NEUROINFLAMMATION AND MODULATING FACTORS IN DEPRESSION AND HIV

THE GROWTH STUDY- GROUP THERAPY IN HIV FOR DEPRESSION IN UGANDA

Neuroinflammation and Modulating Factors in Depression and HIV- The GROwTH Study

Area: HIV and Depression

Type: Comparative Effectiveness

List of investigators and co-investigators:

Investigator	Institution	Role	Email
Sarah Lofgren	University of Minnesota	PI	Lofg0020@umn.edu
Noeline Nakasujja	Makerere University	Ugandan Co-PI	DrNoeline@yahoo.com
David Boulware	University of Minnesota	Mentor of PI	Boulw001@umn.edu
David Bond	University of Minnesota	Psychiatry Advisor	DJBond@umn.edu
Alan Lifson	University of Minnesota	Epidemiologist	lifso001@umn.edu
Katherine Hullsiek	University of Minnesota	Statistician	hulls003@umn.edu
George M. Slavich	University of California- Los Angeles	Psychology Advisor	GSlavich@mednet.ucla.edu

Document History

Document	Version Date	Summary of Changes
Version 3	7 Jan 2020	*Demographics added to screening information collected.* *A 2nd non-depressed control group (100 individuals) added*
Version 2	8 July 2019	*CD4 cutoff removed as an enrollment criteria*
Version 1	21 January 2019	N/A

PROTOCOL SUMMARY

Background and Rationale

Depression in people living with HIV is associated with worse care engagement, drug adherence, and mortality. The prevalence of depression is three times greater in those with HIV than comparable controls. While antiretroviral therapy (ART) enables immune reconstitution, those with depression do worse clinically than those without depression even when controlling for HIV stage. However, treating depression in HIV-infected persons is challenging. Even among those virologically suppressed on ART, a significant percentage are resistant to standard pharmacotherapy or psychotherapy for depression. The reasons for this are complex and poorly understood. An emerging body of evidence indicates that inflammation may perpetuate depression. We therefore posit that CNS inflammation from HIV viral replication and signaling may be a biologic process contributing to the increased depression prevalence and resistance to depression treatment in HIV-infected individuals. While depression is a complex disease with psychosocial and genetic predisposing factors, our overarching *hypothesis* is that HIV induced neuroinflammation contributes to the high prevalence of treatment resistant depression thereby contributing to worse HIV outcomes in individuals and populations both in the United States and globally.

In spite of the recognition of inflammation as a driver of depression in those with HIV the basic underlying pathophysiology must be elucidated. Prior research investigating plasma inflammatory biomarkers in HIV-infected persons reported an association of depression with pro-inflammatory cytokines, such as interleukin-6 (IL-6), and depression. Yet, factors modulating longitudinal changes in depression with therapy, e.g. group support psychotherapy in HIV patients is poorly understood. We will longitudinally evaluate changes in plasma biomarker changes in participants on ART with standard of care depression interventions before and after implementing group psychotherapy. In Ugandans with HIV, IL-6 in plasma is associated increased risk of depression highlighting the importance of IL-6 and innate inflammation.

Objective

Determine if depression, which persists after depression treatment at 26 weeks, is associated with increased innate inflammation in a prospective cohort of HIV-infected Ugandans receiving SSRIs in which group psychotherapy is initiated.

Hypothesis: Among HIV-infected Ugandans with depression (A): initiating ART and SSRI therapy, structured weekly group psychotherapy coupled with SSRIs will reduce depressive symptoms, measured by the PHQ-9 and Hamilton Depression Rating Scale: (B) Those with persisting depression at 26 weeks will have increased plasma IL-6 and cortisol levels, reflective of ongoing systemic stress response.

Prediction: Innate inflammation (e.g. IL-6) and systemic stress responses (e.g. cortisol) will be higher at 26 weeks in those with persistent depression compared with those with resolved depression.

Experimental Plan:

We will enroll a prospective cohort of HIV-infected subjects with depressive symptoms and a control without depressive symptoms.

- The first 100 subjects - standard of care therapy including SSRI therapy
- The second 100 subjects – standard of care including SSRI therapy + Group Support Psychotherapy
- The third 100 non-depressed subjects- standard of care HIV therapy

We will assess PHQ-9 at baseline (pre-ART) and again at 26 weeks. PHQ-9 instrument has been used and validated in several African countries including Uganda.[1-9] The cut-offs for the PHQ-9 tool are “not depressed”

(score ≤4), “mild depression” (score 5-9), “moderate and moderately severe depression” (score 10-19), or “severe depression” (score ≥20).

Enrollment Criteria

- Age ≥18 years old and <65 years
- Depressive Symptoms with PHQ-9 score ≥5
- Not suicidal (PHQ-9 question 9 score ≥2)
- Not severely depression (PHQ-9 score ≥20)
- Not Pregnant or Breastfeeding
- Provision of written informed consent
- Not receiving ART at study entry
- Outpatient, not requiring hospitalization

Non-depressed control group will have PHQ-9 <5 and not suicidal but otherwise identical.

Screening: We will screen participants newly presenting to clinic (<3 months). We will check PHQ-9 score to evaluate for eligibility and record the baseline CD4 count. We will also record baseline demographics including biological sex and age. We will record all screened in screening log. We will also ask all women the date of their last menstrual period, their last pregnancy, and do a pregnancy test on all women ages 18-50 if otherwise eligible.

Baseline Measurements: Those with PHQ-9 ≥5 and ≤19 will be invited to consent as well as a non-depressed (PHQ-9 <5) control group otherwise meeting enrollment criteria. Those consenting will have PHQ-9 recorded as well as Hamilton Rating Depression Scale,[10] which has not been previously validated in Uganda. We will compare depression prevalence between the two scales. Of enrolled participants (PHQ-9 score >5), We will collect plasma and cryopreserve at -80C for biomarker quantification. We will record the medications the participants are prescribed including antidepressants and ART. I will administer a questionnaire about relevant social factors to depression including a validated social support scale as well as the Stress and Adversity Inventory (STRAIN).

Week 12 Measurements of those depressed: At 12 weeks we will assess for depression using PHQ-9. We will record the medications the participants are on including antidepressants and ART. This is primarily a safety check. Those not depressed will not be contacted.

26 Week Follow Up Including HIV Viral Loads: We will again assess for depression using PHQ-9. We will record medications the participants are taking and measure plasma cytokines/biomarkers. We will again administer the social factor questionnaire including a validated social support scale as well as the STRAIN stress inventory tool. HIV plasma viral load will be checked per National Ugandan HIV guidelines. We will collect these data via review of the electronic medical record.

Cytokine measurement will be performed at baseline and 26 weeks.

Statistical Analysis: Our analysis will focus on:

1) Effect of Group Support Psychotherapy: We will compare the proportion of baseline depression with the proportion of persistent depression at week 26. We will use the PHQ-9 as a continuous variable, with changes from baseline to week 26.

2) Effect of biomarkers on persistent vs. resolved depression: We will compare those with persistent depression (PHQ-9 >4 at week 26) versus resolved depression (PHQ-9 <5 at week 26). We will assess baseline demographic and HIV parameters as well as log2-transformed plasma cytokines from week 0, week 26, and the change in biomarker values from week 0 to week 26. We will use Benjamini-Hochberg adjustment for multiple comparisons for the biomarkers unrelated to our a priori hypothesis (i.e. IL-6 association with persisting depression). If the distribution between groups is unbalanced for an important factor (e.g. age, sex as biological variable, anti-depressant use, HIV viral load), we will adjust as needed for differentially distributed variables between the cohorts. We will consider sex as a biological variable in our analyses, considering differential effects in women vs. men.

3) Effect of biomarkers on depressed vs non-depressed control group: We will compare those never depressed (PHQ-9 <5) and those depressed at baseline and at 26 weeks. We will also group those never depressed with those with resolved depression (PHQ-9 <5 at week 26) and compare with those with persistent depression (PHQ-9 >4 at week 26). We will assess baseline demographic and HIV parameters as well as log2-transformed plasma cytokines from week 0, week 26, and the change in biomarker values from week 0 to week 26. We will use Benjamini-Hochberg adjustment for multiple comparisons for the biomarkers unrelated to our a priori hypothesis (i.e. IL-6 association with persisting depression). If the distribution between groups is unbalanced for an important factor (e.g. age, sex as biological variable, anti-depressant use, HIV viral load), we will adjust as needed for differentially distributed variables between the cohorts. We will consider sex as a biological variable in our analyses, considering differential effects in women vs. men.

