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Title: Project INSPireD: Integrating Nuanced Support for Perinatal Adherence and Depression

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PROTOCOL

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Project Title: INSPireD: Integrating Nuanced Support for Perinatal adherence and Depression

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1. SPECIFIC AIMS

Specific Aims. Following standards for developing and initially testing a behavioural intervention, this study will involve an iterative process of intervention development. The main aim is to conduct a pilot field test of a group based counselling intervention with HIV positive women in the perinatal period (N=40) as delivered by a lay counsellor (an individual who has completed the requirements to serve as an HIV counsellor, but who is not a clinical psychologist or social worker). The primary goal of the intervention is to improve the detection of perinatal depression and facilitate treatment, and increase adherence to antiretroviral therapy among HIV infected women during pregnancy and continued adherence during the postpartum period living in a resource limited setting; secondary outcomes will include reductions in stigma, increased social support, and improved adherence to other aspects of the postpartum PMTCT cascade, namely, contraception uptake. We have two hypotheses: Hypothesis 1a: *Women who participate in the intervention will have lower levels of depression and stigma, and increased levels of adherence to antiretroviral therapy, and other aspects of the postpartum PMTCT cascade (e.g., contraception uptake), and social support at the end of the intervention.* Hypothesis 1b: *The intervention will be both acceptable and feasible.*

Please note that this is a follow up (Phase II) study of a previous submission approved and completed under the same investigators (Clearance Certificate M110963).

2. BACKGROUND AND SIGNIFICANCE

"There can be no health without mental health." The United Nations Millennium Development Goals (MDGs) initiative illustrates eight key areas in which the lives of women worldwide are in need of vast improvement, including reductions in child mortality, improvement of maternal health, and the need to address issues related to HIV/AIDS. Researchers have argued that targeting maternal *mental* health is critical to the success of this global call to action[1-3]. Depression is approximately twice as common in women versus men worldwide, with rates highest during the childbearing years[1]. Sub-Saharan Africa (SSA) is one of the areas specifically targeted by the MDGs, where a recent review suggests depression rates of 4-17% during pregnancy and 3-48% in the postpartum period, with the highest rates reported in South Africa [2].

Women of childbearing age in South Africa bear a substantial degree of HIV disease burden. Sub-Saharan Africa remains the epicenter of the HIV pandemic, with well over 24 million people living with HIV in the region at the end of 2013.[3] With respect to concentration of cases, South Africa is currently home to the largest number of HIV infected individuals in the world.[3] Rates of new infections are consistently higher in women than in men, particularly women of reproductive age [3,4]. In South Africa, data obtained from antenatal clinics suggest elevated rates of infection among pregnant women, documenting rates as high as 37% among women presenting for antenatal care[5] .

The synergy between HIV infection and reproductive events may leave women particularly vulnerable to depression. Documented rates of major depressive disorder among HIV infected individuals in South Africa range from 11%-35%[6–8], and one study found elevated depressive symptomatology among 41% of women presenting for an HIV test in the context of antenatal care[9]. HIV related stigma remains present in SSA, and represents yet another factor influencing depression in this setting [10,11]. Thus, the complexities of managing both pregnancy (many of which are unplanned) and a highly stigmatized chronic illness in a resource limited setting may predispose women to additional vulnerability for mood disturbance.

Maternal mental health is critically linked to the health of infants. Reducing childhood mortality is another MDG, and is indisputably tied to maternal behaviour. The consequences of untreated depression alone during pregnancy and the postpartum for mothers and children are well documented and include poor attendance at antenatal care visits, low birth weight, early gestational age, inadequate nutrition, worse overall infant health, maternal disability, and disordered maternal-infant interactions (e.g., [12–16]). Poor maternal mental health has also been associated with subsequent behavioural and mental health disorders in children (e.g., [17]). Patel and colleagues[14] describe the importance of effective maternal care during the first year of life particularly in resource limited settings given the increased environmental challenges that infants in these settings need to negotiate, such as inadequate shelter and sanitation. In these settings in particular, maternal depression may compromise mothers' abilities to provide the best care possible to their infant.

Depression impacts adherence to healthcare behaviours. Preventing mother to child transmission protocols (PMTCT) involve a "cascade" of interventions across several stages (see Figure 1). Utilization of PMTCT is considered suboptimal[18–23] and a WHO report suggests that only 58% of pregnant women in SSA who needed antiretrovirals (ARVs) received them [24]. Few studies to date have examined depression as a risk factor for non-adherence to various stages of PMTCT, though at least one report has documented an association between depression scores and infant HIV testing [11], while depression in general has been associated with poorer adherence to ARVs in resource limited settings [25–27]. Pregnancy has been identified as a risk factor for falling out of HIV care [28,29], though to what extent this is due to depression remains unknown. Depression has also been associated with negative views about the health care system and fear of stigmatization among a sample of women receiving an HIV test during antenatal care; as the authors suggest, this could result in a failure to establish health care, which makes the delivery of interventions meant to optimize maternal and foetal health, such as PMTCT, nearly impossible [9].

