding during the course of this study
- If the participant has develops fever, need for systemic therapy for acute or serious illness, or hypotension after screening that precludes completion of the study visits within the allowed timeframes
- Requirement for prohibited concomitant medication(s)
- Clinical reasons believed life threatening by the physician
- Participant, as judged by the investigators, to be at risk of failing to comply with the provisions of the study protocol as to cause harm to self or interfere with the validity of the study results

9.0 STATISTICAL CONSIDERATIONS AND DATA MANAGEMENT

9.1 General Considerations

Data management and statistical analyses will be the responsibility of the study team. The randomization sequence, though, will be generated by a member of the Department of Biostatistics. Parameter estimates and relevant summary statistics will be reported for both efficacy and side effects. Continuous variables will be summarized by means, medians, minima, maxima, and standard deviations. Categorical variables will be summarized by frequencies and percentages. Additional exploratory analyses will be performed when appropriate. Normality of variables will be checked and, if violated, nonparametric methods will be adopted. Changes from the analysis plan will not require an amendment to the protocol unless it changes a significant feature of the study.

9.2 Sample Size Justification

As a pilot trial, no formal sample size estimation was performed as we do not expect to find significant differences in the comparisons to be performed for either Study I or Study II. The sample sizes of 32 participants (40 screened and consented to identify the 32) with insomnia for the Study I trial and the additional 12 (15 screened and consented to identify the 12) participants without insomnia for the comparison studies for Study II should be sufficient as per Julious (34). We expect a dropout rate of 25% for the RCT based on our ongoing study of depression CBT; thus, approximately 12 in each group will likely complete the proposed trial. It is unlikely that there will be sufficient power with just 12 per study arm for statistical hypothesis testing. However, we do not believe it necessary to find statistically significant differences between study arms at this stage as long as we can demonstrate that the SHUTi intervention can be implemented successfully by our group

and that the effect sizes related to differential outcomes in the two study arms are clinically relevant. Of note, the prevalence rate of ISI scores ≥ 15 in patients from the Eskenazi HIV clinics who would be eligible for the currently proposed pilot trial is 25%. Given that there are over 800 patients on stable HIV therapy in these clinics and our group's proven ability to recruit in these clinics, we should have no difficulties enrolling 32 participants with insomnia into the Aim #1 trial.

9.4 Criteria for Stopping the Study

No early stopping rule will be implemented.

9.5 Analysis Datasets

Datasets	Definition
Intention-to-treat (ITT)	This will comprise all patients who meet the eligibility criteria and are randomized onto the study irrespective of their compliance to the planned course of treatment.
Per Protocol Set	This will comprise all UC patients and SHUTi participants.
Safety	This will comprise the SHUTi patients that attend at least one session of treatment.

9.6 Patient Characteristics and Significant Protocol Violations

Demographic and other baseline data will be summarized descriptively for all patients in the ITT set. Comparisons between the two groups will be performed using Pearson's chi-square tests and Student's t-tests. Significant protocol violations will be documented.

9.7 Disposition

The number of enrolled subjects will be summarized in a flow chart with frequency of completion and discontinuation. The subjects discontinued from SHUTi and their corresponding information will be listed. Significant protocol violations will be tabulated and/or listed.

9.8 Compliance

Compliance status will be tabulated for the SHUTi arm.

9.10 Analysis Plan for the Primary Objective

To test our primary hypothesis, an analysis of covariance (ANCOVA) will be performed to test for treatment group differences in Week 10 ISI adjusted for baseline ISI using the intent-to-treat set. Statistical significance will be considered if two-sided p-value <0.05.This analysis will be also repeated using the per-protocol set.

9.11 Analysis Plan for Secondary Objectives

Both unadjusted comparisons and adjusted comparisons between UC and SHUTi will be performed for secondary outcomes. Safety assessments will be performed using the safety dataset.

9.12 Interim Analysis

No interim analysis will be performed.