4) Baseline Cytokine Analysis: As a secondary outcome, subjects will be categorized into baseline groups of mild depression versus moderate or above depression. We will compare baseline plasma biomarker levels by group via linear regression of log2 transformed data. Any demographic covariates associated with depression will be included in the regression model. We will also compare by 9 am cortisol levels. We will assess whether age or sex are associated with biomarker responses.

5) Virologic Outcomes: As a secondary outcome, proportions of those with 26-week virologic suppression will be compared by those with persisting depression vs. resolved using Fisher's Exact test.

6) Depression Scale Comparison: We will compare prevalence of depression using the PHQ-9 and the HDRS. We will compare the proportions of those depressed at baseline and 26 weeks using McNemar's test.

7) Social Factors and Stress Assessment: We will analyze social factors and the STRAIN stress and adversity tool scores by baseline depression and control groups as well as those with persistent depression at 26 weeks using linear regression.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE	Adverse events
ART	Antiretroviral Therapy
CD4	CD4+ T helper Cells
CRF	Case report form
HRDS	Hamilton Rating Depression Scale
HIV	Human Immunodeficiency Virus
IDI	Infectious Diseases Institute
IL-6	Interleukin-6
IRB	Institutional Review Board
KCCA	Kampala Capital City Authority

MU-JHU	Makerere University – John's Hopkins University Core Laboratory
PHQ-9	Patient Health Questionnaire 9 Item Depression Screening Tool
PI	Primary Investigator
SAE	Serious Adverse Event
SSRI	Selective Serotonin Reuptake Inhibitor
STRAIN	Stress and Adversity Inventory

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1. INTRODUCTION

Depression in HIV is a complex co-morbidity with both social factors such as stigma[11] as well as biologic components.[12] Disruptions in neurotransmitters such as serotonin and catecholamines are known to cause depression.[13] Inflammation caused by diseases such as stroke, diabetes, and HIV is associated with higher rates of depression.[14] HIV causes inflammation throughout the body, but since the virus can cross the blood-brain-barrier, HIV can replicate in and target the brain causing neuroinflammation which predisposes depression.[15] However the pathophysiology of the role of inflammation in comorbid depression and HIV is poorly understood.

1.1. Disease Setting/Patient Population

Participants will be selected from the HIV patients in the IDI or KCCA clinics. We will select ART naïve, adults who are newly enrolled in clinic (<3 months). We will screen them for depression. Those with depression will be followed for 26 weeks and have their charts checked for viral load data at 26 weeks.

1.2. Background and Rationale

Depression in HIV is common and causes poor HIV outcomes. Depression prevalence in HIV-infected persons ranges from 13 to 78% as compared to 5% in the general population.[16, 17] Adherence to antiretroviral medication and subsequently viral suppression is a life-saving treatment in HIV.[18] However, depression has been shown to reduce engagement in care as well as adherence to medication.[19] There is also evidence that depression is associated with poorer levels of viral suppression and even mortality.[20, 21]

Depression in HIV has negative public health implications. Depression decreases the likelihood that people will engage in HIV care, adhere to treatment, and respond to HIV therapy. Those with depression and HIV are less likely to return to health and remain more likely to transmit the virus.[22, 23] Because of this, treatment of HIV is an important key to prevention; lower rates of engagement in and adherence to HIV treatment due to depression means others remain at risk.[24, 25]

Growing evidence shows depression has an inflammatory component. Depression has higher prevalence in neuroinflammatory disorders including stroke, diabetes, and HIV.[14] These conditions alter the blood brain barrier allowing for infiltration of immune cells and increased cytokine signaling. While many diseases make people chronically ill such as hepatitis B, only some have increased prevalence of depression such as HIV. This observation does not suggest that the psychosocial impacts of chronic life-threatening illness do not contribute to depression but does imply that neuroinflammatory effects in diseases such as HIV can be additive or synergistic in the pathogenesis of depression.

Depression in HIV, even when participants have virologic suppression, is often resistant to standard psychiatric treatment, and treatment for depression among people living with HIV is understudied. While there are many treatment modalities for depression, a significant proportion of patients do not respond to treatment.[26] Also, while there are a few studies looking at treatment of depression specific in HIV, the data are scant.[27, 28] More work on depression treatment in those with HIV is needed, particularly in low-income countries in sub-Saharan Africa given the high prevalence of HIV.

Psychotherapy, long known to improve depression, is increasingly being shown to decrease inflammation suggesting the underlying mechanism. Psychotherapy is a mainstay of depression treatment and has been shown to decrease IL-6 and TNF-a two pro-inflammatory cytokines linked with depression,[29] as well as IL-6, and CRP in women post coronary artery bypass.[30] Psychotherapy may work through a neuroendocrine mechanism with decreased psychological symptoms correlating with decreased stress biomarkers such as cortisol. Antoni et al. found cognitive-behavioral stress management interventions decreased both cortisol and depressive symptoms over controls in U.S. men who have sex with men (MSM) and are living with HIV.[31] However, given the differences in cultures, psychological, and social factors between American MSM and sub-Saharan African heterosexual individuals, adjustments to similar interventions are needed.

Psychotherapy: Evidence in sub-Saharan Africa. We recently published a depression intervention review for Africans with HIV.[32] We found multiple interventions feasible and acceptable in their community. Specifically Nakimuli-Mpungu in Uganda has found that group support psychotherapy is a culturally sensitive intervention, which enhances social support, teaching coping skills, and income-generating skills thereby treating depression.[33-36] Given the success in sub-Saharan Africa and that group psychotherapy is scalable, as it can be taught to lay health workers, this presents an opportunity to treat depression even in poor and rural areas.

This work could be helpful not only for people with HIV but also potentially for patients with other inflammatory diseases such as lupus where there is also a higher prevalence of depression.[37] The past work in immunologic differences in those with and without depression in HIV suggests an opening to further investigation.

Resolution of Depression for Some with ART: Our previous work in Uganda has shown that while a portion of HIV-infected people remain depressed even after starting ART, a large percentage resolve with ART alone. In our previous studies in cryptococcal disease, 65% (N=217) of 325 cryptococcal survivors were depressed via the CES-D scale at time of ART initiation and of those depressed, at 8 weeks 47.5% (N= 103) were no longer depressed, 31% (N=67) remained depressed, and 21.7% (N=47) had died or were lost to follow up (unpublished data). Similarly, 59% in those with cryptococcal antigenemia (N=207) were depressed pre-ART compared to 30% in 125 HIV-infected controls pre-ART with a mean CD4 count of 242 $\pm$119 cells/μL.[38] In those with meningitis, we followed depression via CESD and found a significant portion of the depression resolved with HIV therapy but no depression specific therapy. Similarly our co-mentor Dr. Nakasujja recently presented a poster at CROI from a subset of participants in the Rakai cohort with available follow up data.[39] The researchers found among 333 people with HIV and ART naïve, 22% (N=73) were depressed via CESD score at baseline and 8.4% (N=28) 2 years later. Thus, in this cohort 38% (28/73) had persistent depression at 2 years with HIV therapy alone. Dr. Nakasujja co-authored another study looking at ART naïve, HIV-infected Ugandans and found that the rate of persistent depression was 25% over 1 year.[40]

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

1) Among depressed HIV-infected Ugandans, determine if the resolution of depression at 26 weeks of HIV therapy is improved with group psychotherapy.

2) In the same population determine if persistent depression is associated with higher levels of innate inflammation. Also, compare baseline and follow up inflammation among depressed compared to non-depressed control group.

3) Evaluate if viral suppression levels at 26 weeks are improved by group psychotherapy.

Endpoints

1) Depression score via patient health questionnaire (PHQ-9) at screening (total screened and total enrolled) and at 26 weeks (total enrolled) comparing those in the observational cohort and those in the intervention cohort.

2) Biomarkers associated with depression including IL-6 measured from plasma as well as morning cortisol levels at screening and 26 weeks.

2.2. *Study Hypothesis*

Hypothesis: Among HIV-infected Ugandans with depression (A): initiating ART and SSRI therapy, structured weekly group psychotherapy coupled with SSRIs will reduce depressive symptoms, measured by the PHQ-9 and Hamilton Depression Rating Scale: (B) Those with persisting depression at 26 weeks will have increased plasma IL-6 and cortisol levels, reflective of ongoing systemic stress response.

Prediction: Innate inflammation (e.g. IL-6) and systemic stress responses (e.g. cortisol) will be higher at 26 weeks in those with persistent depression compared with those with resolved depression.

STUDY DESIGN

We will enroll a prospective cohort of HIV-infected subjects with depressive symptoms as well as a non-depressed control group.

