Study Protocol and Statistical Analysis Plan

Protocol Title: Depression Care to Improve Adherence to PMTCT Care Continuum and Pregnancy Outcomes

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Brief outline of the rationale for the study

Depression is common among HIV+ pregnant women, in both prenatal and post natal phases and depression often impedes adherence to PMTCT care, parenting, and early child health development. Treating depression could mitigate these consequences and help ensure optimum pregnancy and maternal and child health outcomes. The proposed cluster randomized controlled trial will compare the effects of evidence-based depression care vs. usual care on adherence to each step of the PMTCT care continuum at 8 ANC clinics and with 400 HIV+ depressed pregnant women (50 per site). Four (4) clinics will implement usual care and 4 will implement usual care plus depression care [anti depressant therapy(ADT) and problem solving therapy (PST)]. Peer mothers will be trained to assist in depression screening and implement PST, while nurses will be trained to diagnose depression and provide ADT, under the supervision of psychiatric specialists. PST will be recommended for all women deemed eligible for treatment, while ADT will be recommended for only those with severe or refractory depression.

Primary aims of the study:

1. Integrate evidence-based PST and ADT into usual care, using the gold standard, stepped care approach.
2. Assess whether the integrated depression care model is superior to usual care on (1) adherence to each step of the PMTCT care continuum and maternal viral suppression (primary outcomes); (2) prevention of infant HIV infection, and maternal and child health outcomes (secondary outcomes), and 3) depression treatment uptake and depression alleviation (depression care processes).

Secondary aim;

Examine how (1) depression and (2) depression alleviation are associated with maternal viral load, adherence to each step of the PMTCT care continuum, and mother and child health outcomes; and identify potential mediators (e.g., HIV disclosure; stigma; problem solving skills) of these relationships.

Methods

The two arm cluster RCT will compare the effects of task-shifted, evidence-based depression care vs. usual care on adherence to each step of the PMTCT care cascade at 8 ANC clinics in Uganda. At 4 experimental sites, task-shifted, depression care will include (1) depression screening and psychoeducation, (2) depression diagnosis, and (3) provision of evidence-based problem solving therapy (PST), or antidepressant therapy (ADT) for those with severe and refractory depression (or who decline PST), to be implemented by trained peer mothers and midwife nurses. The 4 control sites will use usual care services for managing depression, which consist of the FSG program and referrals to a mental health specialist. At each site, 50 HIV+ newly pregnant women (total n=400) who screen positive for potential depression will be enrolled and followed until 18-months post-delivery to assess how depression and depression alleviation relate to primary (adherence to each component of the PMTCT care continuum, maternal virologic suppression) and secondary (infant HIV status; post-natal maternal and child health outcomes) outcomes, as well as processes of depression care (treatment uptake and depression alleviation among clinically depressed patients). The PST/ADT treatment will be provided only to study participants, not all depressed clients, because our focus is the effects of depression treatment on PMTCT adherence and pregnancy outcomes, not implementation research for scaling

up the model in ANC care (with HIV and non-HIV women), which is a much broader focus. A cost-effectiveness analysis will be used to compare the two study arms.

We will enroll all consenting eligible clients and survey them at baseline, month 6, 12 and 18 following delivery. For those who miscarry, a final survey will take place 6 months after the miscarriage to assess successful transition to receive HIV care at the HIV clinic. At all sites, HIV+ adult patients who are early enough in their gestation period to be eligible for the study will be informed of the study and screened for potential depression by trained peer mothers using the EPDS-2. The screening will take place in a private room and those who screen positive will receive depression psycho-education. Eligible women who express interest in participating in the study will be connected by the peer mother to the study coordinator (via phone if the coordinator is not at the clinic that day) so that the coordinator can describe the study in detail, confirm eligibility and obtain written consent; these procedures are done during the same clinic visit, or the next day that the coordinator is at the clinic.

