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

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C.3 Research Design and Methods

Aim 1 Determine the effects of an SSRI on innate immunity and inflammation in depressed HIV seropositive individuals.

C.3.1 Summary

This will be the first placebo-controlled RCT to determine the immunomodulatory effects of SSRI therapy among a contemporary, urban cohort of HIV-seropositive individuals whose viral load is well controlled, yet still experiences immune dysregulation due to co-morbid depression and HIV infection Comparing the two depressed groups that are randomly assigned to receive SSRI or placebo will allow us to address novel aims: can SSRI treatment and improvement of depression reverse the immune dysregulation of depression and HIV. Comprehensive biomarkers of innate immunity, and inflammation will be assayed via blood draw at baseline and at 2, 4, and 10 weeks. Additionally, we will monitor adherence to SSRI and antiretroviral medications in all participants using contemporary methodology (i.e., self-reported doses taken and missed, medication electronic monitoring system (MEMS) caps, and, for HIV, plasma viral load).

Aim 1A. Determine whether an SSRI upregulates innate immunity in depressed HIV seropositive individuals. *Hypothesis*: SSRI is superior to placebo in restoring biomarkers of innate immune suppression (LUNK and intracellular IFNγ in NK cells).

Previously we demonstrated that major depression is associated with significant reductions in NK cell activity and resolution of depression resulted in improvement of LUNK (for details see C1.7, C1.8). SSRI enhances LUNK ex vivo (for details see C1.9.a). In addition as a part of our recent project (RO1 MH82670) we demonstrated that increase in severity of depression is associated with decrease in absolute numbers of total NK cells (p=0.008), reduction in perforin+ NK cells (p=0.009) and reduced expression of activation receptors NKP30+ (p=0.011) and NKP46+ (p=0.049) (unpublished observations). NK cell functions are also affected by HIV infection in several ways including decreased cytotoxic activity, changes in receptor expression and cytokine production (123-125). Although NK functions are partially restored by cART(44, 123), several studies demonstrated that recovery is incomplete. NK cells from HIV positive individuals with sustained viral suppression by cART do not completely recover in numbers (44), continue to have increased activation/degranulation profiles (46), show decreased receptor expression (NKp46 and NKp30) (126) and decreased cytokine production (IFNγ, TNF-α) (127).

In this aim we will assess NK cell functions in HIV positive individuals on stable cART at baseline and after 2, 4, and 10 weeks of SSRI therapy. NK cell function will be assessed by the standard chromium release assay, established in our laboratory, using K562 target cells and peripheral blood mononuclear cells (PBMC) at effector to target cell ratios of 6.25 - 50. Percent lysis values will be normalized for percent NK cells within the PBMC preparations and are expressed as lytic units (LU) per 10^7 NK cells or LUNK as previously described (41, 71, 72). In addition intracellular IFNγ will be assessed as described (42) (also see letter from Dr. Luis J. Montaner) in stimulated PBMCs. The number of $IFN\gamma^+$ NK cells will be assessed by flow cytometry gated on $CD45^+/CD3^-$/ $CD16^+/CD56^+$ cells. Nonreactive isotype-matched mAb will be used as control.

Aim 1B. Determine whether an SSRI downregulates inflammation in depressed HIV seropositive individuals. *Hypothesis*: SSRI is superior to placebo in decreasing biomarkers of inflammation (IL-6, CRP). Both MDD and HIV infection are associated with elevated levels of pro-inflammatory cytokines (for review see (7, 128-130). Although increased levels of many cytokines, inflammatory and oxidative stress markers were linked to either of those conditions extensive literature review show that IL-6 and CRP are two markers most consistently associated with both MDD and HIV infection. We propose to use changes in those two markers as a primary outcome of our study. For example in our recent clinical trial with aprepitant, a compound with potential utility as a drug for depression and anti-inflammatory properties in HIV infected subjects, in non-depressed subjects we detected a decrease in plasma levels of IL-6 after 2 weeks of treatment within subjects (p=0.02) and between aprepitant and placebo (p=0.02) (131) (Figure 7). In addition to our primary variables (IL-6 and CRP) associated with inflammation, we will measure several other plasma markers of inflammation in HIV positive depressed subjects receiving SSRI or placebo (see C.4 Further Analyses).

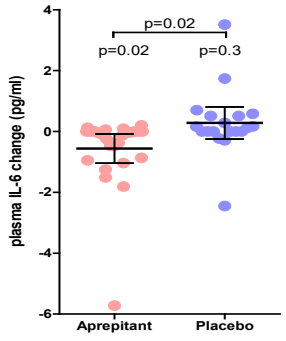

Figure 7. Changes in plasma levels of IL-6 in patients treated with aprepitant. IL-6 levels were measured in plasma of 48 patients HIV positive patients enrolled in aprepitant trial. 29 patients received medication (125, 250 or 375 mg per day), 19 received placebo for 14 days. Changes in IL-6 are shown as delta [IL-6] between baseline and after 2 weeks of treatment with aprepitant measured.