In the depressed groups we will assess PHQ-9 at baseline (pre-ART), 12 weeks and 26 weeks. (**Figure 1**). PHQ-9 instrument has been used and validated in several African countries including Uganda.[1-9] The cut-offs for the PHQ-9 tool are “not depressed” (score $\leq$4), “mild depression” (score 5-9), “moderate and moderately severe depression” (score 10-19), or “severe depression” (score $\geq$20). We will also use the Hamilton Rating Depression Scale (HRDS),[10] which has not been previously validated in Uganda. We will compare depression prevalence between the two scales. We will also have a second non-depressed control group who will be followed similarly to the observational group but without SSRIs or the 12 week safety check.

3. SUBJECT SELECTION

The following eligibility criteria are designed to select subjects for whom protocol treatment is considered appropriate.

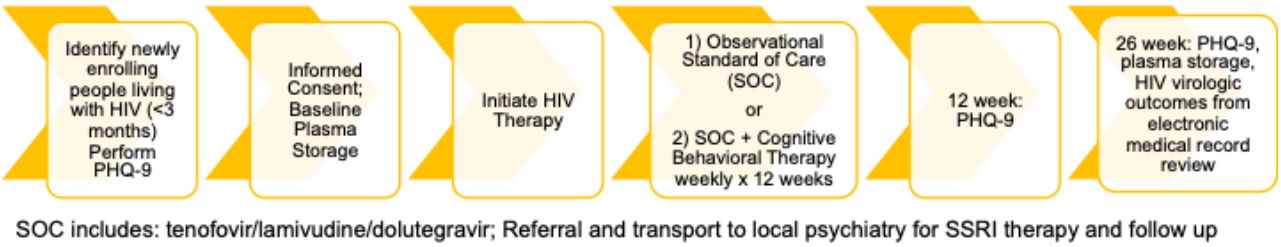
Participating sites:

1) Infectious Disease Institute (IDI)/ Mulago Hill Complex, Kampala, Uganda

2) Kampala Capital City Authority (KCCA) Clinics Kampala, Uganda

- Kawaala
- Kawempe
- Kisenyi
- Kiswa
- Kitebi
- Komamboga

Figure 1. Enrollment Plan



SOC includes: tenofovir/lamivudine/dolutegravir; Referral and transport to local psychiatry for SSRI therapy and follow up

3.1. Inclusion Criteria

Screening: We will screen participants newly presenting to clinic (<3 months). We will check PHQ-9 score to evaluate for eligibility. We will record CD4 counts. We will record all screened in screening log. As screening for depression with PHQ-9 is standard of care in the Uganda HIV guidelines, we ask for a waiver of consent to collect the PHQ-9 score in all screened.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study.

2. Subjects who are willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.

3. Age ≥18 years old and <65 years.

4. Mild to Moderately-Severe Depressive Symptoms with PHQ-9 score ≥5 but <20.

5. Not suicidal (PHQ-9 question 9 score ≥2)

6. Not receiving antiretroviral therapy (ART) at screening.
7. Outpatient, not requiring hospitalization.
8. Non-depressed (PHQ-9 score <5) for 2nd control group but meeting #s 1,2,3,5,6,7.

3.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. Those not meeting enrollment criteria.

4. TREATMENTS OF SUBJECTS

4.1. Allocation to Treatment/Group

The first half of the depressed participants (100 subjects) will be in the observational cohort.

The second half of the depressed participants (100 subjects) will be in the intervention cohort and receive group psychotherapy.

A second non-depressed control group (100 subjects) will be added for another observational cohort.

4.2. Drug Supplies

N/A

5. STUDY PROCEDURES

5.1. Screening

Participants with HIV will be identified in Kampala Capital City Authority Clinics, Kampala, Uganda (KCCA) clinics and IDI through lab personnel, adherence counselors, and clinicians from those newly enrolled. Potential enrollees will be contacted by clinic staff to assess willingness to participate; if willing, participants will be invited to call study personnel or to come and meet study personnel at clinic.

All of those eligible, based on being ART naïve and in clinic <3 months, will be screened for depression via PHQ-9 and score will be recorded. All of those with depression PHQ-9 score >4 will be referred to Mulago psychiatry clinic for SSRI treatment and monitoring. All screened will be logged in a screening log

5.2. Study Period

Those individuals with mild to moderately-severe depression who consent will be enrolled into the study. They will be asked to provide a plasma sample. We will also administer the Hamilton Depression Scale, a stress assessment using the STRAIN, and a social factors questionnaire. I will also as an extra voluntary measure invite the participants to give a CSF sample via lumbar puncture. This will be requested at baseline and at 26 weeks. Those willing will have an extra consent and receive extra compensation of 100,000 Ugandan shillings. This is in addition to the 10,000- 30,000 Ugandan shillings for transportation every visit.

Follow-up Visit

Week 12 Measurements: At 12 weeks we will again assess the depressed groups for depression using PHQ-9. This is primarily a safety check. We will record the medications the participants are on including antidepressants and ART.

26 Week Measurements: We will again assess for depression using PHQ-9. We will record medications the participants are taking and measure plasma cytokines/biomarkers. We will again administer the social factor questionnaire including a validated social support scale as well as the STRAIN tool. HIV plasma viral load will be checked per National Ugandan HIV guidelines. I will collect these data via review of the electronic medical record.

Those who gave a CSF sample at enrollment will again be invited to give another sample. This will again have an extra consent and receive extra compensation.

Cytokine measurements: We will perform cytokine assays at baseline and 26 weeks using linear regression.

5.3. Subject Withdrawal

Subjects may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety or behavioral reasons, or the inability of the subject to comply with the protocol required schedule of study visits or procedures.

If a subject does not return for a scheduled visit, every effort should be made to contact the subject. At enrollment they will provide 3 phone numbers. The participants will be called to remind them of their appointments and will be called if they do not return. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events (AEs).

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6. ASSESSMENTS

6.1. Safety

At screening participants will be screened for depression via PHQ-9. Those enrolled will be asked for a plasma sample and will be evaluated for stress and have a questionnaire to evaluate social factors associated with depression. The participants will be re-

Table 1. ***Schedule of Study Events***

Week	**0**	**12**	**26**
Patient Health Questionnaire-9 (PHQ-9)	X	X	X
Hamilton Depression Rating Scale	X		X
Plasma Inflammatory Biomarkers	X		X
AM Cortisol Levels	X		X
Stress using STRAIN	X		X
Social Factors Questionnaire	X		X
Group Support Psychotherapy		→	
HIV Viral Load (via chart review)			X

assessed at 12 weeks via PHQ-9 mainly as a safety check. Those with worsening depression or signs of suicidality will be sent to the Mulago psychiatry clinic. At 26 weeks all participants will be screened for depression via PHQ-9, will be asked for a plasma sample, and also have their charts to be checked for viral load information.

We will also have a Data Monitoring and Safety Board. See further description in 8.3 Safety Analysis.

6.2. Pregnancy Testing

This study will ask all women the date of their last menstrual period, their last pregnancy, and do a pregnancy test on all women 18-50 who are otherwise eligible.

6.2.1. Sample Handling

All protocol specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650. Culture isolates, if obtained in this study, are to be shipped as specified for UN 2814 Category A Infectious Substances.

Biohazard Containment. Transmission of HIV and other blood borne pathogens can occur through contact with contaminated needles, blood, and blood products. Respiratory pathogens such *Mycobacterium tuberculosis* are transmitted by inhalation of droplet nuclei. Appropriate blood, secretion, and respiratory precautions will be employed by all personnel in the collection of clinical samples and the shipping and handling of all clinical samples and isolates for this study, as currently recommended by the Centers for Disease Control and Prevention in the United States, the WHO internationally, and the NIH.

Sample transfer and analysis will be governed by a material transfer agreement, which will be signed between both parties. At the end of the analysis, unused samples will be retained.

7. ADVERSE EVENT REPORTING

7.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship will be reported.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator.

During each study visit the co-investigator will assess AEs which may have occurred since the previous visit. This will be done by the study coordinator. The patients will be referred and transported if needed to either their HIV primary physician or our psychiatrist at IDI.

7.2. Serious Adverse Events

An SAE is any untoward medical occurrence at any dose that:

Results in death; Is life-threatening (immediate risk of death); Requires inpatient hospitalization or prolongation of existing hospitalization; Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions); Results in congenital anomaly/birth defect,

7.3. Severity Assessment

The severity of adverse events will be graded according to the National Institute of Health Division of AIDS (DAIDS) classification system for reporting adverse experiences in adults.[41]

Causality Assessment

N/A

7.4. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow IRB, local and international regulations, as appropriate. All SAEs will be reported to IDI Scientific Review Committee, the IRB, the Uganda National Council of Science and Technology (UNCST), the Uganda National Drug Authority (NDA). All SAEs will be reported to the sponsor within 24 hours of knowing about the event and to the ethics committee, UNCST and NDA within seven days of knowing about the event. Further relevant follow-up information will be given as soon as possible. Follow-up will continue until the event resolves.

