The Treatment Ambassador Program: A Pilot Intervention to Increase Treatment Initiation

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Study Protocol

PRINCIPAL/OVERALL INVESTIGATOR
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PROTOCOL TITLE
The Treatment Ambassador Program: Pilot Testing a Peer-driven Intervention to Increase Treatment Initiation Among HIV-positive South Africans

FUNDING
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SPECIFIC AIMS

We will conduct a pilot randomized controlled trial of our intervention to determine the acceptability, feasibility and preliminary impact of a peer-support intervention on ART refusal. Up to ninety participants will be enrolled and followed for a total of 6 months (three months of intervention plus three months of follow-up). Participants will be randomized to either standard of care (referral for ART) (up to n=45), or the Treatment Ambassador intervention (up to n=45). The primary outcome will be ART initiation. We will conduct a mixed-methods process evaluation of the different intervention components and their implementation using quantitative, qualitative, and observational methods. The ultimate goal of this work is to contribute to sustainable solutions to tackle ART refusal and promote early and enduring uptake of treatment in South Africa.

BACKGROUND AND SIGNIFICANCE

Data showing treatment-mediated, HIV-1 RNA suppression reduces transmission risk by 96%, has created a global aspiration for an "AIDS-free generation." These findings, combined with the health advantages of Antiretroviral Therapy (ART), have led the World Health Organization to recommend initiating ART immediately upon and HIV diagnosis. South Africa, the country with the largest HIV-epidemic, has adopted a "test and treat" strategy (in which an individual is offered treatment immediately upon learning their HIV status) starting in September 2016. Treatment-refusal, a phenomenon our team identified among newly diagnosed, ART-eligible adults in South Africa, may undermine the potential gains that could be made with earlier treatment. The research proposed here seeks to capitalize on our understanding of ART refusal by designing a feasible and acceptable intervention to improve ART initiation. This multi-component intervention, titled the "Treatment Ambassador Program," will target HIV-infected people who do not initiative treatment within three to six months of learning they are eligible. It will be aimed at addressing barriers to ART initiation identified through our prior qualitative research, as framed through the Theory of Triadic Influence. Our intervention will last approximately twelve weeks and will aim to address the three steams of influences on decision-making through a system of patient navigation and support with an assigned HIV-infected partner trained in motivational interviewing. To develop our intervention, we have formed an interdisciplinary collaboration with expertise in socio-behavioral and biomedical research.

Adopting an explanatory model of ART refusal will optimize intervention-based research. In our recent qualitative research with ART-eligible (CD4 <350 cells/ml) adults in South Africa, our group developed an explanatory model of treatment refusal. We frame our explanatory model within the Theory of Triadic Influence, which focuses on three "streams of influence" that impact health behavior at the individual, social, and structural levels[1]. Central to our model is the meaning of ART initiation for participants. Specifically, at the individual level, the perceived risks associated with starting treatment may be greater than maintaining the status quo. This is often rooted in a pervasive cultural belief that ART is reserved for those who are ill, and not easily considered when one is "feeling healthy." In these circumstances, treatment is often delayed until the known risks of being off of therapy outweigh the unknown risks of ART initiation. As shown in **Figure 1**, there are individual, social, and structural factors that may guide decision-making. This explanatory model provides the basis for the proposed multi-level, multi-component intervention, addressing barriers to ART initiation at individual, social, and structural levels that will be participant-focused and peer-sustained.

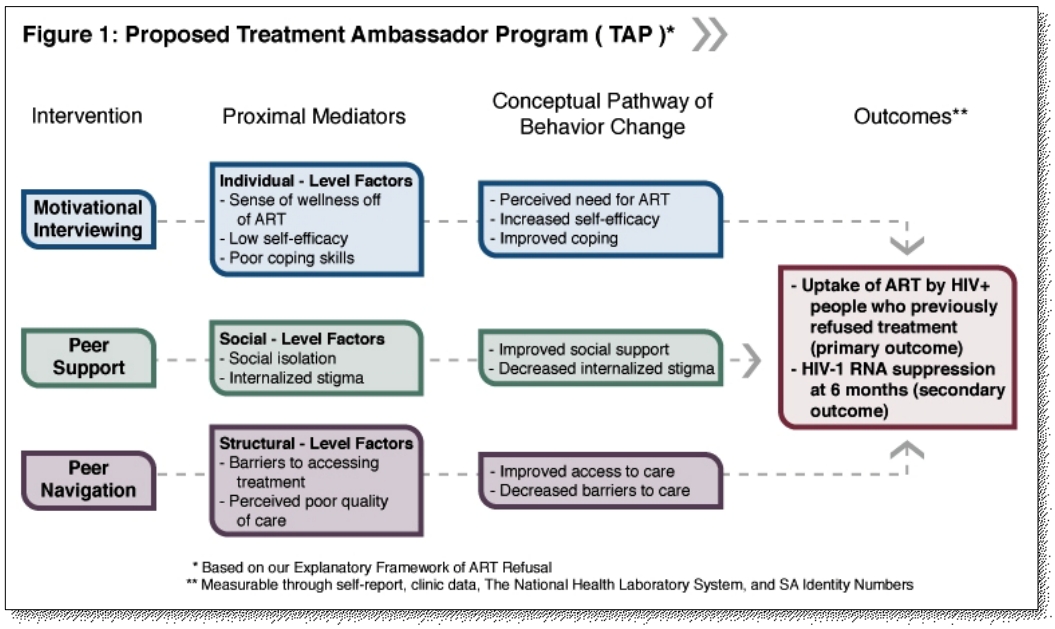

Figure 1. ***Factors guiding decision-making among persons delaying uptake of ART.*** *Individual factors include: a sense of wellness off of ART; low self-efficacy for managing and adhering to daily long-term medications; and poor coping skills. Social-level factors include: concerns about being identified as someone who is sick from HIV, resulting in social isolation due to internalized stigma. Structural barriers include: challenges accessing medication due to cost, travel distance to clinic, and perceived poor quality of care.*

Treatment Ambassadors (TAs) using Motivational Interviewing (MI) techniques is the ideal strategy to engage with people living with HIV (PLWH) who are ambivalent about starting ART. Behavior change requires motivation and readiness as well as the skills needed to engage in the behavior. MI techniques create a collaborative, goal-oriented style of communication that focuses on enhancing intrinsic motivation, which research shows leads to behavior change. Most importantly, MI techniques avoid the use of persuasion, which ultimately can lead to increased resistance. In addition, the promise of MI is the development of "high-quality," durable intrinsic motivation for behavior change, which is vital given the time- limited nature of behavioral interventions. Given our qualitative data identified multiple individual barriers to ART initiation, we believe MI will be an effective and non-confrontational strategy to

engage with participants, and have honest and open conversations about treatment behaviors to promote motivation to start ART.

