

Protocol Title: SSRI Effects on Depression and Immunity in HIV/AIDS

Protocol Description: This a 10 week, double-blind, placebo controlled trial to evaluate SSRI effects for treatment of depression in HIV/AIDS with a focus on innate immunity and inflammation. Depressed population is HIV + on cART, not currently on pharmacotherapy for depression. Subjects will complete cognitive behavior therapy for their depression. Subjects seen weekly to monitor clinical response and possible side effects. Blood samples collected for virologic, neuroendocrine, and immunologic evaluation.

Date: February 9, 2021

Protocol

Abstract

Our prior work established links between depression, immune dysregulation, and HIV disease progression, as well as immune regulating and antiviral effects of SSRI treatment. We found depression was associated with decreased natural killer (NK) cytolytic activity in both medically healthy individuals and in HIV- infected patients, and we showed that depression was associated with accelerated HIV disease progression. We also observed that resolution of depression was associated with increased NK cytotoxicity and we demonstrated that ex vivo SSRI treatment of immune cells enhances NK cytolytic activity. Further, we discovered that an SSRI inhibited HIV infectivity of immune cells ex vivo, and that SSRI treatment significantly down-regulated the expression of HIV receptors and co-receptors (CD4, CXCR4, CXCR5) on macrophages and T-cells. Our studies thus indicate that SSRIs may have a direct action on peripheral immune cells. This work suggests that SSRI treatment could reduce psychiatric morbidity and help reverse immune dysregulation in depressed, People Living with HIV/AIDS. To pursue our long-term objective of successfully treating co-morbid mental and medical disorders in HIV/AIDS, this study aims to determine whether: 1) SSRI treatment significantly increases innate immunity and decreases chronic inflammation and immune activation, and 2) changes in depressive symptoms correlate with changes in immune regulation in HIV/AIDS. This study will be the first double-blind, placebo controlled trial of a SSRI for treating depression in HIV/AIDS with a focus on innate immunity and inflammation.

Objectives

Overall objectives

The overall objectives of this study are to evaluate if SSRI's and improvement of depression lead to

restoration of immune function in aviremic individuals. We will study the effects of SSRI treatment on biomarkers of immune suppression and immune activation that are common in both depression and HIV/AIDS. Our overarching hypothesis is that SSRI treatment of depression and improvement of depressive symptoms leads to increased innate immunity and decreased inflammation, resulting in better control of HIV disease and decreased morbidity.

Primary outcome variable(s)

We are comparing the effects of SSRI Vs Placebo in depressed, HIV+ individuals. We are measuring Lytic Units of Natural Killer cell activity (LUNK) and intracellular IFN γ to evaluate direct SSRI effects on innate immunity. We are measuring IL-6 and C Reactive Protein (CRP), to evaluate direct SSRI effects on systematic inflammation.

Secondary outcome variable(s)

We are measuring Lytic Units of Natural Killer cell activity (LUNK) and intracellular IFN γ to evaluate improvement of depressive symptom effects on innate immunity. We are measuring IL-6 and C Reactive Protein (CRP), to evaluate improvement of depressive symptom effects on systematic inflammation.

Background

Depression is highly comorbid with HIV/AIDS, occurring at nearly double the rate of the general population (1) and is commonly not recognized and not treated (2, 3). Both depression and HIV/AIDS are characterized by immune dysregulation, including suppressed innate immunity and heightened immune activation/inflammation. As described in this section, it may be possible to target shared pathophysiologic immune mechanisms using a SSRI, which could significantly advance the treatment of HIV and comorbid mental disorders involving serotonergic neurotransmission and immune regulation. Biomarkers of impaired innate immunity (decreased NK cell cytotoxicity) and inflammation (elevated IL-6, TNF-, and CRP) have been associated with depression (4-8). There is recent evidence that treatment of depression with SSRIs leads to both decreased immune suppression and decreased immune activation (8-10). Stress and depression are implicated as risk factors in the morbidity and mortality of a wide range of human diseases (11). Stress and depression may impair key components of cell-mediated immunity (12-16) and heighten susceptibility to infectious diseases (17-19), including HIV infection (11, 20-29) both before and after the advent of HAART (27). Although the specific immune mechanisms by which depression may influence immunity and HIV disease progression and mortality remain to be understood, increasing evidence suggests that killer lymphocytes play a key role. Clinical studies of depression in subjects without other medical illnesses (30-32) have demonstrated functional impairment and changes in populations of cells which mediate innate immunity. NK cells as well as CD8 cells, are two immune cell populations that play key roles in regulating HIV infection. NK and CD8 T lymphocytes are involved in the natural resistance against HIV infection through both cytolytic and noncytolytic activity. NK and CD8 cells lyse HIV-1 infected cells and also produce HIV suppressive factors that include chemokines MIP-1 (CCL3), MIP-1 (CCL4), and RANTES (CCL5) and cytokines (IFN, TNF and GM-CSF) that inhibit HIV-1 by suppressing viral entry and replication (33-41). With HIV infection, however, there is a notable decrease in NK cell function early post infection that persists and becomes more pronounced upon progression to acquired immunodeficiency syndrome (AIDS). Numerous experimental and clinical studies have documented this finding (42-44). The negative effects of HIV on NK cells are pervasive, involving both the quantity and functions of NK cells and their subpopulations. These impairments in NK cell number and function have been proposed to result in susceptibility to opportunistic infection and tumorigenesis, as well as decreased control of HIV replication. In general, highly active antiretroviral treatment (HAART) does not fully reverse and correct the NK deficiencies in HIV-infected patients, and NK defects persist. Abnormal NK cytolytic function and production of NK mediators (e.g. gamma interferon) contributes to HIV disease (45). Since the advent of HAART, morbidity and mortality of HIV have been significantly reduced. Nevertheless, immune dysregulation persists with impairment of the innate immune system (43, 46-48) as well as chronic immune activation which has been associated with increased morbidity and mortality (49-54). Numerous pharmacological agents have been studied to reduce chronic immune activation in HIV and the available data are largely from small trials (51, 55-59). Recent studies suggest that the peripheral markers that have promise as biomarkers of activation which may be responsive to therapeutic intervention include IL-6, CRP, sCD14, sCD163, and PD1 (51, 60-62). Immunologic activation may be the consequence of residual HIV in reservoirs and sanctuaries or the result of initial HIV infection and consequential cell, tissue and organ damage (62, 63). Furthermore, the immune system is important in controlling the latent HIV pool (64). Serotonin (5-hydroxytryptophan, or 5-HT)