All AEs will be tabulated and reported to the IRB in annual study reports. Serious adverse events will be reported to IRB and the regulatory authorities within seven days from the time the study team becomes aware of the occurrence of the SAE. All AEs will be reported on the AE page(s) of the CRF.]=For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

7.5. Post-Recruitment Illness

All subjects with post-recruitment illness will be monitored until symptoms resolve, laboratory changes return to baseline or until there is a satisfactory explanation for the changes observed. Patients will receive medical care including admission at Mulago National Referral and Teaching Hospital or Butabika Psychiatric Hospital and patients will be managed in accordance with Uganda national treatment guidelines.

8. DATA ANALYSIS/STATISTICAL METHODS

8.1. Sample Size Determination

Depression Intervention:

We will power for a reduction in IL-6 between those with persistent and resolved depression at 26 weeks. Based on our systematic review, the reduction in depression score for psychotherapy is 73% from baseline.[32] However response rates vary. Another review found the score reduction was 20% when compared to controls.[42] We then calculated a range of possible sample sizes seen in **Statistics Plan.**

Assuming that 25% of the psychotherapy group will have persistent depression at week 26 (with equal sample sizes, 80% power, and two-sided alpha = 0.05) and I want a delta of .5, we need a total sample size of 168

participants. The prior study had a 22% non-completion rate for group therapy.[34] To account for non-completion and up to a 5% loss to follow-up, I estimate a sample size of 200 participants.

Subject Recruitment/Number needed to screen

I postulate that the baseline depression rate in these ART naïve subjects would be about 25%.[43] Thus we would need to screen 800-1000 HIV+ people.

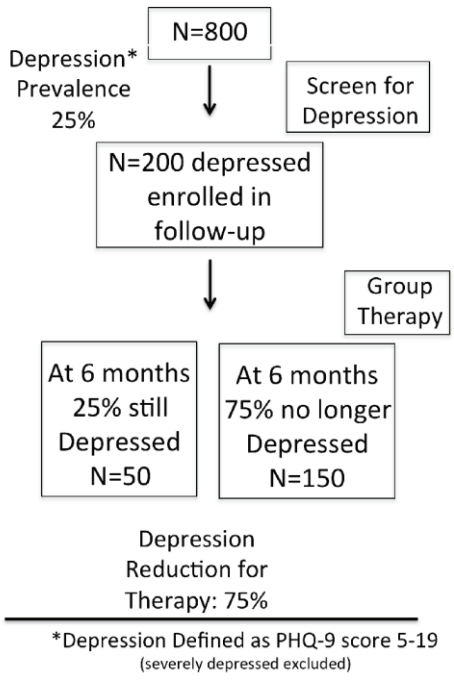
The non-depressed control group will come out of those screened and not add to the total number screened.

These will be enrolled from the Infectious Disease Institute or three clinics that refer to it. As noted in the preliminary data section, we are currently working on a study in those found clinics and have found we can get about 15 new patients with CD4 <100 cells/uL a month (unpublished data). Our experience is that there are many more presenting with higher CD4 cells/uL counts, or about 150 new individuals a month. Taken these patient sources we estimate we could screen 800-1000 participants over 2.2 years from our 4 clinics and given not all participants will agree to participate we estimate that we can enroll the group over 2.5 years.

8.2. Analysis of Endpoints

1) *Effect of Group Support Psychotherapy:* We will compare the proportion of baseline depression with the proportion of persistent depression at week 26. We will use the PHQ-9 as a continuous variable, with changes from baseline to week 26.
2) *Effect of biomarkers on persistent vs. resolved depression:* We will compare those with persistent depression (PHQ-9 $\geq$5 at week 26) versus resolved depression (PHQ-9 <4 at week 26). We will assess baseline demographic and HIV parameters as well as $\log_2$-transformed plasma cytokines from week 0, week 26, and the change in biomarker values from week 0 to week 26. We will use Benjamini-Hochberg adjustment for multiple comparisons for the biomarkers unrelated to our *a priori* hypothesis (i.e. IL-6 association with persisting depression). If the distribution between groups is unbalanced for an important factor (e.g. age, sex as biological variable, anti-depressant use, HIV viral load), we will adjust as needed for differentially distributed variables between the cohorts. We will consider sex as a biological variable in our analyses, considering differential effects in women vs. men.
3) 3) Effect of biomarkers on depressed vs non-depressed control group: We will compare those never depressed (PHQ-9 <5) and those depressed at baseline and at 26 weeks. We will also group those never depressed with those with resolved depression (PHQ-9 <5 at week 26) and compare with those with persistent depression (PHQ-9 >4 at week 26). We will assess baseline demographic and HIV parameters as well as log2-transformed plasma cytokines from week 0, week 26, and the change in biomarker values from week 0 to week 26. We will use Benjamini-Hochberg adjustment for multiple comparisons for the biomarkers unrelated to our a priori hypothesis (i.e. IL-6 association with persisting depression). If the distribution between groups is unbalanced for an important factor (e.g. age, sex as biological variable, anti-depressant use, HIV viral load), we will adjust as needed for differentially distributed variables between the cohorts. We will consider sex as a biological variable in our analyses, considering differential effects in women vs. men.
4)

Figure 1



5) *Baseline Cytokine Analysis:* As a secondary outcome, subjects will be categorized into baseline groups of mild depression versus moderate or above depression. We will compare baseline plasma biomarker levels by group via linear regression of $\log_2$ transformed data. Any demographic covariates associated with depression will be included in the regression model. We will also compare by 9 am cortisol levels. We will assess whether age or sex are associated with biomarker responses.
6) *Virologic Outcomes:* As a secondary outcome, proportions of those with 26-week virologic suppression will be correlated by those with persisting depression vs. resolved using Fisher's Exact test.
7) *Depression Scale Comparison:* We will compare prevalence of depression using the PHQ-9 and the HDRS. We will compare the proportions of those depressed at baseline and 26 weeks using McNemar's test.
8) Social Factors and Stress Assessment: We will analyze social factors and the STRAIN stress and adversity tool scores by baseline depression groups as well as those with persistent depression at 26 weeks using linear regression.

8.3. Safety Analysis

Data and Safety Monitoring Plan

1.0 Introduction: This document describes the Roles and Responsibilities of the Data Monitoring Committee (DMC) convened to monitor the clinical study.

2.0 Composition: This DMC shall have the composition described below. As DMC meetings will be at least annually, the DMC shall have a quorum minimum of three members and the statistician to be required for each DMC meeting. All members have previous experience with clinical trials and/or clinical studies experience with cryptococcal meningitis (Table 1). As the intervention is an open label study, members of the team will participate in the DMC along with external members.

Table 1. DMC Membership

Name	Role	Relevant Experience
Kathy H Hullsiek, PhD	Statistician	Multiple HIV-related trials, U of MN
David Bond, MD, PhD	Member	Psychiatrist, U of MN
Conrad Muzoora, MMed	Member	Multiple clinical trials, Mbarara Univ.
Joshua Rhein, MD	Member	Multiple AIDS-related clinical trials, Mbarara Univ.
Alan R. Lifson, MD	Member	Epidemiologist, U of MN

Additional observers will participate as possible. Observers are non-voting members of the DMC. Observers will receive communicates on DMC reports and recommendations.

3.0 Roles and Responsibilities: It is the role of the DMC to protect trial subjects and to provide impartial advice and assistance to the Principal Investigator regarding the conduct and continuation of the study, so as to protect the validity and credibility of the trial. The DMC will have access to the clinical protocol, interim data, adverse event reports, clinical monitoring reports, annual and/or progress reports submitted to the IRB and/or Regulatory Agency, and correspondence between the Principal Investigator and either the IRB or any Regulatory Agency of competent jurisdiction.

The specific roles of this DMC will be as follows:

- Assess data quality, including completeness.
- Monitor compliance with the protocol by participants and investigators.
- Monitor recruitment progress and losses to follow-up.
- Monitor evidence for treatment differences in the main efficacy outcome measures.
- Monitor evidence for treatment harm (SAE's).
- Advise on protocol modifications suggested by investigators or sponsors.
- Recommend trial continuation or termination as appropriate.

