Treating Insomnia to Reduce Inflammation in HIV: A Pilot Trial
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SCHEMA

OBJECTIVES

The primary objective of this pilot trial is to evaluate the effects of cognitive behavioral therapy for insomnia (CBT-I) on changes in circulating levels of high sensitivity C-reactive protein (hsCRP) at 24 weeks in virologically-suppressed, HIV-positive adults with insomnia, defined as having an Insomnia Severity Index (ISI) score ≥ 11. Secondary objectives include comparing changes in hsCRP at 12 weeks, changes in other circulating inflammation biomarkers (IL-6, sCD14, sCD163, CD14+CD16+ monocytes) at both 12 and 24 weeks, and ISI scores and other self-reported patient outcomes at both 12 and 24 weeks.

DESIGN

The objectives of this study will be met by conducting a 24-week, single-center, single-blinded, two-arm, parallel-group, randomized, controlled pilot trial. A total of 250 participants may be screened to identify the 50 participants who will be randomized into this pilot trial. We aim to enroll at least 25% women into this trial, or 12 of the 50 to be randomized. These participants will be randomized 1:1 (stratified by sex and current use of sleep aids/medications) to either the internet CBT-I program SHUTi (N=25) or an internet sleep education/ hygiene Active Control (N=25). Four study visits are required (Screening, Entry, Week 12, and Week 24).

DURATION

Each individual participant will be followed for up to 30 weeks (up to 6 weeks between Screening and Randomization/Entry and then 24 weeks after Randomization).

POPULATION

All participants will be HIV-positive, 18 years of age or older, have been receiving antiretroviral therapy for at least six months with an HIV viral load < 75 copies/mL at Screening, and have an ISI score ≥ 11 at Screening. Participants will be recruited from the infectious diseases/HIV outpatient clinics of Eskenazi Health Hospital and the Indiana University Health (IUH) Hospitals.

1.0 STUDY OBJECTIVES

1.1 Primary Objective

1.1.1 To compare 24-week changes in hsCRP levels between those undergoing SHUTi vs. Active Control.

1.2 Secondary Objectives

1.2.1 To compare 12-week changes in hsCRP levels between those undergoing SHUTi vs. Active Control.

1.2.2 To compare 12- and 24-week changes in levels of IL-6, sCD14, sCD163, and CD14+CD16+ monocytes between those undergoing SHUTi vs. Active Control.

1.2.3 To compare 12- and 24-week changes in Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Dysfunctional Beliefs and Attitudes about Sleep (DBAS-16), sleep mediation use, insomnia treatment satisfaction, Patient Health Questionniare-9 (PHQ-9), Hopkins Symptom Checklist (SCL-20), Generalized Anxiety Disorder-7 (GAD-7), PROMIS® Fatigue Short Form, Alcohol Use Disorders Identification Test (AUDIT), Pain, Enjoyment, General Activity Scale (PEG-3), and Short Form-36 (SF-36) Health Survey between those undergoing SHUTi vs. Active Control.

1.2.4 To evaluate potential treatment effect moderators including the following baseline factors: age, ISI, insomnia pharmacologic treatment, depression status, substance use, and hsCRP level.

1.2.5 To evaluate the potential treatment mediating effects of insomnia symptom severity, behavioral changes, and HIV virologic rebound on inflammation biomarkers.

2.0 HYPOTHESES, SIGNIFICANCE, AND BACKGROUND

2.1 Hypotheses

2.1.1 Insomnia treatment with SHUTi will reduce circulating hsCRP compared to sleep education/hygiene Active Control at 24 weeks.

2.1.2 Insomnia treatment with SHUTi will reduce circulating hsCRP at 12 weeks and IL-6, sCD14, sCD163, and CD14+CD16+ intermediate monocyte levels at both 12 and 24 weeks compared to sleep education/hygiene Active Control.

2.1.3 Insomnia treatment with SHUTi will reduce ISI scores at 12 and 24 weeks compared to sleep education/hygiene Active Control.

2.1.4 Effects of insomnia treatment with SHUTi on inflammation may be moderated by baseline factors including age, ISI, insomnia pharmacologic treatment, depression status, substance use, and CRP level, and may be mediated by insomnia symptom severity, behavioral changes, and HIV virologic rebound.

2.2 Significance and Background

2.2.1 Significance. With the use of antiretroviral therapy (ART), the lifespans of people with HIV (PWH) are nearing those of the HIV-negative population (1-4). However, this increase in survival is accompanied by a

growing incidence of serious non-AIDS events (SNAE), including diabetes, osteoporosis, chronic kidney disease, neurocognitive decline, pulmonary dysfunction, and cardiovascular disease (5-8).

Persistently elevated systemic inflammation [as measured by circulating high sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6)] and evidence of monocyte activation [as measured by sCD14, sCD163, and pro-inflammatory intermediate CD14+16+ monocytes] are strongly associated with the development of these SNAE, despite virologic suppression with ART (9-16). Because pharmacologic interventions (apart from ART itself and variably with statins) have not yet proven effective in reducing inflammation in PWH, there is a critical need to identify alternative and innovative strategies.

Targeting insomnia may be one such novel strategy to reduce HIV-related inflammation. In the general population, insomnia is associated with greater systemic inflammation (17), as measured by heightened circulating levels of hsCRP and IL-6 (18, 19). Importantly, in a randomized controlled trial (RCT) of 123 older, HIV-negative adults with insomnia disorder (20, 21), cognitive behavioral therapy for insomnia (CBT-I) reduced hsCRP. However, it remains unknown if CBT-I similarly reduces systemic inflammation in PWH on ART.

This single-center, phase II RCT evaluating the effect of Sleep Healthy Using The Internet (SHUTi), on systemic inflammation in PWH is highly significant for several reasons: (1) A positive phase II trial would generate the critical proof-of-concept data and effect size estimates needed to justify and properly design a multicenter, phase III RCT to establish the long-term effects of SHUTi on systemic inflammation and SNAE. As we have ongoing relationships with the AIDS Clinical Trials Group, implementing such a trial is feasible in our hands. (2) A positive phase III trial would identify a novel target (insomnia) for SNAE prevention efforts and would suggest that clinical management guidelines for PWH should, for the first time, include insomnia screening and treatment to improve physical health outcomes. (3) A positive phase III trial would also equip healthcare systems with a new practical and scalable intervention (SHUTi) to help lower SNAE risk. Importantly, SHUTi avoids drug dependence and drug interaction concerns associated with some pharmacologic therapies for insomnia and does not rely on mental health specialty providers trained in CBT-I, which are in short supply. *Thus, given the high prevalence of insomnia in PWH, this application may lead to widespread, clinically relevant changes to improve the lives of PWH.*

2.2.2 Insomnia, Inflammation, and Chronic Diseases in the General Population. *Insufficient sleep* is a highly prevalent and harmful health behavior that contributes to poor mental and physical health outcomes (22). Here, insufficient sleep is defined as the presence of insomnia – frequent and persistent difficulty in initiating or maintaining sleep causing functional impairment or distress (23-25). A 2006 Institute of Medicine report (26) stated that promoting *sufficient sleep* may alter the adverse mental and physical health aging trajectories of vulnerable adults.

Insomnia is the most prevalent sleep disorder and is a major public health concern (27). Insomnia afflicts millions of U.S. adults, with 12-20% having insomnia disorder (28, 29) and 30-50% having insomnia symptoms (30, 31). Insomnia is typically chronic (32, 33), and its serious ramifications include absenteeism and accidents (34); the development of psychiatric disorders (35); the development of chronic diseases, (including diabetes, cardiovascular disease, and dementia) (36-42); and high total annual costs (43, 44).

