A Randomized, Controlled Trial Assessing the Effects of Cognitive Behavioral Therapy to Prevent Worsening Insulin Resistance in Depressed, Virologically Suppressed, Antiretroviral-Treated Adults with HIV

Version 1.0

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SCHEMA

DESIGN

The objectives of this study will be met by performing a 48-week, randomized, controlled, single-blinded, two-arm, parallel group trial at a single center. 150 participants will be enrolled and randomized. These participants will be ≥ 18 years old, have been receiving antiretroviral therapy (ART) for at least 180 days with an HIV viral load < 75 copies/mL at screening, and meet our definition of current depression. These participants will be randomized 1:1 to either depression treatment with the internet cognitive behavioral therapy for depression program (iCBT-D; N=75) Good Days Ahead (GDA) or Active Control (AC; N=75). In the Informed Consent Statement, Good Days Ahead subjects are referred to as 'Group A' and Active Control subjects are referred to as "Group B."

OBJECTIVES

The primary objective of this study is to compare 24-week changes in Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) in depressed adults with HIV receiving virologically suppressive ART who are then randomized to either depression treatment with the GDA iCBT-D program or to AC. Key secondary objectives include comparing changes in HOMA-IR at 48 weeks; HbA1c and glycated albumin levels at 24 and 48 weeks; and monocyte activation, gut integrity markers, and metabolomic profiles between the two groups at 24 weeks.

DURATION

Each individual participant will be followed for approximately 52 weeks (up to 4 weeks from screening to randomization and 48 weeks on study). We expect to enroll 4 participants per month. The total duration of this study will be approximately 48 months.

POPULATION

All participants will be HIV-positive, 18 years of age or older, have HIV-1 viral loads less than 75 copies/mL while receiving stable ART for at least 180 days, have a screening HbA1c <6.5%, and meet our definition of current depression. Participants will be recruited from the HIV outpatient clinics of Eskenazi Health and Indiana University Health.

SAMPLE SIZE

The total sample size for this study will consist of 150 enrolled participants. If a consented and otherwise eligible participant withdraws prior to the Baseline/Entry Visit, this participant will be replaced.

## 1.0 Hypotheses

### 1.1 Primary Hypothesis

- iCBT-D, compared to active control, will prevent worsening insulin resistance as measured by HOMA-IR at 24 weeks.

### 1.2 Secondary hypotheses

- iCBT-D, compared to active control, will prevent worsening HOMA-IR at 48 weeks and prevent worsening HbA1c and glycated albumin levels at 24 and 48 weeks.
- iCBT-D, compared to active control, will reduce circulating sCD163 levels at 24 weeks.
- iCBT-D, compared to active control, will reduce circulating sCD14, REG3α, 16S rDNA, and β-D-glucan levels at 24 weeks.
- Changes in REG3α, 16S rDNA, and β-D-glucan mediate intervention effects on changes in circulating sCD163 and sCD14 levels.
- Changes in circulating sCD163 and sCD14 levels mediate intervention effects on changes in HOMA-IR.
- iCBT-D, versus AC, will produce changes in the circulating metabolome [including increases in PC(P-16:0/18:2) levels] at 24 weeks.
- The metabolites found to be significantly different between study groups mediate intervention effects on changes in HOMA-IR as determined by formal pathway analysis.

## 2.0 Significance and Rationale

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 has been accompanied by a growing incidence of serious non-AIDS events (SNAE) - including cardiovascular disease, renal disease, and cognitive impairment - despite virologic suppression with ART.[5-8] A central driver of these SNAE is diabetes (HIV-DM).[9-11] As such, there is an urgent need to identify causal mechanisms and prevention strategies for HIV-DM to reduce SNAE in PWH.

One often-overlooked potential etiology for diabetes is depression. As we and others have shown, depression is among the most prevalent risk factors globally for chronic diseases and all-cause mortality, regardless of HIV serostatus.[12-19] Specifically, we have found that greater depression severity is linked to higher risk for incident HIV-DM.[19] Of particular relevance here, we have also found that greater depressive symptoms are associated with heightened monocyte activation in PWH,[20] which may be the mechanistic connection between depression and incident SNAE. Importantly, we conducted a pilot randomized trial demonstrating that internet cognitive-behavioral therapy for depression (iCBT-D), compared to usual care, was associated with prevention of worsening insulin resistance, as estimated by Homeostasis Model Assessment-Insulin Resistance (HOMA-IR).[21] HOMA-IR is a validated and commonly used measure of insulin resistance in HIV studies requiring only fasting insulin and glucose levels.[22, 23] HOMA-IR correlates well with insulin resistance assessed by the gold standard method hyperinsulinemic glucose clamp[24] and is predictive of incident DM.[22, 25]

Broadly speaking, insulin resistance is defined as poor responsiveness to insulin by peripheral tissues in taking up glucose. When insulin resistance is combined with underlying beta cell dysfunction, both dysglycemia and overt type 2 diabetes may develop.[26, 27] Systemic inflammation, and specifically monocyte activation,[28] is thought to be a primary contributor to peripheral tissue insulin resistance through various mechanisms, including abnormal insulin receptor signaling, oxidative stress, and mitochondrial dysfunction.[29] Moreover, acute hyperglycemia may, in turn, worsen immune activation, thereby leading to a vicious cycle.[30]

We also found that HOMA-IR changes were positively correlated with changes in circulating sCD163 levels, a marker of monocyte activation. Furthermore, the changes in sCD163 and HOMA-IR were also both positively correlated with changes in REG3α, a marker of gut permeability. To examine other possible mechanistic pathways, we also assessed differential changes in plasma metabolomic profiles and found those in the iCBT-D arm had significant increases in the metabolite 1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-

16:0/18:2), or PC(P-16:0/18:2). This metabolite has been associated with reduced risk of diabetes in the general population[31] and was negatively correlated with HOMA-IR in our trial.

Altogether, our results indicate that successful depression treatment could reduce diabetes risk in PWH by improving gut integrity (and thus limiting microbial translocation), reducing monocyte activation, and preventing worsening insulin resistance. In addition, our data suggest that examining the metabolome could elucidate new mechanistic and potentially therapeutic pathways linking successful depression treatment to reduced HOMA-IR. However, our promising findings are preliminary and require confirmation and extension in a sufficiently powered RCT.

The proposed trial could have a significant impact on science and clinical practice for many reasons. (1) If our results support our hypotheses, it will greatly strengthen the case that depression is a causal risk factor for insulin resistance and diabetes in PWH. (2) If the trial results are positive, these would elucidate novel biological pathways underlying the depression-to-diabetes relationship in PWH and iCBT-D's mechanisms of action. (3) As a set, these results would fill the existing knowledge gaps and generate the critical support to justify the next-step phase III, multi-site RCT to determine the effect of iCBT-D on incident HIV-DM. (4) Demonstrating that successful depression treatment reduces HIV-DM risk in a phase III trial could lead to the inclusion of depression screening in HIV-DM prevention guidelines and incentivize additional use of resources for depression treatment in HIV clinics. (5) Given that the prevalence of depression in PWH on ART is as high as 40%,[32-36] iCBT-D could have population-level effects by reducing morbidity and mortality in this high-risk population. Our non-pharmacologic intervention would also obviate drug interactions, drug dependence, and side effect concerns with pharmacologic antidepressant therapies. Moreover, our internet intervention platform is convenient, accessible, and private for patients; is not be dependent on mental health provider availability; and is scalable for large clinical populations.[37] (6) Finally, elucidating novel biological pathways could lead to the development of adjunctive interventions directly targeting these mechanisms to maximize iCBT-D's beneficial effects on HIV-DM risk.

## 3.0 Background

**Depression, systemic inflammation, insulin resistance, and diabetes.** A 2013 meta-analysis[38] (23 studies) found that depressed adults have a 38% (adjusted for established risk factors) greater risk of developing diabetes than nondepressed adults. This risk conferred by depression is clinically important, as it is on par with established diabetes risk factors, such as smoking.[39-41] A 2008 meta-analysis[42] found that risk ratios for depression predicting diabetes were comparable for women (1.26), men (1.57), older adults (1.50), younger adults (1.96), and groups with higher minority representation (1.79). In addition to clinical diabetes onset, a 2013 meta-analysis[43] (18 studies) revealed that depression is associated with insulin resistance. This finding supports intervening on depression before diabetes onset.

Although the exact pathways through which depression contributes to diabetes development have yet to be determined, several candidate mechanisms have been identified. The leading biological mechanisms are hypothalamic-pituitary-adrenal (HPA) axis hyperactivity, autonomic nervous system dysfunction, and systemic inflammation.[44-48] Maladaptive behavioral mechanisms common in depressed people, such as high calorie diets[49-52] and inactivity,[53] also promote obesity, insulin resistance, and DM.[38, 43, 54] In addition, depression is related to smoking[53, 55] and nonadherence to medical regimens.[56, 57] Compared to nondepressed adults, depressed adults have a 58% greater risk of future obesity,[58] a major DM risk factor.[59] Of note, current conceptual frameworks[60] view systemic inflammation as a final common pathway for both biological and behavioral candidate mechanisms to promote insulin resistance and DM.

**HIV, insulin resistance, and diabetes.** HIV-DM has historically been linked to older generation ART, particularly thymidine analog nucleoside reverse transcriptase inhibitors (stavudine, didanosine) and first-generation protease inhibitors (indinavir) via drug-induced insulin resistance.[61-64] As these regimens were replaced by better tolerated and more easily dosed regimens, other factors are now contributing to insulin resistance and HIV-DM in PWH on ART. These include classic risk factors of age and obesity but may also include indirect effects of tenofovir alafenamide and integrase inhibitors via associated weight gain with these drugs vs. older regimens,[22, 65, 66] although this latter point remains controversial.[67] Other HIV-specific factors contributing to insulin resistance in PWH on ART include persistently elevated systemic inflammation, and specifically monocyte activation, as indicated by elevated circulating levels of sCD14 and sCD163.[68-70] We

have recently published that greater depressive symptoms, potentially via increased monocyte activation, are associated with higher risk for incident HIV-DM.[19, 20] Moreover, we have found that depression treatment with iCBT-D is associated with reduced monocyte activation and prevented worsening insulin resistance in PWH.[21]

**Monocyte activation and gut barrier integrity in HIV.** A key gap in our knowledge, which this trial will address, is how depression treatment causally reduces monocyte activation in PWH. The literature suggests residual low-level viral replication from HIV reservoirs in PWH on ART is not a primary trigger of monocyte activation. [71] Latent cytomegalovirus (CMV) reactivation has been suggested as a cause of increased monocyte activation in PWH,[72, 73] though with conflicting results.[74, 75]

Most research to date has focused on microbial translocation from the intestinal lumen into the circulation as a key driver of monocyte activation in PWH.[76] Even in virologically controlled HIV, there remains persistent intestinal barrier and immunologic disruption with CD4 depletion in gut mucosa. These abnormalities do not lead to overt cultivable bloodstream infections. However, microbial translocation of pathogen products is inferred by higher circulating levels of 16S rDNA (a marker of both gram-positive and gram-negative bacteria)[77, 78] and β-D-glucan (a marker of fungi)[79, 80] in ART-treated PWH compared to people without HIV (PWOH). Moreover, both markers are associated with monocyte activation in PWH.[77, 81, 82]

Circulating markers of impaired gut barrier integrity also remain elevated in PWH on ART compared to PWOH and correlate with markers of microbial translocation. Circulating levels of regenerating islet-derived protein 3α (REG3α), an antimicrobial peptide secreted by intestinal Paneth cells, are increased with disruptions to the gut barrier. A recent study showed that REG3α levels were elevated in PWH not on ART and decreased with virological suppression after ART initiation, although these levels remained elevated compared to PWOH.[83] Another common marker of gut integrity, intestinal fatty acid binding protein (I-FABP), did not change after ART initiation in that study. Moreover, REG3α (but not I-FABP) correlated significantly with HIV-1 viral load, lipopolysaccharide (a marker of gram-negative bacteria), β-D-glucan, and sCD14 levels (sCD163 was not measured). Thus, REG3α is a more accurate and discriminatory marker of gut disruption than I-FABP. Importantly, in our pilot trial, we demonstrated reductions in REG3α in the iCBT-D group compared to usual care and that these reductions correlated with decreases in sCD163.