Secondary Aim. Determine if improvement in depressive symptoms is associated with improvements in innate immunity and inflammation in HIV seropositive individuals.

Hypothesis: Reduced symptoms of depression after acute (10-week) treatment will correlate with increased

levels of innate immunity (LUNK and intra cellular IFNγ in natural killer cells) and decreased levels of systemic inflammation (IL-6 and CRP).

C.3.2 Biostatistical Consideration and Analysis Plan

C.3.2.a Methods and Approach

Primary Aims: For Primary Aims 1A and 1B, participants will provide measures of innate immunity (LUNK and intracellular IFN-γ) and inflammation (IL6 and CRP) 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.
Secondary Aim: In the Secondary Aim, we will examine relationships between the effects of Escitalopram versus Placebo on depressive symptoms and the effects on the primary biological responses. Hamilton scores will be obtained at baseline and at weeks 2, 4, and 10.

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 Hamilton and for the four immunity measures. For each immunity measure and Hamilton, 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 Hamilton 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 Hamilton 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 (135, 136), to test whether changes in Hamilton score at week 2 (and, separately, at week 4) 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 ≤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 (MacKinnon, 2008, 8.10-8.14). 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 (2008) 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.

C.3.2.b Power Analysis and Sample Size Calculation for Primary Aims

We use two-sided hypothesis tests, and assume 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 use the methods of Hedeker et al (122): 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 Cohen's d=0.40 or higher, and 80% power to detect a main effect (from week 2 through week 10) of d=0.4 or higher.

C.3.3 Expected Outcomes, Potential Problems and Alternative Approaches

If successful, this trial will advance the field of HIV care by demonstrating the benefit of SSRI treatment on immune system homeostasis, marked by less innate immune suppression and less systemic inflammation, both of which are implicated in HIV pathogenesis. We expect to detect restoration of NK cell functions and decreases in levels of pro inflammatory markers as a result of SSRI treatment. Pro-inflammatory cytokines are thought to play a role in the pathophysiology of depression (4, 7, 86, 132). Although this is not an aim of the present study, data accumulated during our study will allow us to evaluate this relationship along with other patient characteristics (see C.4 Further Analyses). Both depression and HIV are associated with increased plasma levels of IFNγ (133, 134) however based on previous observations (42) we expect to see decreased

IFNγ production by stimulated NK cells from HIV+ subjects on cART. We will monitor if SSRI treatment or/and depression improvement will restore IFNγ production. However if we do not detect changes in IFN-γ we will analyze other markers of NK activation and degranulation which are associated with both chronic HIV infection and depression (126) as noted below in C.4. Further Analyses.

We expect to see Immune changes prior to depression improvements suggesting direct SSRI effects on peripheral immune cells. Although unlikely, It is possible that a ceiling effect could be observed and both groups exhibit similar and maximal immune changes at a given time point. If that is the case the frequency of our measures will allow us to study the time course of these immune changes over time and over the time course of depression improvement which will further inform us about SSRI direct effects and depression improvement effects on immunity.

If successful, this rigorously designed clinical trial will advance the field of HIV care by demonstrating the immune benefits of SSRIs among depressed patients with well-controlled viral load – an increasingly prevalent population in the era of modern cART. Many large scale clinical trials encounter challenges with recruitment and retention. We will proactively monitor accrual and retention and should we encounter this challenge, we will initiate a response that will include consultation with the PMHARC Community Advisory Board to discuss recruitment barriers, additional avenues of recruitment and retention strategies. We will also maintain close communications with the Philadelphia Integrated Behavioral Health Initiative which has staff embedded within six of the largest HIV care sites in the city. These staff can help promote recruitment and facilitate retention should we need assistance.

C.4 Further Analyses

Innate Immunity, Inflammation and Virology: We will also assess the effects of SSRI on other important innate immune cell populations. These responses will be available at baseline and after 2, 4 and 10 weeks of treatment, so they will be analyzed using the approach described above for the primary outcomes of Aim 1. We will evaluate NK receptor expression before and after 10 weeks of SSRI treatment using Flow cytometry assay. Total NK cells will be characterized as $CD45^{+}/CD3^{-}$/ $CD16^{+}/CD56^{+}$. In addition, the expression of the following receptors will be assessed: NKp44, NKp46, NKp30 and CD107 using appropriate antibodies. CD56 bright and dim cells will be also assessed. CD56bright NK cells are associated with cytokine production while CD56 dim are linked to higher cytotoxic activity (137).

