Building Mobile HIV Prevention and Mental Health Support in Low-resource Settings

NCT #: NCT03912753

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Statistical Analysis Plan

Introduction

The current study aims to test the efficacy of Comunică, a motivational interviewing intervention also informed by minority stress theory, to reduce HIV-transmission-risk behavior in a randomized controlled trial among Romanian gay and bisexual men (GBM). In this study, the primary outcome involves HIV-transmission-risk behavior. Secondary outcomes include depression, anxiety, heavy alcohol use, and suicidality. Exploratory outcomes include HIV and STI (chlamydia, gonorrhea, syphilis) diagnosis and HIV/STI testing patterns. The control condition, referred to as "educational attention control (EAC)" consists of eight educational modules that present information regarding GBM's identity development, HIV/STI prevention, heavy alcohol use and its associations with HIV-transmission-risk behavior, sexual health communication, and the importance of social support. This EAC was created in consultation with Romanian GBM community members and advocates.

Study Design

In this RCT, Comunică is compared to EAC to examine relative change in: (a) the primary outcome, HIV-transmission-risk behavior defined as: frequency of condomless anal sex acts with HIV-positive or unknown-status partners outside of the context of one's own adherent PrEP use or only with a primary partner that has adherent PrEP use or has undetectable viral load and (b) secondary outcomes: depression, anxiety, heavy alcohol use, and suicidality. Sessions for both conditions are to be completed over the course of four months. Outcomes are measured by self-report at pre-intervention (baseline), and at 4-, 8-, and 12-month follow-ups. At baseline and 12-month follow-up, all participants also self-administer at-home rapid testing for HIV and syphilis, and self-collect sampling (urethral, pharyngeal, rectal) for chlamydia and gonorrhea, which are sent to a laboratory for analyses.

Table 1. Primary and Secondary Outcome Measures

Domain	Measure (1˚, 2˚)	Source, Frequency, and Sample
HIV-risk behavior	HIV-transmission-risk behavior (1˚)	Condomless anal sex acts with HIV-positive or unknown-status partners outside of the context of one's own adherent PrEP use or only with a primary partner that has adherent PrEP use or has undetectable viral load. This is measured with an online self-administered Timeline Follow-Back (TLFB) instrument. The TLFB yields past-30-day incidence of HIV risk behavior in terms of type of sexual behavior, condom use, partner'(s) HIV status, self and partner adherent PrEP use (at least 4 days per week), sex while using drugs or alcohol, and number of sexual partners. HIV risk behavior acts as defined above will be measured as the pooled number (count) over 30 days prior to the 4-, 8-, and 12-month follow-up visits. A primary supportive analysis of this outcome will assess the above as any such behavior (binary) during the 30 days prior to the 4-, 8- and 12-month follow-up visits.
Mental health and substance use	Depression (2˚)	Center for Epidemiologic Studies Depression Scale (CES-D) (continuous) at 4-, 8-, and 12-month follow-up visits and using cutoff ≥16 (binary) at 4-, 8-, and 12-month follow-up
	Anxiety (2˚)	Beck Anxiety Inventory (BAI) (continuous) at 4-, 8-, and 12-month follow-up visits and using cutoff ≥ 16 (binary) at 4-, 8-, and 12-month follow-up

	Heavy alcohol use (2˚)	Alcohol Use Disorders Identification Test (AUDIT-C) (continuous) at 4-, 8-, and 12-month follow-up and using cutoff ≥ 4 (binary) at 4-, 8, and 12-month follow-up; Percentage of TLFB-Heavy Drinking Days in the previous 30 days
	Suicidality (2˚)	Suicidal Ideation Attributes Scale (SIDAS) (continuous) at 4-, 8-, and 12-month follow-up and using cutoffs ≥ 21 (binary) at 4-, 8-, and 12-month follow-up

Table 2. Exploratory Outcome Measures

Domain	Measure	Source, Frequency, and Sample
HIV-risk behavior	HIV/STI testing	HIV/STI testing (any/none) (besides study-administered testing) over 12 months
	HIV and STI diagnosis	HIV and STI self-reported testing (gonorrhea; chlamydia; syphilis) (besides study-administered testing) over 12 months

Sample size

The primary and secondary outcome measures are summarized in Table 1.

The Comunică study originally proposed to recruit 326 subjects. This was based on calculations that the study would have 80% power to detect effect sizes ranging from 0.25 to 0.27 if the study attained 80% retention of the study subjects. However, recruitment was slower than planned (due to the COVID-19 pandemic and likely other factors), although retention was better than the 80% estimated.

Therefore, as we approached the end of recruitment for the Comunică study, three factors that were not available when we wrote the proposal transpired: i) While 303 participants were finally enrolled, we had re-estimated that we would likely only be able to recruit 288 subjects by 31 December 2022 (our date of termination of recruitment) and based power re-estimation on this number. ii) The overall participation rate for attending all three post-intervention visits was 86% (with a high proportion of the remaining sample completing 2 post-interventions assessments). iii) From preliminary analysis of our data, we had normative distributions of the study outcomes that could be used in establishing a study design and metrics for powering the primary outcome. To that end, we re-estimated the study power as described below and this new estimate was approved by the Data Safety and Monitoring Board (DSMB).

In the original proposal, a repeated measures mixed linear model (or generalized estimation equation) using all 4 study visits (Baseline, and 4-, 8-, and 12-month follow-ups) was planned. However, the distribution of our primary outcomes (HIV-transmission-risk behavior) based on the data we now had near the end of the study was problematic for fitting this type of model, which is based on a central limit theorem assumption that may not manifest. Namely, there were two issues to consider: 1) at each follow up visit, over 50% of participants manifest no HIV-transmission-risk behavior creating a large point mass at the lower limit of 0. 2) On the other end, the distribution of HIV-transmission-risk behavior acts was very skewed with numbers of acts greater than 50 leading to skewness much > 3, which again contradicts normality-based methods.