neurotransmission is involved in the regulation of mood and is a pharmacologic target in the treatment of depression (65, 66). Several studies have documented the widespread distribution of 5-HT receptors and the 5-HT transporter on monocytes, macrophages, T cells, and possibly NK cells (67-77). Serotonin may have a direct modulating effect on both NK cell function and T-lymphocyte function. Serotonin enhances the cytolytic activity of NK cells, possibly through 5-HT_{1A} receptors on monocytes (69, 78), and may protect the function of NK cells (78). Serotonin also activates 5-HT receptors on T cells (79). In addition, inhibitors of serotonin synthesis and antagonists of 5-HT_{1A} receptors inhibit T-cell function in vitro and cell-mediated immunity in vivo in human and murine T cells; this inhibition is reversed by serotonin and by a 5-HT_{1A} receptor agonist (79). Findings from our ex vivo studies extend these data and suggest that a SSRI may increase NK cytolytic activity and may enhance killer lymphocyte noncytolytic HIV suppression of HIV infectivity (80, 81). Several clinical studies (70, 82-84) have demonstrated a positive effect of SSRIs on NK cytolytic activity in depression. We found a similar increase in NK cytolytic activity associated with the resolution of depression in a naturalistic study of HIV-seropositive women (85). Additional studies (86-88) have also suggested similar serotonin up-regulation of T-cell function in HIV infection. Thus, serotonin and drugs affecting serotonin transmission, including SSRIs, may play important regulatory roles in immune system dysregulation suggesting potential clinical benefits in HIV infection (89, 90). Furthermore, there is clinical evidence of antiviral activity of SSRIs in the central nervous system. Letendre et al. (91) reported that individuals taking SSRIs (citalopram, sertraline or trazodone) were more likely to have lower HIV viral loads in cerebrospinal fluid and better neuropsychological performance. Recent studies have also demonstrated anti-inflammatory effects of SSRIs in microglia (92, 93). Thus, serotonin and drugs affecting serotonin transmission, including SSRIs may play important regulatory roles in central and peripheral immune system dysregulation suggesting potential clinical benefits in HIV infections (89, 90). Further supporting these clinical findings on the effects of serotonin on HIV-related immunity are findings from in vitro experiments indicating that 5-HT decreases acute HIV replication by down-regulating the CCR5 receptor as well as by increasing the secretion of the HIV suppressive chemokine MIP-1 (94). These findings on the direct effects of serotonin are consistent with our finding of the direct effects of the SSRI citalopram on decreasing HIV viral infectivity of human macrophages in an acute ex vivo model as well as a chronic model of both a T cell line and a macrophage cell line (81). Recently, we have found that in additional ex vivo studies, citalopram downregulates CCR5, CXCR4, and CD4 receptors on T cells and macrophages and inhibits infection of macrophages in depressed and nondepressed seronegative individuals. Several clinical studies have demonstrated a beneficial effect of SSRIs on inflammation in depression (95-103). A meta analysis of four studies found that SSRIs were associated with a decrease in IL-6 and a meta analysis of five studies found that SSRIs were associated with a decrease in TNF-alpha. Even though other antidepressants were effective in reducing depression, they were not effective in decreasing cytokine levels (9). A recent meta analysis also reported similar findings for IL-6 as well as CRP (10). Therefore, SSRIs may have dual immune benefits in HIV/AIDS enhancing innate immunity and decreasing chronic immune activation - both of which are implicated in viral control and HIV disease progression. Despite the fact that depression is very prevalent in HIV/AIDS, is associated with immune suppression and immune activation, and is a risk factor for morbidity and mortality in HIV/AIDS, there is a paucity of double-blind, randomized and placebo controlled trials of antidepressant medication among depressed HIV seropositive individuals (104-108). These available trials demonstrated mixed antidepressant effectiveness on depressive symptoms and none examined biomarkers of immune suppression or immune activation. Thus, a randomized controlled trial is highly warranted and essential in order to determine the effects of a SSRI and improvement of depression on biomarkers of immune dysregulation in depression and HIV/AIDS.

Study Design

Phase*

Not applicable

Design

This is a 10 week randomized, parallel-group, placebo controlled trial.

Study duration

The study is planned to last for 5 years. Each subjects participation is planned to be 11 weeks (10 week trial with one week baseline screening prior to randomization). We anticipate beginning the project in December 2015.

Resources necessary for human research protection

Describe research staff and justify that the staff are adequate in number and qualifications to conduct the research. Describe how you will ensure that all staff assisting with the research are adequately informed about the protocol and their research related duties. Please allow adequate time for the researchers to conduct and complete the research. Please confirm that there are adequate facilities for the research.

All research staff working on this project will be thoroughly conversant with details of the study before it begins. The PI will lead weekly meeting prior to the start of the project to review all study procedures. Researchers will be given adequate time to conduct and complete the research. There are adequate facilities here at UPENN to conduct this research.

Characteristics of the Study Population

Target population

Men and Women, 18-70 years old, any race and ethnicity, HIV positive, on cART, depressed but not receiving pharmacotherapy for treatment of depression.

