A Gender-enhanced PrEP-Exposure Prophylaxis Information-Motivational Workshop for Young South African Women – Data analysis plan 24 june 2022

From the original proposal

3.3.9.3 Statistical analysis

Aim 3a. Workshops: *Compare participants (N=100) randomized to Gender-Enhanced or Information-Only Workshops on undergoing PrEP clinical assessment (primary outcome); uptake of PrEP if eligible, and 3-month PrEP retention (secondary outcomes) and hypothesized mediators (risk perception, gender barriers, self-efficacy, outcome expectancies, PrEP-stigma, attitudes, peer norms, information) post-intervention and at 3-months.* To compare the ***primary and secondary outcomes*** across the two workshop conditions, we will use generalized linear models (GLM) with a logit link function and the method of generalized estimating equations (GEE) to account for the effect of clustering within workshop and clustering within recruitment chain. Intervention condition will be the primary predictor. We will adjust for any substantial baseline differences by group on age. To assess if being a PHA, i.e., talking to other women about HIV prevention serves as an additional intervention dose, a secondary analysis will include a variable for whether the woman served as a PHA and recruited other workshop attendees (yes/no).

For the hypothesized mediators, all of which are summary measures from multi-item scales, we will use GLM with an identity link function and GEE (to account for clustering effects) to compare the mean difference between the two intervention groups from post-test to pre-test, and from 3-month follow-up to post-test, to determine if there is an increase, decrease, or no change over time (difference of difference analysis), adjusting for age if necessary.

Accompanying these tests will be point and interval estimates for parameters of interest. Since our aim is not to estimate proportions (or means) from a theoretically representative population, we will *not* use respondent-driven sampling (RDS) weights; our aim is only to account for the greater similarities of individuals by recruitment and intervention-delivery clusters.

Aim 3b. Peer-driven recruitment: 1) *Assess acceptability and feasibility of PDR using pre-specified performance (process) criteria for acceptance and recruitment (on average ≥50% of attendees become PHAs and ≥2 recruitees/PHA attend a workshop); and* 2) *Evaluate reach of PDR* (percent who score high on a new HIV risk tool (10); percent who never tested and never attended family planning. We will estimate these simple proportions from the tracking data and from the pre-workshop assessments.

Power Considerations. The primary goal for this pilot work is to collect preliminary data regarding feasibility, acceptability and target outcomes for the proposed intervention. In line with guidelines from *PA-17-166: Formative and Pilot Intervention Research for Prevention and Treatment*, which caution against using pilot studies (where the sample size is of necessity small) to obtain an estimate of an effect size, we will use these pilot data to rule out unusually large or small true effects through standard 95% confidence interval procedures. We will confirm extrinsic effect sizes are contained within our confidence intervals from the pilot. We will examine the distribution of each variable, and calculate summary statistics by intervention condition. We will *estimate key* intervention parameters with sample means and proportions together with two-sided 95% confidence intervals, and *test the primary null hypotheses* at the traditional two-sided level α=.05 (simulation of the subsequent RCT). For *planning* the RCT, we will also consider one-sided 90% confidence limits for mission-critical *design parameters* such as standard deviations and reference group endpoint rates and proportions in the conservative direction. This is because we intend to plan sample size for the RCT so that power will be "excellent" (at least 80% power) for the clinically relevant effect size to be specified. This strategy will make proper allowance for the limited sample size of the pilot study with its consequent uncertainties, and still yield appropriate sample sizes for the RCT. "Mission-critical" parameters include proportions for dichotomous endpoints (uptake of PrEP clinical assessment, uptake of PrEP yes/no); means and standard deviations for continuous potential mediators of outcome (e.g. gender barriers, PrEP-stigma). Large sample sizes are not required to locate these parameters approximately, but adequately, for planning the subsequent trial, whereas testing the study hypothesis in the pilot