Peer-support can be used as a tool for addressing social barriers to initiating ART. We know that social factors have a profound impact on many HIV-related behaviors. Specifically, social support and social norms are important determinants of ART adherence among PLWH in resource limited settings (RLS). Due to the stigmatization of HIV, PLWH who appear healthy might be less motivated to disclose their status. However, this undermines an individual's ability to access HIV-specific social support. TAs can provide a formal network of peer-support for PLWH. While prior research has shown variable success of peer-support chosen by participants in the setting of ART adherence, there has been significantly less written about the impact of peer-support on pre-ART care. Yet, this research is essential to the success of proposed universal test and treat strategies. Early evidence supports the use of peer-support to improve initiation, particularly when combined with other proven effective interventions. In addition, we have found that peer support proves critical to enhancing PLWH's ability to cope with the life changes that are required to overcome concerns related to ART side-effects, internalized and externalized stigma, potentially increased financial burdens associated with treatment, and the lure of seemingly safer alternative therapies.

Patient navigation can be used as an effective technique for improving linkages-to-care. Data are emerging regarding the impact of patient navigation as an effective strategy for improving engagement in care. Navigation is an efficacious, flexible, individualized approach to assist PLHA in identifying and overcoming barriers to health services. We hypothesize that patient navigation can complement the other facets of our intervention, including social support, and MI techniques, to help PLWH identify barriers to entering care and devise solutions by optimizing the use of available resources.

RESEARCH DESIGN AND METHODS

Overall Strategy for Proposed Study Design: We propose to iteratively develop and conduct a pilot multi-component, socio-behavioral intervention aimed at promoting early and enduring uptake of treatment among PLWH in SA, who otherwise would not avail themselves of the benefits of freely available treatment. We will conduct our work through an ongoing partnership between US and SA academicians, with input from a community advisory board (CAB) consisting of adult members of the community and community-based therapeutic counselors at The Desmond Tutu HIV Foundation. The proposed study is based on our formative research. We will hire and train TAs, who will be identified as "successful" people living with HIV, who will then serve in multiple capacities, including delivering the MI intervention through individual sessions, while providing peer-support and peer navigation. We intend to perform our intervention over three months, a duration that has proven efficacious in our prior domestic research. Our goal is to provide eligible participants with in-person one-on-one weekly contact with their assigned TA as well as weekly phone check-ins. Before pilot testing the intervention, we will perform a phase of iterative development.

The primary outcome will be the proportion of individuals who start ART in the intervention arm compared with those in the control arm (standard of care is to refer to a local clinic to initiate ART). We will ascertain this through the medical record for those who start treatment on site (approximately 80-85% of testers at this site), and through the National Health Laboratory Service (NHLS) for those who start care off site. Participants will complete surveys at baseline and at the end of the intervention. After completing the pilot, we will conduct a process evaluation of a subset of the intervention group. After the process evaluation is completed, we

will use the results to revise the intervention protocol in preparation for a fully powered multi-site RCT. The progression of protocol and manual development, pilot testing for feasibility, and eventual RCT is consistent with the staged model of behavioral intervention development.[2]

Study Site: This study team will be based at the Desmond Tutu HIV Foundation (DTHF) Gugulethu Research Offices, based at the Gugulethu Community Health Centre. DTHF is an internationally- recognized HIV research center that has been involved in community-based research since 2002. Their testing center is based in Gugulethu (population 400,000), South Africa where 48% of residents are unemployed and 64% live on <400 SA Rand (ZAR) [approximately <US$40] per month. The vast majority of the population uses local public sector health services that are provided free of charge. In 2012, the HIV prevalence among women attending local antenatal care services was 27%.

The intervention sessions will be conducted at one of a few local sites identified by our community staff and CAB in Gugulethu e.g. JL Zwane Church, the Gugulethu library, or at their homes. The participant may choose where he/she feels most comfortable.

Eligibility Criteria for Treatment Ambassadors (TA): TAs will be identified through leaders among a community of PLWH who are currently in care in Gugulethu.

Eligibility Criteria for Participants in the Trial:
Inclusion criteria include:
1) HIV-infected adults, 18 years and older, refusing to initiate ART within three to six months of learning eligibility;
2) ART naïve,
3) Live within 60 km of Hannan Crusaid clinic (due to prohibitive costs of following participants to remote locations);
4) English or Xhosa speaking; and
5) Eligible for treatment under current South Africa guidelines
Exclusion criteria include:
1) Unable to provide informed consent (e.g., due to intoxication or mental incapacity,
2) Persons less than 18 years of age,
3) Women who report current pregnancy at the time of consent. We are choosing to not include pregnant women in this study, because the study's recruitment site refers pregnant clients to more specialized care facilities that may better suit their needs.

Development of Components of the Treatment Ambassador Program and Iterative Open Pilot Testing: The core components of our intervention are based on our prior research, and available literature focusing on interventions to improve engagement in care. The structure and intensity of the sessions are based on an attempt to balance the need for sufficient exposure to achieve an effect, with the need for optimizing feasibility and sustainability in community practice. We propose an 8-week intervention, described in detail below. While the components in this intervention will be described separately, they are designed to be synergistic and overlap, with each component providing complementary modalities of support for participants.