9.13 Subgroup Analysis

No subgroup analyses are planned.

9.14 Missing Data

Multiple imputations will be adopted to account for missing data. If differential missing patterns are observed, sensitivity analyses will be performed to evaluate the consequences of potential missing mechanisms.

9.15 Data Management

A comprehensive web-based data management system will be developed for this study using REDCap by the study team which will allow controlled entry through the internet. REDCap provides a secure, web-based environment that provides an intuitive data entry interface and has real-time validation rules (with automated data type and range checks). The system offers easy data manipulation with logged auditing, functionality for reporting, monitoring and querying subject records.

A unique identifier will be assigned to each study participant and their associated study specimens. Patient identifiers will be located only within the subject's study file in a separate, locked cabinet within the Infectious Diseases Research Clinic. Hardcopies of laboratory source records will also be stored in a locked file cabinet. All entryways to the IDRC are secured by padkey codes. Initial screening, consenting of potential subjects, and data abstraction and recording will be completed by either the primary investigators or by the research study coordinators from the IDRC.

10.0 HUMAN PARTICIPANTS RESEARCH AND PROTECTION

10.1 General Considerations/Investigator Training

The Human Participants Research outlined in this proposal meets the definition of a Phase II clinical trial for the purpose of identifying biological and physiological mechanisms of human disease (not for identifying the superiority of one agent over the other). Therefore, a formal Data and Safety Monitoring Board is not required, although appropriate monitoring through the Data and Safety Monitoring Plan with independent monitor as described below will be fully implemented. This trial will be posted on ClinicalTrials.gov and updated regularly as needed for protocol updates and results. All Indiana University personnel involved with this application have successfully completed the training and examination involved with the Collaborative Institutional Training Initiative Course.

10.2 Risks to the Participants

10.2.1 Human Participants Involvement and Characteristics

- Up to 55 HIV-infected participants will be recruited, screened, and consented to participate in these studies. 32 of these will participate and be randomized in the Study I pilot trial investigating the efficacy of cognitive behavioral therapy using the SHUTi computer program to improve insomnia. Another 12 without insomnia will be included in Study II for comparison to the 32 Study I participants.
    - Participants must be at least 18 years of age, have documented HIV infection, and have an HIV-1 RNA level <75 copies/mL while on ART for at least three months. To be in Study I, they must have a screening ISI score ≥ 11; to be in Study II, they must have a screening ISI score <11.
    - The chief exclusion criteria include known CVD, congestive heart failure, treatment for malignancy (besides localized skin cancers) within 6 months of screening, pro-inflammatory conditions besides HIV infection (e.g. autoimmune diseases, but allowing hepatitis B or C co-infection).
        - Potential participants will be recruited from the HIV outpatient clinics of Indiana University Health Hospitals and Eskenazi Health Hospital.

10.2.2 Sources of Materials

- All data for this study will be obtained only after written, informed consent is provided by each participant. Existing medical records will be reviewed for demographics, medical diagnoses, and medications. Questionnaires/surveys to assess insomnia, depression, tobacco use, alcohol use, substance use, physical activity, anxiety, positive/negative affects, and sleep quality/history/beliefs will also be implemented. Measurements of frailty and cognitive functioning will also be performed.
- Results from pertinent medical records and procedures performed for these studies, as outlined above, will be recorded on the human participants involved in the projects in this application.
- Data will be stored in a password-protected computerized database via REDCap that will include only the participants' study identification number (names and other identifiable information will not be included). Therefore, the SID# will be the only link to the participant. Only the principal investigators, co-investigators, and research personnel who will directly obtain the necessary data will have access to the participant identities. All data obtained for this study will be obtained only after written, informed consent is provided by each participant.
- Records will be reviewed manually. SHUTi treatments and questionnaires will be completed in private settings. These data will be collected solely for the purpose of the proposed research projects.