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 comorbidities, including depression* (45, 46). Moreover, research examining the directionality between insomnia and depression consistently finds that insomnia increases the risk of future depression (47, 48) and less consistently finds that depression increases the risk of future insomnia (33, 49-52). This suggests that insomnia manifests independently of depression.

Importantly, there are rigorous genomic association data suggesting causal associations between insomnia and incident chronic diseases, similar to SNAE in PWH, in the general population. In the largest genome-wide association study (GWAS) study to date, Mendelian randomization analyses showed highly

significant ($P<10^{-8}$) direct risk effects of insomnia on type 2 diabetes (OR=1.86) and CVD with no reverse risk effect of these conditions on insomnia (53). Another GWAS study (54) confirmed this significant causal association between insomnia symptoms and CVD (OR=2.15; P<0.001), which was then validated in a second cohort (OR=2.95; $P<10^{-12}$).

It is plausible that the increased risk of chronic diseases due to insomnia is mediated through systemic inflammation (17, 55-62). Insomnia is associated with greater sympathetic activation (63) and subsequent NF-κB upregulation, which, in turn, leads to greater pro-inflammatory activation, as marked by higher circulating hsCRP and IL-6 levels (64). *Critically, evidence suggest that this relationship between insomnia and inflammation is causal.* In a recently completed RCT (21), 123 HIV-negative adults with insomnia were randomized to 4 months of face-to-face CBT-I, Tai Chi Chin (TCC), or sleep seminar (SS) education control. For the primary outcome of insomnia disorder remission at Month 4, CBT-I (54%) outperformed TCC (30%; P<0.05) and SS education control (21%; P<0.01). For the secondary outcome of high hsCRP [≥3.0 mg/L, a commonly used threshold for higher CVD risk (65)], CBT-I also outperformed TCC and SS at Month 16 (both P=0.04). Moreover, hsCRP levels at Month 16 were lower in participants with insomnia remission (1.5 mg/L) versus in those without insomnia remission (2.8 mg/L; P<0.05). The improvement in hsCRP with CBT-I is likely clinically relevant in PWH, as this difference in hsCRP was associated with a significant 2-fold reduction in risk of incident CVD, a key SNAE, in the SMART trial comparing continuous vs interrupted ART (66).

2.2.3 Insomnia and inflammation in HIV. A meta-analysis of self-reported sleep disturbances in 9246 PWH suggested a high insomnia prevalence rate of 58% (67). There are likely multiple contributors to this high prevalence, including HIV stigma, direct effects of HIV on the CNS, stress, substance use, anxiety, cognitive impairment, and adverse effects of certain ART drugs (efavirenz, rilpivirine, integrase inhibitors) on the CNS (68-73). However, CD4 count and HIV-1 RNA level were not associated with insomnia (68).

The literature on the associations between insomnia and heightened inflammation in PWH is more limited than in the general population but appear to support similar relationships. The three studies identified (74-76) used the Pittsburgh Sleep Quality Index and sleep parameters measured by wearable sleep devices to assess sleep disturbances. A total of 641 HIV-positive participants in total were included (70% male, 66% non-white race/ethnicity, 71% on ART). There were greater circulating levels of hsCRP and IL-6 in those with less total sleep time (74); greater circulating IL-13 in those with longer sleep onset (75), and greater circulating IL-6 in those with higher fatigue (76). Thus, sleep disturbances likely do contribute to the greater systemic inflammation known to occur in PWH. However, these observational data could not establish causality. This trial will address this gap.

2.2.4 Treatment of Insomnia with SHUTi. In 2005, an NIH panel concluded that CBT-I is the treatment of choice for insomnia (77). The 2016 American College of Physicians gave their top recommendation that "all adult patients receive CBT-I as the initial treatment for chronic insomnia disorder," given the strong evidence that it is *safe, effective, and broadly applicable with durable benefits* (78). The most recent meta-analysis (79) showed that CBT-I's effect size is large for insomnia symptoms (Hedge's g=0.98); moderate-to-large for sleep efficiency (g=0.71), sleep quality (g=0.65), wake after sleep onset (g=0.63), and sleep latency (g=0.57; all P<0.05). CBT-I's effect sizes are similar regardless of comorbid medical/psychiatric conditions, use of sleep medications, or age (78-80). RCTs with longer-term follow-ups show that the sleep improvements with CBT-I are sustained, whereas those with sleep medications are not (81, 82).

A shortcoming of CBT-I, however, is its limited availability due to a shortage of clinicians trained in this approach (83-85). In addition, patients may not be able to attend sessions with a CBT-I therapist due to financial or time restraints. To address these issues, SHUTi (86) – a self-guided, fully automated, interactive, and tailored internet CBT-I program that is fully accessible via tablets and smartphones – was developed. In one RCT (N=303), adults who received SHUTi, versus insomnia education, exhibited greater improvements in insomnia symptoms [Insomnia Severity Index (ISI) score] at post-treatment, 6 months, and 12 months (Cohen's d=1.90-2.32 in the SHUTi arm) (87). Notably, outcomes did not differ in people with and without

medical/psychiatric comorbidities. In yet another RCT (N=1,149), the SHUTi arm, versus an internet attention-control arm, had lower insomnia symptoms at 6 weeks (d=1.10) and 6 months (d=0.83) (88). Our small pilot RCT found that SHUTi meaningfully reduced insomnia symptoms (ISI score) over a 10-week period compared to usual care in PWH with ISI score ≥ 11. Collectively, these findings indicate that SHUTi has a rapid, meaningful, and lasting positive impact on insomnia.

2.3 Preliminary Studies

2.3.1 Insomnia is associated with SNAE in HIV. Given our group's interest in the relationships between mental health disorders and SNAE in PWH, we have published several studies from the Veterans Aging Cohort Study (VACS) showing that depression, defined either by diagnostic codes or by the validated Patient Health Questionnaire-9 (PHQ-9) scale, is associated with higher rates of incident myocardial infarction, heart failure, and all-cause mortality in HIV-positive adults (89-91). We have now published our VACS study evaluating the associations of insomnia on a key SNAE, incident cardiovascular disease (92). We included 3108 participants (median age 49 years, 97% male, 66% African-American, median CD4 370 cells/μL, median HIV-1 RNA 400 c/mL, 80% on ART) who were enrolled starting in 2002 with follow-up through 2014. Insomnia was measured with the "Difficulty falling or staying asleep" item on the VACS HIV Symptom Index. Response options ranged from 0 ("I do not have this symptom") to 4 ("I have this symptom, and it bothers me a lot"). At enrollment, 59% endorsed some level of insomnia (scores 1-4). We found that PWH who scored a 4, versus those scoring 0, were at a 62-70% increased risk of incident CVD events (myocardial infarction, coronary artery revascularization, or stroke; 267 events) over the 11-year follow-up period. These associations were independent of demographics, traditional CVD risk factors, additional potential confounders (hepatitis C infection, renal disease, anemia, alcohol use, cocaine use), HIV-specific factors (CD4 count, HIV-1 RNA level, ART use), and sleep medication use. Overall, these findings demonstrate that insomnia is another mental health disorder with long-term, clinically significant, adverse consequences in PWH.

2.3.2 CBT for depression in PWH improves measures of inflammation. We have now published our pilot trial of 54 PWH on virologically-suppressive ART with PHQ-9 scores ≥10 (indicating high likelihood of a depressive disorder) who were randomized 1:1 to either the use of an internet CBT program for depression (Beating the Blues-US™ (BtB), N=27), which includes 8 weekly treatment session, or Usual Care (UC, N=27) (93). Three and two participants, respectively, were lost to follow-up over 24 weeks (9% overall attrition). There were no restrictions on use of depression therapies (pharmacologic or behavioral) nor on types of ART regimens. We found that BtB significantly reduced PHQ-9 scores over 24 weeks compared to UC, indicating persistent BtB effects well beyond the initial treatment period. Moreover, the intervention significantly reduced sCD163 levels and proportions of pro-inflammatory, intermediate CD14+CD16+ monocytes (Table 1). The intervention also led to non-significantly greater reductions in hsCRP, IL-6, and sCD14 levels. Overall, these data strongly suggest that internet CBT treatment of a mood disorder can directly improve markers of systemic inflammation and monocyte immune activation in PWH.