4.0 Relationships

4.1 DMC, Principal Investigator, and other Trial Oversight: The DMC shall provide an independent advisory role with investigator input. The DMC will make recommendations to the PI and/or oversight committees regarding trial conduct or continuation. As the trial is open-label, the PI and co-investigators will participate as observers to the DMC, providing their clinical insights. DMC reports will be provided to the oversight IRBs.

4.2 Conflicts of Interest: DMC members shall disclose potential competing interests, both financial and intellectual. None have a conflict of interest at present.

5.0 DMC Meeting Structure and Frequency

5.1 Meeting Structure: DMC Meetings will be held in an open format, as this is an unblinded interventional trial. First, demographic data and trial progress will be discussed. Quality Assurance and Compliance issues may be discussed in this session, and this session is open to investigators, sponsors, funder, patient advocates, and others as appropriate. Open sessions will be followed by closed sections in which only the DMC members, DMC observers, statistician, secretary and specifically invited guests will attend. In closed sessions the outcomes data will be assessed and recommendations formulated. DMC meetings will be conducted by teleconference / Skype.

5.2 Meeting Frequency: The DMC will meet based on the pace of subject recruitment. Initial reviews will be after ~33% and ~66% participants have enrolled into the protocol and have $\geq$12 weeks of data for review.

5.3 Meeting Notes: Meeting notes will be prepared after each DMC meeting.

5.4 Attendance: Members are expected to attend all meetings either in person or by teleconference. A quorum for recommendations/decision making shall be three members and the statistician. Members who fail to attend two consecutive meetings may be removed from the DMC and replaced.

6.0 Data Analysis: The PI will prepare an initial report. The DMC statistician will also perform an independent analysis appropriate to the data presented as per the statistical plan in the protocol. For interim analysis, the primary considerations are:

- Enrollment
- Data completeness.

- Compliance with the protocol by participants and investigators.
- Monitor evidence for treatment differences in the main efficacy outcome measures.
- Monitor evidence for unintended harm(s) or unintended HIV disclosure

6.1 Stopping Criteria

The DMC will give their overall opinion as to the safety to proceed with the study, if there are any suggested protocol modifications, or if the intervention should be stopped.

7.0 DMC Reporting: The DMC will not share confidential information, particularly trial interim data with anyone external to the DMC. The recommendations/decisions of the DMC will be communicated in writing to the PI, IRB, and/or appropriate regulatory agency. The JCRC IRB is the IRB of record.

8.0 Adverse Event Reporting - Summary

Any research-related SAE is required to be reported to the IRB. The summary of Adverse Event reporting and timeline is as follows.

Grade	Serious	Unexpected	Possibly Related	Where is this reported?	Timeline of Reporting
1-2	No	±	±	None	N/A
3-4	No	±	±	*Clinical AE* CRF	DMC & Annual IRB Reporting
Any	Yes	No	±	*Clinical AE* CRF	DMC & Annual IRB Reporting
Any	Yes	Yes	No	*Clinical AE* CRF	≤ 3 working days to IRB, Aggregate reporting to Sponsor
Any	Yes	Yes	Yes	*Clinical AE* CRF	≤ 3 working days to IRB and to Sponsor†
Lab Value	No	No	None	*Blood Results* CRF	DMC & Annual IRB Reporting

8.4. Interim Analysis

N/A

9. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct periodic monitoring may be conducted to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data

recorded on CRFs is accurate. Additionally, the study site may be subject to review by the Institutional Review Board (IRB) and/or to inspection by appropriate regulatory authorities.

10. DATA HANDLING/RECORD RETENTION

10.1. Case Report Forms (CRF)/Electronic Data Record

A CRF is required and should be completed for each included subject.

The investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

10.2. Record Retention

To enable evaluations and/or audits, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls reports).

Investigator records must be kept for as long as required by applicable local regulations (UNCST generally requires a minimum of 5 years). When more than one requirement can be applied, records must be maintained for the longest period provided.

10.3. Confidentiality

Clinical data will be entered into a study specific database by designated staff on a regular basis from completed Case Record Forms (CRF) using REDCap. Consents and other source documents will be kept in locked cabinets. Data will be entered on a regular basis to ensure that it is up to date. The database will be entered on regular basis on a secure PCAccess to database will be given to authorized personnel only (members of the immediate study team) and a log of authorized personnel will be stored in the trial master file. Trial documents will be kept in locked cabinets. No participant identifying information will be disclosed in any publication or at any conference activities arising from the study.

11. ETHICS

11.1. Institutional Review Board (IRB)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents from the IRB. All correspondence with the IRB should be retained in the regulatory or trial master file. Copies of IRB approvals should be filed with other study documents.

11.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects and the Declaration of Helsinki.

In addition, the study will be conducted in accordance with the protocol, GCP guidelines, DSMP, and applicable local regulatory requirements and laws.

11.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any forms, reports, publications, or in any other disclosures, except where required by laws. The informed consent document used in this study, and any changes made during the course of the study, must be prospectively approved by the IRB.

The investigator, or a person designated by the investigator, will obtain written informed consent from each subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

Given these individuals have depression at the start of the study we will re-affirm consent at the second study visit.

12. DEFINITION OF END OF TRIAL

When the last subject has had their chart checked for viral load testing data.

13. PUBLICATION OF STUDY RESULTS

We plan to present the findings of this study at an international conference such as CROI or IAS as well as some smaller mental health conferences. We will also prepare and submit the findings for publication in a peer reviewed scientific journal. We will present at Makerere, IDI or University of Minnesota forums as opportunities arise. Finally, we will hold forums at the clinics from which we enrolled to inform the staff and participants of our findings.

14. CAPACITY BUILDING

A group psychotherapy method, which has been validated in Uganda, will be used at IDI and/or KCCA clinics. Individuals in Kampala will be trained in how to do this and IDI could evaluate if this was something worth continuing.

15. FUNDING

The PI, Sarah Lofgren, as applied for a K23 from the USA National Institute of Mental Health, part of the National Institute of Health, under grant number K23MH121220-01. It is pending funding. She also has additional startup funds at the University of Minnesota.

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17.1. PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

DATE_____

Over the last *2 weeks,* how often have you been bothered by any of the following problems? *(use " to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself - or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed. Or the opposite - being so figety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead, or of hurting yourself	0	1	2	3

	add columns		+	+
(Healthcare professional: For interpretation of TOTAL, please refer to accompanying scoring card).	TOTAL:			

10. If you checked off *any problems,* how *difficult* have these problems made it for you to do your work, take care of things at home, or get along with other people?	Not difficult at all	_____
	Somewhat difficult	_____
	Very difficult	_____
	Extremely difficult	_____

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PHQ-9 Patient Depression Questionnaire

For initial diagnosis:

1. Patient completes PHQ-9 Quick Depression Assessment.
2. If there are at least 4 ✓s in the shaded section (including Questions #1 and #2), consider a depressive disorder. Add score to determine severity.

Consider Major Depressive Disorder

- if there are at least 5 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Consider Other Depressive Disorder

- if there are 2-4 ✓s in the shaded section (one of which corresponds to Question #1 or #2)

Note: Since the questionnaire relies on patient self-report, all responses should be verified by the clinician, and a definitive diagnosis is made on clinical grounds taking into account how well the patient understood the questionnaire, as well as other relevant information from the patient.
Diagnoses of Major Depressive Disorder or Other Depressive Disorder also require impairment of social, occupational, or other important areas of functioning (Question #10) and ruling out normal bereavement, a history of a Manic Episode (Bipolar Disorder), and a physical disorder, medication, or other drug as the biological cause of the depressive symptoms.

To monitor severity over time for newly diagnosed patients or patients in current treatment for depression:

1. Patients may complete questionnaires at baseline and at regular intervals (eg, every 2 weeks) at home and bring them in at their next appointment for scoring or they may complete the questionnaire during each scheduled appointment.
2. Add up ✓s by column. For every ✓: Several days = 1 More than half the days = 2 Nearly every day = 3
3. Add together column scores to get a TOTAL score.
4. Refer to the accompanying **PHQ-9 Scoring Box** to interpret the TOTAL score.
5. Results may be included in patient files to assist you in setting up a treatment goal, determining degree of response, as well as guiding treatment intervention.

Scoring: add up all checked boxes on PHQ-9

For every ✓ Not at all = 0; Several days = 1; More than half the days = 2; Nearly every day = 3

Interpretation of Total Score

Total Score	Depression Severity
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	Severe depression

17.2. Hamilton Rating Scale for Depression (17-items)

Instructions: For each item select the "cue" which best characterizes the patient during the past week.