Component A. Motivational Interviewing (MI)—Channel: Improve self-efficacy and coping, while addressing health beliefs; Duration: 60 minutes each; Number of Sessions: 8 sessions delivered weekly over 8-14 weeks. **Description of MI:** MI is a flexible counseling technique used to elicit behavior change through non-confrontational counseling to enhance motivation and confidence

for behavior change by helping individuals identify discrepancies between stated goals and values, and current behavior. MI will be used to change behaviors and attitudes that are barriers to ART initiation, and develop positive attitudes and beliefs regarding treatment efficacy and expected treatment outcomes. Treatment Ambassadors will help clients develop problem solving skills to identify key barriers, and to implement and evaluate strategies to overcome barriers. MI is designed to maximize feelings of autonomy and increase the likelihood that strategies will be adopted, using a holistic approach to determine what works and does not work for each client. Interventions using MI have demonstrated acceptability, feasibility, and fidelity in South Africa pilot projects, and have shown efficacy when delivered by lay counselors as part of an HIV prevention counseling intervention in KwaZulu-Natal, South Africa. For this planned intervention, we have provided a four-day training for the Treatment Ambassadors to familiarize them with the MI technique and intervention content and structure.

Session Descriptions: Consistent with MI, the sequence of exercises is individually tailored to the participant's level of readiness to engage in care/initiate ART. Refer to **Table 1.**

Table 1. ***Session Descriptions:*** *Eight sessions over 8-14 weeks*

Table 1: MI Training Sessions		
Sessions	**Focus and Goals**	**Description**
Sessions 1 and 2	**Focus:** Personal and culturally grounded barriers to care (e.g., health beliefs, self-efficacy, coping skills, perception of ART efficacy) **Goal:** Reframe the risk perception of participants.	• Assess awareness of the importance of ART initiation, and participants' theories about how treatments work. • Participants asked to describe goals and attitudes about treatment. • TAs develop a brief written plan with participants for short- and long-term goals, and a timeline. • This work-plan will be revisited and updated in each session.
Sessions 3-4	**Focus:** Evaluating and fostering readiness for ART initiation and planning practical steps to achieving these goals. **Goal:** Develop positive attitudes towards ART initiation	• Assess awareness of consequences of not starting ART, and clients' theories about whether and how treatments work. • TAs provide education about ART efficacy, and explain the connection between taking medication and HIV-1 RNA suppression. • Participants asked to describe goals and attitudes about treatment. • MI will be used to help to develop positive attitudes toward ART initiation with the goal of improving treatment, knowledge, self-efficacy, coping skills, and perceptions of ART efficacy (hypothesized social-cognitive mediators of ART initiation).

Sessions 5 - 8	**Focus**: Articulating barriers to and gains/losses associated with ART and evaluating and fostering readiness for initiating ART **Goal:** Reframing barriers to ART initiation and promoting ART readiness	• Participants identify barriers that may contribute to ART refusal, including: internalized stigma; perceived social isolation associated with disclosure; and structural barriers to care. • Emphasis on the initial stages of ART initiation and planning practical steps to achieve goals.

Component B. Peer-support—Channel: Decrease internalized stigma and social isolation.
Description of peer-support: A substantial literature shows linking PLWH with peer-supporters is an efficacious approach to HIV-related behavior change, with effect sizes generally comparable to provider-led interventions. Successful peer-supporters, specifically PLWH who have consistently engaged in care for at least six months and are taking ART with high adherence, can serve as credible role models and challenge negative peer norms about care and ART. Treatment Ambassadors will be carefully selected individuals, who will be PLWH who have been engaged in care, and identified as leaders in their communities. They will be trained to administer the MI-based intervention, while also serving in multiple other capacities, including: acting as a role model regarding care/ART initiation; providing encouragement to link to other services including substance use/mental health as needed; and providing practical tips for initiating ART and staying in care, based on his/her personal experience. Treatment Ambassadors will be highly trained and closely supervised and all contacts will be logged and monitored.

Component C. Peer Navigation—Channel: Address structural barriers to ART initiation.
Description of peer navigation: Navigation has been found efficacious in a large number of studies with endpoints such as engaging and retaining low-income HIV-infected individuals in HIV care, including studies done in sub-Saharan Africa. Peer navigation will be embedded in the Treatment Ambassador intervention as part of the MI-focused approach. Core elements will include: an initial face-to-face meeting (< 60 minutes) as part of the first MI session, to review participants' readiness for and barriers to care/ART and creation of a Change Plan/Action Plan that will be guided by an MI approach. This will be followed by a minimum of weekly phone and in-person meetings during the navigation period, depending on need. The menu of activities will focus on assisting participants in identifying barriers to care and accessing needed services (e.g., transportation, child care, scheduling difficulties, ancillary services for mental health and substance use), while helping to devise effective and sustainable solutions to taking treatment. Treatment Ambassadors will guide participants to the treatment center they identify as best for them, and serve as a liaison between the participant and the healthcare providers on site.

Intervention Fidelity and Treatment Ambassadors Qualifications: We will achieve consistency in intervention implementation through proper hiring and training, and ongoing supervision and monitoring. We will select Treatment Ambassadors who are comparable to those who might lead the program in community settings. They must be PLWH, have a record of proven attendance and leadership in their community, have completed high-school, and

possess relevant interpersonal skills for MI (e.g., empathy, warmth, and respect for individual differences/choices).

Facilitators, Training, and Fidelity: Three Treatment Ambassadors will be trained. Each TA will engage with 12-14 participants. TAs will complete a comprehensive training and demonstrate cultural and treatment education competency, including: basic knowledge of HIV; confidentiality and HIPAA regulations; crisis intervention; referral resources; cultural and social issues; and substance abuse assessment. The training will be led by Dr. Kathy Goggin (Co-Investigator) and a Xhosa-speaking co-facilitator (Ms. Lungiswa Tsolekile, who has worked with Dr. Goggin previously in South Africa on MI interventions). Dr. Goggin and Ms. Tsolekile, with assistance from Drs. Katz and Dr. Laura Bogart (Co-investigator), will conduct a four- day training. The training will cover program content, MI style, and administrative and study details. After Drs. Katz and Bogart introduce the study design and protocol, Dr. Goggin will begin the MI training, using materials (e.g., videos, exercises) from the Motivational Interviewing Network of Trainers. The training will consist of one day of initial MI training. Dr. Goggin and Ms. Tsolekile will then lead the group through simulated program sessions on the second day. The third day will focus on the intervention training that Drs. Katz and Bogart will lead. Facilitators will then role-play potential questions and challenging situations and practice all program activities and components on the fourth day. Facilitators will conduct simulated sessions with each other and be rated for proficiency in both program content and MI by Dr. Goggin. TAs must meet proficiency for at least three consecutive sessions prior to beginning the sessions.