Table 1. Comparison of mean (SD) changes from Entry to Week 24 in depression scores and inflammation/monocyte activation biomarkers between Usual Care (UC) and the Beating the Blues (BtB) study group.

Changes in Endpoint from Entry to Week 24	UC	BtB	Difference BtB vs. UC (95% CI)	P-value
PHQ-9	-1.38 (5.00)	-6.00 (6.60)	-4.63 (-8.00, -1.25)	0.008
hsCRP (mg/L)	0.92 (4.79)	-0.26 (2.55)	-1.18 (-3.50, 1.14)	0.33
IL-6 (pg/mL)	0.56 (2.36)	-0.24 (2.31)	-0.80 (-2.24, 0.64)	0.27
sCD14 (ng/mL)	118 (406)	-134 (571)	-251 (-561, 579)	0.11
sCD163 (ng/mL)	4.71 (9.96)	-1.36 (5.88)	-6.07 (-11.03, -1.11)	0.024
%CD14+CD16+ monocytes	2.23 (6.42)	-1.84 (6.15)	-4.07 (-7.72, -0.42)	0.030

2.3.3 SHUTi improves insomnia symptoms in PWH. We conducted a small pilot RCT to explore the effect of SHUTi versus usual care (UC) on insomnia symptoms in PWH with screening Insomnia Severity Scores (ISI) ≥11, indicating clinically relevant insomnia. Participants were on ART (8 of 10 in each group were receiving dolutegravir or bictegravir; 2 each on rilpivirine, none on efavirenz) with HIV-1 RNA levels <75c/mL; 85% were Black and 85% male. The number of study completers was 6 of 10 and 8 of 10 in the SHUTi and UC arms, respectively. The attrition rate was primarily due to lack of consistent internet availability for some participants. The mean number of SHUTi sessions completed was 4.8 (SD=1.2) out of 6. Mean (SD) baseline ISI scores in the SHUTi [18.3 (7.8)] and UC [20.5 (5.5)] groups were similarly high. Mean (SD) reductions in ISI scores at 10 weeks with SHUTi versus usual care [-9.0 (9.4) vs. -3.4 (2.0); P=0.21] were not statistically significantly different due to low power, but the effect size was large with a Cohen's d=0.82. We found even greater reductions in the SHUTi subgroup ($SHUTi_{4-6}$) who completed at least 4 of the 6 planned sessions [n=4; -12.8 (9.6); P=0.15 compared to UC; Cohen's d=1.36]. Our effect sizes are similar to those found by Ritterband (87) in the large RCT of SHUTi in the general population. These results support the efficacy of SHUTi in the virologically-controlled PWH, most of whom were on integrase inhibitors. Because the budget for this pilot study did not allow for laboratory testing, we could not assess changes in inflammatory biomarkers.

2.4 Study Rationale

The extant literature indicates that insomnia is a risk factor for chronic disease in the general population. Moreover, our published data suggests this relationship holds in PWH, as having highly bothersome insomnia symptoms is associated with incident CVD in PWH. There is strong and rigorous evidence that insomnia is associated with greater levels of systemic inflammation and that treatment of insomnia using CBT-I reduces hsCRP levels in the general population. Similarly, our published pilot trial suggests that treatment of depression using internet CBT reduces systemic inflammation and monocyte activation in PWH. Finally, our small pilot trial indicates that use of internet CBT-I (SHUTi) in PWH reduces insomnia symptoms as measured by ISI scores. What remains unknown is whether treating insomnia with internet CBT-I improves systemic inflammation in PWH. Thus, this trial will fill this critical knowledge gap in preparation for a definitive, end-point driven multicenter RCT of SHUTi on SNAE.

Our long-term goal is to reduce the risk of SNAE in adult PWH. The central objective of this study is to evaluate SHUTi's ability to reduce systemic inflammation, and, in particular, monocyte activation in PWH. A positive phase II trial would provide the proof-of-concept data and effect size estimates needed to justify and properly design an R01-funded phase III RCT to establish the long-term effects of SHUTi (a practical and readily scalable intervention) on HIV-related inflammation and prevention of SNAE.

3.0 STUDY DESIGN

3.1 Overview

The hypotheses of this study will be tested by performing a 24-week, single-center, single-blinded, two-arm, parallel-group, randomized (1:1), controlled pilot trial comparing internet CBT-I (SHUTi) with an internet Active Control (sleep education/hygiene) in 50 HIV-positive patients receiving virologically-suppressive ART and with insomnia. Our primary endpoint will be changes in hsCRP levels based on the Irwin trial (21) in HIV-negative persons. Our secondary endpoints include changes in IL-6 and measures of monocyte activation (sCD14, sCD163, CD14+CD16+ monocytes), given our results with internet CBT in depressed PWH. Importantly, each of these measures is associated with SNAE and thus have mechanistic and clinical relevance.

3.2 Screening Visit/Eligibility Assessment

To be eligible for this trial, the potential participant must have insomnia defined as having an Insomnia Severity Index (ISI) score ≥ 11. To assess for this Screening eligibility criterion, we will employ two methods. First, we will conduct in-person screening using the ISI in the Eskenazi and IUH Hospitals HIV clinics. Second, after provision of verbal consent by the potential participant, we will conduct phone screening using the ISI for patients who either self-refer for the study or who are referred by their HIV provider team members but who have not undergone in-person ISI screening in the clinics. In the latter situation, we will also employ EMR tools in EPIC and CERNER to identify potential participants first and then request approval by the patient's HIV provider to contact the patient.

Patients with ISI scores ≥ 11 will be asked by our in-clinic or phone 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 study team will then further assess eligibility by reviewing the potential participant's medical and laboratory records. HIV-1 RNA levels (viral loads) obtained as standard of care within 30 days (before or after) of the ISI positive screening result can be used to assess eligibility. If the HIV viral load data are not available within this timeframe, then an in-person Screening Visit will be scheduled to perform this test. Those eligible after review of medical and laboratory results will then be scheduled for their Entry/Randomization Visit.

3.3 Entry/Randomization Visit

Participants will be scheduled for this Entry/Randomization Visit within 42 days of the date of the positive ISI score criterion. This visit will occur at the Infectious Diseases Research Clinic located at the Fifth Third Office Building on the Eskenazi Hospital campus.

The study team will first undergo with the participant the written, informed consent process. 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.

For women of reproductive potential, a urine pregnant test (UPT) will then be performed before randomization and other required study procedures. If the UPT is positive, study participation will end. Otherwise, randomization and the other study procedures for this visit will continue. Randomization will be stratified by sex at birth (male/female) and by current regular (≥ 2 times/week) use of prescribed or over-the-counter sleep aids/medications (yes/no) using random number sequences. Sequentially numbered, opaque, sealed envelopes containing treatment assignment will be prepared by the study statistician.

At this visit, updated medical/psychiatric records, current medications, and current behavioral therapies will be reviewed and recorded. Height, weight, and vital signs will be measured and recorded. All participants will complete a questionnaire battery containing the following: standard questions assessing demographics, medical/psychiatric history, sleep mediation use, insomnia treatment satisfaction, and insomnia care received outside of the trial; ISI; PSQI; DBAS-16; PHQ-9; SCL-20; GAD-7; PROMIS® Fatigue Short Form; AUDIT; PEG-3; and SF-36. The questionnaire battery will also include validated scales assessing physical activity level, tobacco use, illicit drug use, medication adherence, and the probability of sleep apnea (STOP-BANG Questionnaire (94)). The questionnaire battery will be administered on a computer 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 questionnaire items.