1. DEPRESSED MOOD
(sadness, hopeless, helpless, worthless)

0 Absent
1 These feeling states indicated only on questioning
2 These feeling states spontaneously reported verbally
3 Communicates feeling states nonverbally, i.e., through facial expression, posture, voice and tendency to weep
4 Patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and nonverbal communication

2. FEELINGS OF GUILT

0 Absent
1 Self-reproach, feels he has let people down
2 Ideas of guilt or rumination over past errors or sinful deeds
3 Present illness is a punishment. Delusions of guilt
4 Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

3. SUICIDE

0 Absent
1 Feels life is not worth living
2 Wishes he were dead or any thoughts of possible death to self
3 Suicide ideas or gesture
4 Attempts at suicide (any serious attempt rates 4)

4. INSOMNIA - EARLY

0 No difficulty falling asleep
1 Complains of occasional difficulty falling asleep i.e., more than ½ hour
2 Complains of nightly difficulty falling asleep

5. INSOMNIA - MIDDLE

0 No difficulty
1 Patient complains of being restless and disturbed during the night
2 Waking during the night – any getting out of bed rates 2 (except for purposes of voiding)

6. INSOMNIA - LATE

0 No difficulty
1 Waking in early hours of the morning but goes back to sleep
2 Unable to fall asleep again if gets out of bed

7. WORK AND ACTIVITIES

0 No difficulty
1 Thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2 Loss of interest in activity; hobbies or work – either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3 Decrease in actual time spent in activities or decrease in productivity. In hospital, rate 3 if patient does not spend at least three hours a day in activities (hospital job or hobbies) exclusive of ward chores.
4 Stopped working because of present illness. In hospital, rate 4 if patient engages in no activities except ward chores, or if patient fails to perform ward chores unassisted.

8. RETARDATION
(slowness of thought and speech; impaired ability to concentrate; decreased motor activity)

0 Normal speech and thought
1 Slight retardation at interview
2 Obvious retardation at interview
3 Interview difficult
4 Complete stupor

9. AGITATION

0 None
1 "Playing with" hand, hair, etc.
2 Hand-wringing, nail-biting, biting of lips

10. ANXIETY - PSYCHIC

0 No difficulty
1 Subjective tension and irritability
2 Worrying about minor matters
3 Apprehensive attitude apparent in face or speech
4 Fears expressed without questioning

11. ANXIETY - SOMATIC

0 Absent — Physiological concomitants of anxiety such as:
1 Mild — Gastrointestinal - dry mouth, wind, indigestion,
2 Moderate — diarrhea, cramps, belching
3 Severe — Cardiovascular – palpitations, headaches
4 Incapacitating — Respiratory - hyperventilation, sighing
Urinary frequency
Sweating

12. SOMATIC SYMPTOMS - GASTROINTESTINAL

0 None
1 Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
2 Difficulty eating without staff urging. Requests or requires laxatives or medications for bowels or medication for G.I. symptoms.

13. SOMATIC SYMPTOMS - GENERAL

0 None
1 Heaviness in limbs, back or head, backaches, headache, muscle aches, loss of energy and fatigability
2 Any clear-cut symptom rates 2

14. GENITAL SYMPTOMS

0 Absent — 0 Not ascertained
1 Mild — Symptoms such as: loss of libido,
2 Severe — menstrual disturbances

15. HYPOCHONDRIASIS

0 Not present
1 Self-absorption (bodily)
2 Preoccupation with health
3 Frequent complaints, requests for help, etc.
4 Hypochondriacal delusions

16. LOSS OF WEIGHT

A. When Rating by History:
0 No weight loss
1 Probable weight loss associated with present illness
2 Definite (according to patient) weight loss

B. On Weekly Ratings by Ward Psychiatrist, When Actual Changes are Measured:
0 Less than 1 lb. weight loss in week
1 Greater than 1 lb. weight loss in week
2 Greater than 2 lb. weight loss in week

17. INSIGHT

0 Acknowledges being depressed and ill
1 Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 Denies being ill at all

Total Score:_____

Citation: Hamilton M: A rating scale for depression. Journal of Neurology, Neurosurgery and Psychiatry 23:56-62, 1960

17.3. Social Support Scale

Emotional/informational support	None of the time	A little of the time	Some of the time	Most of the time	All of the time
1. Someone you can count on to listen to you when you need to talk	○ 1	○ 2	○ 3	○ 4	○ 5
2. Someone to give you information to help you understand a situation	○ 1	○ 2	○ 3	○ 4	○ 5
3. Someone to give you good advice about a crisis	○ 1	○ 2	○ 3	○ 4	○ 5
4. Someone to confide in or talk to about yourself or your problems	○ 1	○ 2	○ 3	○ 4	○ 5
Tangible support	None of the time	A little of the time	Some of the time	Most of the time	All of the time
9. Someone to help you if you were confined to bed	○ 1	○ 2	○ 3	○ 4	○ 5
10. Someone to take you to the doctor if you needed it	○ 1	○ 2	○ 3	○ 4	○ 5
11. Someone to prepare your meals if you were unable to do it yourself	○ 1	○ 2	○ 3	○ 4	○ 5
12. Someone to help with daily chores if you were sick	○ 1	○ 2	○ 3	○ 4	○ 5
Affectionate support	None of the time	A little of the time	Some of the time	Most of the time	All of the time
13. Someone who shows you love and affection	○ 1	○ 2	○ 3	○ 4	○ 5
14. Someone to love and make you feel wanted	○ 1	○ 2	○ 3	○ 4	○ 5
15. Someone who hugs you	○ 1	○ 2	○ 3	○ 4	○ 5
Positive social interaction	None of the time	A little of the time	Some of the time	Most of the time	All of the time
16. Someone to have a good time with	○ 1	○ 2	○ 3	○ 4	○ 5
17. Someone to get together with for relaxation	○ 1	○ 2	○ 3	○ 4	○ 5
18. Someone to do something enjoyable with	○ 1	○ 2	○ 3	○ 4	○ 5

17.4 STRAIN

STRAIN Description

Overview

The Stress and Adversity Inventory (STRAIN) is a secure, online stress assessment system that measures individuals' lifetime exposure to different types of acute and chronic stress that can affect mental and physical health. The system is intended to combine the reliability and sophistication of an interview-based measure of stress with the simplicity of a self-report instrument. To accomplish this goal, the STRAIN enquires about 75 different types of stressors (Adolescent STRAIN) or 55 different types of stressors (Adult STRAIN) that cover all major life domains (e.g., health, intimate relationships, friendships, children, education, work, finances, housing, living conditions, crime, etc.) and several social-psychological characteristics (e.g., interpersonal loss, physical danger, role change, entrapment, etc). Users are presented with one question at a time, which are written in colloquial English, and questions can also be read aloud to users. In turn, users register their responses by simply touching their answer, if an iPad is being used, or by clicking their answer using the computer mouse, if a computer monitor is being used. For each stressor that is endorsed, users are asked a series of short follow-up questions that ascertain the severity, frequency, timing, and duration of the stressor. Using sophisticated interviewing logic, the STRAIN system can guide users through what would amount to a 157-page interview in as little as 20 minutes. Based on the information collected, the system produces 445 raw variables that can be combined to create 115 different stress exposure summary scores and life charts. Analyses can in turn be based on a number of basic factors, including stress severity and exposure timing (e.g., Childhood vs. Distant vs. Recent Life Stress). Because each stressor in the STRAIN is tagged with several attributes, more sophisticated analyses can also be performed by focusing on stressors occurring in specific life domains or that involve particular social-psychological characteristics.

Security Information

The STRAIN was developed in accordance with the best practices in online web security. The online interviewing platform that the STRAIN utilizes is written in PHP and based on a very fast, efficient, and state-of-the-art back-end database software package (LimeSurvey). That package resides on a website that has a dedicated IP address and is hosted on a secure, Comodo SSL-certified internet server that is protected by a comprehensive firewall and continuously monitored by the global leader in website security, SiteLock, for the possibility of a malicious attack. Participant data, which is entirely anonymous, is transferred from users' computers to the server in a secure data channel that utilizes private cookies in conjunction with advanced SSL technology. Finally, all data are stored anonymously on a database that utilizes encrypted password-protected entry to prevent possible participant identification.

Risk Information

Participants will answer questions anonymously through an online survey. No identifying or protected health information will be collected. An Excel file linking participants' identifying information and their STRAIN responses will be kept in an offline location, which will be separate from all STRAIN and other study data. Consequently, participants will not be identifiable or linked to their responses. Prior research using the STRAIN has demonstrated that the interview does not induce negative mood, and that usability and acceptability of the interview is very high. Nevertheless, it is possible that some individuals may feel mildly uncomfortable answering personal questions about their life. Before beginning the interview, individuals are reminded that they are not required to answer questions that they do not feel comfortable answering. Moreover, they may terminate the interview at any time.