10.2.3 Potential Risks

- There are minimal risks to the participants enrolled in the proposed research. There is the potential loss of participant confidentiality. There are no known risks related to the implementation of the SHUTi cognitive behavioral therapy program. Participants may feel unease in completing the questionnaires. There may be some muscle soreness and a very minor theoretical risk of falls when performing the physical functioning assessments.
- The study team is trained to perform these assessments in order to minimize these potential risks. Of note, no falls have occurred to date when performing these assessments.
- The principal alternative to these procedures would be not to participate in the research.

10.3 Adequacy of Protection Against Risks

10.3.1 Recruitment and Informed Consent

- Recruitment will only begin once the Indiana University Institutional Review Board has approved this study. All participants will be recruited from the outpatient HIV care clinics at Indiana University Health Hospitals and Eskenazi Health Hospital. Self-referrals from other venues will also be considered. If the primary caregiver for the patient believes he or she is eligible for the study and allows the patient to be approached for screening, one of the study investigators or a study nurse will approach each potential participant during his or her regularly scheduled clinic visit or by phone if the patient is not present in clinic. If eligibility is confirmed, then the purpose, procedures, and risks and benefits of the study will be discussed with the participant. Participants will have ample opportunity to ask questions and to have all concerns addressed. If the participant wishes to pursue screening, then written informed consent will be obtained (and a copy given to the participant). All consent forms will be stored in a locked file cabinet.

10.3.2 Protection Against Risk

10.3.2.1 Confidentiality. To minimize the risk to participant confidentiality, patient identifiers will be removed once his or her data is abstracted and recorded, and only the random study identification number (generated when consent is provided) will be used. All hardcopy study data will be kept in a secured and locked file cabinet. All electronic data will be kept in a password-protected computer database. The only link between patient identifiers and the randomized study identification number will be kept in separate files. Identifiers will never be used in the analysis or presentation of study results.

Information collected from the participant for this research may be used for future research studies or shared with other researchers for future research. If this happens, information which could identify the participant will be removed before any information are shared. Since identifying information will be removed, we cannot ask for your additional consent.

10.3.2.2 Questionnaires. Participants may feel uneasy or discomfort in completing the depression, treatment adherence, and physical activity questionnaires. To minimize this risk, questionnaires will be completed in private settings with any questions regarding completion of the questionnaires addressed by trained study team psychology personnel.

10.3.2.3 Suicidal ideation and management. Although not an inherent risk of the study intervention or study procedures, participants may have depression as determined through completion of the PHQ-9 questionnaire. As such, these participants may have suicidal ideation at screening or develop suicidal ideation during the course of the study. We have already put into place a protection protocol for just this event in our previous studies in HIV-uninfected depressed patients (please see Appendix at end of this protocol). If a participant reports having thoughts of being better off dead or of hurting him/herself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation), the visit will be immediately stopped, and the research assistant will interview the participant to complete the Patient Suicidality Form (see Appendix). If the participant answers "no" to all three suicide questions or if the patient answers "yes" only to Question 3 (previous attempt) and the most recent attempt was ≥ 10 years ago, the visit will proceed as normal, and the completed Patient Suicidality Form will be given to the principal investigator.

If the participant answers "yes" to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), the research assistant will immediately contact the principal investigators. Dr. Stewart (a clinical psychologist) and Dr. Gupta (a physician) will review the case as soon as possible, but no later than the same day, to determine the appropriate course of action (e.g., immediately contact the patient's primary care provider, primary HIV provider, clinical social worker, or care coordinator, consult with clinicians at Midtown Community Mental Health Center, and/or escort the patient to the Crisis Intervention Unit at Eskenazi Health). Additional authorities, including the police, may be contacted if immediate harm is of concern. Participants may be withdrawn from the study.

A letter, both an email and a hard copy version, will also be sent to the potential participant's primary provider notifying him/her of the situation (see below).

If an enrolled participant reports having thoughts of being better off dead or of hurting him/herself during any telephone calls (e.g., a scheduling call or a call to the study team initiated by the participant), the exact same process as outlined above will be initiated. Please see the Appendix for the full Suicide Management Plan.