We will then obtain whole blood samples for laboratory testing of the inflammation biomarkers of interest and for updated HIV-1 RNA levels and CD4 cell counts. We will also archive blood samples for future testing if consent for this is provided by the participant. 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) will be urged to follow-up with their primary HIV provider and/or clinical social worker regarding their depression.

In the 14-day sleep diary window immediately after the Entry Visit (see section 5.2), a trained research assistant will call each participant to administer the Structured Clinical Interview for DSM-5 Sleep Disorders-Revised (SCISD-R; initial interview on pp. 1-3 and the insomnia module p. 4) (95).

3.4 Week 12 Visit (70-100 days after Entry/Randomization Visit)

The SHUTi intervention and the internet sleep education/hygiene Active Control will be implemented between Entry/Randomization and Week 12. A UPT will be performed for women of reproductive potential; if positive, study participation will end and no further study procedures will be performed at this visit. Otherwise, once again, medical/psychiatric records, current medications, and current behavioral therapies will be reviewed and recorded. Weight and vital signs will be measured and recorded. All participants will complete a questionnaire battery containing the following: standard questions assessing demographics, medical/psychiatric history, sleep mediation use, insomnia treatment satisfaction, and insomnia care received outside of the trial; ISI; PSQI; DBAS-16; PHQ-9; SCL-20; GAD-7; PROMIS® Fatigue Short Form; AUDIT; PEG-3; and SF-36. The questionnaire battery will also include validated scales assessing physical activity level, tobacco use, illicit drug use, and medication adherence. The questionnaire battery will be administered on a computer 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 questionnaire items.

We will then obtain again whole blood samples for laboratory testing of the inflammation biomarkers of interest and for updated HIV-1 RNA levels and CD4 cell counts. We will also archive blood and samples for future testing if consent for this is provided by the participant.

Participants who exhibit elevated depressive symptoms (PHQ-9 $\geq$ 10) will be urged to follow-up with their primary HIV provider and/or clinical social worker regarding their depression.

3.5 Week 24 Visit/Closeout (150-190 days after Entry/Randomization Visit)

At this final/closeout study visit, a UPT will be performed for women of reproductive potential; if positive, study participation will end and no further study procedures will be performed at this visit. Otherwise, once again, medical/psychiatric records, current medications, and current behavioral therapies will be reviewed and recorded. Height, weight, and vital signs will be measured and recorded. All participants will complete a questionnaire battery containing the following: standard questions assessing demographics, medical/psychiatric history, sleep mediation use, insomnia treatment satisfaction, and insomnia care received outside of the trial; ISI; PSQI; DBAS-16; PHQ-9; SCL-20; GAD-7; PROMIS® Fatigue Short Form; AUDIT; PEG-3; and SF-36. The questionnaire battery will also include validated scales assessing physical activity level, tobacco use, illicit drug use, and medication adherence. The questionnaire battery will be administered on a computer 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 questionnaire items.

We will then again obtain whole blood samples for laboratory testing of the inflammation biomarkers of interest and for updated HIV-1 RNA levels and CD4 cell counts. We will also archive blood and samples for future testing if consented by the participant.

Participants who exhibit elevated depressive symptoms (PHQ-9 $\geq$ 10) 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 if the participant still has clinically significant insomnia (ISI $\geq$ 8). The study team will also provide a list of local mental health services to the patients' primary HIV providers or social workers. After the procedures for this study visit have been performed, participation in this study will end, with no further active follow-up apart from notification of final study results.

3.6 Study Duration and Participant Retention

The maximum study period for each participant will be between 24 and 30 weeks, accounting for the 42-day period from Screening to the Entry Visit. To promote retention in the study, participants will be financially compensated at the Entry, Week 12, and Week 24 Visits.

4.0 SELECTION AND ENROLLMENT CRITERIA

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) 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 180 days prior to the date of the HIV-1 RNA value determining eligibility.
4.1.4 HIV-1 RNA level < 75 copies/mL at Screening.

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

4.1.5 ISI score ≥ 11 at Screening.

NOTE: Use of sleeping aids/medications is permitted as long as the ISI score criterion is met.

4.2 Exclusion Criteria

4.2.1 Inability to complete written, informed consent.
4.2.2 Inability to read and understand English as seen on a computer screen.
4.2.3 Incarceration at the time of any study visit.
4.2.4 Active suicidality at Entry, 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).
4.2.5 Diagnosed disease or process, besides HIV infection, associated with increased systemic inflammation (including, but not limited to, systemic lupus erythematosus, inflammatory bowel diseases, or other collagen vascular diseases).

NOTE: Hepatitis B or C co-infections are NOT exclusionary, but treatment for hepatitis C cannot be provided during study participation.

4.2.6 End stage renal disease requiring renal replacement therapy (dialysis, transplantation).
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 the Entry Visit.

NOTE: Therapy for serious medical illnesses that overlaps with a 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 immunosuppressive therapies, 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 bipolar disorder or a psychotic disorder, including schizophrenia.

NOTE: Depressive disorders are not exclusionary.

4.2.13 Current sleep disorder diagnosis other than insomnia disorder (e.g., sleep apnea).
4.2.14 Have a schedule requiring a bedtime earlier than 8:00pm or later than 2:00am or arising time earlier than 4:00am or later than 10:00am (thus preventing adoption of SHUTi interventions).

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 TREATMENTS

5.1 The Intervention Group: SHUTi. SHUTi is the empirically supported, internet CBT-I created by our consultant, Dr. Lee Ritterband, that is fully accessible via tablets and smartphones. It uses a self-guided, fully automated, interactive, multimedia format to deliver six 45-minute sessions, the structure and content of which mirror traditional face-to-face CBT-I (96, 97). Session content includes sleep restriction, stimulus control, sleep hygiene, cognitive restructuring, and relapse prevention. The primary model of behavior change on which SHUTi is based is Social Cognitive Theory, the most widely used model of behavior change in the internet intervention literature (98). Each session has the same structure: objectives, sleep diary and homework review, new intervention material, homework assignment, and summary. Session content was created to be engaging and is based on learning theory and instructional design (99). SHUTi is enhanced through a variety of interactive features, including personalized goal setting, graphical feedback based on inputted symptoms, animations and illustrations to enhance comprehension, quizzes to test user knowledge, patient vignettes, and video-based expert explanation. Across sessions, patients also receive tailored sleep recommendations and feedback based on the sleep diary data they enter into the program. SHUTi has been shown to be acceptable, feasible, and effective in several RCTs published in high-impact journals (87, 100-103) with effect sizes comparable to face-to-face CBT-I (79).

SHUTi was developed and studied in patients who were 18 years and older (100, 102). The prescription digital therapeutic platform for chronic insomnia marketed as Somryst™ utilizes SHUTi principles but carries an FDA approval only for those aged 22 and greater, as the FDA considered those under age 22 (e.g. ages 18-21) to be children and would thus require a separate pediatric indication using pediatric insomnia measures. As this study will use SHUTi (which is licensed for research purposes by Dr. Ritterband's group for those 18 and older), and not Somryst™, we will include HIV-positive patients with insomnia who are 18 years or older to increase external generalizability and extend the study's potential impact across the lifespan as per our NIH application.

To minimize treatment barriers, attrition, and subject burden, SHUTi sessions will be delivered remotely at a location selected by the participant where s/he can access a computer with internet, such as the participant's home, the participant's work, a family member's/friend's home, or a public library. We will loan study tablet

computers with data plans to patients without reliable internet access to maximize intervention update and decrease attrition. Dr. Stewart's laboratory and the Infectious Diseases Research Clinic at Eskenazi Health Hospital will serve as backup locations for SHUTi session delivery if a participant prefers in-person delivery. All intervention patients will also be given new earbud headphones and a binder containing printouts of SHUTi worksheets.