**HIV, depression, and monocyte activation.** Depression is highly prevalent in the HIV-infected population, including in those receiving ART, with rates up to 40%.[84-87] Several studies have suggested that the rate of depression in HIV is two-fold greater than in uninfected individuals.[88] Given this high prevalence of depression, it is plausible that this comorbidity could appreciably contribute to HIV complications. In fact, we have published multiple epidemiologic studies showing that depression predicts incident myocardial infarction, stroke, heart failure, and overall mortality in PWH.[14, 89-91]

There is a rapidly growing literature supporting a bidirectional 'gut-brain' axis linking depression and systemic inflammation. These relationships may be biologically connected via the central and peripheral (including intestinal) nervous systems and the hypothalamic-pituitary-adrenal axis.[92] Depression, therefore, may trigger these neurohormonal pathways leading to downstream impaired gut integrity with consequent microbial translocation and monocyte activation. In fact, we have now shown that depression is associated with both elevated sCD14 levels[20] and incident DM in PWH on ART[19] and that depression treatment with iCBT-D may be effective in preventing worsening changes in HOMA-IR.[21]

Heightened monocyte activation, but not systemic inflammation in general, may be a unique feature in depressed PWH that may predispose this group to worse clinical outcomes. In the VA Cohort Study (VACS), we demonstrated that somatic depressive symptoms were associated with significantly higher circulating sCD14 levels in PWH (but not in PWOH).[20] Moreover, interleukin-6 (IL-6, a marker of systemic inflammation) was not associated with depressive symptoms in either HIV-serogroup [high sensitivity C-reactive protein (hsCRP) and sCD163 were not measured].

These data are limited in that they included mostly men not receiving integrase inhibitors (ART drugs that we and others have suggested are linked to reduced monocyte activation).[93, 94] However, our published trial of iCBT-D in ART-treated PWH, which included both sexes and those receiving integrase inhibitors, found significant reductions in sCD163 and CD14+CD16+ pro-inflammatory monocytes (but not hsCRP or IL-6) in those allocated to the iCBT-D arm compared to usual care.[21] These results suggest depression in PWH may be causally linked to heightened monocyte activation. This trial will examine whether heightened microbial

translocation due to HIV-induced impaired gut integrity or other yet to be identified mechanistic pathways are responsible.

**HIV, insulin resistance, and metabolomics.** At present, there is a small but growing literature suggesting that specific metabolites are associated with insulin resistance in PWH. A large study comparing PWH not yet receiving ART compared to PWOH found that PWH have higher levels of saturated triacylglycerols and 3-OH-kynurenine, but lower levels of N-acetyl-tryptophan (leading to higher kynurenine/tryptophan, K/T, ratios). When initiated on ART, the PWH receiving the integrase inhibitor raltegravir (with tenofovir DF and emtricitabine), compared to those receiving protease inhibitors, had increased triacylglycerol turnover, associated heightened IL-6 and hsCRP levels, and positive correlations between HOMA-IR and medium/long chain acylcarnitines and palmitate.[95] Thus, ART-induced changes in the metabolome/lipidome may negatively affect insulin resistance in PWH. Another study of PWH receiving efavirenz/tenofovir disoproxil fumarate/emtricitabine found that HOMA-IR was associated with higher plasma C3 acylcarnitines (but not branched chain amino acids or C5 acylcarnitines) and with lower levels of short-chain C2 acylcarnitines. The authors concluded that their results suggest insulin resistance is associated with impaired fatty acid uptake or mitochondrial oxidation.[96, 97] While these initial studies have observed relationships between specific metabolites and insulin resistance in PWH, no published studies have examined the effect of depression treatment on the metabolome in this population. Thus, this trial may confirm and extend our preliminary data suggesting that depression treatment with iCBT-D results in changes in the metabolome that are linked to HOMA-IR in PWH on ART.

**Depression is associated with incident diabetes in PWH on ART.** In a study now published,[19] we examined the association between depressive symptoms and incident HIV-DM in the VACS. Participants were free of diabetes at baseline and were followed over a median of 11.5 years for incident HIV-DM identified using validated Kelly's criteria.[98] Depressive symptoms were assessed using the Patient Health Questionnaire (PHQ)-9 survey, a validated screening tool for depression and validated in PWH.[99] In the 1,510 PWH on ART, each 1-SD increase (6 points) in PHQ-9 score at baseline (indicating greater depressive symptoms) was associated with an 11% increase in incident DM (adjusted hazard ratio (HR) 1.11; 95% CI, 0.99 to 1.25; p=0.07) after adjustment for potential confounders (body mass index, age, sex, race, hepatitis C serostatus, CD4 count, and history of stavudine, didanosine, or protease inhibitors use at baseline). Moreover, compared to those without depression (PHQ-9 <5), PWH with moderately severe depression symptoms (PHQ-9 score of 15-19) had significantly greater risk for incident HIV-DM (adjusted HR 1.64; 95% CI, 1.04 to 2.60; p<0.05). These findings indicated that depression may be an important risk factor for HIV-DM.

**Depression treatment with iCBT-D is associated with reduced depressive symptoms and prevented worsening insulin resistance in depressed PWH on ART.** We have now published our pilot trial[21] of internet CBT for depression (iCBT-D) in 54 PWH on virologically suppressive ART (viral loads <75 c/mL), screening glucose levels <140 mg/dL or HbA1c <8.0%, and with PHQ-9 scores ≥10, indicating high likelihood for major depressive disorder.[100] Participants were randomized 1:1 to an established iCBT-D program (which involved 8 weekly sessions completed within the first 12 weeks of the trial) called Beating the Blues US™ (BtB, n=27) or usual care (UC, n=27). UC participants did not receive any study-provided depression education or treatment, though their HIV providers for all participants were notified of the randomization assignments and were allowed to provide additional antidepressant treatments. There were no exclusions based on use of depression therapies (pharmacologic or non-pharmacologic), types of ART regimens, or CD4 counts at Entry. Two and three participants, respectively, were lost to follow-up over 24 weeks (9% overall attrition). The baseline characteristics of the study groups are shown in Table 1, including the subgroup of 15 participants randomized to BtB who completed at least 6 of the 8 therapy sessions ($BtB_{6\text{-}8}$). The cohort were primarily overweight Black men with the majority already receiving antidepressant medications. No participant had additions or changes in their antidepressant regimen during the trial.

As shown in Table 2, we found that BtB significantly reduced PHQ-9 and Hopkins Symptom Checklist-20 (SCL-20) depression scores over 24 weeks compared to UC, indicating persistent BtB effects beyond the initial

**Table 1. Characteristics of the Beating the Blues (BtB) and Usual Care (UC) study groups at trial Entry. Data presented as mean (SD) or n (%). The $BtB_{6-8}$ subgroup comprised those randomized to BtB and who completed at least 6 of the planned 8 sessions.**

| Characteristic | BtB (n=27) | $BtB_{6-8}$ (n=15) | UC (n=27) | Total (n=54) |
|---|---|---|---|---|
| Age, years | 44.6 (9.8) | 47.5 (10.1) | 45.6 (11.9) | 45.1 (10.8) |
| Female sex | 4 (15) | 4 (27) | 5 (19) | 9 (17) |
| Black race | 21 (78) | 12 (80) | 15 (56) | 36 (67) |
| Current smoker | 10 (37) | 2 (13.3) | 12 (44) | 22 (41) |
| CD4 cell count, µL | 713 (243) | 760 (245) | 743 (396) | 728 (325) |
| Body mass index, kg/m² | 30.0 (7.0) | 30.4 (8.7) | 30.1 (6.7) | 30.1 (6.7) |
| Hemoglobin A1c, % | 5.6 (0.5) | 5.7 (0.6) | 5.4 (0.7) | 5.5 (0.6) |
| HOMA-IR | 4.50 (5.00) | 5.12 (6.22) | 3.73 (2.90) | 4.10 (4.10) |
| PHQ-9 score | 17.13 (4.96) | 17.13 (5.08) | 14.04 (4.32) | 15.58 (4.87) |
| SCL-20 score | 2.27 (0.92) | 2.27 (1.06) | 2.09 (0.63) | 2.18 (0.78) |
| Antidepressant medication use | 18 (67) | 10 (67) | 19 (70) | 37 (69) |
| Tenofovir alafenamide use | 18 (67) | 11 (73) | 19 (70) | 37 (69) |
| Dolutegravir use | 6 (22) | 3 (20) | 7 (26) | 13 (24) |
| sCD163, ng/mL | 466.1 (120.3) | 507.7 (101.4) | 433.0 (212.7) | 448.6 (171.9) |
| sCD14, ng/mL | 2325 (849) | 2302 (829) | 2233 (621) | 2279 (732) |
| CD14+CD16+ monocytes, % | 11.00 (4.51) | 11.19 (4.99) | 8.28 (4.04) | 9.61 (4.45) |
| REG3α, ng/mL | 10.32 (5.14) | 10.56 (4.65) | 12.81 (8.26) | 11.64 (7.02) |

treatment period. The magnitude of benefit was even more pronounced for the $BtB_{6-8}$ subgroup compared to the UC group [PHQ-9, -6.87 vs. -1.38, p=0.007; SCL-20, -0.83 vs. -0.35, p=0.061].