Qualitative data will be collected from peer mothers and midwife nurses at baseline, 12 and 24 months, at the intervention sites to assess: successes and challenges in screening, diagnosing and treating patients for depression; the training and supervision process; and impact of depression and its treatment on pregnancy and PMTCT care, clinic functioning, and provider job satisfaction and burnout. We will also interview 40 client participants (20 clinically depressed who were treated, and 20 not treated) at their final study assessment to assess their experiences with pregnancy.

Data analysis

Statistical Analysis. We will first compare clinic-level differences, using standard t-tests or, where the observations per clinic vary, t-tests weighted by cluster-size. Like most cluster RCTs, we do not have the 20+ clusters needed to reliably adjust standard errors for clustering, so we will use the conventional approach of using regression methods on individual level data for most analyses, but will conduct sensitivity analyses using a range of plausible ICC values for the outcomes.

Primary Aim 1: intervention effects on primary outcomes. We will use logistic regression to test for differences between the two study arms on (i) PMTCT adherence, coded as a binary variable, at each stage of the PMTCT care continuum, and (ii) maternal viral suppression. The regression models will include patient characteristics such as age, CD4 and HIV disclosure status that may explain variance in observed differences. We will also explore significant interactions between the covariates and study arm to assess which patient types are likely to be adherent and virally suppressed in depression care vs. usual care. The effect of depression care on PMTCT adherence will be examined using intention to treat as the primary approach. We will use a repeated-measures model that will allow us to incorporate correlation in measurements of each person over time. The sample size of individuals for such models is adequate. The model formulation is: $\text{adherence}_{it} = \alpha + \beta G_i + \gamma(t) + \delta G_i x\ t + \theta_i + \varepsilon_{it}$ where *i* is individual, *t* is continuous time, G is binary indicator of treatment group, β allows for baseline differences between the two groups, γ is the time trend in the outcome common to both groups, and δ is the interaction of treatment group and time, and shows the intervention effect (i.e. effect of depression care relative to usual care). Further, $\theta_i$is an individual-level random effect (to allow for variation across participants) and ε_{it} is time period-specific error. With a vector of individual-level covariates X_i included in the model, we can assess main effects of patient characteristics and interactions between these X_i and indicator of treatment group. Such a model will allow us to test for significance of potential mediators: e.g., do effects of the depression care model vary by the patient's physical health at baseline? As the primary approach is intention-to-treat, the estimates will capture the average benefit for depressed patients, regardless of compliance or use of depression treatment. A secondary "completers only" analysis will be conducted as well. In addition, we will conduct a dose-response type analysis to explore the relationship between continuous implementation variables (e.g. treatment sessions attended), which are collected for all participants, and primary outcomes. Further, to better understand how or why the intervention exerted its effect, we will model the relationship

between fidelity measures (e.g. quality) and primary outcomes, as well as conduct mediation analysis including fidelity as a mediator, in the subgroup of patients enrolled in clinics receiving the intervention arm (depression care).

Secondary Aims 1 & 2: Explore relationship of depression and depression alleviation with primary and secondary outcomes. *Hypothesis: Depression will be associated with lower adherence to each step of the PMTCT care continuum, maternal viral suppression and maternal and child health, while depression alleviation will be associated with better adherence, viral suppression and health outcomes*. We will conduct (unadjusted) bivariate analysis to initially examine significant associations between baseline depression (EPDS≥13) and depression alleviation over time with the primary and secondary outcome measures. Next, longitudinal analysis will be conducted to incorporate repeated observations of individuals and to explore the relationship between change in depression and outcomes over time, and to test whether depression alleviation (EPDS≤6) is related to change in these outcomes. Models will control for observed individual characteristics and unobservables through a random effect term to incorporate characteristics that may affect both depression and the dependent variables. However, this model does not control for simultaneity (e.g., change in viral suppression leads to lower depression). With multiple time-points, instrumental variable approaches combined with fixed effects potentially can deal with this problem, using baseline depression to predict change in depression from time 2 to time 3, if baseline depression is strongly correlated with change in depression over time. The fixed effects model will indicate important time trends in depression and the primary and secondary outcomes.