We will deliver SHUTi with support, as it increases the efficacy of internet interventions (104-106). Specifically, the Intervention RA, a clinical psychology PhD mentee of Dr. Stewart's, will track each participant's progress through the SHUTi dashboard and will check-in with each participant every two weeks to address any questions or issues.

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 completed by the participant between the Entry Visit and the Week 12 Study Visit at rate of a session every 1-2 weeks. No physiologic or biologic assessments will be performed during these sessions. The participants need not be fasting for these sessions.

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.

5.2 The Active Control Group: Internet Sleep Education/Hygiene, Symptom Monitoring, and Usual Care.

In our pilot trial, our comparator was usual care. However, in the proposed trial, we will use an active control comparator (107) for two reasons. First, we wish to obtain precise effect size estimates for the next-step trial, and a usual care comparator could overestimate efficacy. Of note, Irwin's RCT (21) found moderate-to-large improvements in insomnia remission and CRP with CBT-I versus a sleep education/hygiene active control. Second, our active control arm will help to ensure that the groups have similar expectancy of benefit.

The Active Control RA, another clinical psychology PhD mentee of Dr. Stewart's, will oversee and deliver the active control procedures. First, the RA will give participants access to the internet sleep education/hygiene program, which was created by our consultant, Dr. Lee Ritterband, to serve as a standardized active control condition for SHUTi. This educational program was developed at the University of Virginia with funding from the National Institutes of Health and is fully accessible via tablets and smartphones. This program provides static information about: insomnia symptoms; the impact, prevalence, and causes of insomnia; when to see a doctor; and basic lifestyle, environmental, and behavioral strategies to improve sleep (i.e., sleep hygiene recommendations). The content for this program was informed based on a review of insomnia-focused websites at the time of development. Second, just after giving participants access the internet sleep education/hygiene program, the RA will email or mail a list of local behavioral health services to patients and will encourage them to follow-up with their HIV provider. To engender expectancy of benefit, the RA will stress that our notifications should prompt actions by their provider and that the available treatments are evidence-based. We will then notify the HIV provider, which will encourage them to address their patient's insomnia and provide the same list of local services. The same RA will also call each control participant every 4 weeks to assess insomnia symptoms (ISI) and will notify clinical staff to encourage additional care when indicated. Furthermore, the RA will encourage continued use of the sleep hygiene practices. Each control participant will receive usual primary care for insomnia, which in our local HIV clinics is typically limited to sleep hygiene

practices (CBT-I is not offered) and use of antihistamines and trazodone (hypnotics and benzodiazepines are rarely used).

Participants randomized to either the Intervention group or the Active Control group will complete sleep diaries based on consensus sleep diary questions (108) that are incorporated into the online platforms for SHUTi and Active Control for the 14 days immediately after the Entry visit and the 14 days immediately before the Week 12 and Week 24 visits.

We will also assess treatment credibility/expectancy of benefit (109) (end of first SHUTi session or active control call) and insomnia treatment satisfaction with an item from our past trials (Week 12 Visit).

Of note, there will be no restrictions on the care that the participants can receive by their primary care providers, although we will assess changes in such care during the trial.

5.3 Prohibited Medications

- Investigational agents
- Cytotoxic chemotherapy
- Systemic immunosuppressive medications
- 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)
- Hepatitis C medications

6.0 CLINICAL EVALUATIONS

6.1 Schedule of Events

[1]The HIV-1 RNA screening laboratory can be abstracted from routine clinical care if performed within 30 days (before or after) the Screening ISI used for determining eligibility. If HIV-1 RNA is not available from routine clinical care within this window around the Screening ISI, then the participant must complete an in-person Screening Visit for blood HIV-1 RNA measurement.

[2]The Screening ISI can be performed by phone to assess eligibility after verbal consent is provided. If the ISI score is <11, then the patient is not eligible for the study. If the ISI score is ≥11, then the participant may be eligible.

Evaluation	Screening Visit	Entry/Randomization Visit (within 42 days of positive ISI screening)	Interventions: SHUTi vs. Sleep Education/Hygiene Active Control	Week 12 Visit (70-100 days after Entry Visit)	Week 24 Visit/Closeout (150-190 days after Entry Visit)
Verbal Informed Consent for Screening	X				
Written Informed Consent for Randomization		X			
Documentation of HIV Status	X				
Medical/Psychiatric History	X				
Medication/Supplement Use History	X				
Diagnoses	X				
Laboratory History [hepatitis C antibody status (positive, negative), hepatitis C RNA level (HCV viral load), hemoglobin, glucose, albumin, creatinine, and estimated GFR (per CKD-EPI equation)]		X			
Updated Psychiatric Treatment History		X		X	X
Updated Medications		X		X	X
Updated Diagnoses		X		X	X
Height (in cm)		X			
Weight (in kg)		X		X	X
Vital Signs (blood pressure, heart rate, temperature)		X		X	X
Screening laboratories (HIV-1 RNA)[1]	X	X			
HIV-1 RNA and CD4 cell count		X		X	X
Inflammation biomarkers (hsCRP, IL-6, sCD14, sCD163, CD14+CD16+ monocytes)		X		X	X
Urine pregnancy testing		X		X	X
Archived blood samples		X		X	X
Screening ISI[2]	X				
Questionnaires: ISI; PSQI; DBAS-16; PHQ-9; SCL-20; GAD-7; PROMIS® Fatigue Short Form; AUDIT; PEG-3; and SF-36		X		X	X
STOP-BANG Sleep Apnea Questionnaire		X			
Sleep History and Beliefs Survey (PRE-Treatment)		X			
Sleep History and Beliefs Survey (Post-Treatment)				X	X
Alcohol, tobacco, substance use; physical activity; medication adherence questionnaires		X		X	X
SCISD-R		X			
Sleep Diaries		X (14 days after)		X (14 days before)	X (14 days before)
Randomization		X			
SHUTi vs. Active Control Interventions			X		

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 the Screening Visit:

- Birthdate
- Sex at birth
- Patient's self-report of ethnicity (Hispanic vs. Non-Hispanic) and race (White, Black, Asian, Native American, Pacific Islander)
- Year of initial documentation of HIV positivity
- 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
- Any behavioral treatments within one year of Entry Visit

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 in cm will be recorded on CRFs at the Entry Visit.

6.2.6.2 Weight

Weight in kg will be recorded on CRFs at Entry, Week 12, and Week 24 study visits.

6.2.6.3 Resting Blood Pressure

Blood pressure measurements (systolic and diastolic) will be recorded on the CRFs at Entry, Week 12, and Week 24 study visits. Blood pressure measurements should be performed on the same arm throughout the study. The participant will 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 on 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 Entry, Week 12, and Week 24 study visits. This may be done prior to the first blood pressure measurement. The participant will first sit quietly for five minutes prior to measurement of heart rate.

6.2.6.5 Laboratories obtained through routine clinical care

Laboratories obtained through routine clinical care before the Entry/Randomization visit will be abstracted and recorded onto CRFs. These include most recent hepatitis C antibody status (positive, negative), hepatitis C RNA level (HCV viral load), hemoglobin, glucose, albumin, creatinine, and estimated GFR (per CKD-EPI equation). If available, the most recent HIV-1 RNA level obtained within 30 days of the positive ISI score meeting the insomnia inclusion criterion will also be recorded on CRFs.

6.2.6.6 Laboratories

An HIV-1 RNA level will be obtained at an in-person Screening visit if none are available through routine clinical care within 30 days of the positive ISI score meeting the insomnia inclusion criterion. This will be performed at the IUH Pathology Laboratory.