We then examined changes in HOMA-IR between study groups (Table 2) and found significantly greater increases in HOMA-IR in the UC group compared to the BtB group. When excluding participants who had screening HbA1c levels ≥6.5% (the cutoff for a diagnosis of DM), the differences in HOMA-IR at 24 weeks between the BtB (n=24) and UC groups (n=23) were more pronounced [0.21 vs. 3.24, p=0.07; Cohen's d=0.58]. Importantly, HOMA-IR declined in the $BtB_{6-8}$ subgroup vs. UC (-0.46 vs. 2.92, Cohen's d=0.69, p=0.053), thereby suggesting greater adherence to the iCBT-D treatment may *reduce* insulin resistance.

**Table 2. Comparisons between the Beating the Blues (BtB) and Usual Care (UC) groups for 24-week *changes* in depressive symptoms scores (PHQ-9, SCL-20) and insulin resistance (HOMA-IR).**

| Outcome, mean (SD) for 24-week *changes* | BtB (n=25) | UC (n=24) | Difference BtB vs. UC (95% CI) | P-value | Cohen's d |
|---|---|---|---|---|---|
| PHQ-9 score | -6.00 (6.60) | -1.38 (5.00) | -4.63 (-8.00, -1.25) | 0.008 | 0.79 |
| SCL-20 score | -0.72 (0.73) | -0.35 (0.44) | -0.37 (-0.70, -0.04) | 0.029 | 0.61 |
| HOMA-IR | 0.33 (5.61) | 2.92 (4.80) | -2.59 (-5.78, 0.60) | 0.11 | 0.51 |

**Depression treatment and BMI in PWH**. As obesity is a major determinant of insulin resistance and incident DM, we examined the effects of iCBT-D on 24-week changes in BMI (kg/m²) in our pilot trial. There was no significant between mean (SD) group changes in BMI in the BtB arm vs. UC [0.37 (1.35) vs. 1.32 (3.97); p=0.28]; these differences were similar when comparing the $BtB_{6-8}$ subgroup with UC [0.04 (1.22) vs. 1.32 (3.97); p=0.15]. Moreover, changes in BMI were not correlated with changes in either PHQ-9 (ρ=-0.037, p=0.80) or SCL-20 (ρ=0.098, p=0.52) depression scores or changes in HOMA-IR (ρ=0.063, p=0.69). Thus, the beneficial effects of iCBT-D on insulin resistance were not due to changes in BMI.

**Depression and monocyte activation in PWH**. In 2005-2006, the Veterans Aging Cohort Study (VACS) Biomarker Cohort prospectively assessed depressive symptoms [PHQ-9 scores] and circulating biomarkers predictive of cardiovascular disease and mortality (sCD14, IL-6, D-dimer)[101, 102] in 1546 PWH. As shown in Table 3 from our published results,[20] we found that sCD14 was elevated in depressed PWH; however, IL-6 or D-dimer were not. Among PWH, the sCD14-depression association, especially for the somatic depressive symptoms, held after adjustment for demographics, clinical confounders, antidepressant use, HIV-1 viral load, and CD4 cell count.

**Table 3. Relationships between depression and cardiovascular biomarkers in the VACS Biomarker Cohort.**

| CVD biomarker, median (IQR) | Depressed (n=348) | Not Depressed (n=1179) | P-value |
|---|---|---|---|
| ***sCD14, ng/mL*** | ***1822 (1511-2137)*** | ***1694 (1432-2073)*** | ***0.002*** |
| IL-6, pg/mL | 2.20 (1.47-3.55) | 2.03 (1.41-3.35) | 0.14 |
| D-dimer, µg/mL | 0.29 (0.16-0.53) | 0.26 (0.15-0.48) | 0.091 |

Note. Patient Health Questionnaire-9 (PHQ-9) score ≥10: depressed; <10: not depressed.

Although sCD163 was not assessed in the VACS Biomarker Cohort, a recent publication from the Multicenter AIDS Cohort Study (MACS) did examine this biomarker's relationships with depression.[103] The authors provided additional analyses to our group with permission to present these in support of this application (Albert Anderson, personal communication, September 25, 2022) that included only ART-treated PWH with viral loads <200 c/mL to reduce confounding from HIV viremia. As shown in Table 4, sCD163 levels were elevated in depressed (Center for Epidemiologic Studies-Depression (CES-D) score ≥16) vs. not depressed (CES-D <16) PWH. Of note, there were no differences in sCD14 levels (nor in hsCRP or IL-6 levels, data not shown) between groups.

**Table 4. Relationships between depression and monocyte activation markers in the MACS.**

| Monocyte activation marker, mean (SD) | Depressed (n=126) | Not Depressed (n=304) | P-value |
|---|---|---|---|
| ***sCD163, ng/mL*** | ***733.9 (261.5)*** | ***669.5 (245.9)*** | ***<0.05*** |
| sCD14, ng/mL | 1684.0 (494.4) | 1674.4 (421.4) | NS |

Note. Center for Epidemiologic Studies-Depression (CES-D) score ≥16: depressed; <16: not-depressed (CES-D <16). NS=not significant.

As a set, however, these results support a relationship between depression and monocyte activation in PWH on ART.

**Depression treatment, monocyte activation, and gut barrier integrity in PWH**. To assess for potentially causal relationships between depression and monocyte activation in PWH, we examined circulating sCD14, sCD163, and cellular monocytes fractions (by flow cytometry) in our pilot trial. As shown in Table 5, BtB led to significantly reduced sCD163 levels and proportions of CD14+CD16+ monocytes. Interestingly, the difference in changes in sCD163 between BtB and UC (-60.7 ng/mL) is nearly identical to the difference between non-depressed and depressed PWH in the MACS study (-64.4 ng/mL; Table 4), suggesting that successful depression treatment may normalize heightened monocyte activation found in depressed PWH. Of note, there were no significant differences between groups in changes in CD14+CD16- and CD14$^{dim}$CD16+ monocyte fractions (data not shown). There also were non-significantly reduced sCD14 and REG3α levels with BtB vs. UC. The effect sizes for iCBT-D on these outcomes approached medium to large (Cohen's d>0.5).

**Table 5. Comparisons between the Beating the Blues (BtB) and Usual Care (UC) groups for 24-week *changes* in monocyte activation and gut barrier integrity.**

| Outcome, mean (SD) for 24-week *changes* | BtB (n=25) | UC (n=24) | Difference BtB vs. UC (95% CI) | P-value | Cohen's d |
|---|---|---|---|---|---|
| sCD14, ng/mL | -134 (571) | 118 (406) | -251 (-561, 579) | 0.11 | 0.51 |
| sCD163, ng/mL | -13.6 (58.8) | 47.1 (99.6) | -60.7 (-110.3, -11.1) | 0.024 | 0.74 |
| %CD14+CD16+ monocytes | -1.84 (6.15) | 2.23 (6.42) | -4.07 (-7.72, -0.42) | 0.030 | 0.65 |
| REG3α, ng/mL | -0.83 (3.11) | 2.01 (10.00) | -2.85 (-7.34, 1.65) | 0.20 | 0.38 |

Importantly, the changes at 24 weeks in REG3α correlated with changes in sCD163 (ρ=0.28, p=0.08), thus suggesting a relationship between improved gut barrier integrity and reduced monocyte activation with depression treatment. Moreover, 24-week changes in REG3α were nearly significantly correlated with changes in HOMA-IR (ρ=0.27, p=0.09). There were no significant correlations between 24-week changes in sCD14 and CD14+CD16+ monocytes and changes in REG3α (both |ρ|<0.12, both ps>0.50) or with HOMA-IR (both |ρ|<0.20, both ps>0.25), thereby suggesting sCD163 as the preferred monocyte activation marker for the proposed trial. However, as the lack of significant correlations with sCD14 and CD14+16+ may reflect lack of power, we will measure these monocyte activation markers in secondary analyses in this trial. We did not assess microbial translocation markers in our pilot trial, though we will address this limitation in this protocol.

**Effects of depression treatment on metabolomic profiles in PWH**. In our pilot trial, we performed longitudinal metabolomic (including lipidomic) profiling (Metabolon, Inc.) of plasma collected at Entry and Week 24 in BtB (n=20) and UC (n=19) study participants with available paired samples to determine whether depression treatment was associated with perturbations in plasma metabolites. One metabolite, the plasmalogen 1-(1-enyl-palmitoyl)-2-linoleoyl-GPC (P-16:0/18:2) [or PC(P-16:0/18:2)] was significantly increased in BtB but not UC (Figure 1A). Moreover, PC(P-16:0/18:2) negatively correlated with HOMA-IR and BMI across all samples (Figure 1B). PC(P-16:0/18:2) is in a class of glycerophospholipids that are cell membrane structure components and are involved with cellular signaling.[104] They also putatively have antioxidant properties,[105] which may limit insulin resistance and risk for DM.[106] In a large metabolomic study that included 996 and 2618 adults in respective discovery and in validation cohorts,[31] PC(P-16:0/18:2) was shown to be negatively associated with Type 2 DM (β=-0.58, p value =1.17E-15, replication p = 5.70E-5). A recent metabolome-wide association study demonstrated that PC(P-16:0/18:2) was positively associated with vigorous physical activity, thereby suggesting a potential role of this metabolite in the beneficial effects of exercise on diabetes risk.[107] These initial data suggest that iCBT-D in PWH may improve insulin resistance via mechanisms that result in the induction of the metabolite PC(P-16:0/18:2).

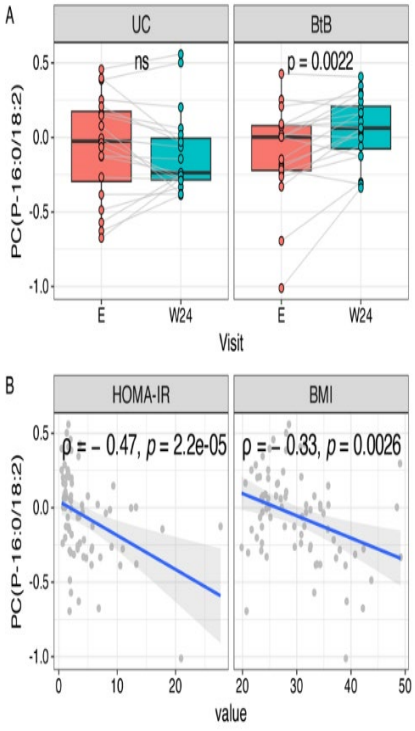


**Figure 1. (A) PC(P-16:0/18:2) scaled abundance by treatment and visit. Significance determined by paired t tests. ns = not significant. (B) Spearman's correlation between PC(P-16:0/18:2) and HOMA-IR or BMI across all samples (n=79).**

These results demonstrate our ability to use metabolomics/lipidomics to identify pathways that may provide novel insight into the mechanisms underlying the beneficial effect of depression treatment on HOMA-IR in ART-treated PWH, even with relatively small samples size. We would expect that additional metabolites will be identified in this larger trial will elucidate more pathways amenable to therapeutic intervention.