HIV-infected women in resource limited settings are required to negotiate complex barriers in order to maintain their health and the health of their infants. Structural barriers to healthcare, such as limited financial resources, distance from healthcare facilities, and availability of ARVs are commonplace in SSA [29,30]. Social support is the term used to describe resources that are the result of social ties [31,32], and is emerging as a critical component of adherence to health behaviours in resource limited settings, and among individuals living with HIV [29]. HIV related stigma may jeopardize one's ability to leverage social support, and may thus impact adherence to health care behaviours such as attending clinic and taking ARVs. Pregnancy and postpartum health care behaviours may be especially vulnerable to stigma, as many interventions designed to help protect the infant from acquiring HIV (e.g., delivering in a hospital, modifications to breastfeeding behaviour) may lead to inadvertent disclosure of serostatus. Symptoms of depression, including social isolation, hopelessness, or decreased problem solving may represent yet another barrier to the utilization of social support.

Better understanding of the role of modifiable, behavioural factors associated with non-adherence to PMTCT may improve uptake of these cost-effective interventions. In South Africa overall, 29.5% (37.4% in KwaZulu-Natal) of antenatal women are HIV positive, and approximately 21,000 children become infected with HIV in South Africa alone every year[5]. According to the PMTCT Country Report for South Africa, only 51.7% of HIV infected women received treatment [33]. Modelling studies have proposed that without increasing rates of adherence to PMTCT protocols, we will not see significant reductions in vertical transmission [34]. It is important to maintain the health of HIV positive mothers in its own right, but mothers are

also the gateway to care for HIV exposed infants, and the eradication of vertical transmission cannot be achieved without them. Resource limited settings are different from resource rich settings such that individuals with HIV have to overcome a myriad of social and structural barriers to care. Alone, depression is a significant barrier to adherence, but adherence is likely compromised further by high levels of stigma and inability to effectively use social support. There is no "one-size-fits-all" approach to HIV care or prevention, thus understanding the way in which modifiable psychosocial factors contribute to PMTCT non-adherence is essential.

2. Innovation

The proposed study seeks to develop a scalable depression and adherence intervention that can be delivered by healthcare workers. While effective psychosocial treatments for depression exist, few studies to date have attempted to investigate the acceptability or feasibility of delivering these treatments to HIV infected women during the perinatal period in resource limited settings[35,36], and none have attempted to treat diagnostic levels of depression. In a setting where there is a dearth of mental health providers or antidepressant medication, identification of such an intervention is critical. Maternal mental health has a direct impact on the well-being of children, including vertical transmission of HIV, and the current study seeks to identify modifiable barriers to PMTCT adherence in a resource limited setting. The proposed work will allow for the development of a targeted mental health intervention, which is based on empirical evidence.

3. RESEARCH STRATEGY

3.1 Conceptual framework. Our preliminary conceptual framework (see Figure 2) which was examined in phase 1 of this project (Clearance Certificate M110963) is based on a model of ART adherence developed by Bangsberg and Deeks [30], who propose that HIV-infected individuals living in Sub-Saharan Africa have to manage both "standard" barriers to HIV adherence (such as side effects and forgetting), and unique economic and structural barriers such as high transportation costs and "opportunity costs," or loss of income that may result from time spent obtaining HIV related care. Their work suggests that individuals in resource limited settings need to rely on their community resources (or social support) in order to overcome structural barriers to ART adherence. Bangsberg and Deeks propose that high levels of HIV-related stigma disrupt this system by making it difficult for individuals to access their community as a potential source of help (e.g., financial support, help with transportation to appointments). Stigma, inadequate social support, and mental health issues have all been cited as reasons for nonadherence to antiretroviral therapy [25–27]. High levels of stigma have been described in postpartum women with HIV in South Africa [37], and may be especially salient during the perinatal period, due to fears of disclosure amid the demands that managing a pregnancy and HIV infection place on women, including regular PMTCT appointments, delivering in healthcare facilities, and breastfeeding behaviour [22,38]. Inability to get to a healthcare facility due to a lack of transport or inability to pay for the cost of transport have been identified as barriers to adhering to PMTCT [19,21,37], barriers that could possibly be circumvented by being able to make use of one's social support. We have expanded the Bangsberg and Deeks original model to include depression as an additional determinant of whether an individual will access their community or individual support network. We have also expanded the definition of adherence to include not only ART adherence, but adherence to other behaviours that are part of preventing mother to child transmission (PMTCT) in South Africa.

While data analysis from phase I (approved by HREC, Clearance Certificate M110963) is still underway, some preliminary analyses have been conducted. Specifically, we have explored the data collected during pregnancy examining depression, stigma, social support and structural barriers to PMTCT. An adherence score was created using principal components analysis on

the response to four questions assessing adherence over the past 30 days. Depression was defined as a Hopkins score > 1.75 and was examined as a predictor of the adherence score in a linear regression model. Separate linear regression models also examined relationships between (1) social support and structural barriers (income and time spent traveling to clinic) and (2) depression and stigma as predictors of social support. We found that depression predicted adherence: participants with elevated depressive symptoms had significantly lower adherence scores ($p<0.01$). Neither income ($p=0.10$) nor time spent traveling to clinic ($p=0.28$) predicted adherence; thus, moderation with social support was not examined. Depression significantly predicted social support (est=-0.46 $p<0.01$): those with elevated depressive symptoms had a lower social support score. Similarly, a higher stigma score was significantly associated with a lower social support score (est=-0.09, $p<0.01$). We therefore conclude thus far that while PMTCT programs are effective, adherence to these services is suboptimal. Depression may play an important role in adherence to these behaviours. HIV infected pregnant women with elevated depressive symptoms may also suffer from low social support and high stigma; interventions targeting these factors may support maternal and foetal health.

Anticipated enrolment.