HIV-1 RNA and CD4 cell counts will be measured at the Entry, Week 12, and Week 24 study visits. These will be performed at the IUH Pathology Laboratory.

Whole blood [THREE (3) 6.0-mL, purple-top EDTA tubes] will be drawn for the inflammatory biomarker measurements at Entry, Week 12, and Week 24. These tubes are to be filled completely. These whole blood samples are not to be spun after collection and are to be kept at room temperature and upright pending transfer to the Angio BioCore. These 3 tubes for the Angio BioCore will be labeled “WB ABC”. These will be given to the Angio BioCore laboratory (under Dr. Karen Pollok’s supervision) for same day measurement of monocyte fractions using standard flow cytometry procedures. The residual sample will be processed for plasma aliquots and stored. These aliquots will later be used for batch testing of hsCRP, IL-6, sCD14, and sCD163 in the Analyte Core of the Diabetes Center (under Dr. Robert Considine’s supervision) and for longer term archival for measurement of proteins and chemicals of future research interest.

Computer labels will be generated and affixed to the appropriate specimen containers and will include the specimen number, participant number, specimen date, specimen type, and aliquot number. Labels must be affixed prior to freezing the vials.

Urine pregnancy testing will be performed for women of reproductive potential at Entry, Week 12, and Week 24.

6.2.6.7 Questionnaires

At Entry, Week 12, and Week 24, participants will complete a questionnaire battery (see Appendix) containing the following: standard questions assessing demographics, medical/psychiatric history, sleep mediation use, insomnia treatment satisfaction, and insomnia care received outside of the trial; ISI; PSQI; DBAS-16; PHQ-9; SCL-20; GAD-7; PROMIS® Fatigue Short Form; AUDIT; PEG-3; and SF-36. The questionnaire battery will also include validated scales assessing physical activity level, tobacco use, illicit drug use, medication adherence and the probability of sleep apnea (STOP-BANG Questionnaire; Entry only). The questionnaire battery will be administered on a computer in private with availability of the study team to assist only when asked by the participant.

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 for the full Suicide Management Plan). 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 or with the psychiatrists assigned to the LifeCare clinic, 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 email will also be sent to the potential participant's HIV 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.

Because it is unknown if insomnia 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 IU 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 develops a 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

9.0 STATISTICAL CONSIDERATIONS AND DATA MANAGEMENT

9.1 General Considerations

To test our hypotheses, we will use intention-to-treat (ITT) analysis of covariance models to test for treatment group differences in Week 24 levels of inflammation biomarkers adjusted for baseline levels. P-values will be two-sided and considered significant at $\alpha=0.05$. Adjustments for multiple comparisons will not be performed due to the relatively small sample size and exploratory nature of this phase II trial.

In secondary/exploratory analysis, multivariable linear regression models will be constructed to include treatment group and other potentially confounding baseline and time-updated variables that differ significantly between groups and which may account for differences in outcomes. Baseline characteristics that may be included in the models are demographics (age, sex, race/ethnicity), ISI scores, PHQ-9 and SCL-20 scores, tobacco/adherence questionnaire results, ART drugs/regimens (including efavirenz, rilpivirine, and integrase inhibitors), insomnia medication use, comorbidities, CD4 cell counts, HIV-1 RNA levels, levels of the inflammation biomarkers, and nonprescription substance use. Time-varying characteristics that may be included are changes in ISI scores, questionnaire results, CD4 cell counts, ART drugs/regimens, and HIV-1 RNA levels.

We will also perform 'per protocol' secondary analyses comparing the $ISI_{4\text{-}6}$ subgroup (defined as participants who completed ≥4 of the 6 SHUTi sessions) vs. the active control group to determine if greater SHUTi engagement leads to greater differences in the endpoints of interest.

We will also examine relationships between changes in questionnaire scores, especially ISI scores, and the inflammatory endpoints using Pearson correlations.

All of these models will be repeated for comparing 12-week changes in the endpoints in addition to the primary models for 24-week changes.

9.2 Missing Data Approach

Missing data mechanisms will be examined by comparing completers with incompleters on the baseline factors. Multiple imputation (SAS proc mi and mianalyze) will be used if a substantial amount (>10%) of missing data exist. If differential missing patterns are observed, sensitivity analyses will be performed to evaluate the consequences of potential missing mechanisms.

9.3 Potential Moderators, including Biological Sex, of Intervention Effects

In exploratory analyses, we will test interactions between the following baseline factors and treatment group to examine these factors as potential moderators of intervention effects: age, sex, inflammation biomarkers levels, ISI scores, PHQ-9 and SCL-20 scores, use of sleep aids/medications, and nonprescription substance use. Given that the proposed trial is not powered to detect such interactions, specific models will also be run separately for males and females to assess whether there are clinically important differences in the treatment group-outcome relationships between sexes.

9.4 Mediation Analyses

Preliminary mediation analyses to assess for intervention-related decreases in ISI scores, behavioral changes, and HIV virologic rebound (either singly or in combination) to explain reductions in the inflammation/monocyte activation endpoints will be performed.

9.5 Sample Size Justification

The goal of this application is to provide proof-of-concept data and effect sizes of SHUTi on inflammation/monocyte activation endpoints in support of a future, definitive trial. As such, the proposed sample size is based on the enrollment time period and the funding allowance of the R21 mechanism, not for definitive superiority testing. We will enroll 50 participants with the expectation that 40 (20 in each arm) will complete the 24 week study. Using the standard deviations and correlations between baseline and week 24 for hsCRP (this trial's primary endpoint) from our previously published depression trial, we have 80% power (α=0.05) to detect mean differences between study groups of 3.41 mg/L. This detectable difference is clinically meaningful, as it is similar to that found to be predictive of CVD events and overall mortality in the SMART trial (66, 110).

For the primary and secondary endpoints, the following table demonstrates the effect sizes that can be observed between study groups (N=20 in each arm), assuming similar variances and correlations as observed in our pilot trial of internet CBT for depression in PWH. Of note, the detectable difference in IL-6 is also clinically meaningful, given that differences of 1.3-2.2 pg/mL were associated with greater risks of CVD and mortality in the SMART trial (66, 110).

Outcome	SD	Correlation	Detectable mean difference (N=20 per group)
hsCRP (mg/L)	4.87	0.64	3.41
IL-6 (pg/mL)	2.34	0.32	2.02
sCD14 (ng/mL)	751	0.70	488
sCD163 (ng/mL)	19.12	0.89	7.97
%CD14+CD16+ monocytes	5.54	0.31	4.77

Our group has access to ~3000 HIV-positive outpatients engaged consistently in care within the Indiana University Health system (Eskenazi Health with 1200; IU Methodist Hospital with 1800). As part of our pilot trial, we found that ~30% of the virologically-suppressed PWH in our HIV clinics have ISI scores ≥11. Thus, there are ~900 patients eligible for recruitment. Based on review of our clinic population characteristics, we estimate ~800 will fulfill the other eligibility criteria.

9.6 Criteria for Stopping the Study

No early stopping rule will be implemented.

9.7 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.

9.8 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.

9.9 Adherence

Adherence status will be tabulated for both arms.

9.10 Analysis Datasets

Intent-to-treat set will include patients as randomized regardless their adherence status and data completeness.

Per-protocol set will include patients with 24-week hsCRP measurements and who completed at least 4 out of 6 SHUTi sessions.

9.11 Interim Analysis

No interim analysis will be performed.

9.12 Subgroup Analysis

Our analyses will be repeated comparing the Active Control group with the SHUTi intervention group who complete ≥4 of the 6 planned treatment sessions (the $SHUTi_{4\text{-}6}$ subgroup).