10.3.2.4 Adverse event financial management, grading, and reporting. In the event of an adverse event, necessary medical and professional intervention will be provided immediately and billed to the participant's medical insurance (if available). If the participant does not have insurance, care will be provided via the indigent care program at Eskenazi Health Hospital. Standard procedures for reporting deviations from protocols will be followed; serious adverse events that meet the Indiana University IRB prompt reporting requirements will be reported within 10 business days. All adverse events will be graded using The Division of AIDS Table for Grading Adult Adverse Experiences is located at: http://roc.s-3.com/members/download/adulttox.pdf.

10.3.2.5 Data and Safety Monitoring. Dr. Lana Dbeibo of the Division of Infectious Diseases, Indiana University will serve as the independent chair and monitor for this trial. She will receive reports at least every six months regarding the progress and participant safety during the trial.

10.4 Potential Benefits of the Proposed Research to the Participants and Others

- Potential benefits to the participants include an evaluation of their insomnia, depression, functional capacity, and frailty status. They may also derive short-term benefits from the SHUTI insomnia treatment program, although this is not guaranteed. Finally, the participants may also benefit from knowing that their participation will accrue knowledge that could benefit other HIV-infected patients.
- Although there are no guaranteed clinical benefits from those who are randomized to treatment with SHUTi, this program appears quite safe when used in HIV-uninfected participants. The standard of care will not be altered in the control participants. Therefore, the ancillary benefits to the participants in the proposed studies significantly outweigh the minimal risks in this study. Moreover, the proposed research may lead to other prevention and therapeutic studies that would eventually demonstrate how to reduce inflammation and improve endothelial function, which consequently may reduce future cardiovascular events in the HIV-infected population, and to improve frailty and functional status in the aging HIV population. This would benefit society directly by impacting clinical practice.

10.5 Importance of the Knowledge to be Gained

- The knowledge that will be gained from this study will determine the relationships between HIV, insomnia, functional capacity, and frailty. This would potentially impact the clinical care of HIV-infected patients at risk for worse long-term outcomes. Furthermore, prevention and therapeutic strategies for these highly prevalent diseases can then be formulated, thereby reducing morbidity, mortality, and cost to the patients and society in general.
- Again, the risks to the participants are considered minimal. Even if the results are negative, the results of these investigations will add substantially to our knowledge on effects of an internet-based cognitive behavioral program on insomnia in virologically-suppressed, HIV-infected persons. Therefore, the importance of the knowledge gained outweighs the risks to the participants.

10.6 Data and Safety Monitoring Plan

- Progress of these studies, including data monitoring, participant enrollment, protocol deviations, and all SAE, will be reviewed by a panel including the PIs (Drs. Gupta and Stewart) and an HIV expert investigator at Indiana University not directly connected with this study (Dr. Lana Dbeibo of the Division of Infectious Diseases, Indiana University School of Medicine). Reports, which will include descriptions of all adverse events, will be prepared for review by this panel every 12 months. Any study participant prematurely discontinued due to an adverse event will be reviewed immediately. Standard procedures for reporting deviations from protocols to the Indiana University ICRC, IRB, and NHLBI will be implemented. Serious Adverse Events (SAEs) will also be reported to the IRB within 30 working days and subsequently forwarded to NHLBI as required.

10.7 Inclusion of Women and Minorities

There are no exclusion criteria based on gender, racial category, or ethnicity. Based on our previous cumulative experience and the general HIV-infected population cared for at the study sites at the Indiana University Health Medical Center (Eskenazi Hospital, Methodist Hospital, VA Roudebush Hospital, and Indiana University Health Hospital), it is anticipated that approximately 25% of the study participants will be women.

It is also anticipated that approximately 50% and 10% of the study participants will be black and Hispanic, respectively. American Indians, Alaskan Natives, Asians, Native Hawaiians or Other Pacific Islanders are not expected to be represented in the proposed study population due to extremely low representation of these groups within the Indiana University Health Hospitals HIV outpatient clinics and in Indianapolis in general.