Study setting. Prince Mshiyeni Memorial Hospital (PMMH) is a 1200-bed government hospital, situated 10 miles (16KM) southwest of Durban city centre which serves the population of Umlazi, the second largest township in South Africa. Umlazi District has one of the highest seroprevalence of HIV in South Africa, with 39% seroprevalence in antenatal clinic attendees in of 2012[5]. The antenatal clinic serves approximately 150-200 clients per day.

Inclusion and exclusion criteria. We will obtain consent prior to screening participants for the current study. Inclusion criteria include (1) female sex; (2) age 18-45; (3) currently pregnant; (4) HIV positive and diagnosed with HIV during the index pregnancy; (5) meet criteria for a current major depressive episode; (6) currently on antiretroviral therapy and eligible for lifetime therapy; (7) receiving antenatal care at PMMH Gateway clinic; (8) primary language English or isiZulu; (9) access to a phone and willing to give researchers permission to reach them via phone; (10) resident of Umlazi; and (11) able and willing to give informed consent. Participants will be screened for eligibility (after consent is obtained) using a screening script. The screening script contains a screener (the Patient Health Questionnaire; PHQ-2) to assess for the presence of depressive symptoms; participants who meet all other criteria, endorse depressive symptoms, and would like to participate will sign an informed consent document and complete a full baseline assessment to determine presence of a major depressive episode. Participants who do not meet criteria for a major depressive episode after completion of the baseline evaluation will be informed that they do not meet full study criteria, and will be referred to a health care provider. Participants who do meet criteria for a major depressive episode will be randomized to study condition (see Figure 4 for Flow Chart) and also provided with a referral to counselling services at PMMH. Women with active or untreated major mental illness that would interfere with participation (e.g., untreated psychosis, bipolar disorder, dementia, or active suicidality), will also be excluded and referred for mental health treatment via counsellors at PMMH. Acutely distressed or suicidal participants will be escorted to on-site mental health services immediately. A potential participant may also be excluded if, in the opinion of the Principal Investigator, participation in the study would be unsafe, would complicate interpretation of study findings, or otherwise interfere with achieving study objectives.

Recruitment procedures. We are requesting approval to enrol/randomize up to 40 (20 treatment and 20 control) HIV infected women meeting the aforementioned inclusion criteria from PMMH Gateway clinic. Potential participants will be approached about study participation by a trained research assistant (experienced in sexual and reproductive health fieldwork) as

they wait in the clinic queue. Those who express interest will be invited to speak with the study research assistant to learn more about study participation and be screened for eligibility; written signed consent to screening will be obtained. Those who volunteer to participate will complete the informed consent process. These procedures will be completed in a private setting, and procedures will be undertaken to ensure women do not lose their place in line. This strategy has successfully been used for other studies at PMMH antenatal clinic. Phase I of this protocol was approved by HREC (Clearance Certificate M110963), which utilized the same procedures. The research assistant will use an eligibility screening script to track all screened potential participants. These data will be recorded for study data reports. Review of the inclusion/exclusion checklists will be part of regular supervisory meetings between the local site PI, project manager and the research assistant.

Intervention development. The preliminary intervention content is based on two established cognitive-behavioural interventions: problem-solving therapy (PST; [39]) and Cognitive Behavioural Therapy for Adherence and Depression (CBT-AD; [40]). PST was selected as it is an effective depression treatment in its own right,[41] but because many of the challenges that HIV infected women in the perinatal period face (e.g., managing stigma, overcoming barriers to PMTCT adherence) are strong targets for a problem-solving intervention, and the group setting may contribute to a rich range of potential solutions to these problems. Furthermore, PST is straightforward to deliver, increasing the likelihood of successful delivery by a wider variety of individuals with varied training in psychosocial interventions. CBT-AD combines traditional cognitive-behavioural skills (including problem-solving) for depression with adherence counselling skills. The “Lifesteps” module of CBT-AD has been modified to reflect the adherence needs of HIV-infected women during the perinatal period. The intervention manual is included as an Appendix.

The intervention has been conceptualized as a group intervention as it has been proposed that interventions that make use of and foster social support may be helpful in decreasing social isolation and stigma among individuals living with HIV [10]. In addition, interventions that target social networks and strengthen group ties have also been used to empower marginalized groups, and to effect health related behaviour change related to HIV prevention (e.g., [42–44]). Lastly, group mental health interventions are cost-effective, which is of particular benefit in resource-limited settings [44,45]. The ideal number of participants per group will be approximately 2-10. In the event that enough participants cannot be recruited to participate in group-based sessions (i.e. due to scheduling concerns), individual sessions will be conducted. This data will be recorded and analysed as part of the feasibility and acceptability data.

Study procedures. After the informed consent document has been reviewed and signed, participants will be scheduled to complete a study intake assessment with the Project Manager or a Research Assistant. Once eligibility is determined, participants will be randomized to study condition. To allow an estimate of effect size for a larger trial, we will use a “treatment as usual” control group, and participants will be randomly assigned to a group. The treatment as usual group will consist of a referral to counselling services at PMMH, with the option of participating in the group sessions later (i.e. the next time the group is offered). Participants who will be postpartum by that time will be offered the option of attending a series of open problem-solving groups. With permission of the participants, we will send a referral letter documenting that criteria for depression have been met to a public health facility of the participants’ choosing to facilitate treatment for all participants who complete the baseline evaluation. Participants who do not wish to have a letter of this nature sent to a facility will be provided with a letter directly, if desired. We will also refer ALL participants who meet study inclusion criteria (or, those who do not meet criteria but could benefit from, or wish to be referred) to counselling services at PMMH,

where there is a social worker, psychiatrist, and trauma specialist on site. To facilitate referral, we developed a referral letter in collaboration with staff at PMMH (included with this application) that has been used in other studies with similar populations. Acutely distressed or suicidal participants will be escorted directly to counselling services by study staff. The screening that occurs as part of this study goes beyond the standard of care for depression screening and thus, women may actually benefit from the screening process. The specific referral path is described below.