will generally not have sufficient statistical power. Estimation of mission-critical design parameters with point and confidence interval estimates will be considered highly important; continuous outcome measures make it feasible to detect promising effect effects even in small samples. For the continuous measures, means and standard deviations (sd) will be estimated. For approximately normally distributed variables, an upper one-sided 90% confidence limit for the sd, σ_U, will be constructed from $\sigma_U = s\ \chi^2_{\nu,.10}{}^{1/2}$, where s is the sample sd and $\chi^2_{\nu,.10}$ is the upper 10^{th} percentile of the chi-squared distribution with ν degrees of freedom. For approximately log-normally distributed variables, a logarithmic transformation will be applied to achieve approximate symmetry and normality. For the dichotomous variables (such as the primary and secondary outcomes, or the PDR performance criteria), exact binomial methods will be employed for the CIs for proportions. As an example, the width of the exact 95% confidence interval around a point estimate of 40% (e.g., percent women who score high-risk) would be 30%-50% with 100 participants.

While testing the primary null hypothesis is not the primary goal for this pilot study, if we assume the proportion of women who undergo PrEP clinical assessment in the information-only group ranges from 20% to 50%, with total sample size of 100 participants we are still able to declare a difference of 33 to 36 percentage points as statistically significant at 0.05 level with power of 80% if the within recruitment chain and within intervention-delivery group correlation coefficient is no greater than 0.1. As an illustration of how this can be used for planning the large randomized trial, suppose in this pilot study, proportion of participants take PrEP risk screening is 85% and 50% for Gender-Enhanced workshop and Information-Only Workshop respectively while the minimally clinically relevant improvement, on extrinsic grounds, is an improvement of 15 percentage points. Then, N=240 per group would be required in the RCT. The above plan will allow us to assess feasibility and acceptability, estimate factors influencing intervention parameters, and examine the range of possible effect sizes for our primary outcome. Therefore, the information collected from this pilot study should put us in an excellent position to conduct a future full-scale RCT.

December, 2020 Revisions.

In December, 2020, we revised the specific aims of the study as a consequence of being unable to conduct in-person workshops and therefore shifting to a virtual format. The following is taken from the proposal that was submitted to and approved by our program officer:

Because of the shift to a virtual group workshop, we have also reconceived our comparison condition. Previously, the comparison condition for the gender-enhanced group workshop was an information-only group workshop. However, since the enhanced condition is now the virtual group-based interactive workshop, we believe that an appropriate comparison condition would be individually-accessed web-links without any group interaction. The weblinks will include a PrEP motivational video (also included in the Gender-enhanced condition), a South African government PrEP website, and a South African government contraception options website. PrEP motivational videos have been used in other PrEP studies and PrEP information websites are becoming widely available, making this a reasonable “standard of care” condition. The main study question thus becomes, ***is a virtual group-based gender-enhanced group workshop more effective in prompting women to consider PrEP for themselves than individually-accessed PrEP information and motivation?***

We are also proposing a small change in how we operationalize the study outcome. The original protocol specified that after the workshop, women who were willing to consider PrEP for themselves would be escorted from the workshop location to the Addington Hospital PrEP access site (Pink House) just outside the Hospital clinic. ***Undergoing individual PrEP counseling including HIV-testing*** was the primary study outcome. At this time, asking women to attend a clinic for PrEP counseling is no longer feasible, as many people in South Africa are foregoing care for even more urgent conditions. We have been able to obtain the services of the nurse employed

by the Gender and Health Research Unit of the Medical Research Council to counsel women around PrEP and conduct HIV counseling and testing, either in person at the MRC office or via a telehealth nurse visit. HIV testing will be done using Oraquick®, an MRC-approved HIV self-test kit, either at the MRC office or offsite by the woman herself, with guidance from the nurse. We therefore propose to revise the primary study outcome to the following: ***having an individual discussion with the study nurse about taking up PrEP (either in-person or via telehealth)***. ***Undergoing HIV self-testing guided by the study nurse (either in-person at the GHRU office or via telehealth visit) will be a secondary outcome, as will initiating PrEP if eligible for PrEP (HIV-negative).***

These outcomes will be measured as follows: On the post-test assessment, women will be asked if they wish to speak with the study nurse about PrEP (and/or about any other issues). A "yes" response will trigger a notification to project staff, who will inform the study nurse. The study nurse will then contact the individual participant to arrange the counseling session. The study outcome will be considered to have been enacted when the participant has a PrEP counseling session. This, along with the result of PrEP counseling (e.g., underwent HIV testing or not, PrEP-eligible or not, and will initiate PrEP or not), will be documented by the nurse.