Subjects enrolled by Penn Researchers

180

Subjects enrolled by Collaborating Researchers

0

Accrual

Recruitment Procedures The enrollment of 180 depressed HIV positive, cART suppressed individuals will be accomplished through the implementation of a series of structured and well-coordinated recruitment and screening activities. These activities include: 1) the use of the Penn CFAR HIV clinical registry; 2) traditional advertising via fliers and print media; 3) networking with MH and HIV clinicians, clinic staff, case managers and patients; and 4) regular presence at clinic staff meetings to provide project visibility and feedback on project enrollment. We will post the IRB approved flyers in key locations and on the PMHARC HIV Research Bulletin Board, a web site that provides a central location for posting IRB recruitment flyers. We will begin recruitment by targeting the five adult HIV clinics that operate under the umbrella of the University of Pennsylvania Health System (UPHS). The UPHS clinics serve approximately 2,000 patients each year and are linked administratively, share a common database and electronic medical record system. We will also recruit participants from the Drexel Partnership Clinic, the Temple HIV Clinic and the Lax Clinic of Philadelphia Fight. Thus, collectively the clinics from which we will be recruiting see approximately 7,500 patients each year. Recruitment will be initiated upon notice of grant award and enrollment will begin in the fourth month of the study and continue for 53 months. **Power Analysis and Sample Size Calculation for Primary Aims** We used two-sided hypothesis tests, and assumed 10% loss to attrition over the 10 weeks. We set an overall alpha level of 5% within the innate immunity and inflammation hypotheses, so each Hypothesis is tested at $\alpha=0.025$. We used the methods of Hedeker et al. (152): assuming a within person correlation of 0.6 between visits, we have 80% power to detect a linear group by time effect (from week 0 through week 10) of Cohens $d=0.42$ or higher, and 80% power to detect a main effect (from week 2 through week 10) of $d=0.41$ or higher. **Biostatistical Consideration and Analysis Plan for Primary Aims** For Primary Aims 1A and 1B, participants will provide measures of innate immunity and inflammation at baseline, and at weeks 2, 4, and 10. The measures will be continuously distributed, and we will use linear mixed effects models, probably after log transformation of a response, to estimate the effects of medication group and time on the distribution of the responses across the 10 week period. The explanatory variables in these models will be a binary indicator of medication group, variables representing time effects, together with possible group by time interaction terms. Time will be modeled as a discrete factor. For the covariance structure, we expect that a random intercept model will provide a good fit to the data, and will also compare other possible specifications using BIC comparisons. **Biostatistical Consideration and Analysis Plan for Secondary Aim First**, we will examine whether participants showing improvement in depression measures are also those showing improvement in primary biological measures. Here, we will calculate change from baseline scores for the HAM-D and for the four immunity measures. For each immunity measure and HAM-D, we will use bivariate mixed

effects models to simultaneously model the pattern of depression change scores and immunity change scores across weeks 2 through 10. Here, for each of the four immunity measures, we are modeling the three HAM-D change scores and the three immunity change scores as a six-dimensional response, with explanatory variables of week, medication, and type of response (depression versus immunity). Our hypotheses, that decreases in HAM-D will be associated with increases in innate immunity, and with decreases in inflammation, will be tested by modeling the covariance structure, and testing individual covariances for significant differences from zero. We will perform these analyses separately for the four immunity responses. Second, we will test whether escitalopram has direct and indirect effects on the immune responses. The primary analyses (for Aims 1A and 1B) have addressed the total effect of escitalopram on the four immunity measures. One set of analyses will use the confidence limit approach of MacKinnon et al. (153, 154), to test whether changes in HAM-D score at week 2 (and, separately, at week 4 and 8) mediate the change in immunity measures at week 10. To obtain a complete picture of the possible mediation effects of depression, we will also perform these analyses using 50% reduction in HAM-D, and HAM-D less than or equal to 7, as the measures of the direct effect of escitalopram on depression. We will perform these analyses on the four innate immunity and inflammation responses separately. These mediation analyses focus on the end of treatment time point. To obtain information on longitudinal mediation across the full period, we will use latent growth curve mediation models (154). These models are similar to the bivariate mixed effects models describe above, but here we include additional regression terms to isolate effects of depression on immunity across time, and random intercepts and slopes for the repeated depression scores and the repeated immunity scores, with the intercept and slope of the immunity response regressed on the intercept and slope of the depression response. MacKinnon (154) describes how the estimated coefficients of these models can be used to provide estimates and confidence intervals for the indirect and direct effects of escitalopram on immunity. Note: Subjects that are withdrawn from the study will be replaced.

Key inclusion criteria

1) Men and women aged 18-70 years, of any race and ethnicity, 2) HIV-seropositive by ELISA and Western Blot assays, infected by behavioral transmission (perinatal HIV excluded), 3) Willing and able to comply with antidepressant medication regimen and scheduled follow-up visits, 4) Currently on a regimen of cART and Viral load less than 200 RNA copies/ml, 5) Current depressive symptoms (HAM-D- 17 score greater than or equal to 13 and a SCID diagnosis of either Major Depressive Disorder, Persistent Depressive Disorder (Dysthymia), Unspecified Depressive Disorder, or Other Specified Depressive Disorder, 6) Able to understand and provide informed consent.

Key exclusion criteria

1) Acute suicidal ideation, gestures, or attempts (e.g., HAM-D suicide item score of 3 "Ideas or gestures of suicide" or 4 "Attempts at suicide" at intake or HAM-D suicide item score of 4 "Attempts at suicide" during study), 2) Significant cognitive impairment or dementia (including HIV Associated Dementia (HAD)), 3) Use of a medication known to alter immune function within 4 weeks prior to randomization (the following are not excluded: a. acyclovir and related antiviral medications, b. topical corticosteroids, c. corticosteroid nasal sprays or inhalers, d) statin medications.), 4) Immunization with HIV vaccine, 5) Presence of psychotic symptoms or known diagnosis of a primary psychotic disorder, 6) Currently taking an anti- psychotic medication, 7) Pregnant or within nine months post-delivery, lactation, 8) Current or chronic medical condition that would likely preclude adherence to protocol or completion of the trial (per investigator judgment), 9) bipolar disorder (I or II) or schizophrenia, 10) Current pharmacotherapy for treatment of depression, 11) A history of intolerance or nonresponse to an adequate trial of escitalopram (or other SSRIs), 12) Renal failure, including those who require dialysis, 13) History of epilepsy or seizure disorder, 14) Taken MAOIs within 14 days of randomization, 15) On the antibiotic Linezolid and taking IV methylene blue, 16) On a regular regime of medication known to have anticoagulant properties such as NSAID, aspirin or warfarin, 17) A history of acute narrow/closed angle glaucoma, 18) Currently taking CNS drugs (the following are not excluded: gabapentin, pregabalin, varenicline, antihistamines, and hypnotics (e.g. zolpidem, zaleplon, eszopiclone), 19) On any triptan medications, 20) Undergoing ECT.