The study staff will be trained to identify participants with symptoms of depression during data collection through self-reporting or using the assessment measures. Study staff will complete a referral letter and refer the participant to the project manager/coordinator. The project manager/coordinator will then discuss the depression symptoms identified with the participant, as outlined on the referral letter. She will explain to the participant the purpose of referral to the clinic healthcare provider for assessment, counselling and further management. Each participant will be escorted by the study staff to the service point healthcare provider. The healthcare provider will assess the patient, counsel, treat or refer to the hospital Social Worker or Psychologist or Crisis Centre for further appropriate management.

The initial intervention will consist of 5 to 8, 90-minute, weekly sessions. Each session will begin with a brief “open” check-in among group members to foster relationships and social support among group members. The remaining session time will consist of teaching problem-solving skills for managing depression and adherence. While participants will be encouraged to attend group sessions at a regularly scheduled time to facilitate group cohesion, a total of three group sessions will be offered each week to facilitate group attendance.

Baseline assessments will occur until it is deemed that enough participants are available for randomization and to run a group. For example, baseline assessments may occur until a minimum of four participants are identified (two intervention participants, and two control participants). In the event that recruitment is difficult, the investigators may run sessions with as few as two participants (one intervention participant, and one control participant). Participants will complete assessments with an interviewer (constructs described below in Table 1) at the following time points: once before the intervention begins, once after all intervention sessions are completed, and once at approximately three months postpartum. Control participants will be assessed at times mirroring that of the intervention participants.

As noted above, we will use an iterative process of intervention development. Interventions will be held in waves whereby an intervention group will be conducted, feedback collected from participants on the intervention, and another intervention group conducted. This process will be completed up to three times. In order to collect feedback from participants, the opportunity to participate in a brief qualitative interview will be offered to a random sample of intervention participants at the conclusion of each wave of intervention sessions. This qualitative interview is optional, and would be in addition to the aforementioned assessments. Approximately 3-5 participants per wave of intervention sessions will be randomly selected (a total of 10-15 interviews, maximum) to provide feedback on the intervention. If data from the qualitative interviews suggests that changes be made to the intervention (e.g., changing the number of sessions, changing the length of sessions, etc.), the investigators will propose changes and submit them to the ethics committee for consideration prior to starting the next wave of group sessions.

Sources of Materials: In order to maximize the integrity of the data, a racially and ethnically concordant female interviewer, fluent in both English and isiZulu, and who is different from the

study interventionist, will complete assessments with each participant. After eligibility is determined, assessments will occur immediately pre and post intervention; a third and final assessment will occur at approximately three months postpartum (see Table 1 for constructs and measures). In addition to a self-report measure of adherence, each participant will also be provided with a Medication Event Monitoring System (MEMS) to monitor their adherence to ARVs. Data from the MEMS caps will be uploaded at the beginning of each intervention session, and at all assessment visits. Feasibility will be documented as depicted in Figure 3. Qualitative interviews will be conducted with a sub-sample of participants at the end of the group in order to describe the acceptability and perceived usefulness of the intervention. Interviews will follow a structured interview guide, with flexibility to explore probes and content that may not specifically be in the guide to begin with. Questions will be open-ended to most effectively elicit information without biasing participants' responses.

Minimization of risks. All research study staff will be thoroughly trained in assessment procedures. In the event that a subject is determined to be in distress or actively suicidal and at risk for self-harm during any study procedure, study staff will refer to the local site Principal Investigator (Professor Smit) and the Project Manager so that appropriate clinical intervention is executed. Participants who are in distress or seemingly depressed will be assessed by the study staff and the Project Manager. The study staff will complete a referral letter, and the participant will then be referred via an in-charge at the antenatal clinic to either a psychologist, social worker, or other relevant person in at PMMH for further evaluation and treatment. All participating study institutions have been involved with numerous local, national, and international studies of persons living with HIV and each have considerable experience in implementing measures to protect confidentiality. Some of these steps include in-service trainings on confidentiality and the assignment of study ID numbers. Staff at all sites who conduct participant recruitment, screening, enrolment, and assessments will have been trained in ethical human subjects research and screening and interviewing techniques, to minimize participant risk as much as possible. Each research assistant employed by MatCH Research is required to sign a confidentiality agreement as part of their employment contract; oversight is managed carefully by Human Resources. In addition, all research assistants are required to have a valid Good Clinical Practice certificate and undergo training in the ethical conduct of studies. All data will be kept confidential, under lock-and-key, accessible only to trained study staff. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept separately under lock and key.

Foreseeable risks and discomforts. It is unlikely that participants will be at any risk for physical harm as a result of study participation. However, subjects may find some of the questions asked during the interviews to be emotionally upsetting. If this occurs, or if participants endorse active suicidality or exposure to intimate partner violence, they will be given the opportunity to cease study participation, and will be referred for counselling services as described above. As with any study, there is always the risk of inadvertent breach of confidentiality. This is of particular importance here because participants are infected with HIV, which may be stigmatizing. An additional discussion of how we minimize these risks is described above under "Minimization of risks".