The revised specific aims of this study are as follows:

1. **Formative Work (no changes):** To ***inform intervention development*** through
   a. Focus groups (six) with at-risk AGYW aged 18-25, grouped by age and recruitment venue (community, family planning clinic) to explore knowledge of, beliefs about, motivators for, and concerns about PrEP in the context of gendered relationship dynamics and PrEP-related stigma;
   b. Qualitative interviews with men (10 known HIV-positive and 10 HIV-negative or of unknown status) who have female partners aged 18-25 to understand men's views of PrEP and of their partners' use of PrEP.
2. **Intervention development (revised):** In collaboration with an Intervention Development Working Group (IDWG) of AGYW, to ***develop a virtual group-based Gender-Enhanced PrEP Information-Motivational workshop,*** drawing on our formative Aim 1 data and strategies from our prior HIV prevention interventions, **and to choose a PrEP video and a PrEP informational website for the individual digital access control condition.**
3. **Pilot (revised):** To evaluate acceptability, feasibility, and outcomes of the intervention components:
   a. Intervention: Compare women randomized to the virtual group-interactive workshop with those randomized to individually-accessed links to a PrEP promotional video and PrEP information on the ***primary outcome of having an individual discussion with the study nurse about the possibility of taking up PrEP***; **undergoing HIV self-testing guided by the study nurse (either in-person at the GHRU office or via telehealth visit) (secondary outcome); if eligible for PrEP, initiating PrEP (secondary outcome)**, and, for all women, changes in hypothesized mediators (information, risk perception, gender barriers, outcome beliefs, PrEP-stigma, peer norms) post-intervention and at 3-month follow-up.
   b. Peer-driven recruitment: 1) Assess *acceptability and feasibility* of peer-driven recruitment (PDR) using pre-specified performance criteria for acceptance and recruitment (on average ≥50% attendees agree to recruit other women (i.e., become Peer Health Advocates [PHAs] and ≥2 recruitees/PHA enroll in the study); and 2) evaluate *reach* of PDR (percent who score high on HIV risk assessment; percent who never tested or never attended family planning).

Data Analysis

Workshops: Compare women randomized to the virtual group-interactive workshop with those randomized to individually-accessed links to a PrEP promotional video and PrEP information on the ***primary outcome of having an individual discussion with the study nurse about the possibility of taking up PrEP***; **undergoing HIV self-testing guided by the study nurse (either in-person at the GHRU office or via telehealth visit) (secondary outcome); if eligible for PrEP, initiating PrEP (secondary outcome)**, and, for all women, changes in hypothesized mediators (information, risk perception, gender barriers, outcome beliefs, PrEP-stigma, peer norms) post-intervention and at 3-month follow-up.)

To compare the ***primary and secondary outcomes*** across the two workshop conditions, we will use generalized linear models (GLM) with a logit link function and the method of generalized estimating equations (GEE) to account for the effect of clustering within recruitment chain. The logit link function is appropriate because the primary and secondary outcomes are dichotomous and characterized as yes/no if achieved at any time over the course of the study by the time of the 3-month follow-up interview. Intervention condition (Gender-Enhanced or Individual Access) is the primary predictor. Although the original data analysis plan also specified accounting for clustering by workshop group attended, we will not account for clustering by workshop group because women in the IA condition received the intervention as individuals rather than as groups.