10.8 Inclusion of Children

Subjects over the age of 18 will be eligible for enrollment. However, participants under age 18 will be excluded to minimize confounding from developmental changes that may affect the studies' endpoints of behavioral and functional measures.

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Appendix: Suicide Management Plan

Suicide management plans very similar to the one described below have previously been approved by the Indiana University IRB and were successfully implemented in the two other depression trials conducted by our team (IRB #'s 1105005448 and 1110007119). Those suicide management plans were constructed with input from Eskenazi Midtown Community Mental Health Center leadership (Dean Babcock, Associate Vice President, and Michael Hughes), who concluded that the plans provide a high level of protection while minimizing disruption to usual clinical activities. In the present trial, we will assess suicidal ideation at every study visit, and we are prepared to appropriately handle the situation should one of the enrolled patients exhibit suicidal ideation.

(a) In-Person Study Visits

Suicidal ideation will be assessed using Item #9 of the PHQ-9 at the Screening Visit and all Main Study Visits (see Section 6.1). If a participant reports having thoughts of being better off dead or of hurting him/herself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation) during any of the Study Visits, the visit will be immediately stopped, and the study coordinators running these visits will interview the participant to complete the Patient Suicidality Form (see below). If the potential participant answers "no" to the clarifying question, the visit will proceed as normal. If the potential participant answers "yes" to the clarifying question, the participant will be asked the three suicide questions. If this interview is required at one of the Weekly SHUTi Sessions, the graduate student research assistants will perform this interview, as they will conduct these treatment sessions.

The study coordinators have been trained by Dr. Stewart, a clinical psychologist, in conducting the interview to complete the Patient Suicidality Form and in following this protocol. Dr. Stewart will also serve as the primary supervisor to these study coordinators when it comes to their tasks related to this suicide management plan. In Dr. Stewart's completed (IRB #'s 1105005448 and 1110007119) and ongoing (IRB # 1411802537) clinical trials, he has trained ResNet research assistants to effectively conduct this interview and provide a high degree of protection to patients.

The graduate student research assistants are doctoral students enrolled full-time in IUPUI's clinical psychology Ph.D. program, which is accredited by the American Psychological Association and of which Dr. Stewart is a core member. The research assistants have completed graduate coursework in psychological assessment, psychological interventions, psychopathology, and ethics and have acquired supervised clinical experience in local healthcare settings. The graduate student research assistants have also been trained by Dr. Stewart in conducting the interview to complete the Patient Suicidality Form and in following this protocol. Dr. Stewart is also the primary supervisor of graduate student research assistants.

It is worth noting that neither the study coordinators nor the graduate student research assistants will be making any decisions regarding how to handle a situation. Instead, they will collect information by administering a highly structured, 3-question interview (Patient Suicidality Form, found below) and will follow the straightforward, step-by-step protocol described in the next paragraph. They will be instructed to call Dr. Stewart if they are unsure about a participant's response to any of the three questions. As he has done in his past depression trials and is described above, Dr. Stewart will train the study coordinators and the graduate student research assistants in administering the brief interview and in following the protocol. This training will be repeated periodically during the study period.

If the participant answers "no" to all three suicide questions or if the patient answers "yes" only to Question 3 (previous attempt) and the most recent attempt was ≥ 10 years ago, the visit will proceed as planned, and the completed Patient Suicidality Form will be given to Dr. Stewart.

If the participant answers "yes" to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), the study coordinators or the graduate student research assistant will immediately stop the visit, will contact Drs. Stewart and/or Gupta, and will stay with the participant until a decision is made. If clinically indicated (e.g., the situation is an emergency), a graduate student research assistant and/or Dr. Stewart will go to the visit location (Infectious Diseases Research Clinic or ICRC) to assist the study coordinators.