In addition to IL-6 and CRP we identified several other markers for further analyses based on the literature and our own immunologic investigations. Specifically, in the aprepitant trial, in addition to IL-6 we also detected a decrease in plasma levels of TNFα and soluble CD163 (sCD163) and decreased expression of Programmed Death 1 (PD-1) receptor on CD4+ cells. PD-1 is known to suppress T cell activation (138). The assays will be done in conjunction with PMHARC Core E. sCD163 and TNF-α will be measured by standard ELISA techniques and PD-1 by flow cytometry. We will use a PD-1 panel established in our laboratory as a part of clinical the trial U01 MH090325 (CD3/CD4/CD8/CD45RO/CD197/CD62L/CD95/PD-1/CD38/HLA-DR). We will also use the monocyte activation/polarization panel which we have developed (CD3/CD14/CD19/CD56/CD16/ CD163/CD97/CD312/CD38/HLA-DR). Further we will quantitate expression of CD4, CCR5, and CXCR4 receptors on PBMCs and macrophages to evaluate SSRI effect we observed ex vivo (see C1.9.c). We will measure both fluid phase (plasma) and cellular markers of innate immunity and inflammation using multiplex and flow cytometry technology. These measures will be performed on stored plasma samples and cryopreserved PBMCs.

We expect to find undetectable levels of virus in plasma (<40 copies/ml) in most subjects because all subjects will be on a stable cART regimen. Therefore, data on plasmas viral load will be used primarily for monitoring cART adherence. In contrast, we expect to find low but detectable levels of viral DNA in most subjects. Restoration of NK functions may lead to decreased viral DNA levels. We will analyze if such a decrease is linked to SSRI treatment or improvement of depression in general. We will also establish a repository of plasma and frozen PBMC samples from the 180 depressed HIV+ subjects. This repository will allow us to evaluate other markers associated with depression and/or chronic HIV infection such as oxidative stress (e.g. malondealdedyde), markers of monocyte activation (e.g. neopterin) and any other newly identified molecules during the period of the current study. We will evaluate monocyte activation/polarization profile since we expect that changes in plasma cytokines may affect monocyte polarization which in turn may influence both depression and HIV infection (30-33).

Effects of patient characteristics: Differences in patient demographics (such as age and gender) and characteristics (such as depression severity, levels of life stress, social support, neurocognitive capacity, time since HIV diagnosis, endocrine status, and systemic inflammation level) could potentially moderate the effects of SSRI treatment on our primary outcomes. Some research has suggested that baseline levels of CRP (139), IL-6 and TNF-α (7, 86, 140, 141) and of other biological indicators (7, 86, 132) may influence the effects of

SSRI on depression. We will perform a series of moderator analyses (142) to address these questions. The potential moderators will be included as main effects and as interactions with group in the analyses described above for the primary responses. We will use multivariate analyses analogous to the univariate analyses to examine SSRI effects on a wider range of biological responses to include endocrine hormones (cortisol, ACTH, DHEA), as well as the flow cytometry panels noted above.

C.5 Missing Data and Nonadherence For the primary analyses described above, premature discontinuation from treatment and occasional missing weekly appointments will lead to incomplete data. The mixed effects models for Aim 1, Hypothesis 1 described above can make use of all available data provided by subjects, but the inferences drawn from them will be unaffected by the missing data only if the missing data can be regarded as ignorable. For the other primary responses, dropouts will not provide any responses, so the basic models require ignorable dropout. To assess the sensitivity of our analyses to this assumption, we will also use selection models (143) to examine the effects of missing data: we will explicitly model the probability of premature discontinuation at a time point as a function of baseline characteristics and responses at previous time points, using a logistic regression model. For the longitudinal analyses of Aim 1, Hypothesis 1, these probabilities will provide time varying (inverse) weights for reruns of the primary analysis. For the other primary hypotheses, the overall probability of dropout will be used as a weight, and incorporated into a weighted analysis of these hypotheses. We will perform these analyses in a range of assumptions on the dropout process and assess the sensitivity of results to them. To account for possible non-adherence to assigned intervention, we will use self-report of pill ingestion and MEMS caps, as well as RNA viral load for cART. We will use the methods of Nagelkerke et al (144, 145), to obtain estimates of the intervention effect in a population compliant with treatment i.e. the Complier Average Causal Effect (CACE).

C.6 Data Management Data will be gathered using an internet-based direct-entry data system developed and used over the last ten years by the U Penn Center for Studies on Addictions in the Department of Psychiatry. Interview data and self-report data are entered directly onto computers at the research sites by research technicians and study subjects respectively. Field validation (e.g., no out-of-range or otherwise invalid responses will be accepted) and form validation (e.g., logically impossible responses to different questions will not be accepted) are built into this entry process. Data are transmitted (128-bit encrypted form) over the Internet to the DMU servers. After online reviews, the data are archived on secure servers located in the U Penn School of Medicine Data Center. No identifying information is stored on the DMU servers. Certain DMU staff members have permission to modify the archived data. Audit logs record any modification to the original entry. Password protection allows members of the research team appropriate levels of data access.

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