Vulnerable Populations

Children Form

Pregnant women (if the study procedures may affect the condition of the pregnant woman or fetus) Form

Fetuses and/or Neonates Form

Prisoners Form

Other

None of the above populations are included in the research study

The following documents are currently attached to this item:

There are no documents attached for this item.

Populations vulnerable to undue influence or coercion

The compensation offered is commensurate with travel and time-related expenses and is not coercive to participation. Study populations will be informed that their decision to participate or not participate will in no way prejudice their care. Patients who are not capable of giving informed consent will be excluded from this study. Employees and students at Penn will be informed that their decision to participate or not participate will in no way be indicated on their record or shared with their department.

Subject recruitment

As described above in the Accrual section, the enrollment of 180 depressed HIV positive, cART suppressed individuals will be accomplished through the implementation of a series of structured and well-coordinated recruitment and screening activities. These activities include: 1) the use of the Penn CFAR HIV clinical registry; 2) traditional advertising via flyers and print media; 3) networking with MH and HIV clinicians, clinic staff, case managers and patients; and 4) regular presence at clinic staff meetings to provide project visibility and feedback on project enrollment. We will post the IRB approved flyers in key locations and on the PMHARC HIV Research Bulletin Board, a web site that provides a central location for posting IRB recruitment flyers. We will begin recruitment by targeting the five adult HIV clinics that operate under the umbrella of the University of Pennsylvania Health System (UPHS). The UPHS clinics serve approximately 2,000 patients each year and are linked administratively, share a common database and electronic medical record system. We will also recruit participants from the Drexel Partnership Clinic, the Temple HIV Clinic and the Lax Clinic of Philadelphia Fight. Thus, collectively the clinics from which we will be recruiting see approximately 7,500 patients each year. Recruitment will be initiated upon notice of grant award and enrollment will begin in the fourth month of the study and continue for 53 months. We will screen an average of 20 potential participants each month, 4 of whom we expect to be eligible, willing and enrolled. Thus, the screening to enrollment ratio for this study is projected to be 5:1. These recruitment projections are based on our extensive experience in recruiting HIV-positive individuals and our access to an existing clinic-based recruitment infrastructure supported by the Penn Mental Health AIDS Research Center and the Penn CFAR and our teams affiliation with the Philadelphia Integrated Behavioral Health Initiative, a network of behavioral health specialists who are embedded within six HIV provider agencies and last year identified 2,065 patients who met criteria for depression. The project will include an experienced recruitment staff with knowledge of the HIV treatment community in Philadelphia. Screening appointments will be scheduled by the recruitment staff and conducted at the subject's convenience at our research offices located in close proximity to bus, trolley, and subway stops. Enrollment numbers and participant characteristics will be closely monitored by investigators at weekly project meetings using screening and enrollment data reports produced by Participant File. This is a research study tracking software that retains relevant data and produces custom reports clearly showing the number of participants screened, their recruitment source, the number eligible, reasons for ineligibility, and the enrollment status of those who were eligible. The database is housed on a UPHS protected server and meets all NIH and University requirements for protection of confidentiality of personal health information (PHI).

Will the recruitment plan propose to use any Penn media services (communications, marketing, etc.) for outreach via social media avenues (examples include: Facebook, Twitter, blogging, texting, etc.) or does

the study team plan to directly use social media to recruit for the research?

Yes

Please identify which method(s) of social media you will utilize, the content of the text to be used, and the method(s) for posting this information (i.e., using Penn supported communication services). When proposing the text to utilize, please be aware of any social media limitations (i.e., number of characters allowed in a tweet) and any appropriate confidentiality practices necessary to be compliant with posting research recruitment text.*

We will post ads which have the same images and text as previously approved recruitment flyers; we would just be posting this in different locations, such as Craigslist, Facebook, etc. In addition, if we wish to post a new advertisement, we will submit these to the IRB for approval before posting them.

The following documents are currently attached to this item:

There are no documents attached for this item.

Subject compensation*

Will subjects be financially compensated for their participation?

Yes

The following documents are currently attached to this item:

There are no documents attached for this item.

If there is subject compensation, provide the schedule for compensation per study visit or session and total amount for entire participation, either as text or separate document

Subjects will receive \$100 for completing the baseline assessment. This may be done as a single visit or divided into two shorter visits. If done in two shorter visits they will receive \$50 for each. For each weekly assessment study visit at weeks 1,3 ,5 ,6 ,and 8, the subject will receive \$30 for each visit. For weeks 2 and 4, which include a blood draw, the subject will receive \$40 for each visit, and for the final visit at week 10, which also includes a blood draw and longer visit, subjects will receive \$50. Thus, If the subject completes the baseline visit(s) and all weekly assessment visits (8) they would receive \$380 total. Research participants may be compensated via the Greenphire Clincard for their study participation. In addition, if a participant is required to travel to the research site to complete any missed parts of a study visit, and the participant is traveling from a location within Philadelphia, we may add up to \$5 to their payment as needed to cover the costs of this additional transportation. Also if a participant is traveling from a location outside Philadelphia for their study visit, we may add up to \$10 to their payment as needed to cover the costs of additional transportation. In some cases, the study may provide a ride to the research location by a ride share service. In such situations, this additional compensation to cover transportation will not be provided to the participant.

Study Procedures

Suicidal Ideation and Behavior

Does this research qualify as a clinical investigation that will utilize a test article (ie- drug or biological) which may carry a potential for central nervous system (CNS) effect(s)?