Expected benefits. Participants in an intervention group may experience a reduction in depressive symptoms and an increase in adherence to the PMTCT cascade, including antiretroviral therapy. Study staff will refer participants to appropriate social services as needed or upon request. The data collected as part of this study may ultimately help researchers and

clinicians better care for HIV infected women and their children.

Equitable selection of participants. All women presenting for care at antenatal clinic at PMMH and meeting inclusion criteria will be invited to participate in the current study. We have budgeted time for research assistants to be physically located at the antenatal clinic to encourage and insure adequate recruitment. Men have been excluded from study participation because the aims of the study relate specifically to women. Children under the age of 18 are excluded as we are interested in studying the phenomenon of adherence to PMTCT among adult women; women under the age of 18 likely face additional and different barriers to PMTCT adherence than women 18 years or more.

Remuneration. Refreshments will be served at all assessment and intervention visits. There are three main interviews in this study. Participants will be reimbursed R100.00 for each interview where we collect data from participants (at the beginning of the study, after the group counselling intervention / 8-10 weeks after participant first interview, approximately three months postpartum). There is also an optional qualitative interview; participants who are selected to participate and complete this interview will be reimbursed R100.00. In order to support transport costs to sessions, participants in the intervention group will also be reimbursed R50.00 at each intervention session.

Consent procedures. Two informed consent procedures will occur; the first will occur before the eligibility screening, and the second will occur before study enrolment.

A detailed pre-screening informed consent form will be signed by each participant willing to participate in the eligibility screening questions. The consent form will include information about the study procedures, and the nature of the screening questions. It will also state that participants do not have to answer any questions they do not want to answer, and that they may stop the screening at any time. Participants will be informed that they do not have to answer any question they do not want to answer, they may stop the screening at any time, and that their answers will remain anonymous and confidential.

A detailed study consent form will be signed by each participant willing to participate in the study, following the explanations of the study procedures by the research project staff. The study consent form will include all of the study procedures, information about potential risks and benefits of participation, and information regarding who they can contact for further questions. It also will state that participation is voluntary, that participants can refuse to answer any question, that they can withdraw from the study at any time, and that study participation is in no way related to their care. Participants will also be reminded to take care when storing the consent document to avoid inadvertent disclosure of HIV status. Participants will also be informed that depression treatment is available via a referral for mental health treatment at PMMH, and thus they do not need to participate in the study in order to receive depression treatment. Participants will have as much time as they require to decide if they want to participate, even if this requires re-scheduling other portions of the visit to allow the participant more time to review the informed consent document. All procedures and protocols will have been approved by the Massachusetts General Hospital (MGH) institutional review board (IRBs) and the Wits University Human Research Ethics Committee and by PMMH and local and KwaZulu-Natal provincial health authorities before the inception of any study procedures.

Data analytic plan. All analyses conducted as part of this field test intervention are meant to lay the groundwork for future work, and it is not necessarily powered to detect statistically significant changes in depression, adherence, stigma, or social support. Because this is an

exploratory study, we will first examine the outcome variables continuously. We may determine cut-off scores that are appropriate to the sample and make clinical sense, and examine dichotomous outcomes (e.g., a reduction of 30-50% in depressive symptoms and/or the percentage of the sample scoring lower than >/= 9 on the Edinburgh Postnatal Depression Scale (EPDS) and achieving ≥90% adherence) when assessing the effect of the intervention. Descriptive measures (such as mean, standard deviation, median, and range) will be used to summarize continuous patient characteristics (such as age, income) and categorical patient characteristics (such as ethnicity, employment status) will be summarized using frequencies and percent's. Descriptive data on the feasibility outcomes depicted in Figure 3 will be presented. With respect to qualitative exit interviews, data will be analysed using standard qualitative methodologies described by Miles and Huberman[46]. After transcripts are translated to English, they will be reviewed for errors and omissions. NVivo software (version 9) will be used to organize data and to facilitate analyses. Two investigators, one of whom will be a South African study staff member (to ensure accurate interpretation), will independently review the transcripts in order to generate an overarching thematic framework for data interpretation, in which major and minor themes are identified.

Data and safety monitoring. Data collection occurs in the form of a series of quantitative assessment interviews. The principal investigator (Dr. Psaros) and her primary mentor (Dr. Safren) will work closely with the South African site PI (Professor Smit), to oversee all data management and analysis issues. The proposed study team has extensive experience collecting data on reproductive health among women in Durban, South Africa, and a quality management plan will be developed to specify daily quality control and monthly quality assurance measures. The research assistant will review all assessments prior to the end of all interviews to minimize missing data. Data will be entered in an on-going fashion (into REDCap data management system), and will be analysed using the Statistical Package for the Social Sciences (SPSS), version 18, and QSR NVivo qualitative software, version 9, after being thoroughly checked and cleaned as appropriate. Data files will be sent to Dr. Psaros from the site using secure (password protected) file transfer. The MGH IRBs will review the data-monitoring plan along with the full study protocol at least annually.

Data will be obtained from participants recruited specifically for this protocol and will include sociodemographic information (e.g., age, level in school, race and ethnicity, etc.), depression, stigma, social capital utilization, and adherence to PMTCT (see Table 1). A research assistant will collect data from the participants' record on CD4 cell count, viral load, and antiretroviral regimen during the last trimester of pregnancy and immediately postpartum, the stage of HIV as determined by World Health Organization's staging criteria, and the gestational age, date of birth, and weight of each participant's infant at birth. No other information will be abstracted from the medical record. Only trained study staff will have access to these data. Participants' data will be identified by an ID number only, and a link between names and ID numbers will be kept separately under lock and key.