We will record each session, and 20% will be reviewed for fidelity. Independent Xhosa raters will code the extent to which key elements are covered; $\kappa \geq .80$ will indicate adequate coder consistency. To ensure facilitator fidelity to MI, we will use the Motivational Interviewing Treatment Integrity (MITI) Code, which rates global empathy and MI spirit and has frequency assessments of MI-consistent and inconsistent behaviors (e.g., open/closed questions). In Dr. Goggin's research with similar trainings, counselors were independently rated as highly MI adhered Dr. Goggin will train our RA to supervise TAs weekly and will hold monthly Skype supervision calls. If performance during the study drops below the threshold on any criterion (e.g., ≤6 on 7- point scales) or protocol elements are not completed, each of that facilitator's subsequent sessions will be monitored until three consecutive sessions meet the threshold again.

Data Collection: *Primary outcome* will be ART initiation, which will be assessed at the completion of the intervention (month 3) and monthly through 6 months post-randomization. This will be measured through both self-report, medical records at GCHC, and accessing data through the National Health Laboratory Service (NHLS).

Baseline Demographic Data and HIV Clinical Data (diagnosis date, clinical history, most recent CD4 count): Laboratory testing. Standard protocol at the testing center is testing of the participant's blood to determine HIV status and CD4 and participant eligibility. This is done routinely already at GCHC. Self-Report Measures. For the pilot RCT, we will administer three sets of surveys (baseline, three months (at the completion of the intervention), and at six months (completion of the study)). Our current study in Gugulethu utilizes an interviewer-administered survey that has been shown to be feasible. Code numbers will link data over time. Intervention participants who drop out of the program will be encouraged to complete all surveys. Incentives and Efforts to Improve Response Rates. We have extensive experience retaining participants over time in South Africa. We will offer participants choices as to where they would like to do the survey, and they will receive a stipend equal to $10 USD for each of the surveys, with a bonus of $20 US at the end for completing all surveys.

Quality Assurance: For each session, TAs will fill out a quality assurance form to assess the extent to which key elements and activities from the program manual were covered. We will record each session, and independent raters on the SA team will code the extent to which key elements were covered; $\kappa \geq .70$ will indicate adequate consistency between coders.

Curriculum Revision: The curriculum development team (Drs. Katz, Bogart, and Goggin) will thoroughly review and discuss results with the Community Advisory Board annually. These discussions will help us to optimize our pilot randomized controlled trial.

Survey Measures: We will draw on our formative South African research and community input to adapt measures. We will provide surveys in English and Xhosa. Pilot data will allow us to gain valuable information about psychometric properties of the proposed scales in both languages.

Data Analysis Plan (Open pilot): Data from the small pre-pilot sample (*N*=10) will be analyzed and will be primarily used to inform ongoing modifications to the TAP intervention to maximize acceptability and retention. Baseline and follow-up quantitative data will be examined for within-group trends in ART initiation.

RCT - Randomization. Participants will be identified from those in previous studies who gave permission to be contacted for future research, through links with the Community Advisory Board or at the VCT rooms of 4 local clinics, where we will also review daily testing logs and treatment logs, and will contact those found to be eligible and not starting ART within 3 months of testing. Those who then go on to meet eligibility criteria will be selected to enroll and asked to complete a baseline questionnaire. HIV testing itself is not part of this study.

We will use a blocked randomization design based on gender, with a goal of equal representation of males and females. Participants will be randomized to the standard of care (referral to initiate ART) or the intervention arm. A computerized random-number generator will be used to formulate an allocation schedule; participants will be given their assigned allocations within sealed opaque envelopes. The RA enrolling patients will be blinded to the randomization assignment. Upon completion of the baseline questionnaire, the randomization assignment will be revealed. For participants randomized to the TAP arm, the RA will notify the TA, who will come to meet the participant immediately upon completion of the survey. We will seek to prevent control group contamination (i.e., controls being influenced by what the intervention group is learning). For contamination to threaten the ability to detect intervention effects, statistical models suggest that ≥30% of the control group must receive the equivalent of a full-strength intervention[2], which we believe to be highly unlikely. Nevertheless, we will survey participants about possible contamination (e.g., whether they discussed this study with community members) upon study completion.

Data collection.

Primary Outcome. ART initiation – Assessed at the completion of the intervention (month 3) and monthly through 6 months post-intervention. This will be measured through both self-report, medical records at GCHC, and accessing data through the NHLS.

Demographics. We will collect baseline demographic data, and HIV clinical data (diagnosis date, clinical history, most recent CD4 count).

Laboratory testing. Standard protocol at the testing center is testing of the participant's blood to determine HIV status and CD4 and participant eligibility. This is done routinely already at GCHC.

Self-Report Measures. We will administer two sets of surveys to the pilot groups (baseline and at completion of the intervention) to test survey questions and tracking procedures. Our current

study in Gugulethu utilizes an interviewer-administered survey that has been shown to be feasible. Participants will complete the baseline survey before randomization. Code numbers will link data over time. Intervention participants who drop out of the program will be encouraged to complete all surveys.

Incentives and Efforts to Improve Response Rates. We have extensive experience retaining participants over time in SA. We will offer participants choices as to where they would like to do the survey, and they will receive a stipend of Rand 100 (roughly $8 U.S for each of the surveys, with a Rand 200 bonus at the end for completing all 3 surveys.

Quality Assurance. For each session, TAs will fill out a quality assurance form to assess the extent to which key elements and activities from the program manual were covered. We will record each session, and independent raters on the SA team will code the extent to which key elements were covered; $\kappa \geq .70$ will indicate adequate consistency between coders.