Yes

Procedures

Screening and Baseline Assessments Prospective subjects will be screened for eligibility via a phone interview. Eligible subjects will be invited to complete further screening and baseline assessments, which will be conducted either remotely or in person. Visit locations may include our Mobile Clinical Trials Unit. Trained clinicians with on-going monitoring and feedback to ensure reliability will perform assessments. Following study review, consenting subjects will complete the following: 1) SCID-RV to verify inclusion and exclusion criteria, as well as for diagnostic purposes; 2) HAM-D, to determine depression severity; 3) HAM-D Anxiety Subscale to determine the severity of anxiety symptoms; 4)

BDI II for subjective ratings of depressive symptoms; 5) C-SSRS to assess suicidal ideation; 6) Medical history and vital signs; 7) Neuropsychological assessment to exclude HAD; 8) HIV plasma RNA viral load test; 9) Biological assessment: comprehensive immune, virologic and neuroendocrine measures, a complete blood count (CBC), and a comprehensive metabolic panel (CMP); and 10) Pregnancy test. These procedures may happen at our research offices, remotely via private video or telephone call, or on our Mobile Clinical Trials Unit (MCTU). The SCID-RV, HAM-D, and C-SSRS will be audio recorded for training purposes on a digital audio recorder or on Bluejeans. Subjects will also sign a release of information to allow us to communicate with their HIV primary care provider. The baseline assessment may be completed in one longer visit (8-10 hours) or two shorter visits (each 4-5 hours).

Randomization The 180 HIV-seropositive eligible and consenting depressed subjects will be randomized to 10 weeks of double blind therapy with either escitalopram or placebo. Study medication may be sent to participants via mail. All participants will concurrently begin CCBT. Stratification based on race, sex, and baseline depression symptom severity, will be incorporated to ensure an even distribution of more severely depressed subjects (i.e., those with HAM-D scores greater than or equal to 20) in each treatment condition. Neither the research nurse nor the study clinicians will be aware of the assigned treatment condition for each subject nor will any research staff having any clinical contact with the study participants be aware of the treatment assignment during each subjects participation in the study. Only the research pharmacist will be unblinded to the treatment condition during each subjects participation.

Treatment To address ethical concerns about withholding active treatment, all study subjects will receive CCBT in combination with pharmacotherapy. We have selected a computer-assisted model of cognitive behavior therapy because it is less resource intensive and has been recommended for depression in primary care (119, 120). We have chosen the Good Days Ahead (121) model of CCBT because our mood disorders group has extensive experience with this approach (122) and we have recently completed a two-center study of outpatients with Major Depressive Disorder that demonstrated noninferiority to conventional Cognitive Behavioral Therapy (CBT) conducted by therapists trained at our Center for Cognitive Therapy (R01-MH082794; ME Thase, PI). Escitalopram, which is the active isomer of citalopram, was selected for its efficacy and pharmacologic properties. A meta analysis conducted by the Cochrane Collaboration concluded that escitalopram was one of only 2 (along with sertraline) newer generation antidepressants that was superior in terms of both efficacy and tolerability (123). Furthermore, it is well-suited for a study of medically complex patients because it has relatively simple dosing and few drug-drug interactions. Escitalopram and placebo will be prepared in the form of identical capsules by the Investigational Drug Service (IDS) research pharmacy at University of Pennsylvania School of Medicine. The active capsules will contain 5mg, 10mg, or 20mg of escitalopram. Patients will be started at 10mg daily (or placebo equivalent) for the first week. Upward titration will be permitted after one week based on tolerability and clinical response, (maximum dose is 20mg/day). Downward titration will be permitted if side effects are severe. We anticipate that about 3/4th of the patients will be taking 20mg/day (or placebo equivalent) by week 10. In the case of a medical emergency or serious adverse event, the blind will be broken by the research pharmacist and the information provided to an independent study psychiatrist. Subjects that do not tolerate the study drug will be withdrawn and replaced and referred for treatment of their depression. Treatment(s) they receive after being withdrawn are their financial responsibility. Also, at the end of ten weeks or if the study needs to be stopped for some reason that we do not currently anticipate, or if the subject needs to be withdrawn for any reason, we may need to wean the subject off the medicine as opposed to stopping it abruptly. We have stated this in the Informed Consent. Over a maximum two week period we will gradually decrease the amount of study medicine a subject is taking, and by phone we will monitor the subject for any discontinuation or worsening of depression symptoms. We will speak with the subject about options for continued care and will provide appropriate referrals. This may include treatment by staff and faculty of the Penn Department of Psychiatry, Mood and Anxiety Disorders Treatment and Research Program or by the subject's primary care provider, or by an alternate care provider the subject chooses. We will encourage subjects to speak with their physician about continued care. If we need to taper the subject off the study medicine we will continue to supply and pay for the study medicine. In addition to the possibility of tapering, in some circumstances we might also provide at no cost to the subject two weeks of escitalopram to participants who had been receiving active medication at the final week 10 visit, when subjects are unblinded to their treatment assignment, to maximize patient care. After the two week period, if the subject has not been able to receive a prescription from their provider or referral physician, our study psychiatrist will prescribe an additional two weeks of escitalopram which will be the financial responsibility of the subject. Any treatments, including medication, that the subject receives elsewhere after they leave or are withdrawn from the study are their financial responsibility and will not be paid for by the study. At the first visit following randomization, a certified cognitive therapist will meet with the participant for 60 minutes in person or remotely to

provide an overview about cognitive therapy and to demonstrate how to log in to the Good Days Ahead program. This therapist will serve as the patients coach and will meet either in person or via private video or telephone call to review progress or trouble shoot for thirty minute sessions every other week. More frequent sessions, either in person or by phone, can be scheduled if problems arise. Good Days Ahead consists of 8 distinct modules and it is recommended that participants work at a pace of one module per week. Computer-assisted sessions can be done at home or, if no computer or internet access is available, at the clinic. We anticipate that the average participant will have about 3 hours of therapist contact during the 10 week protocol. Pharmacotherapy visits will occur either in person or via private video or telephone call weekly for the first 6 weeks and then at weeks 8 and 10. The treating clinician will assess side effects, review symptomatic progress, and adjust the study medication as clinically appropriate. These visits typically last 15-30 minutes. An independent clinical evaluator or clinician will assess patients with the HAM-D and C-SSRS at baseline, and weeks 1-6, 8 and 10 during double blind therapy. During each assessment visit, adherence to research medication will be assessed. At the end of the 10-week treatment phase, all participants will be referred for appropriate clinical treatment of their depression.