## 4.0 Study Design

### 4.1 Overview

The study hypotheses will be tested by conducting a prospective, randomized, parallel-group, clinical trial in which 150 depressed PWH will be randomized 1:1 (75 in each group) to either iCBT-D or AC. The primary endpoint is change in HOMA-IR, as a measure of insulin resistance, at Week 24. We chose Week 24 as our primary endpoint to confirm our previous results; we chose Week 48 as our secondary endpoint to assess for longer-term effects.

We will ensure at least 40% of the participants are female at birth; enrollment of males will be capped at 90 to ensure enrollment of 60 female PWH. Study visits include a Screening Visit, an Entry Visit, a Week 24 Visit, and a Week 48 Visit. The study will be single-blinded, i.e. the participants will not be blinded to the intervention, but the assessors will be blinded to randomization assignment.

### 4.2 Screening Visit

To be eligible for this trial, potential participants must meet our definition for current depression (section 5.1). To pre-assess for this screening eligibility criterion, we will employ one of two methods (within 90 days of the formal Screening Visit). Wemay conduct in-person screening using the PHQ-9 in the HIV clinics of Eskenazi and IUH hospitals, which is considered standard of care in the clinics. (Note: if a current [less than 90 days old] PHQ-9 is in the EMR, it may be used instead.) Alternatively, after provision of verbal phone consent by the potential participant, we will conduct phone screening using the PHQ-9 for those who either self-refer for the trial or who are referred by their HIV provider team members but who have not undergone recent in-person PHQ-9 screening in the clinics. In the latter situation, we will also employ search/filter tools in the electronic medical record system to identify potential participants first and then request approval by the person's HIV provider to contact their patient.

Potential participants with PHQ-9 scores ≥10 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 and scheduled for a formal, in-person Screening Visit to fully determine eligibility and where written, informed consent will be provided.

At the Screening Visit, current depression will be confirmed by (1) repeat PHQ-9 ≥10[100] result at the Screening Visit (suggesting moderate to severe depressive symptoms); (2) PHQ-9 depressive disorder diagnosis (2 or more of the 9 depressive symptoms, including depressed mood or anhedonia, present in the past 2 weeks);[108] (3) functional impairment (using the tenth PHQ-9 item assessing social/occupational impairment); (4) no evidence that the direct physiological effects of a substance, medication, or medical condition clearly account for the depressive symptoms; and (5) no bipolar or psychotic disorders. We have a comprehensive Suicidal Ideation Protection Protocol in place from our prior depression trials for properly handling reports of suicidal ideation during screening and trial participation (see Appendix for details).

After depression diagnosis is confirmed, blood and urine samples will be obtained to assess laboratory eligibility criteria. The participants do not need to be fasting at the Screening Visit.

The participants will be provided a Fitbit and instructed in the use of Fitbits for recording physical activity so that they can properly use this instrument for 7 days prior to the Entry Visit. They will be asked to return their Fitbits at the Entry Visit.

Antiretroviral therapy (ART) will not be provided by the trial, and the trial will not mandate specific regimens (although we will explore for ART interactions in secondary analyses). Use of antidepressant medications or other depression treatments during the trial will not be prohibited in either treatment group for ethical reasons as well as to enhance external generalizability. We will track depression treatments received during the trial and may include depression treatment variables as covariates in our models. As in our pilot trial, the

participants' primary HIV providers will be allowed to initiate any depression treatment that they deem warranted. However, this never occurred in our pilot trial as assessed by participant report, review of prescription records, or by antidepressant metabolite measurement. Thus, we do not expect that the AC group will have appreciably greater use of added depression treatments compared to the iCBT-D group during the trial.

### 4.3 Entry Visit

Within 30 days of the Screening Visit, the participants will attend an Entry Visit. This visit will occur at either the Infectious Diseases Research Clinic located at the Fifth Third Office Building on the Eskenazi Hospital campus or at the Indiana Clinical Research Center at University Hospital (or future IUH Academic Health Center). The participants will need to fast for 8 hours prior to obtaining blood samples at this visit.

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.

All medications (including HIV antiretrovirals), depression therapies (pharmacological and non-pharmacological), and over the counter and homeopathic treatments will be recorded. Vital signs/weight/height/waist circumference, HIV-1 RNA levels, CD4 cell counts, fasting insulin and glucose (to calculate HOMA-IR), HbA1c, and glycated albumin will then be measured. Additional blood and urine samples will be obtained and stored for future laboratory testing.

A stool sample will also be collected. The stool sample will be self-collected at the study visit using the OMNIgene-Gut DNA/RNA kit. Alternatively, the sample may be collected using these kits at home within 7 days prior to the visit and then brought to the visit or returned to the study team within 7 days after the study visit.

All participants will complete a questionnaire battery containing the following: standard questions assessing demographics, medical/psychiatric history, current depression treatments, tobacco/nicotine use, alcohol use (AUDIT), illicit drug use, and medication adherence. In addition, the following surveys will be completed: PHQ-9, SCL-20, GAD-7, ISI, PROMIS® Fatigue Short Form, PANAS-PA, and SF-20. This 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.

Next, participants will complete the web-based VioScreen Food Frequency Questionnaire (FFQ). Study personnel will assist participants in completing the FFQ. Based on study staff's previous experience with this FFQ, we have found that almost all subjects benefit greatly from staff assistance in getting started with this detailed questionnaire. Once particpants become familiar with the flow of the FFQ and are functioning independently, staff may leave the room. Because of the software's design, it is impossible to skip a question. However, the participant may refuse to fill out the FFQ.

The Fitbits provided at the Screening Visit will be returned at this Entry Visit.

Randomization will then take place and will be stratified by sex at birth (male/female) and by current use of prescribed antidepressant medications (yes/no) using random number sequences. Treatment credibility/expectancy of benefit[123] will then be assessed once the participant is aware of their assigned treatment group.

Participant diagnosed with diabetes during the trial will be referred to their HIV primary providers for further diabetes standard of care management but will still be allowed to complete the trial and be included in intention-to-treat analyses. Those lost to follow-up will not be replaced to maintain the integrity of randomization, though we have accounted for potential attrition with an appropriately greater sample size.

## 4.4 Week 24 Visit (145-190 days after the Entry Visit)

The iCBT-D or AC interventions will be implemented between the Entry Visit and the Week 24 visit. While it is not possible to blind participants and members of the study team involved in iCBT-D and AC delivery, participants will be blinded to trial hypotheses, and assessors will be blinded to treatment assignment. We will assess depression treatment satisfaction at this visit.

For women of reproductive potential, a urine pregnant test (UPT) will then be performed before required study procedures. If the UPT is positive, study participation will end with no further assessments completed at this visit and the participant will be discontinued from the trial.

All medications (including HIV antiretrovirals), depression therapies (pharmacological and non-pharmacological), and over the counter and homeopathic treatments will be recorded. Vital signs/weight/height/waist circumference, HIV-1 RNA levels, CD4 cell counts, fasting insulin and glucose (to calculate HOMA-IR), HbA1c, and glycated albumin will then be measured. Additional blood and urine samples will be obtained and stored for future laboratory testing.

A stool sample will also be collected. The stool sample will be self-collected at the study visit using the OMNIgene-Gut DNA/RNA kit. Alternatively, the sample may be collected using these kits at home within 7 days prior to the visit and then brought to the visit or returned to the study team within 7 days after the study visit.

All participants will complete a questionnaire battery containing the following: standard questions assessing demographics, medical/psychiatric history, current depression treatments, tobacco/nicotine use, alcohol use (AUDIT), illicit drug use, and medication adherence. In addition, the following surveys will be completed: PHQ-9, SCL-20, GAD-7, ISI, PROMIS® Fatigue Short Form, PANAS-PA, and SF-20. This 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.

Next, participants will complete the web-based VioScreen Food Frequency Questionnaire (FFQ). If needed, study personnel will assist participants in completing the FFQ. As noted in the Entry Visit section, participants may benefit from staff assistance in initiating the FFQ. Once participants become familiar with the flow of the FFQ and are functioning independently, staff may leave the room. Because of the software's design, it is impossible to skip a question. However, the participant may refuse to fill out the FFQ.

Fitbits will be mailed to the participants prior to the Week 24 Visit so that they can complete the 7-day assessment just prior to this visit and then return the Fitbit at this visit.

Participant diagnosed with diabetes during the trial will be referred to their HIV primary providers for further diabetes standard of care management but will still be allowed to complete the trial and be included in intention-to-treat analyses. Those lost to follow-up will not be replaced to maintain the integrity of randomization, though we have accounted for potential attrition with an appropriately greater sample size.

## 4.5 Week 48 Visit (315-360 days after the Entry Visit)

For women of reproductive potential, a urine pregnant test (UPT) will then be performed before other required study procedures. If the UPT is positive, study participation will end with no further assessments completed at this visit.

All medications (including HIV antiretrovirals), depression therapies (pharmacological and non-pharmacological), and over the counter and homeopathic treatments will be recorded. Vital signs/weight/height/waist circumference, HIV-1 RNA levels, CD4 cell counts, fasting insulin and glucose (to calculate HOMA-IR), HbA1c, and glycated albumin will then be measured. Additional blood and urine samples will be obtained and stored for future laboratory testing.

A stool sample will also be collected. The stool sample will be self-collected at the study visit using the OMNIgene-Gut DNA/RNA kit. Alternatively, the sample may be collected using these kits at home within 7 days prior to the visit and then brought to the visit or returned to the study team within 7 days after the study visit.

All participants will complete a questionnaire battery containing the following: standard questions assessing demographics, medical/psychiatric history, current depression treatments, tobacco/nicotine use, alcohol use (AUDIT), illicit drug use, and medication adherence. In addition, the following surveys will be completed: PHQ-9, SCL-20, GAD-7, ISI, PROMIS® Fatigue Short Form, PANAS-PA, and SF-20. This 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.

Next, participants will complete the web-based VioScreen Food Frequency Questionnaire (FFQ). If needed, study personnel will assist participants in completing the FFQ. As noted in the Week 24 section, participants may benefit from staff assistance in initiating the FFQ. Once participants become familiar with the flow of the FFQ and are functioning independently, staff may leave the room. Because of the software's design, it is impossible to skip a question. However, the participant may refuse to fill out the FFQ.

We will again assess treatment credibility/expectancy of benefit[123] and depression treatment satisfaction at this visit. The participant may refuse to complete any of the questionnaire items.

Fitbits will be mailed to the participants prior to the Week 48 Visit so that they can complete the 7-day assessment just prior to this visit and then return the Fitbit at this visit.

### 4.6 Study Duration and Participant Retention

The maximum study period for each participant will be between 315 to 390 days, accounting for the 30-day period from Screening to the Entry Visit. To promote retention in the study, participants will be financially compensated at the Entry, Week 24, and Week 48 Visits.