Curriculum Revision. The curriculum development team (Drs. Katz, Bogart, Goggin, and Gwadz) will thoroughly review and discuss results with the CAB annually. These discussions will help us to optimize our RCT. For this phase, we intend to pilot test the Treatment Ambassador intervention on a sample of up to 45 PLWH in each group (up to n=90) who have not started ART within 3-6 months of learning eligible. This phase of the study is focused on assessing acceptability and feasibility to inform a larger RCT. Inclusion criteria, recruitment, intervention, TA training and supervision, outcomes and measures, are described above, pending refinement based on our iterative design. In preliminary analyses, randomized groups will be compared with respect to baseline demographic and clinical variables using t-tests and chi-square tests; if significant group differences are identified in any variables known to be highly predictive of ART initiation outcome, these variables will be adjusted for via their inclusion as covariates in analyses. These covariates will also be summarized with descriptive statistics and graphical methods to determine the most appropriate way to incorporate them in the analyses (e.g., continuous or categorical representation of the variable).

Primary data analysis will be an intent-to-treat analysis, which includes all randomized participants. Of note, every attempt will be made to continue assessing participants even if they drop out of treatment. In addition, we will replicate all analyses with the completers only. The hypothesis that The Treatment Ambassador Program will yield higher rates of ART initiation by the completion of the intervention will be tested using Fisher's exact test; the treatment effect estimate will be summarized in terms of a relative risk and 95% confidence interval. Any baseline demographic or clinical variables identified as necessary covariates in preliminary analyses will be included in a logistic regression analysis that examines the main effect of treatment condition on the rates of ART initiation.

Power/Sample Size Considerations. Because this is a pilot study, power considerations for testing null hypotheses are somewhat less relevant than having adequate degrees of freedom to estimate treatment effects with a reasonable degree of precision for potential use in a future fully-powered trial. However, for completeness, we present a summary of the power analyses for the primary hypothesis below. With a sample size of up to 45 per treatment group, the probability is greater than 80 percent that the study will detect a difference of 25% in the percent who initiate ART. This is based on the assumption that the percent who initiate ART in the control group is approximately 10%, as seen in our prior research in SA. Thus, the study is adequately powered to detect medium-to-large effect sizes (corresponding to a relative risk = 3.5) for the primary outcome. Finally, allowing for a dropout or attrition rate anticipated to not be greater than 10%, we plan to recruit a total of up to 90 participants (45 per group) to ultimately guarantee our complete sample of 80 participants. This proposed sample size provides more than sufficient degrees of freedom to obtain a precise estimate of the primary outcome event rate and a preliminary relative risk

comparison of the two treatment groups, even when allowing for up to 10% loss to follow-up. If promising results are detected, these data will provide an estimate of the reliability of the intervention effect to inform power calculations for a larger RCT.

Process Evaluation to Examine the Feasibility and Acceptability of the Intervention. Process evaluation data, integral to the development of cluster RCTs, will be collected to assess the implementation, feasibility and acceptability of the different intervention components. Using a mixed-method approach, we will collect data from qualitative and quantitative sources throughout the pilot study. Data collection will include:

Attendance registers to provide data on enrollment, dropout and attendance of the intervention. Registers will be filled out by intervention staff, beginning with the enrollment visit. Staff will collect information on training attendance and participation levels (assessed on a 1-5 scaled rubric).

Weekly meetings with detailed minutes including research staff and TAs will document challenges and problems with recruitment and study procedures. The RA will document challenges in both the intervention and control conditions, including reactions by participants, difficulties encountered, areas for improvement, and overall assessment of project implementation. Twice monthly debriefings to review these notes will occur with the intervention team and study investigators.

In-depth interviews will be conducted at two points in the study. The first time will be after completion of the open, non-randomized pilot, at which time we will interview all 10 participants (all of whom received the pilot intervention) and the Treatment Ambassadors. Our goal in performing interviews at this stage is to inform intervention design and get feedback on study acceptability. Secondarily, we will be conducting interviews after the full pilot RCT, with up to 30 study participants. To gain diverse perspectives among study participants, we will aim to interview both male and female participants who completed the study. These interviews will be conducted in either English of Xhosa, last approximately 60 minutes and will be digitally recorded and transcribed. The purpose of interviews will be to further understand challenges and facilitators of each intervention component from the perspective of those who received and delivered the intervention. Themes of the interviews will include: a) barriers to participation and attendance; b) barriers to MI protocol; c) relevance of peer-support, d) relevance of peer navigation; e) interaction between program participation and clinic attendance; f) unanticipated problems with the control condition. Among staff, we will also ask about issues related to study recruitment, participation and retention.

Process evaluation analysis. We will use an inductive content analytic approach to analyze qualitative data. This approach consists of the following steps: (1) data reduction through coding, (2) category construction, (3) comparison, and (4) interpretation.

Coding. Coding will begin with a provisional start-list of themes based on prior research. Twenty percent of the interviews will be independently read and new themes iteratively generated based on identifying themes not present in the start-list, which will result in a codebook. The team members will code 20% additional interviews to calibrate the methods of evaluation, and one individual, using the standards established, will code the remaining interviews (Cohen's Kappa ≥0.80). For each of the seven survey measures, we will compare responses at 6 months by computing the mean response for each arm, a 95% bootstrap confidence interval for the between-arm difference in means, and a permutation test p-value for the between-arm difference in means adjusted for each participant's baseline score. To assess preliminary efficacy, rates of ART initiation at 3 months for the two arms will be

compared by computing the relative "risk" of initiation and testing for an association between arm and initiation rate using Fisher's exact test.

We will use NVivo10© (QSR International Pty Ltd 2014) software to code and manage the data. The result will be a reduced data set consisting of an initial set of concepts and corresponding sections of interview/field note text -- the basis for category construction. Categories will be developed by grouping codes and coded data into meaningful clusters to form larger concepts. We will formulate labels and definitions for each new concept. Final versions of categories will include: (1) the category label or name, which should convey a category's essential meaning; (2) the operational definition and/or an indication of the variety of specific forms the category takes; and (3) evidence of validity in the form of examples of the data from which the category was formulated. The role of interpretation here is to develop conceptual categories into larger explanations to guide process evaluations.