The following documents are currently attached to this item:

There are no documents attached for this item.

Deception

Does your project use deception?

No

International Research

Are you conducting research outside of the United States?

No

Analysis Plan

We have included this in the accrual section of the detailed protocol and in the attached grant.

The following documents are currently attached to this item:

There are no documents attached for this item.

Data confidentiality

- x **Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.**
- x **Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.**
- x **Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.**
- x **Wherever feasible, identifiers will be removed from study-related information.**
- x **A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.**
A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
- x **Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.**
Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.

Subject Confidentiality

Confidentiality Risks: There is a small risk of breach of confidentiality related to collection of sensitive health and psychological information. We recognize the serious adverse effects that can occur with a

breach of confidentiality. Our research team is trained and experienced in the ethics of medical research and operating procedures will be enforced to insure that all subject interactions are treated confidentially and all data are protected by use of only a unique study ID number to identify the subject. Furthermore, the University of Pennsylvania has developed policies and guidelines to ensure HIPAA compliance in the collection of research data. Compliance for research data will be reviewed by the IRB as part of the human subjects approval process. The investigators will assure that the data collection instruments and consent forms are in compliance with Penn policies in this area. We are particularly sensitive to the issues of subject confidentiality with respect to HIV and depression. Consequently, we have adapted extensive procedures for our HIV and depression studies and will adapt similar procedures for the proposed study. We are committed to a system that maximally protects the confidentiality of our subjects. All subjects who consent to participation in this study receive a research identification number. Only this number, not subject name, will identify the subject in all research records. In no case will names or other personal identifiers such as social security numbers be used. The majority of data collected in this study will be entered in real time directly into the study's REDCap (Research Electronic Data Capture) database, a password-protected on-line database. Only authorized staff working on the study will have access to this database. All hard copy data will be stored separately from documents with identifying information, such as signed informed consent forms, in locked file cabinets. The security and confidentiality of the data in paper and hard copy form will be the responsibility of the P.I. Access to these locked file cabinets will be limited to the research staff under the supervision of Dr. Evans or the study coordinator.

Sensitive Research Information*

Does this research involve collection of sensitive information about the subjects that should be excluded from the electronic medical record?

No

Subject Privacy

Privacy refers to the person's desire to control access of others to themselves. Privacy concerns people, whereas confidentiality concerns data. Describe the strategies to protect privacy giving consideration to the following: The degree to which privacy can be expected in the proposed research and the safeguards that will be put into place to respect those boundaries. The methods used to identify and contact potential participants. The settings in which an individual will be interacting with an investigator. The privacy guidelines developed by relevant professions, professional associations and scholarly disciplines (e.g., psychiatry, genetic counseling, oral history, anthropology, psychology).

The research team has considerable experience relating to depressed and HIV infected subjects and understands and respects the need for patient privacy. We anticipate being able to maintain a high degree of privacy in this research project and will do everything we can to protect the privacy of individuals participating in this research. The consenting process will take place in a closed private setting or via a remote method per IRB guidance issued on 5/22/2020, such as REDCap and/or telephone or video call. All assessment visits will be kept as private as possible and generally will happen in a closed private office or via a private telephone or video call. If and when the study coordinator or study recruiter calls a subject they will only leave their name and a phone number. They will not leave anything in a message that could identify the study, or department, or status of the subject. Study procedures conducted remotely (such as informed consent, psychiatric evaluations, cognitive therapy sessions, etc.) will be conducted via either a private video or phone call. Procedures conducted through REDCap (such as informed consent or completing survey questionnaires) will be private because the study team will generate a secure survey to be sent to and completed by the participant.

Data Disclosure

Will the data be disclosed to anyone who is not listed under Personnel?

No, unless we are required by law to disclose specific data.

Data Protection*

- x **Name**
- x **Street address, city, county, precinct, zip code, and equivalent geocodes**
- x **All elements of dates (except year) for dates directly related to an individual and all ages over 89**
- x **Telephone and fax number**
- x **Electronic mail addresses**
- x **Social security numbers**
- x **Medical record numbers**
 - Health plan ID numbers**
 - Account numbers**
 - Certificate/license numbers**
 - Vehicle identifiers and serial numbers, including license plate numbers**
 - Device identifiers/serial numbers**
 - Web addresses (URLs)**
 - Internet IP addresses**
 - Biometric identifiers, incl. finger and voice prints**
 - Full face photographic images and any comparable images**
 - Any other unique identifying number, characteristic, or code**
- None**

Does your research request both a waiver of HIPAA authorization for collection of patient information and involve providing Protected Health Information ("PHI") that is classified as a "limited data set" (city/town/state/zip code, dates except year, ages less than 90 or aggregate report for over 90) to a recipient outside of the University of Pennsylvania covered entity?

No

Tissue Specimens Obtained as Part of Research*

Are Tissue Specimens being obtained for research?

Yes

Tissue Specimens - Collected during regular care*

Will tissue specimens be collected during regulator clinical care (for treatment or diagnosis)?

No

Tissue Specimens - otherwise discarded*

Would specimens otherwise be discarded?

No

Tissue Specimens - publicly available*

Will tissue specimens be publicly available?

No

Tissue Specimens - Collected as part of research protocol*

Will tissue specimens be collected as part of the research protocol?

Yes

Tissue Specimens - Banking of blood, tissue etc. for future use*

Does research involve banking of blood, tissue, etc. for future use?