We will adjust for any substantial baseline differences by condition on age. We will also adjust for any substantial differences by other demographic and behavioral characteristics, such as education level, whether attending school, has a primary partner, sexual risk behaviors (to be defined), relationship power, reported intimate partner violence **if** these factors differ substantially by condition at baseline and are also associated with the outcome (i.e., meet the conditions of confounding).

To assess if being a PHA, i.e., talking to other women about HIV prevention serves as an additional intervention dose, a secondary analysis will include a variable for whether the woman served as a PHA and recruited other workshop attendees (yes/no).

Mediators. "Other outcomes" include those measures designed to tap constructs that are hypothesized in our theoretical model to be mediators, i.e., on the pathway between the intervention and the outcome. These are factors that we believe influence the outcome (women considering PrEP for themselves) and that if changed by the intervention will lead to an increase in this outcome. We want to know if these factors are influenced by the gender-enhanced intervention and help explain (mediate) any changes in the main outcomes. These hypothesized mediators, most of which are summary measures from multi-item scales, include PrEP information, perceived risk for HIV, perceived effectiveness of PrEP, positive outcomes of taking PrEP, gendered HIV prevention barriers related to partner disclosure, PrEP-related stigma, normative beliefs, medication beliefs. Please see the related document entitled "Table of pilot study measures 2022 June 22." for descriptions.

An additional variable—stage of change for adopting PrEP--was added when we revised the study. This will also be considered a mediator, although at 3month followup, the last option of this measure is "I am taking PrEP". This is the indicator for the outcome of initiating PrEP.

For the mediators, we will first test if the intervention had any effect on them, using generalized linear models (GLM) with an identity link function and GEE (to account for clustering effects) to compare the mean difference between the two intervention groups from post-test to pre-test, and from 3-month follow-up to post-test, to determine if there is an increase, decrease, or no change over time (difference of difference analysis), adjusting for age and other confounders if necessary. As per Cheng-Shiun: the model is of the form: $E(Y|X,T1,T2))=constant+b1*X+b2*T1+b3*T2+b4*X*T1+b5*X*T2$, where X is the intervention indicator, T1 and T2 are post-intervention and 3-month FU indicator respectively. The regression coefficient b4 represents the group difference in change of the outcome Y (i.e., the potential mediators) from pre- to

post-intervention, however, it is b5-b4 (NOT b5) that represents the group difference in change of Y from post-intervention to 3-month FU.

As a second step, we want to know whether, apart from the intervention, any of the hypothesized mediators are associated with the outcomes, e.g., whether women who at pre-test have low PrEP stigma, high perceived risk, low gender barriers for example, were more likely to have a nurse conversation, undergo HIV testing, initiate PrEP. These analyses will be conducted adjusting for intervention condition.

Finally, any mediators that are altered by the intervention will be included in the earlier models testing intervention effects of gender-enhanced intervention on primary study outcomes. A substantial reduction in the estimate of effect for the gender-enhanced intervention once the mediator is included in the model gives evidence that the hypothesized mediator explains in part the effect, i.e., that the intervention worked, for example, by reducing PrEP stigma or increasing risk for HIV.

Effect measure modifiers. (updated with definitions on Dec 19 2022)

We will also want to evaluate whether the intervention was more (or less) effective among any particular sub-groups of women. Although these effect measure modifiers were not specified in the proposal, we included some in our pre-test measures (see measures document). I propose we examine the following:

1. Women with elevated depressive symptoms – using cutpoint of 10 on the CESD-10

   If Depress10 = 1. (however, n is only 27 so may not be possible)

2. Women reporting intimate partner violence themselves or whose social network includes women who experience IPV.

   If networkAbuse =1 or IfIPV = 1. (n = 57)

3. Women whose network includes those who engage in transactional sex

   If O_1 = 1 or O_1 = 2. (n = 45)

4. Women with higher (or lower) sexual relationship power

   If relatcontrol3 = 1. (however, N is only 28 in this group so may not be possible)

5. Women who have a primary male partner

   IfMalePartner = 1. (N = 85)

6. Women with higher levels of sexual risk.

   IfSexRisk1 = 1. (n = 64)