## 5.0 Selection and Enrollment Criteria

### 5.1 Inclusion Criteria

- HIV-1 infection, documented as listed clinically in the participant's electronic medical record <u>by any of the following tests</u>: (1) any licensed rapid HIV test, (2) HIV enzyme test kit at any time prior to study entry, (3) at least one detectable HIV-1 antigen, or (4) at least one detectable plasma HIV-1 RNA viral load.
- Age ≥ 18 years.
- Ongoing receipt of stable antiretroviral therapy of any kind for at least 180 days prior to Screening
- Meets the depression definition for this trial:
    - (1) repeat PHQ-9 ≥10[100] result at the Screening Visit (suggesting moderate to severe depressive symptoms), AND
    - (2) PHQ-9 depressive disorder diagnosis (2 or more of the 9 depressive symptoms, including depressed mood or anhedonia, present in the past 2 weeks), AND
    - (3) functional impairment (using the tenth PHQ-9 item assessing social/occupational impairment), AND
    - (4) no evidence that the direct physiological effects of a substance, medication, or medical condition clearly account for the depressive symptoms, AND
    - (5) no bipolar or psychotic disorders

      NOTE: The use of antidepressant medications is <u>not</u> exclusionary.

- HbA1c < 6.5% at Screening
- HIV-1 RNA level < 75 copies/mL at Screening

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

5.2 Exclusion Criteria

- Inability to complete written, informed consent
- Inability to read and understand English as seen on a computer screen
- Diagnosed diabetes mellitus or any previously recorded HbA1c ≥6.5%
- History of bipolar disorder or a psychotic disorder, including schizophrenia

NOTE: Depressive disorders are not exclusionary.

- Incarceration at the time of any study visit

- 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).
- 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

- End stage renal disease requiring renal replacement therapy (dialysis, transplantation).
- Known or suspected malignancy requiring systemic treatment within 180 days of the Entry Visit.

NOTE: Localized treatment for skin cancers is not exclusionary.

- 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.

- Pregnancy or breastfeeding during the study.
- 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

NOTE: Use of NSAIDS and aspirin are allowed

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

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.

## 6.0 Study Treatments

### 6.1 The Intervention Group: Good Days Ahead (GDA)

Intervention participants will receive the empirically supported, HIPAA-compliant, therapist-assisted iCBT-D called Good Days Ahead (GDA; MindStreet, Inc.). We have delivered GDA in our prior (IRB# 1908716624) and ongoing (IRB# 22761) depression trials involving Eskenazi Health and IU Health patients.

GDA uses an interactive, multimedia format (including video, exercises, calls to action, newsfeeds, and customized feedback) to deliver nine 45-minute sessions, the structure and content of which mirror traditional face-to-face CBT. Topics include identifying and modifying automatic thoughts, using behavioral activation and other behavioral methods, identifying and modifying schemas, using effective coping strategies, and employing other core CBT methods. Characters appearing in GDA represent diverse racial, ethnic, age, and cultural backgrounds. GDA includes a clinician portal to allow therapists to track progress, view completed exercises, and check comprehension. In addition, the therapist assistance (~20 minutes/session) is manualized and includes orienting patients to GDA, coaching patients on use of GDA, assessing understanding of CBT concepts, reviewing GDA content and homework assignments, troubleshooting problems in implementing CBT skills, and providing empathic support.

Intervention participants will have access to GDA between the Entry and Week 24 Visits. The intervention will be completed preferably within 12 weeks. They will be instructed to complete sessions in their homes when convenient at a pace of one session every week, leaving time to practice CBT skills between sessions and to review sessions at the end of the period. A Clinical Psychology PhD student supervised by Dr. Stewart will provide therapy assistance via phone at the start of the period and after each session. These PhD students have clinical training and experience delivering CBT and working with populations with medical comorbidities. As we have done in prior trials, we will provide basic tablet skills training and loan study tablets with unlimited data plans to all intervention participants when needed. Providing such training and devices will maximize trial participation, intervention accessibility, and intervention engagement.

### 6.2 Active Control (AC)

Our AC comparator, modeled after that used in our NIDDK-funded RCT (NCT04437485), will include depression education and depressive symptom monitoring along with usual depression care as provided in our HIV clinics. First, trial staff will have a 30-minute call with AC participants to review depression materials, including their HIV provider's role in its management and treatment options. Trial staff will also provide a list of local mental health services. To engender expectancy of benefit, trial staff will stress that our notifications should prompt HIV provider actions and that the available treatments are effective. We will message their HIV provider indicating that their patient screened positive for depression and was randomized to the AC group, note that there are no care restrictions, and provide the same list of mental health services. Second, trial staff will call AC participants every month to assess depressive symptoms (PHQ-9) and will notify clinic staff to encourage additional care when indicated. We elected to use an AC group in this application to further isolate the effects of iCBT-D itself on the study endpoints and to control for potential benefits simply from the study team interactions. Moreover, as noted above in our other primary care study of depression using GDA, improvements in depression symptom scores remained strongly robust compared to an AC group, mitigating concerns about a smaller effect size compared to a usual care control in this trial.

### 6.3 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

## 7.0 Schedule of Events

| Evaluation | Screening Visit | Entry Visit (within 30 days of the Screening Visit) | Interventions: GDA vs. AC (to be completed, preferably, within 12 weeks of Entry) | Week 24 Visit (145-190 days after Entry Visit) | Week 48 Visit (315-360 days after Entry Visit) |
|---|---|---|---|---|---|
| Written Informed Consent for Randomization | X | | | | |
| Documentation of HIV Status | X | | | | |
| Depression diagnosis assessment | X | | | | |
| Medical/Psychiatric History, including review of historical HbA1c levels | X | | | | |
| Medication/Supplement Use History | X | | | | |
| Diagnoses | X | | | | |
| Screening laboratories: UPT, HbA1c, HIV-1 RNA (6 mL whole blood EDTA) | X | | | | |
| Laboratory History [hepatitis C antibody status (positive, negative), hepatitis C RNA level (HCV viral load), hemoglobin, glucose, HbA1c, 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 |
| Waist and hip circumferences (cm) | | X | | X | X |
| Vital Signs (blood pressure, heart rate, temperature) | | X | | X | X |
| HIV-1 RNA, CD4 cell count, HbA1c (13 mL whole blood EDTA) | | X | | X | X |
| Fasting serum glucose, insulin, glycated albumin (6 mL whole blood SST) | | X | | X | X |
| Urine pregnancy testing | | X | | X | X |
| Whole blood for inflammation biomarkers, gut integrity and translocation biomarkers, metabolomics, and storage (3 x 6 mL tubes of whole blood EDTA for plasma, 1 x 6 mL tubes of whole blood SST for serum) | | X | | X | X |
| Whole blood for PBMC isolation (2 x 10 mL tubes whole blood heparin for PBMCs) | | X | | X | X |
| Urine for renal function/injury biomarkers and storage | | X | | X | X |
| Stool samples for microbiomics | | X | | X | X |
| Questionnaires: Tobacco/nicotine, substance use; medication adherence; PHQ-9; SCL-20; ISI; PROMIS® Fatigue Short Form; AUDIT; PANAS-PA, and SF-20 | | X | | X | X |
| VioScreen FFQ | | X | | X | X |
| Fitbit physical activity assessments | | X | | X | X |
| Randomization | | X | | | |
| Expectancy of treatment benefit | | X | | | |
| Depression treatment satisfaction assessment | | | | X | |
| GDA vs. Active Control Interventions | | | X | | |

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

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) with option to self-report more than one race
- 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)
- Historical HbA1c levels

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 antidepressant treatments
- Any other prescription medications within 30 days of Entry Visit
- Any supplements (non-prescription) used within 30 days of Entry Visit
- Any vaccinations within 30 days of Entry Visit
- Any behavioral treatments within one year of Entry Visit

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.

Updated Medications: All new and/or discontinued prescription medications (including antiretroviral and antidepressant medications), supplements, and vaccinations taken since the Entry Visit will be recorded on CRFs with start and stop dates.

Height: Height in cm will be measured using a standard stadiometer and recorded on CRFs at the Entry Visit.

Weight: Weight in kg will be measured using standard automatic scales and then recorded on CRFs at Entry, Week 24, and Week 48 study visits.

Waist circumference: A standard tape measure will be used for measuring waist circumference in cm. The tape measure will be placed halfway between the top of the hip bone and the bottom of the ribs (in line with the navel). The participant will be instructed to breathe out normally. Place the tape measure midway between these points, in line with your belly button, and wrap it around your waist loose enough to fit one finger inside the tape.

Hip circumference: A standard tape measure will be used for measuring waist circumference in cm. The tape measure will be placed around the widest part of the buttocks, loosely enough to fit one finger inside the tape.

Temperature: Temperature will be measured using a standardized thermometer and recorded in Celsius.

Resting heart rate: Resting heart rate will be measured manually. Measurements will be recorded on the CRFs at Entry, Week 24, and Week 48 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.

Resting blood pressure: Blood pressure (systolic and diastolic) will be measured using a manual sphygmomanometer. Measurements will be recorded on the CRFs at Entry, Week 24, and Week 48 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. Therefore, two blood pressure measurements are to be documented in the CRFs.

Laboratories obtained through routine clinical care: Laboratories obtained through routine clinical care before the Screening and Entry Visits will be abstracted and recorded onto CRFs at the Entry Visit. 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).

Study Laboratories:

HIV-1 RNA levels [6 mL whole blood EDTA to be collected with goal to provide 3 mL plasma for testing] will be obtained at Screening, Entry, Week 24, and Week 48. These will be performed at the IUH Pathology Laboratory.

CD4 cell counts [3 mL whole blood EDTA] will be measured at the Entry, Week 24, and Week 48 study visits. These will be performed at the IUH Pathology Laboratory.

HbA1c levels [4 mL whole blood EDTA] will be measured at Screening, Entry, Week 24, and Week 48. These will be performed at the IUH Pathology Laboratory.

Whole blood [THREE (3) 6.0 mL, purple-top EDTA tubes; ONE (1) 6.0 mL, gold-top serum separator tube (SST); and TWO (2) 10.0 mL green-top sodium heparin tubes] will be drawn for the metabolomic and inflammatory biomarker measurements at each of the Entry, Week 24, and Week 48 visits. These tubes are to be filled completely. EDTA and SST tubes will be used for plasma and serum, respectively. Heparin tubes will be used for isolation of PBMCs. These whole blood samples are not to be spun after collection and are to be kept at room temperature and upright pending processing by the Indiana CTSI Biospecimen Management Core (CTSL/SSF). The whole blood samples will be processed for plasma, serum, and PBMCs by the CTSL and then stored in the SSF.

The PBMCs will be stored in liquid nitrogen vapor phase for future genomic and single cell transcriptomic testing in the Indiana CTSI Biospecimen Management Core (CTSL/SSF). The plasma and serum aliquots will be stored for future batched testing of glucose and insulin (for calculation of HOMA-IR), glycated albumin, hsCRP, IL-6, sCD14, sCD163, REG3α, and β-D-glucan in the Analyte Core of the Diabetes Research Center (under Dr. Considine's supervision). Additional samples will be used for 16S rDNA via Dr. Tran's laboratory and metabolomics via Metabolon Inc (Morrisville, North Carolina), which is IUSM's preferred metabolomics vendor. The remaining samples will be held for longer term archival for measurement of proteins and chemicals of future research interest.