The data files from the interviews will be sent by a secure file transfer system between South Africa and Boston without names and other personal identifiers. These files will be sent with a password lock known only to the key study staff. These files without any personal identifiers will be kept in Boston for 10 years, and then destroyed. Study results will be reported only in summary form so that no individual participant can be identified.

Adverse events reporting. As a result of participation in the interview, study staff may become aware of an adverse event, including participant distress or disclosure of current or past physical or sexual abuse. Study staff will be trained to make appropriate referrals for clinical or

psychological care in consultation with the PIs and/or antenatal clinic staff and in accordance with South African law regarding the reporting of sexual or physical abuse. Adverse events will be reported according to the local South African ethics committee procedures and these will be discussed on calls between the overall PI (Psaros) and the site PI (Smit).

4. TABLES AND FIGURES

Figure 1: The PMTCT "cascade"

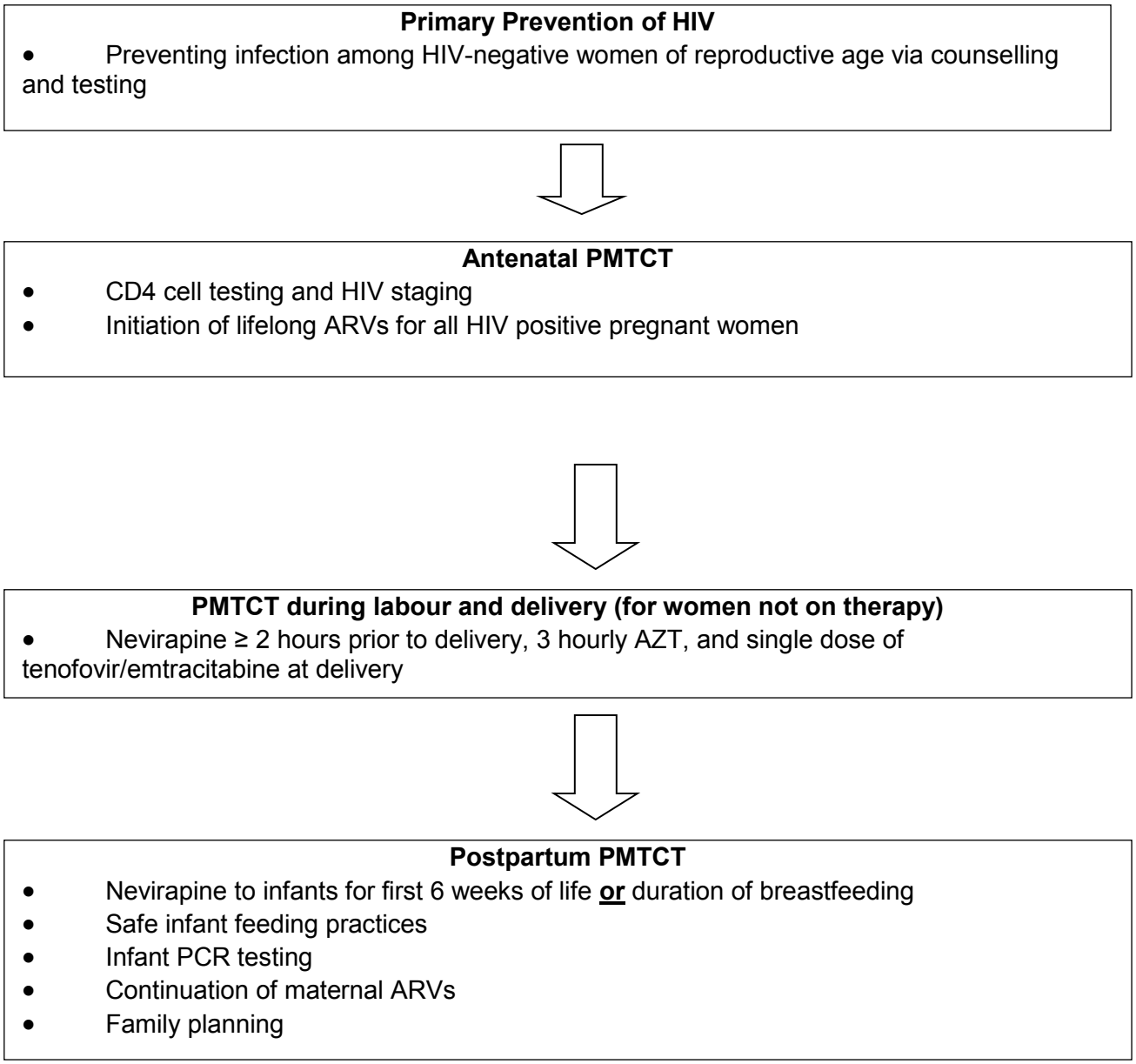

Figure 2: Conceptual model

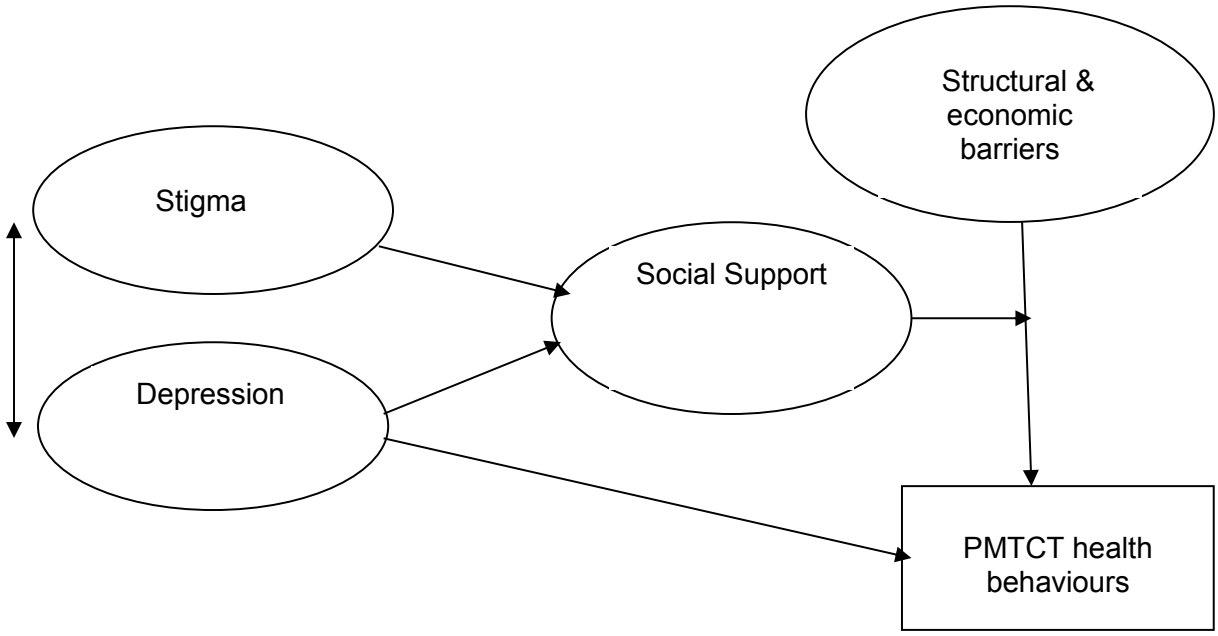

Figure 3: Intervention feasibility

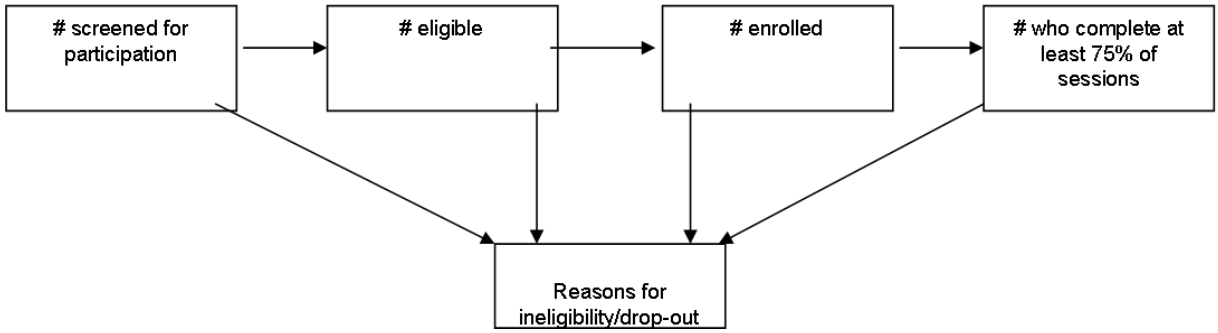

Figure 4: Participant Flow Chart

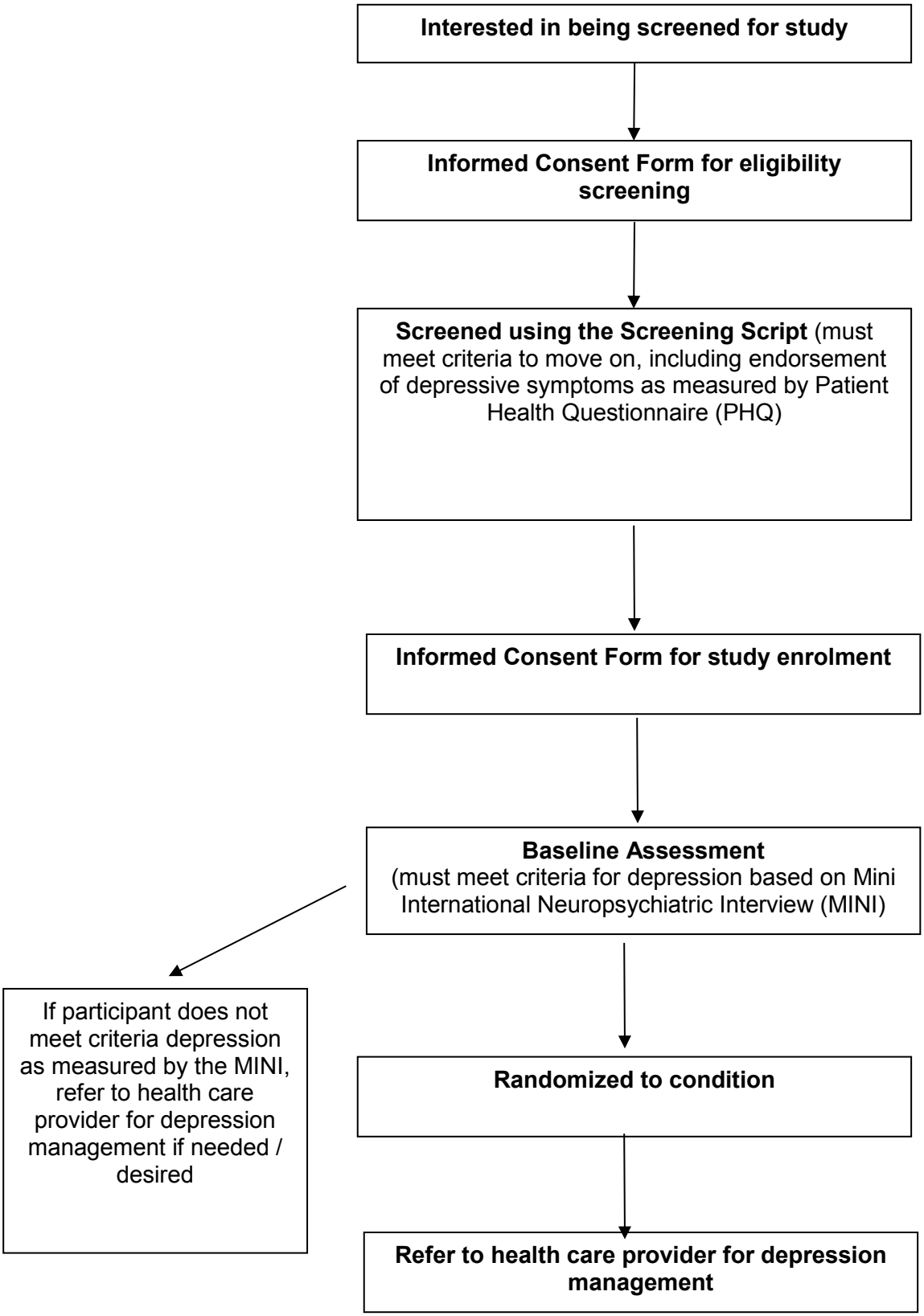

Table 1: List of proposed measures and assessments

Construct	Measurement tool and schedule
Sociodemographic and structural barriers	Age; ethnicity; educational level; employment status; occupation; income; distance to clinic; time spent travelling to clinic; mode of transportation to clinic.
Clinical information	Approximate due date, number of pregnancies, number of children, date of HIV diagnosis, number of children who are HIV positive