Drs. Stewart and/or Gupta will review all cases screening positive for suicidal ideation immediately to determine the appropriate course of action – e.g., interview the patient to obtain further information, immediately contact the patient's HIV provider or clinical social worker to involve them in the decision-making process, consult with clinicians at the Eskenazi Health Midtown Community Mental Health Center to aid in the decision-making process, escort the patient to the Eskenazi Health Crisis Intervention Unit ('warm handoff'), and/or contact the police if the patient is at imminent danger of harm and is refusing all care. Either Dr. Stewart or Dr. Gupta will also call the participant's HIV provider notifying him/her of the situation if the provider was not involved in the decision-making process. Regardless of the exact course of action, the study team will ensure that the participant is connected to the appropriate existing clinical services. If the patient's HIV provider no longer believes that the patient is appropriate for this trial following this situation, the patient will be withdrawn from the trial.

Of note, because patients exhibiting active suicidal ideation are not eligible for this trial, we expect that it will be a rare occurrence that an enrolled patient will screen positive for suicidal ideation. Zero enrolled participants in our two prior depression trials have exhibited suicidal ideation during their involvement in the studies.

(b) Study Telephone Contacts

If a participant reports having thoughts of being better off dead or of hurting him/herself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation) during a study call (e.g., the start or end of a remote SHUTi session, a scheduling call, or a call to the study team initiated by the participant), the study coordinator or a graduate student research assistant will interview the participant to complete the Patient Suicidality Form (found below).

If the potential participant answers "no" to all three suicide questions, the call will proceed as planned and the completed Patient Suicidality Form will be given to Dr. Stewart. If the participant answers "yes" to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), the study coordinator or a graduate student research assistant will immediately contact Drs. Stewart and/or Gupta. Drs. Stewart and/or Gupta will review the case immediately to determine the appropriate course of action – e.g., interview the patient to obtain further information, immediately contact the patient's HIV provider or clinical social worker to involve them in the decision-making process, consult with clinicians at the Eskenazi Health Midtown Community Mental Health Center to aid in the decision-making process, escort the patient to the Eskenazi Health Crisis Intervention Unit, and/or contact the police if the patient is at imminent danger of harm and is refusing all care. If a participant prematurely terminates a call after reporting suicidal ideation, the study coordinator or a graduate student research assistant will immediately contact Drs. Stewart and/or Gupta. Once again, Drs. Stewart and/or Gupta will review the case immediately to determine the appropriate course of action. Either Dr. Stewart or Dr. Gupta will also call the participant's HIV provider notifying him/her of the situation if the provider was not involved in the decision-making process. Regardless of the exact course of action, the study team will ensure that the participant is connected to the appropriate existing clinical services.

If the patient's HIV provider no longer believes that the patient is appropriate for this trial following a situation, the patient will be withdrawn from the trial.

It should be noted that the informed consent form for this trial contains a section describing the steps that will be taken if an enrolled participant reports suicidal ideation on a questionnaire or spontaneously.

Patient Suicidality Form (administered verbally by the research assistant)

*****CONFIDENTIAL*****

Research Assistant: _____ Date: _____

Patient's Name: _____ Hospital ID: _____

Patient's Address: _____

Patient's Phone Number: _____ Patient's PCP: _____

****

Clarifying Question
Over the past 2 weeks, have you been having thoughts of hurting yourself in some way?

Yes ____ No ____
(Continue) (Stop)

Comments:

I'm going to ask you a few questions that are part of this study, because we have seen that in some patients with these symptoms, these are important concerns.

1. Do you have a suicide plan? Yes _____ No _____

Comments:

2. Have you been struggling against thoughts about committing suicide? Yes _____ No _____

Comments:

3. Have you attempted suicide in the past? Yes _____ No _____

If YES, in what year was the most recent attempt? _____

Comments:

If the participant answers "yes" to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), you must carefully follow the procedures described in the Suicidal Ideation Protection Protocol.