At least 6 plasma aliquots of 0.5 mL each will be processed and frozen at -80C within 4 hours of processing. One aliquot (≤0.5 mL) will be in de-identified, barcoded specimen tubes that will be specifically for metabolomics at Metabolon. Another 6 serum aliquots of 0.5 mL each will be processed and frozen within 4 hours of processing.

Computer labels will be generated and affixed to the appropriate specimen containers and will include the specimen number, participant number, specimen date, specimen type ('PBMC', 'PLA', or 'SER'), and aliquot number. Labels must be affixed prior to freezing the vials.

Urine will be collected for urine pregnancy testing of women of reproductive potential at Screening, Entry, Week 24, and Week 48. Urine will also be collected and stored from all participants at Entry, Week 24, and Week 48 for future, archived testing of renal function and injury biomarkers.

At least 5 mL of urine will be collected using a standard collection cup using clean catch technique. This sample will be processed by the CTSL/SSF into at least 4 aliquots containing at least 0.5 mL in screw-top plastic vials and stored at -80C. Computer labels will be generated and affixed to the appropriate specimen containers and will include the specimen number, participant number, specimen date, 'URI', and aliquot number. Labels must be affixed prior to freezing the vials.

Stool will be collected and stored at Entry, Week 24, and Week 48. The stool sample will be self-collected at the study visit using the OMNIgene-Gut DNA/RNA kit, which has collection equipment and appropriate microbiome tubes using buffers for preservation of nucleic acids. Alternatively, the sample may be collected using these kits at home within 7 days prior to the visit and then brought to the visit or returned to the study team within 7 days after the study visit.

These samples will then be transferred to Dr. Tran's laboratory and cryopreserved at -80º C for future testing of intestinal microbiomics. Computer labels will be generated and affixed to the appropriate specimen containers and will include the specimen number, participant number, specimen date, 'STL', and aliquot number. Labels must be affixed prior to freezing the vials.

Questionnaires: At Entry, Week 24, and Week 48, participants will complete a questionnaire battery containing the following: standard questions assessing demographics, medical/psychiatric history, current depression treatments, tobacco/nicotine use, alcohol use (AUDIT), illicit drug use, medication adherence, PHQ-9, SCL-20, GAD-7, ISI, PROMIS® Fatigue Short Form, PANAS-PA, and SF-20. 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.

VioScreen Food Frequency Questionnaire (FFQ): At each visit (Entry, Week 24, Week 48), participants will complete the VioScreen Food Frequency Questionnaire (FFQ). This 20-minute, web-based FFQ has been validated against repeated 24-hour dietary recalls and allows for complex skip patterns, portion size estimation based on images, and real-time error checking.[109] Study personnel will assist participants in initiating and completing the FFQ as needed. The FFQ will provide measures of usual kilocalories and macro- and micro-nutrients over the past month. We will calculate the USDA Healthy Eating Index (HEI) from the FFQ data[110] as our index of overall diet quality.

Fitbit physical activity assessments: Participants will be asked to complete 7 consecutive days of monitoring to measure objective physical activity using Fitbit Inspire 3 devices and the Fitabase platform. The Fitbit Inspire 3 is a wrist-worn health and fitness tracker that is unobtrusive, lightweight, and water-resistant. It has a long battery life (~10 days) and will be configured to provide minimal feedback to participants. Fitabase is a secure data management and analytics platform designed to facilitate the collection, storage, and analysis of data from Fitbits for research projects.

Before each visit, participants will be given or mailed a FitBit and a simple instruction sheet showing proper placement on the nondominant wrist. Participants will also complete a 15-minute Fitbit training session via phone before the Entry visit. At each study visit, participants will return their Fitbit to the study team, and their data will be uploaded to Fitabase. Our index of overall physical activity will be average daily step count (mean across the 7 days), given that (a) Fitbits have been shown to provide accurate and reliable step counts[119-121] and (b) daily step counts have an inverse dose-response relationship with cardiometabolic disease incidence and all-cause mortality.[122] From the Fitbit data, we will also extract average daily energy expenditure, time spent in different activity intensities, and sedentary time (means across the 7 days).

## 9.0 Adverse Event Management

Although not an inherent risk of the study interventions or procedures, participants may have suicidal ideation at screening or develop suicidal ideation during the study, given that they will all have current depression. We have already put into place a protection protocol for just this event in our previous clinical trials in HIV-positive patients and primary care patients with depression. See the Appendix for our full Suicidal Ideation Protection Protocol.

If a participant reports having thoughts of being better off dead or of hurting him/herself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation), the visit will be immediately stopped, and the research assistant will interview the participant to complete the Patient Suicidality Form (see Appendix). If the participant answers "no" to all three suicide questions or if the patient answers "yes" only to Question 3 (previous attempt) and the most recent attempt was ≥ 10 years ago, the visit will proceed as normal, and the completed Patient Suicidality Form will be given to the principal investigator.

If the participant answers “yes” to any of the three questions (for Question #3 the previous attempt must be within the past 10 years), the research assistant will immediately contact the principal investigators. Dr. Stewart (a clinical psychologist) and Dr. Gupta (a physician) will review the case as soon as possible, but no later than the same day, to determine the appropriate course of action (e.g., immediately contact the patient’s primary care provider, primary HIV provider, clinical social worker, or care coordinator, consult with clinicians at the Sandra Eskenazi Mental Health Center or with the psychiatrists assigned to the Methodist Hospital 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 Suicidal Ideation Protection Protocol.

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

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

## 10.0 Criteria for Study Discontinuation

- Request by the participant to withdraw
- Request of the primary care or primary HIV 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 this study
- If the participant develops a need for systemic therapy for acute or serious illness 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

## 11.0 Statistical Analysis Plan

### 11.1 Sample Size Justification and Power Analysis

The primary endpoint of this application is to determine the 24-week effects of iCBT-D on insulin resistance measured as HOMA-IR in people with HIV (PWH) on antiretroviral therapy (ART) (primary endpoint). Secondary endpoints include determining the 48-week effects of iCBT-D on HOMA-IR, the 24- and 48-week effects of iCBT-D on monocyte activation (sCD163, sCD14), the circulating metabolome, HbA1c and glycated albumin, gut integrity (REG3α), and microbial translocation markers (16S rDNA, β-D-glucan). We will also assess if monocyte activation and/or the metabolome mediates the relationships between trial group (iCBT-D vs AC) and HOMA-IR and if gut integrity and microbial translocation mediate the relationships between trial group and monocyte activation.

HOMA-IR: Based on our pilot RCT, we would require 67 participants per group to find a difference in HOMA-IR at Week 24 (Aim 1 primary endpoint) with 80% power at a two-sided $\alpha=0.05$. With an assumed 10% attrition rate (based on our pilot RCT), we will increase the sample size to 75 per group (150 total). We are assuming a further 10% attrition between Weeks 24 and 48; thus, we expect at least 120 participants (60 per group) to

complete the Week 48 visit. Of note, these sample sizes would provide >99% power to detect differences in PHQ-9 and SCL-20 depression symptom scores at Week 24.

To our knowledge, there are no established changes in HOMA-IR that are proven to be clinically relevant. However, in the Diabetes Prevention Program trial, a 0.5 SD improvement in insulin sensitivity (the reciprocal of HOMA-IR) corresponded to a clinically relevant 30% lower hazard ratio (HR) of incident DM.[137] Thus, we would expect that a 0.5 SD reduction in HOMA-IR would lead to a similar decrease in DM. Based on the variance observed in our pilot trial, to detect a difference of 0.5 SD in HOMA-IR change quates to needing 64 participants per group. Thus, our sample size of 75 per group should detect this minimally and clinically relevant effect size.

Monocyte activation: Based on our pilot trial data, with the expected 67 participants in each group completing the Week 24 measurements, we will have >99% and 80%power (at α=0.05) to detect differences between changes in the iCBT-D and AC groups for sCD163 and sCD14, respectively. In regards to the mediation analysis, we used Fitz & MacKinnon's widely cited simulation results[147] for determining the required sample size to detect clinically meaningful mediation effects. Assuming medium effect sizes for the paths in our mediation models and α=0.05, a sample size of 71 *total* is required to achieve 80% power for bias-corrected bootstrap tests of mediation, which have consistently been shown to be the most powerful mediation tests.[147] Thus, with 134 total participants expected to complete the Week 24 visit, we have more than sufficient power for assessing mediation at even lower effect sizes.

Assuming medium effect sizes for the paths in our mediation models is reasonable given our preliminary data and results from others. The effect sizes for iCBT-D on depressive symptoms (PHQ-9 d=0.79; SCL-20 d=0.61), gut barrier integrity (REG3α d=0.38), monocyte activation (sCD163 d=0.74), and insulin resistance (HOMA-IR d=0.58) in our pilot RCT ranged from approaching medium to large.[27] In addition, substantial epidemiologic literature support large effect sizes between our markers of gut barrier integrity, microbial translocation, and monocyte activation in PWH.

Metabolomics: Our main comparison will examine whether iCBT-D differentially affects abundance of plasma metabolites versus usual care at 24 and 48 weeks relative to Entry baseline. To estimate power for the longitudinal metabolomics studies, we used actual dispersions and mean scaled abundance within each group-visit parameterization from our pilot metabolomic study to perform a simulation-based power analysis for various group sample sizes and log2 fold-change (LFC) cut-offs, assuming an FDR of 10% and 1332 metabolites, of which ≥5% are differentially abundant between changes in the BtB and UC groups. Assuming even distribution between groups, 42 completers per group would provide >80% power for detecting differences at |LFC| of 0.585 (1.5 in linear space) at 10% FDR. Therefore, our estimated 67 and 60 completers/group at 24 and 48 weeks, respectively, should be sufficiently powered to detect differences between the iCBT-D and AC groups in the proposed trial.

### 11.2 Randomization, Data Management and Validation

Randomization: Randomization with varying block sizes will be implemented at Entry. We will stratify randomization on sex at birth (male, female) and use of pharmaceutical antidepressants (yes, no) at Screening.

Data Management Systems: IU REDCap – an easy-to-use tool for creating secure, web-based data entry systems – will be used to capture demographics, vital signs, medications, medical/psychologic history, diagnoses, interview, survey, and EMR data. The following IU REDCap databases will be created: Recruitment and Screening, GDA Intervention Delivery, Active Control Delivery, Screening Visit, Entry Visit, Week 24 Visit, and Week 48 Visit. Data will be exported from IU REDCap in SAS format. Assay data from the various IU Core labs and Dr. Tran's lab will be converted from Excel to SAS format and merged with the IU REDCap data by our data manager.

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 if due to data entry errors. If these values cannot be corrected, they will be deleted and set to missing. 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 (≤ -7 or ≥ 7) 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.