Data Analyses

In this study, participants' responses to the STRAIN will be used to calculate a standard set of 20 lifetime stress exposure scores, which are based on the type of stressors experienced, when they were experienced, their primary life domain, and their core social-psychological characteristics. More specifically, this summary score data will include the following computed variables: Lifetime stressor count, lifetime stressor severity, early life stress (before age 18) stressor count, early life stress (before age 18) stressor severity, adulthood stressor count, adulthood stressor severity, lifetime count of acute life events, lifetime count of chronic difficulties, lifetime severity of acute life events, lifetime count of chronic difficulties, lifetime stressor count and severity by primary life domain (i.e., housing, education, work, treatment/health, marital/partner, reproduction, financial, legal/crime, other relationships, death, life-threatening situations, possessions), and lifetime stressor count and severity by core social-psychological characteristic (i.e., interpersonal loss, physical danger, humiliation, entrapment, role change/disruption). In addition, we will compute indices relating each participant's actual overall stress burden, as compared to what would be expected given his or her sex and age (based on prior STRAIN validation data), and their actual overall health status (i.e., number of mental and physical health problems), again, as compared to what would be expected given his or her sex and age (based on prior STRAIN validation data).

17.5. Enrollment Consent Form- Observational PID_____

Study Title: **The "GROwTH" GROup Therapy in Hiv in Uganda Study**

Study Purpose

Depression in HIV is associated with worse HIV outcomes including worse engagement in care, medication adherence, and retention in care. Depression is also three times more prevalent in those with HIV than in the general population. While there are complex reasons including psychosocial, there is a growing body of evidence that inflammation is linked to mental illness including depression although the underlying pathophysiology is not well understood. Better understanding of the pathogenesis will help identify new treatments. Better depression treatments may thereby lead to engagement/retention in care and better HIV outcomes including virologic control. Better HIV control will help achieve the UNAIDS 90/90/90 goals to diagnose 90% of all HIV-positive persons, provide ART for 90% of those diagnosed, and achieve viral suppression for 90% of those treated.

The goal of this study is to determine if prevalence of depression at 26 weeks of HIV therapy is improved with group psychotherapy and determine if persistence of depression is associated with higher levels of innate inflammation.

Given you were screened and found to have depression and HIV we would like to follow you over 26 weeks.

You confirm that the following has been explained to you, and you have had a chance to ask questions:

1. You were previously screened for this study. You were found to be eligible and to have depression. As such we would like to follow you for 26 weeks.
2. In 12 weeks we would like to have you back to clinic. We will ask you a few questions and screen you for depression again.
3. In 26 weeks we would like and take another plasma (blood) sample.
4. You also authorize study doctors or designated representative of the sponsor to acquire follow up information from your clinic including subsequent clinic attendance, adherence on your medications, CD4 counts, and viral load tests.
5. You may benefit from this study by helping others in the future with HIV treatment.

6. You will not be paid for participating in this study, but you will be given money to refund your actual transport expenses up to 30,000 Shillings if you need to come to a visit outside your regular clinic visits.
7. Any information about you shall be kept private, and your data will be used without your name or identity.
8. Agreeing to participate in this study is voluntary and you can withdraw from the study at any time if you so wish by telling the study doctors. If you withdraw from the study, you can continue to receive your ARV medicines free at the clinic.
9. You will not be giving up any of your legal rights by signing this consent form.
10. You are going to be given a copy of this form.

Risks

The study has the following risks:

We will be discussing sensitive topics around your HIV disease and depression. This discussion will be private and the forms we will out will be confidential

Pregnancy:

Pregnant and breastfeeding women can participate, as there is only minimal risk.

Study approval

Approval to conduct this study has been granted by the Uganda National Council for Science and Technology.

Contacts and Questions

You may ask any questions you have now. If you have questions later or any urgent health concerns or return of your headache, you are encouraged to contact:

- Dr. David Meya in **Kampala** on phone number **077-254-3730,**

In case of any questions regarding the Welfare and rights of participants, you should contact Dr. Nakwagala Frederick Nelson at the Mulago Research and Ethics Committee at **+256-41554008/1** or admin@mulago.or.ug.

If you have any questions about the use of your samples, you can ask them now or contact the above individuals later.

Informed consent

I hereby consent to participate in this study, "Timing of Presentation to HIV Care"

Participant Signature

_____ **OR**

Thumb print

Participant Name _____ Date _____

Signature of Witness (if needed)…….……. Date

_____

Relationship of the Witness: _____

Signature of who administered consent:

_____

Date:_____ Time:_____

17.5. Enrollment Consent Form- Interventional PID_____

Study Title: **The "GROwTH" GROup Therapy in Hiv in Uganda Study**

Study Purpose

Depression in HIV is associated with worse HIV outcomes including coming to clinic, taking medication, and continuing to come to clinic. Depression is also three times more prevalent in those with HIV than in the general population. While there are complex reasons including family, finances, and work, there is a growing body of evidence that inflammation is linked to mental illness including depression although how it works is not well understood. Better understanding of how it works will help find new treatments. Better depression treatments may lead to people coming to clinic more and better HIV control in people. Better HIV control will help achieve the UNAIDS 90/90/90 goals to diagnose 90% of all HIV-positive persons, provide medications for 90% of those diagnosed, and achieve HIV viral control for 90% of those treated.

The goal of this study is to determine if the amount of depression at 26 weeks of HIV therapy is improved with group psychotherapy and determine if persistence of depression is associated with higher levels of inflammation.

Given you were screened and found to have depression and HIV we would like to follow you over 26 weeks.

A Ugandan researcher has found that group support psychotherapy is a culturally sensitive intervention, which enhances social support, teaching coping skills, and income-generating skills thereby treating depression. We will ask you to participate in the group therapy 1 time a week for 8 weeks for about an hour a time.

You confirm that the following has been explained to you, and you have had a chance to ask questions:

11. You were previously screened for this study. You were found to be eligible and to have depression. As such we would like to follow you for 26 weeks. We are going to assess your stress levels, take a plasma (blood) sample and fill out a questionnaire today.
12. We will ask you to participate in 8 weekly sessions of group therapy.

13. In 12 weeks we would like to have you back to clinic. We will ask you a few questions and screen you for depression again.
14. In 26 weeks we would like to have you back to clinic. We will again screen you for depression. We will again assess your stress levels, administer a questionnaire and take another plasma (blood) sample.
15. The study doctors or designated representative of the sponsor would like to get follow up information from your clinic including subsequent clinic attendance, adherence on your medications, CD4 counts, and viral load tests. This consent will authorize them to do so.
16. You may or may not benefit from this study by having your depression improve. You may gain friends and job skills through the group therapy. You may also benefit by helping other people with depression and HIV in the future.
17. You will not be paid for participating in this study, but you will be given money to refund your actual transport expenses up to 30,000 Shillings/visit if you need to come to a visit outside your regular clinic visits.
18. Any information about you shall be kept private, and your data will be used without your name or identity.
19. Agreeing to participate in this study is voluntary and you can withdraw from the study at any time if you so wish by telling the study doctors. If you withdraw from the study, you can continue to receive your HIV medicines free at the clinic.
20. You will not be giving up any of your legal rights by signing this consent form.
21. You are going to be given a copy of this form.

Risks

The study has the following risks:

1. We will be discussing sensitive topics around your HIV disease and depression. This discussion will be private and the forms we will out will be confidential.
2. We are asking you to participate in group therapy. By being in the group therapy people will know you have HIV and depression. The other participants will also have HIV and depression. This information will be expected to be confidential by all involved but there is a risk of disclosure. However, this intervention was developed in Uganda and has been judged by prior people with HIV and depression that the benefits outweigh the risks.
3. You will be asked to give a blood sample. This will require a blood draw which will hurt. You could get a bruise at the site.

Pregnancy:

Pregnant and breastfeeding women can participate.

Study approval

Approval to conduct this study has been granted by the Uganda National Council for Science and Technology.

Contacts and Questions

You may ask any questions you have now. If you have questions later or any urgent health concerns, you are encouraged to contact:

- Dr. David Meya in **Kampala** on phone number **077-254-3730,**

In case of any questions regarding the Welfare and rights of participants, you should contact Prof. Johnson Acon, JCRC IRB Chairman, Telephone (Office): 0414-201 148; Mobile: 0706300300.