Yes

Genetic testing

If genetic testing is involved, describe the nature of the tests, including if the testing is predicative or exploratory in nature. If predictive, please describe plan for disclosing results to subjects and provision

of genetic counseling. Describe how subject confidentiality will be protected Note: If no genetic testing is to be obtained, write: "Not applicable."

Not Applicable

Consent

1. Consent Process

Overview

The PI or his designee will review all study procedures and answer all questions that a potential study subject has. Only after the study has been explained thoroughly will the study staff offer the subject to sign the Informed consent. This will take place in one of the research offices used by this study on the UPENN campus (TBD), on our Mobile Clinical Trials Unit, via a private telephone or video call and/or via REDCap. The PI/ or designee will explain the study using lay language. If a subject is not capable of providing consent they will not be consented into this study. Under no circumstance will study staff try to unduely influence a subject to consent.

Children and Adolescents

Not Applicable

Adult Subjects Not Competent to Give Consent

Adult subjects not competent to give consent will not be eligible to participate in the study.

2. Waiver of Consent

Waiver or Alteration of Informed Consent*

No Waiver Requested

Minimal Risk*

Impact on Subject Rights and Welfare*

Waiver Essential to Research*

Additional Information to Subjects

Written Statement of Research*

No

If no written statement will be provided, please provide justification

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit

Potential Study Risks

All potential risks that might occur as a result of the participation in this study are detailed in the Informed Consent form and will be fully discussed with each subject by the research staff. General: It will be explained to each subject that in the event of physical injury directly resulting from the research procedures, every effort will be made to make available the facilities and professional skills of the University of Pennsylvania Health System. It will be further explained that while some risks are not predictable, every precaution consistent with the best medical practice to protect the health and safety of the subjects will be taken. We will explain to each subject that participation in the research study is completely voluntary. The subject has the right to refuse participation or withdraw at any point in the

study, without influencing any aspect of medical treatment that they may require. Medication and Placebo Use: The study clinicians will closely monitor subjects for adverse effects throughout the trial. Adverse effects can be treated by lowering the dose, or discontinuing it when necessary. Although there are no clinically proven adverse effects associated with escitalopram with regard to pregnancy, as a safety precaution we will not study pregnant women. All consenting females of childbearing potential will be tested for pregnancy prior to receiving treatment. They will be required to use an effective contraceptive method during the trial (such as a condom with spermicide or diaphragms with spermicide; oral, injectable, or implantable birth control; intrauterine devices (IUDs); surgical sterility). This will be explained in the consent form. There are no reported drug-to-drug interactions between escitalopram and antiretrovirals. However there are few clinical trials using the particular combination of agents our study participants will be on; therefore, the lack of reported interactions does not ensure that previously unknown adverse effects will not arise. Nonetheless, escitalopram is not known to have any significant effects on the cytochrome p450 isoenzyme system and no drug interaction effects are anticipated. Adverse effects will be monitored vigilantly. All serious adverse events will be fully documented and reported to the Penn IRB within 24hrs of knowledge of the event. The following safety procedures will be maintained in order to identify the presence of worsening depressive symptoms. A careful clinical psychiatric assessment, including the HAM-D scale, which is a sensitive symptom severity rating instrument, and the C-SSRS, which measures suicidal ideation, will be obtained at each assessment study "visit" whether conducted in person or remotely via private video or telephone call. In addition, study subjects will be instructed by the study clinicians about the signs and symptoms of worsening depression, and will be instructed to call the study in the event that they experience these symptoms. Information about depressive symptoms will be provided to all subjects at the beginning of the study and throughout the course of the study to enhance patient safety and study compliance. Subjects will be provided with a 24-hour emergency phone number in case of untoward events or worsening depressive symptoms. The magnitude and frequency of the clinical monitoring schedule during all aspects of the study should easily permit the study clinicians to determine the presence of symptomatic worsening. Rapid clinical intervention will be instituted in the event of significant clinical worsening. In this event, the subject will be treated as clinically warranted. Given these safeguards, we believe that the use of a placebo condition is safe when applied in accordance with the proposed treatment guidelines of our study. Risk of Computer-assisted Cognitive Behavior Therapy (CCBT): There are no known or foreseeable risks associated with receiving treatment with computer-assisted cognitive behavior therapy. Like other treatments for depression, CCBT is not effective therapy for all people and there is a chance depressive symptoms could worsen. The safeguards noted above reduce risk associated with symptomatic worsening. Risk of Phlebotomy: The potential risk of an approximately 70cc blood draw are minimal, and include the discomfort of an IV, a bruise, or rarely, an infection of the vein. To reduce these risks, blood will be collected by an experienced phlebotomist following aseptic procedures. Risk of Psychological Evaluation: Although the potential psychological risks are also minimal, participation in psychiatric interviews and psychiatric and psychological questionnaires can, for some subjects, be psychologically provocative. We will make every effort to be sensitive to the psychological response to the assessments of each individual subject. Specifically the research associates will inquire about each subjects psychological experience during each assessment. In rare instances where psychological and psychiatric evaluation evokes distressful feelings we will provide support as needed and appropriate. If a subject becomes very seriously or suicidally depressed there is a rescue procedure which involves breaking the blind on the study medication and providing or, if necessary, referring them for appropriate clinical treatment.