Quantitative data will be described using frequency tables and descriptive statistics (e.g. means, standard deviations, medians, interquartile ranges, proportions) as appropriate. Major barriers and facilitators to study implementation will serve as the basis for revision of the intervention manual, and study operating procedures.

Potential Risks:

The primary risks associated with this study include: anxiety due to a new HIV diagnosis; a potential loss of confidentiality; a risk of fatigue from interviewing; discussion of sensitive topics regarding sexual practices, which may lead to personal discomfort or embarrassment; and ensuring access to ART during the study. As discussed above, we intend to minimize any loss of confidentiality, by ensuring that participants are interviewed in a private location.

Special issue #1: Anxiety due to a new HIV diagnosis – All subjects presenting for testing have come to learn their HIV status. All HIV testing is voluntary, and clients can choose to opt-out at any time. We anticipate that some clients who are diagnosed with HIV and are found to be treatment-eligible will experience anxiety in dealing with their new diagnoses. There are social-workers on the staff of GCHC, who are trained to deal with issues relating to new HIV diagnoses. Clients who need counseling are given up to 6 free one-on-one sessions to discuss their concerns with a social worker. Study participation is voluntary and participants may withdraw at any time. Participants will be reminded of this during the study.

Special issue #2: A potential loss of confidentiality - Performing research on this topic with a vulnerable population requires careful attention to ethical issues associated with confidentiality. This is particularly the case in communities where there is a history of exploitation and social and economic disparities, and an HIV diagnosis can be highly stigmatizing. We will adhere to strict guidelines regarding confidentiality, and ensure interviews with participants will be performed at a private location of the interviewees choosing. All family members and friends will be asked to wait in the waiting room while the interview is conducted. Participants' HIV status will be kept in a secure file in the HIV testing area that can only be accessed by research and clinic staff, to document test results when no one else is present in the room. All study forms will be kept in locked file drawers, and immediately transcribed onto password-protected computers equipped with anti-virus software. All survey information and HIV test results will be linked by a de-identified patient number, to protect privacy. In addition, NHLS data will be stored in a protected data base, and will only be accessed to verify information related to ART uptake and/or mortality.

Special issue #3: Risk of interview fatigue – Given the in-depth nature of the proposed research, we will need to spend time interviewing clients during a time of potentially high stress for them. We will ensure that interviews last no more than 45-60 minutes with regularly scheduled breaks throughout the session. Participants will be informed in advance that they can take a break or stop at any time. Our RA has performed extensive qualitative research in the past, and is trained in assessing interviewee fatigue and will stop accordingly.

Special issue #4 - Discussion of sensitive topics– As part of our interview with these subjects, we will be discussing sensitive topics relating to HIV acquisition and stigma. This raises the question of trust that clients must be able to put into researchers in order to speak about these issues. Study personnel will undergo training to ensure interviews are performed in a non-judgmental manner.

Special issue #5 - Access to ART during the study: ART usage has clearly been shown to decrease morbidity and mortality, as well as decrease heterosexual transmission of HIV. For patients who refuse ART, it is our ethical duty to ensure that access to ART is optimized, and we provide a standard of care that provides free and accessible ART. All participants will be counseled on the benefits of ART and provided with direct referrals if they meet treatment criteria. While we recognize this may impact our findings, and possibly result in our underestimating the impact of our intervention due to a Hawthorne effect in the control arm, we believe that we have an ethical obligation to ensure refusers receive proper information, referral, and access to ART during the course of the study.

Special issue #6 – *Psychological Distress*: Participants may experience psychological distress resulting from the assessment questions. Using strategies established in our previous SA and US studies, including the pilot study (NYSPI IRB # 6848), steps will be taken to minimize the risk of psychological distress resulting from assessment questions (see page 15 below)

Adequacy of Protection Against Risks:

Informed Consent: We will obtain written informed consent for all persons in this study. We do this through a process of continuous informed consent, such that research assistants will remind subjects throughout their initial intake and interview process that participation is voluntary, and they can seek to opt-out and/or speak with a counselor at any time. If there is any concern that the client is unable to give full informed consent due to anxiety, we will not pursue further questioning and discount the interview.

ART will be provided through the Hannan-Crusaid Treatment Centre in Gugulethu per usual routine. When a subject agrees to participate, he or she will sign a consent form drafted in the appropriate language (English or Xhosa). Participants will be asked to summarize the study and to explain the reasons why they want to participate, prior to seeking a signature. If there are cultural literacy reasons why a signature is not appropriate, individuals will be allowed to mark consent forms with an X. At this point, any misunderstandings regarding procedures, risks, or benefits can be clarified. Individuals will be provided with information on how to contact the study staff to report adverse events or other concerns associated with the study. Approval of the consent form will be sought from both the Partners Human Research Committee and the Ethics Committee at the University of Cape Town in South Africa prior to study initiation.

Measures to Protect Against Risk:

Anxiety due to a new HIV diagnosis – Social workers will be available on site free of charge for any subject needing additional counseling. If there is any concern that the client is unable to give full informed consent due to anxiety, we will not pursue further questioning and discount the interview.

Potential loss of confidentiality - To ensure confidentiality of all participants, all data will be coded by subject number. We will store NHLS data in separate files and will only link data by subject number. Data will be stored in Research Electronic Data Capture (REDCap), which is a secure, web-based application for building and managing online surveys and databases.[3] REDCap Software is supported by Partners Healthcare. Dr. Katz has used this database previously, because of the rigorous standards set to maintain privacy and security. All transactions are fully encrypted, and logins use secure authentication. It is widely used in the academic research community: the REDCap Consortium is a collaborative, international network of more than 900 institutional partners in over 70 countries, with more than 100,000 total end-users employing the software for more than 100,000 ongoing research studies. Interviewers and support staff will be trained on procedures for maintaining privacy and will sign a pledge of confidentiality. Risks to subjects are minimized through informed consent, strict confidentiality, and HIV counseling provided at GCHC.