17.6. Enrollment CRF GROwTH Study PID_____

Date today _____

Age _____ DOB_____

HIV clinic registered _____ Date Enrolled in

Clinic_____

Ever Been on ART Yes[] No[]

HIV Status_____ CD4 Count_____

Have you seen Psychiatry?_____

Have you seen Dr. Noeline at IDI?_____

Ever been diagnosed with Depression_____

Ever been diagnosed with Anxiety_____

Ever been diagnosed with Psychosis_____

Ever been diagnosed with other thinking disorder?_____

Ever been on an antidepressant medication (check chart and give patient examples- Prozac or fluoxetine, Zoloft or sertraline, etc)_____

If yes, which antidepressant medication_____

If yes, dates on antidepressant medication_____

Current Medications_____

Do you have any illnesses other than HIV? _____

Last fever? _____(weeks)

PHQ-9 Score_____

Suicidal? (score ≥2 on question 9)_____ If yes, refer to psychiatry.

Social Support Scale_____ STRAIN score_____

Social Factors Questionnaire

1. Monthly income <100k [ ] 100k-500k [ ] >500k [ ]

2. Patient works outside home Yes [ ] No [ ]

3. Occupation_____

4. Alcohol Frequency? Never []<1x/week [] <daily [] 1-2x daily [] >2x daily

5. History of war Yes [] No [] 5b.Where? _____ 5c.

Date_____

6. History of attack/been beaten/trauma Yes [] No [] If yes date_____

7. History of Domestic abuse (partner hit, slapped, kicked, raped, kept from food) Yes [] No

[] 7b. Date most recent abuse _____

8. Told partner I have HIV Yes [] No []

9. Told household members I have HIV Yes [] No []

10. Told other friends and family I have HIV Yes [] No []

Other psychosocial Factors

11. Religion: Roman Catholic [] Anglican [] Other Protestant [] Muslim [] Other

[]_____

12. Frequency of Services: Yearly [] Monthly [] Weekly [] > weekly []

13. I worry my family will not have enough to eat? Yes [] No []

17.7. Enrollment Consent Form- Voluntary Lumbar Puncture PID_____

Study Title: **The "GROwTH" GROup Therapy in Hiv in Uganda Study**

Study Purpose

Depression in HIV is associated with worse HIV outcomes including worse engagement in care, medication adherence, and retention in care. Depression is also three times more prevalent in those with HIV than in the general population. While there are complex reasons including psychosocial, there is a growing body of evidence that inflammation is linked to mental illness including depression although the underlying pathophysiology is not well understood. Better understanding of the pathogenesis will help identify new treatments. Better depression treatments may thereby lead to engagement/retention in care and better HIV outcomes including virologic control. Better HIV control will help achieve the UNAIDS 90/90/90 goals to diagnose 90% of all HIV-positive persons, provide ART for 90% of those diagnosed, and achieve viral suppression for 90% of those treated.

The goal of this study is to determine if prevalence of depression at 26 weeks of HIV therapy is improved with group psychotherapy and determine if persistence of depression is associated with higher levels of innate inflammation.

You have been enrolled in the study and this is an additional request, which is completely voluntary and will not affect your enrollment into the rest of the study.

You are being asked to give a cerebral spinal fluid sample via lumbar puncture.

You confirm that the following has been explained to you, and you have had a chance to ask questions:

22. You were previously enrolled in this study. You are eligible for this extra test.
23. This is completely voluntary and your willingness will not impact your participation in the larger study.
24. You may benefit from this study by helping others in the future with HIV treatment.
25. You will be compensated 100,000 UgSh for this lumbar puncture
26. Any information about you shall be kept private, and your data will be used without your name or identity.

27. Agreeing to participate in this study is voluntary and you can withdraw from the study at any time if you so wish by telling the study doctors. If you withdraw from the study, you can continue to receive your ARV medicines free at the clinic.
28. You will not be giving up any of your legal rights by signing this consent form.
29. You are going to be given a copy of this form.

Risks

The study has the following risks:

A lumbar puncture, or LP is a standard procedure. An LP takes about 20 minutes. During an LP, a needle is used to draw fluid from the lower back – this is called spinal fluid. Spinal fluid is made in the brain, but is also around the spine. When the needle is first inserted, you may feel a shooting pain and/or a tingling sensation. The doctors will give you a medicine to block the pain. It is possible that you could develop a local infection with redness and swelling where the needle was inserted, or that some of the fluid could leak out. You may have pain in your lower back for a short time (several hours to a day).

Pregnancy:

Pregnant and breastfeeding women can participate, as a lumbar puncture should not impact

Study approval

Approval to conduct this study has been granted by the Uganda National Council for Science and Technology.

Contacts and Questions

You may ask any questions you have now. If you have questions later or any urgent health concerns or return of your headache, you are encouraged to contact:

- Dr. David Meya in **Kampala** on phone number **077-254-3730,**

In case of any questions regarding the Welfare and rights of participants, you should contact Dr. Nakwagala Frederick Nelson at the Mulago Research and Ethics Committee at **+256-41554008/1** or admin@mulago.or.ug.

If you have any questions about the use of your samples, you can ask them now or contact the

above individuals later.

Informed consent
I hereby consent to participate in this study, "Timing of Presentation to HIV Care"

Participant Signature

_____ **OR**

Thumb print

Participant Name _____ Date _____

Signature of Witness (if needed)…….……. Date

_____

Relationship of the Witness: _____

Signature of who administered consent:

_____

Date:_____ Time:_____

GROwTH Study PID_____

Follow up CRF Week 14

Date today _____

Age _____

Have you seen Psychiatry?_____

Have you seen Dr. Noeline at IDI?_____

Ever been on an antidepressant medication (check chart and give patient examples- Prozac or fluoxetine, Zoloft or sertraline, etc)_____

If yes, which antidepressant medication_____

If yes, dates on antidepressant medication_____

Current Medications_____

PHQ-9 Score_____

Suicidal? (score ≥2 on question 9)_____ If yes, refer to psychiatry.

Do you have any illnesses other than HIV? _____

Last fever?_____(weeks)_____

17.8. Follow-up CRF Week 26 GROwTH Study PID_____

Date today _____

Age _____

Have you seen Psychiatry?_____

Have you seen Dr. Noeline at IDI?_____

Ever been on an antidepressant medication (check chart and give patient examples- Prozac or fluoxetine, Zoloft or sertraline, etc)_____

If yes, which antidepressant medication_____

If yes, dates on antidepressant medication_____

Current Medications_____

Do you have any illnesses other than HIV? _____

Last fever?_____(weeks)_____

PHQ-9 Score_____

Suicidal? (score ≥2 on question 9)_____ If yes, refer to psychiatry.

STRAIN score_____ Social Support Score_____

1. Monthly income <100k [ ] 100k-500k [ ] >500k [ ]

2. Patient works outside home Yes [ ] No [ ]

3. Occupation_____

4. Alcohol Frequency? Never []<1x/week [] <daily [] 1-2x daily [] >2x daily

5. Told partner I have HIV Yes [] No []

6. Told household members I have HIV Yes [] No []

7. Told other friends and family I have HIV Yes [] No []

8. I worry my family will not have enough to eat? Yes [] No []

Is patient in the Observational or Interventional Cohort.

If Observational, thank the participant. They are finished.

If Interventional, continue.

5-point scale

This example uses a five-point scale from strongly agree to strongly disagree.

QUESTIONS ABOUT THE PRESENTER

Please state the extent to which you agree or disagree with the following statements, where 1 is Strongly Agree and 5 is Strongly Disagree (tick one per statement).

Q1.	SA				SD
	1	2	3	4	5
A. A. The facilitator communicated the information clearly.					
A. B. The facilitator engaged the audience.					
A. C. The facilitator made the subject matter compelling.					
A. D. The facilitator was able to answer questions.					
A. E. The content was presented in a well-structured manner.					
A. F. The pace of the therapy was right for me.					

QUESTIONS ON THE EFFECTIVENESS OF THE PRESENTATION

Please state the extent to which you agree or disagree with the following statements, where 1 is

Strongly Agree and 5 is Strongly Disagree (tick one per statement).

Q2.	SA				SD
	1	2	3	4	5
B. A. The group therapy sessions were relevant to me.					
B. B. The group therapy was interesting.					
B. C. The group therapy content was meaningful to me.					
B. D. The group therapy met my purpose in attending.					
B. E. The group therapy content was related to the skills and knowledge I needed.					
B. F. The group therapy made me think about my own actions.					
A. G. The group therapy motivated me to take action.					
A. H. I want to tell others about what was presented.					
A. I. I have the confidence to use the knowledge gained from the group therapy in my life.					
A. J. The group therapy has given me ways to become more sustainable.					