Partnership characteristics	Marital/partnership status; partner's HIV status; length of relationship with partner; if live with partner; disclosure to partner; partner involvement in pregnancy (yes/no).
HIV characteristics	CD4, viral load, year of diagnosis; disclosure status. World Health Organization staging classification for HIV stage, as available. Antiretroviral therapy regimen.
Pregnancy characteristics	Attitudes towards pregnancy and pregnancy intention as measured by the CDC PRAMS instrument;[33,47,48] parity. Instrument is scored using an accompanying variable codebook, with answers "Yes" scoring '1' and "No" scoring '0'. Number of antenatal care visits.
Depression	Diagnosis of current and past Major Depressive Disorder will be made using the Mini International Neuropsychiatric Interview (MINI), Major Depressive Episode Module. The Edinburgh Postnatal Depression Scale will also be utilized to measure depression at baseline, post treatment, and postpartum. This 10 item measure has been validated for broadly African and specifically South African populations specifically for perinatal and postpartum participants. [49,50]
Stigma	HIV/AIDS Stigma Instrument-People living with AIDS (HASI-P) has been developed and tested broadly in five African countries (including South Africa). The instrument was validated with a sample of 1,477 persons living with HIV/AIDS in those five countries. This is a large measure from which we are utilizing 3 sub-scales: negative self-perception items (n=5), social isolation (n=5), and verbal abuse (n=8).[51]
Social support	Modified version of the Duke-UNC Functional Social Support Questionnaire.[52] 10-item scale evaluating availability of emotional, informational, and tangible support. Items are rated on a 4-point Likert scale; number of persons providing support is also assessed.