Planned procedures for protecting against fatigue - Interviews will last 45-60 minutes. Regular breaks will be scheduled throughout the session. Additionally, subjects will be informed that they can take a break or stop at any time. Staff will be well-trained and supervised under the direction of experienced clinical researchers.

Discussion of sensitive topics- Efforts will be made to minimize discomfort by assuring that interviewers are well-trained and that they will inform participants beforehand about the nature of the questions and assure participants of privacy. The interviewer will be available after the interview to debrief with the participant if s/he is in any way concerned by the nature of the questions. Routine demographic questions will be asked first, followed by more personal questions. Participants will be informed that they have the right to decline participation in the study, to refuse to answer any questions, or to withdraw at any time without adverse consequences. In addition, researchers will be sensitive to any potential concerns regarding mistrust of providers. We will review all data collection materials with our community advisory board to guide our research. The CABs have helped to foster a culture of trust and mutual understanding with the community and to ensure that the research conducted through the Desmond Tutu HIV Foundation respects the values and cultural differences among those who participate. As an added level of protection for clients, we will ensure that the research assistant working on this project is not a healthcare provider on staff at the clinic.

Ensuring access to ART - We will offer “minimal wait” referrals to either medical providers or counselors at every study encounter to minimize structural barriers to ART initiation. A “minimal wait” visit means that the participant will be referred to a medical provider and/or counselor and will be the next individual seen as needed. We recognize that this enhanced referral strategy will produce a Hawthorne effect by decreasing the impact of our planned intervention. This, however, does not represent a significant change from clinic policies that are currently in place, and is consistent with the overarching philosophy of GCHC and The Desmond Tutu HIV Foundation. In addition, it fulfills our ethical obligation to provide access to lifesaving therapy, and is a conservative bias towards the null.

Ensuring Minimization of Psychological Distress – We will provide the following to participants:

1. Participants will be informed that the assessments include questions about sensitive behaviors (e.g., mental health, drug use, non-adherence), and that they can decline to answer any questions with which they are uncomfortable.

2. Procedures for emergency and nonemergency situations will involve the interviewer informing the SA SCO of any such incidents of distress so that s/he can monitor compliance with distress-related protocol.

3. Participants who experience mild to moderate distress will be referred to the clinic mental health staff for counseling. Because the study will take place near the Hannan Crusaid Treatment Centre, we will be able to make immediate referrals as needed to health care providers.

All surveys will take place in a private location and all data will be stored in secure a location accessible only to study researchers. Any study participant has the option of stopping the survey or intervention. Study participants may ask to be de-enrolled at any time. Research staff will remind participants that participation is completely voluntary and they may choose to withdraw from the study.

EXPECTED BENEFITS

Subjects may become more aware of the importance of HIV treatment and therefore initiate ART sooner, with a potential decrease in morbidity and mortality, as well as a decreased risk of transmission to HIV-uninfected partners. They may also benefit from knowing that their participation may help others like them in the future. Otherwise, there are no known direct benefits to subjects.

EQUITABLE SELECTION OF SUBJECTS

Our inclusion criteria do not exclude any group of persons other than women who are currently pregnant and persons under 18 years of age. These groups are not included in the proposed research study because of the study's recruitment site, which refers pediatric and pregnant clients to more specialized care facilities that may better suit their needs.

While English is the recognized language for commerce and science in South Africa, there are over 11 official languages. In Cape Town, Xhosa and Afrikaans are the most commonly spoken languages. However, Xhosa is the most widely spoken language among the population likely to enroll in this study (i.e., specific location of clinic). The consent form and subsequent surveys/questionnaires will be translated by a local multilingual research assistant into Xhosa.

RECRUITMENT PROCEDURES

Our goal is to recruit ART-eligible, treatment-naive persons living with HIV (PLWH) who have undergone testing at GCHC within the last three to six months and have failed to initiate ART. Based on our preliminary studies, we estimate about 8-10 participants will be recruited per month for our randomized control trial (RCT). Therefore, we estimate it will take 12 months to fully recruit our full sample for our RCT. This will allow approximately 18 months to implement the full intervention.

In order to identify and reach this population, we initially will approach individuals who gave permission to contact for future research in our previous study, “Examining the Correlates and Outcomes of HIV Treatment Refusal in an Adult South African Cohort”; University of Cape Town Human Research Ethics Committee HREC REF: 328/2014 Approved on 11 August, 2014. Should we need to approach more people than agreed to future research in this previous study, we will recruit from the Gugulethu CHC, Nyanga CHC, Vuyani clinic and Gugulethu clinics. The study team has a known relationship with these clinics. We will apply to the City of Cape Town and the Provincial research committees for permission to recruit at these sites. In addition, this study has been presented to the Emavundleni Community Advisory Board (the CAB used by the Desmond Tutu HIV Foundation) for community participation and buy-in.

If participants sign our initial consent form, our research assistant (RA) will contact eligible PLWH to assess their interest in participating in the study. We will use medical records and pharmacy on site (80-85% of participants) and data from the NHLS to track whether an ART-eligible individual has started treatment within six months of testing. While NHLS only provides lab data, we will be following participants for a total of 6 months (three months of intervention plus an additional four months post intervention), and will be able to monitor standard labs that are sent within four to six months on treatment.

For participants who qualify and agree to enroll in our study, we will obtain written informed consent in English or Xhosa for all study phases. We will do this through a process of **continuous informed consent**, such that research assistants will remind participants throughout their initial intake and interview process that participation is voluntary, and they can seek to opt-out and/or speak with a counselor at any time.

This protocol is an iterative pilot intervention where all participants will be part of the intervention. This step will inform and further develop/modify our full intervention of up to 90 where participants will be randomized to intervention or control after baseline data collection (1:1). We will ensure gender balance throughout the study. ART will be provided through the Department of Health (DOH) treatment center per standard of care.