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.

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 depression 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 the DSMB report.

Policies and Methods for Ensuring Blinding of Study Results: To ensure unbiased results, all laboratory 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 (GDA vs. Active Control) will not be blinded by necessity. Dr. Liu will create the master randomization list to be implemented by the REDCap system. The master randomization list will not be shared with the blinded PIs and laboratory personnel performing the endpoint assays. At the Entry Visit, randomization will occur at the end of the session after all data collection for that visit is complete.

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 Indiana Clinical Research Center. 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 the internet CBT-D program (Good Days Ahead). 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 GDA sessions in private rooms or areas in their homes or other locations they choose.

Methods for Monitoring the Quality and Consistency of Interventions (Treatment Fidelity): We will use treatment fidelity strategies consistent with the NIH Behavior Change Consortium recommendations.

Strategies will include: (1) using standardized intervention protocols and training; (2) using adherence checklists to track fidelity; and (3) holding regular meetings to address any issues. At weekly and separate GDA delivery and AC delivery meetings, fidelity to the intervention will be monitored in real time by MPI Stewart, and corrective feedback will be provided as needed. In addition, MPI Stewart will closely supervise the graduate student research assistants responsible for GDA and AC delivery. He will also audit a random subset of 20% of GDA and AC patients every 6 months and perform an assessment of treatment fidelity using our adherence checklists. We will develop GDA Delivery and AC Delivery IU REDCap databases for this trial. These databases, which will include the graduate student research assistants' de-identified notes, will allow for assessments of treatment fidelity. To sustain high fidelity, MPI Stewart will provide timely corrective feedback and any needed training to the graduate student research assistants to maintain a minimum threshold of 80% on the adherence checklists. Although there are no clear guidelines on the optimal level of adherence, ≥80% typically constitutes high fidelity. Treatment fidelity metrics will be reported to the DSMB every 6 months in the DSMB report.

### 11.3 Statistical Analyses

We will test our hypothesis using the intention-to-treat approach. Normality of variables will be checked with appropriate transformations performed when necessary. Tests will be two-tailed with $p<0.05$ considered significant. We will assess for (but do not expect) treatment group differences in baseline factors that are not balance by randomization by calculating their standardized mean differences (SMDs). Even so, we will construct supplemental, hypothesis-testing models adjusting for any baseline factors exhibiting imbalance between groups.

Primary endpoint of HOMA-IR and secondary endpoints of glucose homeostasis markers: To test our primary hypothesis (iCBT-D will prevent worsening HOMA-IR at 24 weeks), an analysis of covariance (ANCOVA) will be performed. The independent variable will be treatment group (iCBT-D versus AC), the covariate will be Entry HOMA-IR, and the dependent variable will be Week 24 HOMA-IR. We will use the same approach to test the secondary hypotheses involving the secondary outcomes (Week 24 HbA1c and Week 48 HOMA-IR, HbA1c, glycated albumin).

Additional potential covariates and/or mediators to be included in secondary models include demographics and both Entry levels and changes in PHQ-9 scores, CD4 cell counts, BMI, smoking/alcohol/cannabis/illicit drug use, ART (both regimen and individual drugs, e.g. integrase inhibitors and tenofovir alafenamide), and dietary/physical activity parameters (HEI, Fitbit step counts). We will specifically assess study group-sex interactions and sex-stratified analyses to address sex as a biological variable.

We will also conduct sensitivity analyses excluding those assigned to iCBT-D who complete fewer than 6 of the 9 planned treatment sessions in GDA. Such 'per-protocol' analyses will provide insights into any potential dose-response, causal relationships.

Secondary endpoints of monocyte activation, gut integrity, and microbial translocation biomarkers: We will use similar ANCOVA models and sensitivity analyses as outlined above to determine the differences between the iCBT-D and AC study groups in changes in the various endpoints at Weeks 24 and 48.

We will use PROCESS version 4.2[148] to test for mediation effects. First, we will compute residualized change scores for each measure of gut barrier integrity, microbial translocation, monocyte activation, and HOMA-IR by regressing 24-week level on baseline level. Second, for H2c, we will use PROCESS Model 4, to run parallel mediation models to simultaneously test the indirect effects of Good Days Ahead (X) on each monocyte activation marker (Y) via 24-week changes in REG3α and microbial translocation (M's). We will then run similar models for 48-week changes in mediators and outcomes. Third, for H2d, we will again use PROCESS Model 4 to run a parallel mediation model to simultaneously test the indirect effects of Good Days Ahead (X) on 24-week changes in HOMA-IR (Y) via 24-week changes the monocyte activation markers (M's). We will then run similar models for 48-week changes in the mediators and outcomes. To assess the statistical significance of mediation effects, we will use bias-corrected bootstrap 95% confidence intervals with 10,000 bootstrap samples. Mediation will be considered statistically significant if the 95% confidence interval for the indirect effect does not cross zero. We will specifically assess study group-sex interactions and sex-stratified mediation analyses to address sex as a biological variable.

Secondary endpoint of plasma metabolomics: The metabolomics data generated by UHPLC/MS/MS will be normalized and scaled by Metabolon using their quality control and reference standards. We will determine the differentially abundant metabolites between the study groups at 24 and 48 weeks with FDR of 5% using the limma package with duplicateCorrelation.[154] Differentially abundant metabolites with p<0.10 will be assessed for enrichment of canonical pathways and upstream regulators by Fisher's exact test using QIAGEN Ingenuity Pathway Analysis, with FDR<0.10 considered significant. As a complementary approach, significant pathways and an activity network will also be computed using mummichog.[155] Monotonic relationships between each of the differentially abundant metabolites and HOMA-IR will be assessed using Spearman's correlation with significance reported as Benjamini-Hochberg adjusted p values. We will specifically assess study group-sex interactions and sex-stratified analyses to address sex as a biological variable.

An additional pathway analysis will include more comprehensive data using integrated machine learning to determine which of the metabolomic, monocyte activation markers, and participant features (e.g. demographics and changes (if any) in ART regimen/drugs, BMI, FFQ and Fitbit assessments, smoking, alcohol, illicit drug use) obtained at Entry and 24 weeks best predict changes in HOMA-IR from baseline to 48 weeks. Here, we will use permutation importance of random forests for feature selection[156] with nested cross-validation and gradient boosted decision trees[157] as a classifier with 4-fold cross-validation.

Missing Data Approach: Missing data mechanisms will be examined by comparing completers with non-completers on the baseline factors. Multiple imputation (SAS proc mi and mianalyze) will be used if a substantial amount (>10%) of missing data exist. Of note, our trial biostatistician (Dr. Liu) is an expert on longitudinal and missing data analysis, which are critical for contemporary trial analysis.

Sex as a Biological Variable: In exploratory analyses, we will examine sex as a potential moderator of treatment effects on all outcomes by testing treatment group x sex interactions. Given that the proposed trial is not powered to detect such interactions, 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.

Moderation Analyses: To assess the potential influence of certain psychiatric comorbidities, we will examine clinically significant depression symptoms (PHQ-9 ≥10), clinically relevant insomnia symptoms (ISI ≥11), clinically significant anxiety symptoms (GAD-7 ≥10), and alcohol use suggestive of dependence (AUDIT ≥15) at pre-treatment as candidate predictors of intervention adherence (e.g., the number of iCBT-D sessions completed; intervention arm only) and trial attrition (both arms). In addition, we will examine these three psychiatric comorbidities separately as candidate moderators of treatment effects on the endpoints by testing treatment group x psychiatric comorbidity x time interactions in the models. These models will also be run separately for both levels of each psychiatric comorbidity to assess whether there are meaningful differences in the treatment group-outcome relationships based on the presence of these psychiatric comorbidities.

## 12.0 Human Participant Protections

The Human Participants Research outlined in this proposal meets the definition of a Phase II mechanistic trial for the purpose of identifying biological and physiological mechanisms of human disease (not for identifying the superiority of one agent over the other). A Data and Safety Monitoring Plan with independent monitor will be implemented to include appropriate monitoring 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.

### 12.1 Risks to the participants

a. Human Participants Involvement and Characteristics

- A total of 150 HIV-positive participants will be recruited to participate in this pilot randomized, controlled trial investigating the efficacy and underlying mechanisms of internet cognitive behavioral therapy for depression using the GDA internet-based computer program in preventing worsening insulin resistance and reducing monocyte activation.

- Participants must be at least 18 years of age (no upper age limit), have documented HIV infection, be English literate, have a screening HbA1c <6.5%, have a screening HIV-1 RNA level <75 copies/mL while on ART for at least six months, and have depression per PHQ-9 score ≥10.
- The chief exclusion criteria include ever having a recorded HbA1c ≥6.5%; active suicidality; history of bipolar, manic, or psychotic disorder; any other pro-inflammatory condition (e.g., autoimmune diseases); malignancy requiring treatment within 2 months of screening; are receiving systemic daily anti-inflammatories besides ASA/NSAIDS; or are currently pregnant or breastfeeding.
- Potential participants will be recruited from Indiana University Health University Hospital and from the Ryan White HIV outpatient clinics of Eskenazi Health Hospital and Indiana University Health Methodist Hospital. Self-referrals from other clinical sites will also be allowed.

b. Sources of Materials

- All data for this study will be obtained only after written, informed consent is provided by each participant. Existing medical records will be reviewed for demographics, medical diagnoses, and medications. Blood samples will be obtained for testing of HIV-1 RNA levels, CD4 cell counts, insulin, glucose, HbA1c, glycated albumin; biomarkers of monocyte activation, intestinal permeability, microbial translocation biomarkers; and metabolomics. Urine samples will be obtained for pregnancy testing. Urine, serum, plasma, cells, and stool will be obtained and stored for batch testing of our endpoints of interest and/or for future studies. Questionnaires to assess depression, insomnia, tobacco and alcohol use, anxiety, medication adherence, and quality of life will also be implemented. In addition, dietary questionnaire assessments (the FFQ) and Fitbit physical activity measurements will be collected.
- 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. Stool samples will be self-collected. Questionnaires will be completed in private settings. These data will be collected solely for the purpose of the proposed research projects.

c. 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 of the three main study visits are 6 mL (one-half tablespoon) and 60 mL (4 tablespoons), respectively. The total amount of blood to be obtained over the 48-week study period would be approximately 186 mL (12-13 tablespoons), which is well within the accepted standards for blood donation over a 12-month period. There are no known risks related to the implementation of the Good Days Ahead cognitive behavioral therapy program for depression in the Intervention Group or of the education and more frequent symptoms monitoring in the Active Control group. Participants may feel unease in completing the questionnaires.
- Adverse events expected because of the underlying condition include worsening depression and suicidality, both of which are closely monitored and screened for during the trial. The adverse events associated with antiretroviral-treated HIV infection are manifold, but much less so compared to untreated HIV infection. Our eligibility criteria should exclude any participant for whom their HIV disease may lead to adverse events during the trial.