Potential Study Benefits

All subjects may benefit from the comprehensive medical and psychiatric diagnostic assessments in the study. Half of the depressed subject in the study will receive CCBT and antidepressant medication for their depression and will be monitored weekly (weeks 0-6) or biweekly (weeks 6-10). The other half of the depressed subjects will receive CCBT and placebo but will also be monitored weekly (weeks 0-6) or biweekly (weeks 6-10). Based on previous studies, we expect that ~ 60% of the depressed subjects receiving placebo will see an improvement in their depression. The ~40% that do not see an improvement will be referred for treatment after their participation in the study is completed. All subjects in the study will be referred for treatment of their depression and will receive follow-up to maximize treatment initiation, and or continuation. All subjects will receive free of charge medical, neurologic, immunologic and psychiatric assessments. Any subject needing immediate medical treatment, including psychiatric treatment will be referred for treatment. Being evaluated weekly/biweekly, the risks to subjects in this study are minimal and reasonable compared to the benefits gained by their participation. Subjects will also make important contributions to others via the further

development of clinical information on the best treatment approach for HIV+ subjects suffering with depression. Subjects may also contribute to a better understanding of the immune mechanisms that underlie the relationship between depression and HIV disease progression. The potential immune mechanisms by which depression may influence HIV disease progression and mortality remain to be understood. Knowledge gained from this study will advance the field of HIV care by clarifying if there exists dual benefits of pharmacotherapy for clinical depression among HIV+ patients with well-controlled viral load. This knowledge, and the good it may lead to, outweighs the minimal risks associated with this study. The study will specifically show if escitalopram given to aviremic, HIV+ depressed subjects will result in: (1) immune system homeostasis, marked by less innate immune suppression and lower levels of inflammation and immune activation; (2) if improvement in depressive symptoms are associated with improvements in innate immunity and inflammation. The proposed study is designed to determine if escitalopram will upregulate innate immunity (LUNK and intracellular gamma interferon in NK cells) and downregulate inflammation (IL-6 and CRP) in depressed, aviremic HIV+ individuals. This proposal also has the potential to produce new knowledge on the depression/ endocrine/immune mechanisms that will determine whether traditional pharmacotherapy (escitalopram), might benefit HIV+ individuals.

Alternatives to Participation (optional)

The alternative to participating in this study is not to participate.

Data and Safety Monitoring

The study will be monitored by the Principal Investigator and the Data Safety Monitoring Board (DSMB). Data and Safety Monitoring Plan In order to ensure the safety of participants and the validity and integrity of the data, we will appoint a Data and Safety Monitoring Board (DSMB) whose chief function will be to ensure safe and effective conduct of the trial. The DSMB will monitor our project and serve as a reporting body to the Penn IRB. Composition of the DSMB The DSMB will consist of 3 investigators, who are external to this study, selected from a number of scientific disciplines (including, a psychiatrist, an infectious disease practitioner, and a biostatistician) needed to interpret the data and ensure patient safety. None of the board members will be directly associated with the proposed research study. Activities of the DSMB: The primary goals of the DSMB will be: - To monitor and advise on scientific and ethical issues related to the study implementation for the protection of human subjects. - To review and approve the protocol and subsequently conduct annual reviews to determine whether patient safety has been adequately safeguarded - To review procedures and decisions regarding the adequate protection of specific patients when investigators break protocol because of adverse events or clinical deterioration. - To review progress to see that enrollment goals have been met. - To monitor and advise on ethical issues related to adverse events. - To oversee the confidentiality of data, and quality of data collection, management, and analysis - To recommend if necessary, discontinuation, modification, or termination of the study based upon emerging data (in the study and literature) and evaluation of risk/benefit ratio. - When possible, to serve as the final arbiters of whether individual patients should be removed from the protocol. The DSMB will receive quarterly reports of study progress and of any adverse effects or protocol violations. The DSMB will meet once per year, or more often as needed. In event of emergencies, the DSMB may meet via teleconference. For each annual meeting, the DSMB will first meet in an open session attended by the principal investigator and co-investigators, and the project statistician. The group will first review the research protocol and plans for data safety monitoring. The group will be used to review any problems in implementing the safety plan and for suggesting any necessary modifications to the safety plan. The DSMB will then meet in a closed session for the purpose of reviewing emerging trial data. Confidentiality will be maintained by providing data without any patient identifying information to the committee. At the conclusion of the meeting, the DSMB will make recommendations to the investigators and the IRB. The DSMB will make recommendations concerning the continuation or conclusion of the study. Data Monitored by the DSMB The DSMB will monitor both safety and outcome data as part of the yearly review. Outcome evaluations will include review of data quality and timeliness, participant recruitment, accrual and retention, and review of interim masked outcome results on primary and secondary efficacy measures. Safety evaluations will include review of adverse events and weekly symptom measures for each patient. In addition to serious adverse events, the board members will be presented with all adverse event information. The DSMB will further consider external factors such as scientific and therapeutic developments that may impact the safety or the ethics of the study. Procedures for reporting Adverse Event All serious adverse events will be reported to the members of the DSMB and the IRB within 24 hours. A report of all non-serious adverse events will be provided to the board members and the IRB yearly. NIH will be informed of all actions taken by the IRB as part of its continuing review. Oversight

of DSMB The investigators will ensure that the Data and Safety Monitoring Plan is reviewed and approved by the IRB before the initiation of the study protocol. The DSMB will then provide a report to the IRB following each yearly meeting, including recommendations concerning continuation or conclusion of the study. Data Safety Management Data will be gathered using an internet-based direct-entry data system in REDCap (Research Electronic Data Capture). REDCap is a secure web-based application designed to support data capture for research studies. REDCap provides 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. Interview data and self-report data are entered directly onto computers and/or tablets at the research sites by research study staff and study subjects respectively. When data are entered into REDCap remotely, research study staff enter data directly into REDCap. When links to self-report surveys are sent to a participant, the participant enters their own responses and submits from their own device. While their responses cannot be accessed by another person, if someone else has access to a participants email, they may see that the person is being asked questions about depression and HIV. In cases where the participant cannot complete the surveys online, a research staff member will ask them the questions and enter their answers into REDCap. Data are transmitted over a secure web connection with authentication and data logging. Password protection allows members of the research team appropriate levels of data access.

The following documents are currently attached to this item:

There are no documents attached for this item.

Risk / Benefit Assessment

The risks of participating in this study are minimal and are outweighed by the potential benefits the study has not only to each individual subject but to society at large. Subjects in this study are depressed but not receiving treatment for their depression. Whether they receive active drug or placebo they all will participate in a cognitive behavioral therapy program for their depression. Additionally, at the conclusion of their participation each subject will be referred for appropriate treatment of their depression.