9.13 Data Management

9.13.1 Data Management Systems.

IU REDCap will be used to capture demographics, vital signs, medications, medical/psychologic history, diagnoses, interview, survey, and EHR data. The following IU REDCap databases will be created: Recruitment and Screening, SHUTi Intervention Delivery, Active Control Delivery, Screening Visit, Entry Visit, Week 12 Visit, and Week 24 Visit. Data will be exported from IU REDCap in SAS format. Assay data from the Translation Core Analyte Laboratory (hsCRP, IL-6, sCD14, sCD163) and the Angio BioCore (CD14+CD16+ intermediate monocytes) will be converted from Excel to SAS format and merged with the IU REDCap data.

9.13.2 Methods of Data Cleaning

Data cleaning procedures will assess for out-of-range values, outliers, normality, and very low frequency classes for each variable using SAS statistical software. Frequencies will be examined to identify out-of-range (i.e., impossible) values. Identified out-of-range values will be checked against the source data and corrected (any data entry, coding, or computational errors will be fixed and/or assays will be rerun, as appropriate). Z

scores (≤ -3.3 or ≥ 3.3) for all continuous variables will be computed to identify outliers. Identified outliers will be checked against the source data and corrected if due to data entry errors. If not due to data entry errors, these values will be noted, retained in primary analyses, and may be altered or removed in sensitivity analyses. Skew (≤ -3 or ≥ 3) and kurtosis (≤ -10 or ≥ 10) values will be examined to assess normality of continuous variables. If the normality assumption is not met, variable transformations to normalize distributions and/or distribution-free nonparametric tests for the primary analyses will be considered.

9.13.3 Tracking of Emergency Department Visits and Hospitalizations

For the DSMB reports prepared by Dr. Gupta every 6 months, Ms. Danielle Grounds will query the relevant EMR to extract data (type of medical visit and diagnostic codes) to be stored in an Excel file. Dr. Gupta will report the total number of emergency department visits and hospitalizations among randomized participants in the DSMB reports. If evidence of treatment group imbalance emerges, further investigation by Dr. Gupta will be initiated (e.g., examining reasons for the visits), and the results will be reported to the DSMB for their consideration.

9.13.4 Methods for Monitoring the Quality and Consistency of Data Collection

We will use our IU REDCap assessment databases to ensure the collection of high-quality data in a consistent fashion over time. These databases will serve as both the operations manual and the data collection instrument for study contacts. Specifically, each database will include step-by-step instructions (e.g., from the scheduling call to the closing of a visit) with a box to be checked by the team member when each step is completed. All interview questions and questionnaire items will be embedded in the databases, along with radio buttons, checklists, drop-down menus, or open fields to capture participant responses. There will be open fields to capture height, weight, and vital signs. Instructions for the electronic health record chart reviews and the corresponding data fields will also be embedded to capture relevant data (e.g., concomitant medications and insomnia care received outside the trial). Data quality (e.g., % missingness) will be assessed every 6 months before DSMB meetings, and data quality metrics will be reported to the DSMB every 6 months in Dr. Gupta's DSMB report.

9.13.5 Policies and Methods for Ensuring Blinding of Study Results

To ensure unbiased results, all outcomes assessors will be blinded to treatment group assignment, and all patients will be blinded to study hypotheses until the proposed trial is complete. Drs. Gupta and Stewart and the study personnel involved in treatment delivery (SHUTi vs. sleep education/hygiene) will not be blinded by necessity. Dr. Liu and Ms. Grounds will have the master randomization list but will not share it with the blinded co-investigators and laboratory personnel performing the endpoint inflammation assays (Drs. Considine and Pollok). At the Entry Visit, randomization will occur at the end of the session after all data collection for that visit is complete.

9.13.6 Data Confidentiality and Subject Privacy

All research material will be kept strictly confidential. All investigators and study personnel have completed or will complete the Collaborative Institutional Training Initiative (CITI) courses in Human Subjects Research and Good Clinical Practice and will make every effort to ensure confidentiality. All electronic and hard copy data will be identified using only the unique participant identification number assigned when each patient is enrolled (participant identifying information will not be included). All electronic data will be saved on password-protected and encrypted computers and secure servers, and all hard copy data will be stored in secure and locked file cabinets. The key linking participant names with the participant identification numbers will be

kept in a separate secure and locked file cabinet. Data will be analyzed and reported as an aggregate, with no individual identifying information.

To protect participant privacy, all in-person data collection will be conducted in private rooms at the Infectious Diseases Research Clinic. In addition, all study phone calls will be conducted from private rooms in Dr. Stewart's Cardiovascular Behavioral Medicine Laboratory. No identifying information will be entered into SHUTi. Instead, participants will log on using their participant identification number and a password they create. Finally, participants will be instructed to complete study calls and SHUTi sessions in private rooms or areas in their homes or other locations they choose.

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). Although the NIH does not require a formal Data and Safety Monitoring Board, we will still employ one with an independent monitor as described below. 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

- A total of 50 HIV-positive participants will be recruited to participate in this pilot trial investigating the efficacy of internet cognitive behavioral therapy for insomnia using the SHUTi computer program to reduce systemic inflammation and monocyte activation.
    - Participants must be at least 18 years of age (no upper age limit), have documented HIV infection, have a screening HIV-1 RNA level <75 copies/mL while on ART for at least six months, and have insomnia disorder per the Structured Clinical Interview for DSM-5 Sleep Disorders.
    - The chief exclusion criteria include if they have another sleep disorder diagnosis (e.g. sleep apnea); have a schedule requiring a bedtime earlier than 8:00pm or later than 2:00am or arising time earlier than 4:00am or later than 10:00am (thus preventing adoption of SHUTi); have any other pro-inflammatory condition (e.g. autoimmune diseases); malignancy requiring treatment within 6 months of screening; are receiving systemic daily anti-inflammatories; have a history of bipolar or psychotic disorder; or are currently pregnant or breastfeeding.
    - Potential participants will be recruited from the Ryan White HIV outpatient clinics of Eskenazi Health Hospital and Indiana University Health Methodist Hospital.

10.2.2 Sources of Materials

- All data for this study will be obtained only after verbal consent is provided during the Screening process and after written, informed consent is provided by each participant for the formal randomized, clinical trial portion of the study. Existing medical records will be reviewed for demographics, medical diagnoses, and medications. Blood samples will be obtained for testing of HIV-1 RNA levels, CD4 cell counts, and inflammation biomarkers. Urine samples will be obtained

for pregnancy testing. Plasma will be obtained and stored for future studies of interest. Questionnaires to assess insomnia, depression, tobacco and alcohol use, anxiety, medication adherence, physical activity, and fatigue will also be implemented.

- 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. Urine specimens will be obtained via standard clean-catch technique. Blood specimens will be obtained via peripheral venipuncture. 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. The first is the potential loss of participant confidentiality. The second consists of the risks associated with blood drawing/needle sticks, which include pain, bruising, infection, and phlebitis. The amounts of blood to be drawn at screening and at each main study visit are 5 cc (one teaspoon) and 18 cc (1-2 tablespoons), respectively. The total amount of blood to be obtained over the 24 week study period would be approximately 60 cc (4 tablespoons), which is well within the accepted standards for blood donation over a 6 month period. There are no known risks related to the implementation of the SHUTi cognitive behavioral therapy program in the Intervention Group or of the sleep education/hygiene program in the Active Control/Comparator group. Participants may also feel unease in completing the questionnaires.
- 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

- In brief, recruitment will only begin once the Indiana University Institutional Review Board has approved this study. All participants will be recruited from the outpatient Ryan White HIV care clinics at Eskenazi Health Hospital and Indiana University Health Methodist Hospital. Self-referrals from other venues will also be considered. The EMR filter functions (EPIC for Eskenazi Health, Cerner for Methodist Hospital) will be used to identify potentially eligible participants from the clinic databases. We will then ask each patient's primary HIV caregiver for permission to approach their patient for recruitment into the trial. If permission is granted, our dedicated trial recruiters will approach these potentially eligible patients either in person or by telephone to discuss the trial and screen for insomnia using the Insomnia Severity Index (ISI). For those with an ISI score $\geq$11 and who are willing to participate in the trial, the recruiters will then refer these patients to Ms. Grounds, the primary study coordinator, to schedule a formal Screening Visit. If eligibility is confirmed at the Screening Visit, 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 some of the questionnaires (e.g., those assessing depressive symptoms). 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 Blood draws. The risks of blood drawing will be minimized by having only experienced medical personnel perform this procedure. The amount of blood that will be drawn falls well within safety standards for blood donation.