Specific inclusion criteria and eligibility criteria to participate in the study are as follows:

- HIV-infected persons eligible for treatment under current South African treatment guidelines and choosing not to initiate ART within three months of learning their eligibility;
- Antiretroviral therapy (ART) naive;
- Age 18 years or older;
- Capable of providing informed consent; and
- Live within 60 kilometers of the Hannan Crusaid ART clinic.

Specific exclusion criteria disqualifying an otherwise eligible person from participating in this study include:

- Anyone previously on ART;
- Age less than 18 (initiation patterns and determinants may differ from those of adults);
- Residence greater than 60 kilometers from the clinic (due to prohibitive cost of following participants);
- Unable to provide informed consent (e.g., due to intoxication or mental incapacity); and

- Women who report current pregnancy at the time of consent (women pregnant at time of ART initiation may have different motivations of initiating ART and adherence patterns).

Each study participant will be reimbursed a total of 100 Rand per survey completed – for a total of 300 Rand. In addition, they will receive a 200 Rand bonus for completing all three surveys. If participants are randomized to the intervention arm, they will receive 20 Rand per session to cover their transport costs.

CONSENT PROCEDURES

Consent is a step-wise process: First, prospective participants consent to be contacted regarding participation in the study; then we explain the study and its risks; and finally, participants must sign the consent form in order to participate in the study.

The interviewee does not have to participate in the interview at that time, if it is inconvenient for them. We will obtain consent in a private location and it will either be obtained by the study principal investigator (PI) or by a research assistant directly trained and working with the PI. There is no time-table for consent, and a study participant can agree to consent and be part of the study at any time. Oral consent serves as an assurance that the required elements of informed consent have been presented orally to the participant or the participant's legally authorized representative.

All forms used in this study, including the consent form, have been translated into English and Xhosa, the two official languages most-widely used in the study area. The local research assistants will explain any risks that a reasonable person would want to understand regarding their potential participation in this study.

DATA AND SAFETY MONITORING

The risks associated with this study are less complex than those of larger, multisite phase I or II trials. Thus, the data and safety monitoring plan for this study will be limited. We will assume primary responsibility for data safety and monitoring. In this research, the primary risk to subjects is social harm due to loss of confidentiality associated with the survey and motivational interviewing process and possible physical harm (e.g., acts of physical violence directed at people who have been disclosed as HIV-infected). In this study, there is risk of embarrassment and stigma (e.g., being questioned about sexual behavior).

We have set up several mechanisms to ensure confidentiality of subjects. All surveys will occur in a private space. Contact with the interviewer will only occur with prior written consent from the subject. The nature of any information that might be disclosed is included as part of this consent. All paper files will be in locked file cabinets, and electronic files will be stored in password-protected files. Furthermore, both paper and electronic files will be identified only by the subject's identification number. The Project Manager will retain identifying information linking subjects to their study identification number off site in a locked cabinet only accessible to her, and myself. Finally, I will review confidentiality policies and procedures with all staff on an annual basis. We will monitor confidentiality practices on a weekly basis. I will notify University of Cape Town and Partners' institutional review boards of any breaches in confidentiality or other adverse events attributable to this study within ten days of the event.

MONITORING AND QUALITY ASSURANCE

A project manager will be involved in the oversight of the study and will continually monitor the data. The principal investigator and the research assistants will monitor the data. Weekly quality assurance checks will be performed by the research assistants to ensure validity and integrity of the data.

All study staff will go through a training program to promote standardized and objective collection of participant information. To ensure fidelity of data collection, I will use random supervisor contact (the Project Manager working with me) to verify the accuracy of survey data. Data will be managed in a relational database. Questionnaires are automatically read by optical character recognition into a Microsoft SQL-server database; human verification of key text fields provides a second level of quality assurance. Data entry verification will include algorithms that automatically check completed forms for missing, out-of-range, or inconsistent values. Aberrant entries are reported immediately on the project's website so that the original interviewer can reconcile the problem immediately. This method of rapid error reporting and resolution by field staff quickly results in improved interviewer accuracy. Databases will be maintained in an NT-operating system in a password protected partitioned drive, and backed-up daily and quarterly (24G NT Backup). A relational database will link socio-demographics, behavior, and survey results by a unique subject identifier and date.

PRIVACY AND CONFIDENTIALITY

All surveys will be performed privately at a mutually convenient time and location. Research records will be kept confidential to the level allowed by the law. To ensure confidentiality of all participants, all data will be coded by subject number. Physical records will be kept in locked cabinets and will be accessibly only to study personnel. Computerized records will be kept on a secure, password-protected computer server via REDCap. Any identifying information that links a patient to HIV status or laboratory records shall be stored only in REDCap and not in paper form. REDCap keeps all linked data password-protected and encrypted to prevent loss of confidentiality.

All Support staff (includes research assistants) will be trained on procedures for maintaining privacy and confidentiality and obtaining informed consent. All SMS messages will be arranged during baseline to ensure no identifying information or stigmatizing messages are sent. Treatment Ambassadors will be trained on procedures for maintaining privacy and confidentiality; however, their role is verbal and they will not have access to written data. We will not disclose study information to anyone other than the participant.

SENDING SPECIMENS/DATA TO RESEARCH COLLABORATORS OUTSIDE PARTNERS

Only people directly involved in this study will have access to these data. This includes Dr. Ingrid Katz (principal investigator of this study), Dr. Catherine Orrell (site principal investigator for the parent trial in South Africa), Dr. Laura Bogart (Co-I), Dr. Kathy Goggin (Co-I), Ms. Ingrid Courtney (on-site study coordinator), Dolphina Cogill (data manager in South Africa), Regina Panda (research assistant), and a research assistant at Brigham and Women's Hospital. In addition, Vincent Staggs (who works with Kathy Goggin at Children's Mercy in Kansas City) will help conduct analyses with our REDCap data.

There are no specimens used as part of this study; only data from survey responses and the intervention, which uses the technique of motivational interviewing. Additionally, we are submitting an IRB at the University of Cape Town in South Africa.

RECEIVING SPECIMENS/DATA FROM RESEARCH COLLABORATORS OUTSIDE PARTNERS

There are no specimens used as part of this study; only data from survey responses and the intervention, which uses the technique of motivational interviewing.

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