Adherence to ARVs during pregnancy and PP (self-report and objective measure)	(1.) Adherence with ARV medications over the past month with three different response formats: (1) frequency, (2) percent, and (3) rating response. Category scores of 0, 20, 40, 60, 80, and 100, with 100 being the best adherence are calculated[53] (2.) 30-day visual analogue scale (VAS) for overall adherence assessment for one month. Adherence is calculated as the % of doses taken over those prescribed and categorized into full, partial, and non-adherence. The VAS has been used in South Africa.[23] MEMS caps will be brought to each session and each assessment and read for quantifiable adherence value (i.e. when the pill was opened every day).

Adherence to labour and delivery practices	Method of delivery (vaginal or Cesarean section); delivery in a healthcare setting (yes/no; [21])
Infant nevirapine administration	Select questions from the ACTG Paediatric International Adherence Questionnaire (NIAID Paediatric AIDS Clinical Trials Group). Assesses missed doses and reasons for missed doses. This measure has been used in South Africa.
Initiation of family planning methods	Initiation of family planning (yes/no); means of family planning (including intrauterine devices, oral and injectable hormonal contraception, implants, condoms).[54,55] These questions have been used in South Africa and Zambia.
Infant outcomes	HIV testing (yes/no);[11] HIV status; gestational age; birth weight; mortality; birth date.
Breastfeeding	Assesses breastfeeding practices (breast, formula, mixed); reasons why participants may have chosen to opt out of breastfeeding or why they may have chosen to supplement breast milk.

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