10.3.2.4 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 for the full Suicide Management Plan). 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.

10.3.2.5 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.

10.3.2.6 Data and Safety Monitoring. Upon discussion with the NIH/National Institutes of Mental Health, this trial is considered a minimal risk study that does not require independent monitoring. As such, only Level 1 monitoring by the co-PIs (Drs. Gupta and Stewart) is required. The co-PIs under supervision of the IU IRB will meet every 6 months to review and ensure participant safety; monitor recruitment, accrual, randomization, retention, treatment delivery and fidelity; and review data collection and quality; suicidal ideation protection protocol triggers; any adverse events; any protocol deviations; and any IRB amendments. The IU IRB and NIH will receive copies of all monitoring reports and responses at the time of continuing review.

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

- Potential benefits to the participants include an evaluation of their insomnia, immunology, and pro-inflammatory status. They may also derive short-term benefits from the SHUTi and sleep education/hygiene treatment programs, although this is not guaranteed. Participants will also be provided with the final trial results via their HIV providers. Finally, the participants may also benefit from knowing that their participation will accrue knowledge that could benefit other HIV-positive patients.
- Although there are no guaranteed clinical benefits from those who are randomized to treatment with SHUTi, this program appeared safe in our pilot trial involving PLW and in the thousands of HIV-negative patients in published trials. Therefore, the ancillary benefits to the participants in the proposed trial significantly outweigh the minimal risks in this study. Moreover, the proposed research may lead to other prevention and therapeutic studies that would demonstrate how to reduce inflammation in PLW, which consequently may reduce future serious non-AIDS events in the HIV-positive 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, insomnia treatment, and inflammation. This would potentially impact the clinical care of HIV-positive patients at risk for serious non-AIDS events. 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.
- The risks to the participants are considered minimal. Even if the trial results are negative, the ensuing knowledge will add substantially to our understanding on the mechanisms underlying inflammation in HIV-positive patients with insomnia. Therefore, the importance of the knowledge gained outweighs the risks to the participants.

10.6 Data and Safety Monitoring Plan and Board

For this phase II trial, we have developed a Data and Safety Monitoring Plan to ensure the safety of participants and to monitor participant recruitment, accrual, randomization, and retention; treatment delivery and fidelity; and data collection and quality.

10.6.1 Data and Safety Monitoring Plan (DSMP)

10.6.1.1 Adverse Event Monitoring.

We will systematically identify potential adverse events (AEs): (a) by conducting Eskenazi Health and IUH Health Methodist EMR searches every 6 months for all emergency department visits, outpatient visits, and hospitalizations that occurred among randomized patients and (b) by reviewing responses on a self-report questionnaire assessing for the occurrence of any potential adverse events since the last study visit/call. Any potential AEs spontaneously reported by participants will be evaluated. We will fully investigate, rate, and prepare a Case Report Form for those events that are plausibly related to insomnia, insomnia treatment, suicidal ideation, or any study procedure. For all other captured events (emergency department visits or hospitalizations typically for chronic medical conditions that are unrelated to study involvement), we will provide frequency counts for the SHUTi Intervention and Active Control study arms. We will fully investigate these events only if there is evidence of group imbalance. It is worth noting that that: (a) we are delivering safe and established insomnia interventions, (b) we are not delivering any new or experimental interventions or restricting usual care, and (c) all study procedures are noninvasive (except for the blood draw) and standard.

10.6.1.2 Adverse Event Rating and Reporting

All events plausibly related to insomnia, insomnia treatment, suicidal ideation, or any study procedure will be promptly rated using the anticipation, severity, and attribution scales below. These ratings will be included in the Case Report Form for the adverse event and signed by Dr. Gupta or Dr. Stewart.

<u>Anticipation</u>
1. Anticipated
2. Unanticipated

<u>Severity</u>
1. Mild: Awareness of sign or symptom but easily tolerated
2. Moderate: Interference with normal daily activities
3. Severe: Inability to perform normal daily activities
4. Life-Threatening: Immediate risk of death from the reaction as it occurred

<u>Attribution</u>
1. Definite: Adverse event clearly related to study involvement
2. Probable: Adverse event likely related to study involvement
3. Possible: Adverse event may be related to study involvement
4. Unlikely: Adverse event doubtfully related to study involvement
5. Unrelated: Adverse event clearly not related to study involvement

All AEs that meet the IU IRB prompt reporting requirements (unanticipated; definitely, probably, or possibly related to study involvement; and suggest that the research places participants or others at a greater risk of harm than was previously known or recognized) will be immediately reported to the IU IRB and NIH. All severe or life-threatening AEs will be immediately reviewed by the co-PIs and reported to the IU IRB and NIH. All other

AEs will be reported to these entities at the time of continuing review. A summary of AE data (e.g., frequency, types, and corrective actions) will be provided to the IU IRB and NIH at the time of continuing review.

10.6.2 Data and Safety Monitoring Board (DSMB)

For this phase II trial, upon discussion with the NIH/National Institutes of Mental Health, this trial is considered a minimal risk study that does not require independent monitoring. As such, only Level 1 monitoring by the co-PIs (Drs. Gupta and Stewart) is required. Every six months, a written report will be prepared describing study updates; participant recruitment, accrual, randomization, and retention; treatment delivery and fidelity; data collection and quality; suicidal ideation protection protocol triggers; any adverse events; any protocol deviations; and any IRB amendments. The IU IRB and NIH will receive copies of all monitoring reports at the time of continuing review.

10.7 Inclusion of Women and Minorities

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

It is also anticipated that approximately 50% and 5% 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 HIV outpatient clinics of Eskenazi Health and Indiana University Health Methodist Hospitals and in Indianapolis in general.

10.8 Inclusion of Children and Inclusion across the Lifespan

Participants under the age of 18 are excluded from the proposed studies as inflammation and monocyte activation markers may be affected by hormonal fluctuations during puberty. In addition SHUTi has not been fully evaluated yet in those under 18 years. However, there will be no upper age exclusion to ensure that older participants that are now more representative of the aging HIV population in the United States are included in this trial.

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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 prior depression trials conducted by our team (e.g., IRB #'s 1409114254 and1411802537). Those suicide management plans were constructed with input from Eskenazi Midtown Community Mental Health Center leadership, 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 with the PHQ-9 at Entry, Week 12, and Week 24, and we are prepared to appropriately handle the situation should one of the enrolled patients exhibit suicidal ideation.

(a) <u>In-Person Study Visits</u>
Suicidal ideation will be assessed using Item #9 of the PHQ-9 at Entry, Week 12, and Week 24. 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.

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 depression trials (IRB #'s 1409114254 and1411802537), he has trained various 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, 4-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.

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 or with the associated psychiatrist to LifeCare clinic 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.

(b) Study Telephone Contacts

If a participant reports having thoughts of being better off dead or of hurting him/herself spontaneously during a study call (e.g., a scheduling call), 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 or with the associated psychiatrist with the LifeCare clinic 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

Interviewer:_____ 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, no SMP trigger)

Comments:

****

I'm going to ask you a few questions that are part of the study protocol, 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? In other words, are you afraid you might act on these thoughts?

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 patient 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 Suicide Management Plan.