- The principal alternative to these procedures would be not to participate in the research.

12.2 Adequacy of protections against risks

a. 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 and from the outpatient infectious diseases/HIV clinic at Indiana University Health University Hospital. Self-referrals from other venues will also be considered. The electronic medical record search/filter functions 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 by telephone to discuss the trial and screen for depression using the PHQ-9 survey. For those with an PHQ-9 score ≥10 criterion and who are willing to participate in the trial, the recruiters will then refer these patients to our study team 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.

b. Protection Against Risk

1. Confidentiality. To minimize the risk to participant confidentiality, patient identifiers will be removed once his/her/their data are 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.

2. 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.

3. Questionnaires. Participants may feel uneasy or discomfort in completing the questionnaire battery. 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. Participants may also refuse to answer any questionnaire item.

4. Suicidal Ideation. Although not an inherent risk of the study interventions or procedures, participants may have suicidal ideation at screening or develop suicidal ideation during the study, given that they will all have current depression. We have already put into place a protection protocol for just this event in our previous clinical trials in HIV-positive patients and primary care patients with depression. See the Appendix for our full Suicidal Ideation Protection Protocol.

- 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 will be recorded on CRFs and reported to the IRB annually; *unexpected* serious adverse events will be reported to the IRB within 10 days. All adverse events will be graded using The Division of AIDS Table for Grading Adult Adverse Experiences.

- Dr. Dennis Fortenberry (Indiana University Division of Adolescent Health, Department of Pediatrics) will serve as the Chair and independent monitor of the Data and Safety Monitoring Board for the proposed trial. Drs. Gupta, Stewart, Tran, and Liu (as protocol biostatistician) will also be members of this Board.

12.3 Potential benefits of the proposed research to the participants and others

- Potential benefits to the participants include an evaluation of their depression risk, immunology, pro-inflammatory status, dietary and physical activity assessments, and diabetes risk. They may also derive short-term benefits from the GDA or education/monitoring 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 PWH.
- Although there are no guaranteed clinical benefits from those who are randomized to treatment with GDA, this program was safe in our pilot trial involving people without HIV. 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 monocyte activation and diabetes risk in PWH. This would benefit society directly by impacting clinical practice.

12.4 Importance of the knowledge to be gained

- The knowledge that will be gained from this study will identify the determinants underlying the relationships between depression, monocyte activation, and diabetes risk in ART-treated PWH. 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 monocyte activation in HIV-positive patients with depression. Therefore, the importance of the knowledge gained outweighs the risks to the participants.

12.5 Data and safety monitoring plan

- For this phase II mechanistic trial, we have developed a Data and Safety Monitoring Plan and Board to ensure the safety of participants and to monitor participant recruitment, accrual, randomization, and retention; treatment delivery and fidelity; and data collection and quality. Per NIDDK instructions (https://www.niddk.nih.gov/research-funding/human-subjects-research/policies-clinical-researchers/data-safety-monitoring-plans), because this is a phase II trial; does not include a masked, high risk, or invasive intervention; is a single-center trial, and does not include vulnerable populations, the proposed Board includes the study principal investigators and an independent safety monitor.
- Adverse Event Monitoring: We will systematically identify potential adverse events (AEs): (a) by conducting Eskenazi Health and IUH Health Methodist and University 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 in-person study visit. 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 depression, depression 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 GDA 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 depression interventions, (b) we are not delivering any new or experimental interventions or restricting usual care, and (c) all study procedures are considered standard and noninvasive (except for the blood draw).

- Adverse Event Rating and Reporting: All events plausibly related to depression, depression treatment, 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.

  Anticipation
  1. Anticipated
  2. Unanticipated

  Severity
  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

  Attribution
  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 the IU IRB, DSMB, and NIH. All severe or life-threatening AEs will be immediately reported to and reviewed by the DSMB. 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, DSMB, and NIH at the time of continuing review.

- Data and safety board/monitor: For this phase II trial, we will implement a Data and Safety Monitoring Board (DSMB) consisting of Drs. Gupta, Stewart, Tran, Liu and an independent monitor, Dr. Dennis Fortenberry. Dr. Fortenberry is Professor of Pediatrics and a behavioral physician-scientist in the Division of Adolescent Health, Department of Pediatrics at the IU School of Medicine. Dr. Fortenberry is familiar with the team's ongoing research program in HIV-related health psychology and has led research himself in HIV behavioral psychology. Being outside the home departments of Drs. Gupta, Stewart, and Tran facilitates his independent status on the DSMB. Moreover, he has not published with the PIs and has no ongoing research projects with them.
  - This four-person DSMB will meet every six months to ensure participant safety; monitor recruitment, accrual, randomization, retention, treatment delivery and fidelity; and review data collection and quality.
  - Every six months, Dr. Gupta will submit a written report to the DSMB 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. At that time, the DSMB will determine whether the trial should continue unchanged, be modified, or be stopped, and the DSMB independent monitor (Dr. Fortenberry) will provide a written response with all recommendations. The IU IRB and NIH will receive copies of all DSMB reports and responses at the time of continuing review.

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## Appendix: Suicidal Ideation Protection Protocol

Through our clinical trials involving primary care and HIV-positive patients with depression, we have developed and successfully implemented a detailed and effective suicidal ideation protection protocol (SIPP). SIPPs very similar to the one described below have been approved by the Indiana University IRB for these prior depression trials (IRB#'s 1105005448, 1110007119, 1409114254, 1411802537, and 1908716624) and have been reviewed and approved by Eskenazi Health leadership to ensure a high level of protection while also being minimally disruptive to usual clinical activities. Of note, the informed consent statement contains a section describing to patients the steps to be taken if a patient reports suicidal ideation on a questionnaire or spontaneously. In the present trial, we will assess suicidal ideation with the PHQ-9 during the phone screening interview, Entry Visit, AC depressive symptom monitoring calls, Week 24 Visit, and Week 48 Visit, and we are prepared to appropriately handle the situation should a patient exhibit suicidal ideation.

In the description below, "trial staff" refers to study coordinators and research assistants interacting directly with potential participants or participants. Trial staff have or will be trained by Dr. Stewart, a clinical psychologist, in conducting the interview to complete the Patient Suicidality Form and in following the SIPP. Dr. Stewart will also serve as the primary supervisor to trial staff when it comes to their tasks related to the SIPP. In our prior depression trials, he has trained various research staff 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 the IU Indianapolis Clinical Psychology PhD program, which is accredited by the American Psychological Association and of which Dr. Stewart is a core member. These 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 the SIPP. Dr. Stewart is also the primary supervisor of graduate student research assistants. It is worth noting that trial staff will not be making any decisions regarding how to handle a situation. Instead, they will collect information by administering a highly structured interview (Patient Suicidality Form) and will follow the straightforward, step-by-step protocol described below. They will be instructed to call Dr. Stewart if they are unsure about a patient's response to any of the questions.

### Phone Screening Interview

If a potential participant reports having thoughts of being better off dead or of hurting themself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation) during a phone screening interview, the interview will be immediately stopped, and trained trial staff will interview the potential participant to complete the Patient Suicidality Form (see below). If the potential participant answers "no" to the clarifying question ("Over the past 2 weeks, have you been having thoughts of hurting yourself in some way?"), the interview will proceed as normal. If the potential participant answers "yes" to the clarifying question, they will be asked these three suicide questions:

1. Do you have a suicide plan?
2. Have you been struggling against thoughts about committing suicide? In other words, are you afraid you might act on these thoughts?
3. Have you attempted suicide in the past? If yes, in what year was the most recent attempt?

If the potential participant answers "no" to all three suicide questions or if the patient answers "yes" only to Question 3 and the most recent attempt was ≥10 years ago, the interview will proceed as normal, 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), trial staff will inform the patient that the interview must be stopped and that a clinical social worker in the patient's HIV clinic must be contacted according to the study protocol. The patient will also be told that a clinical social worker will call them back shortly. Trial staff will then contact a clinical social worker in the patient's HIV clinic, who will contact the patient before the end of that day to determine the appropriate course of action and will notify the patient's HIV provider. After the situation is handled, trial staff will contact the clinical social worker. If the clinical social worker or the patient's HIV provider considers the patient to be at acute risk of suicide (an exclusion criterion), the patient will be coded as ineligible. If the clinical

social worker or the patient's HIV provider considers the patient not to be at acute risk of suicide, trial staff will attempt to contact the patient again to readminister the screening interview.

In-Person Study Visits

If an enrolled participant reports having thoughts of being better off dead or of hurting themself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation) during an in-person trial visit, the visit will be immediately stopped, and trained trial staff will interview the participant to complete the Patient Suicidality Form. If the potential participant answers "no" to the clarifying question, the visit will proceed as normal. If the participant answers "yes" to the clarifying question, the participant will be asked the three suicide questions. If the participant answers "no" to all three suicide questions or if the patient answers "yes" only to Question 3 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 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), trial staff 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 to assist trial staff. 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 Sandra Eskenazi Mental Health Center or with the associated psychiatrist to the LifeCare clinic to aid in the decision-making process, instruct the patient to go 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. Either Dr. Stewart or Dr. Gupta will also notify the participant's HIV provider if they were not involved in the decision-making process. Regardless of the exact course of action, the study team will ensure that the participant is quickly 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 during the phone screening interview are not eligible for this trial, we expect that it will be a rare occurrence that an enrolled participant will screen positive for suicidal ideation.

Study Calls

If an enrolled participant reports having thoughts of being better off dead or of hurting themself (i.e., responds with a 1, 2, or 3 to PHQ-9 Item #9 or spontaneously reports suicidal ideation) during a study call, trained trial staff will immediately interview the participant to complete the Patient Suicidality Form. If the participant answers "no" to the clarifying question, the call will proceed as normal. If the potential participant answers "yes" to the clarifying question, the participant will be asked the three suicide questions. If the participant answers "no" to all three suicide questions or if the patient answers "yes" only to Question 3 and the most recent attempt was ≥10 years ago, the call will proceed as normal, 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), trial staff will inform the patient that the call must be stopped and that the trial PIs must be contacted according to the study protocol. The participant will also be told that trial staff or one of the PIs will call them back shortly. 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 Sandra Eskenazi Mental Health Center or with the associated psychiatrist to the LifeCare clinic to aid in the decision-making process, instruct the patient to go 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, trial staff will immediately contact Drs. Stewart and/or Gupta. Once again, Drs. Stewart and/or Gupta will review the case to determine the appropriate course of action. Either Dr. Stewart or Dr. Gupta will also notify the participant's HIV provider if they were not involved in the decision-making process. Regardless of the exact

course of action, the study team will ensure that the participant is quickly 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 during the phone screening interview are not eligible for this trial, we expect that it will be a rare occurrence that an enrolled participant will screen positive for suicidal ideation.

**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 ____ (Continue) No ____ (Stop, no SIPP 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 Suicidal Ideation Protection Protocol.**