Although generally accepted approaches for power estimates for this situation do not readily exist, we found one approach that will satisfy assumptions for standard normal methods and that is also amenable to conducting a power estimation. That approach is to take the average behavior over all three post-intervention timepoints (4-, 8-, and 12-month follow-ups) as a single within-person outcome, rather than evaluation of the repeated measures at 4-, 8-, and 12-month follow-ups as separate within-person outcomes. For example, if a person reported 0, 1 and 2 high risk acts respectively at the 4-, 8-, and 12-month follow-up visits, these would be summed together (0 + 1 + 2) = 3 and averaged over the 3 visits (3/3 = 1) as a single outcome of 1 high risk sex act over the previous 30 days per trimester. The details on what happened when we examined this outcome in our (still unblinded to intervention) data follow in the next paragraphs.

When we took the average of all three timepoints of HIV-transmission-risk behavior acts (i.e., during the previous 4 months), only 24% of participants had no HIV-transmission-risk behavior acts over the entire 12-month time period (i.e., the point mass at 0) which given our projected sample size of 288 (or 246 evaluable assuming 14% loss of data as we have been observing) is low enough to treat this average as a continuous variable in a normal approximation. However, due to a few individual(s) reporting very high numbers of risk acts (i.e., > 50), this variable was still skewed (> 3) so we capped (i.e., Winsorized) the maximum number of average per-assessment HIV-transmission-risk behavior acts at 15 acts the upper 97^{th} percentile of HIV-transmission risk behavior. When this was done, the HIV-transmission-risk behavior outcome was close enough to normal (i.e., skewness = 1.5) for the central limit theorem to apply to the linear model presented below:

The power estimation approach assumes that a linear model will be fit $Y = a + b X + c T + \varepsilon$

Where

Y = Averaged (during prior 4 months) prior 30-day high-risk sex behavior over 12-month behavior
a = intercept
X = baseline prior 30-day high-risk sex behavior
T = 0 for control, 1 for intervention
ε is random error with mean 0 and constant variance

And a, b, c are unknown parameters that are estimated in the model fit

The null hypotheses c = 0 will be tested with an overall two-sided type 1 error of 0.05.

Importantly for power estimation, the correlation of baseline and the average 12-month HIV-transmission-risk behavior acts was 0.37, which means that after adjustment for the pre-intervention behavior, the standard deviation of the post-intervention behavior would be the square root of $(1-0.37^2) = 0.93$ that of the unadjusted outcome. Based on this and with 288 subjects, 86% of whom participated in all 3 visits as we have been observing will happen (or conservatively 123 in each treatment arm), there is 80% power to detect an effect size of 0.33, slightly greater than our originally estimated effect size of 0.25-0.27 and at the upper end of the range of effect sizes found for behavioral interventions addressing multiple health outcomes among sexual minority men (Pantalone et al., 2020). We believe that 0.33 represents a plausible effect size to detect in this trial given the strong distinction between the two intervention conditions, with one involving an active therapist-guided intervention and the other consisting of self-guided psychoeducation only. The standard deviation of the (Winsorized)

averaged outcome over 12 months per-assessment HIV-transmission-risk behavior acts was 3.46 acts. Multiplying this standard deviation by the effect size of 0.33 gives 1.14 HIV-transmission-risk behavior acts. This means that the study will have 80% power to detect an overall mean reduction of 1.14 HIV-transmission-risk behavior acts in the prior 30 days per assessment period in the intervention compared to the control condition.

It should be noted that our final analysis will most likely incorporate the partial information from men with only 1 and 2 post-intervention follow-up visits through imputations or more exactly adjustment of the partial information for number of trimesters reported, If so, this would increase power, by a very modest amount.

DRAFT ANALYTIC PLAN FOR COMUNICĂ STUDY

1. Overview

The analysis of the primary and secondary outcomes will use intent-to-treat with participants analyzed according to their original treatment assignment. SAS 9.4, SPSS 26.0, Stata and/or R software will be used for all analyses.

2. Comparability of Treatment Groups

Differences in baseline demographic characteristics between the two treatment arms will be assessed using appropriate graphical and statistical methods including summary statistics and *p*-values from exact, rank, chi-square, *t*-tests and ANOVA. Of note, later on in the analysis, we will control for variables related to the study outcome in the analyses. We will also investigate if the randomization scheme was compromised.

3. Analysis of Primary Outcome: Number of condomless anal sex acts in the past 30 days with HIV-positive or unknown-status partners outside of the context of one's own adherent PrEP use or primary partner's adherent PrEP use or undetectable viral load in the past 30 days (HIV-transmission-risk behavior)

The statistical significance threshold for an intervention (vs. control) arm effect will be a two-sided $p \leq 0.05$. The primary outcome will be evaluated between the treatment arms at 4-, 8-, and 12-month follow-ups combined in a repeated measures analysis that adjusts for baseline behavior. This will be analyzed using negative binomial regression with baseline, and 4-, 8-, and 12-month follow-ups clustered within the same person. Main effect terms for 4-, 8-, and 12-month follow-ups post-baseline (each timepoint vs. baseline) will be included in the model. A single interaction term between the 4-, 8-, and 12-month measures with the intervention arm will be included in the model to test for pooled post-baseline treatment arm differences. The relative number of HIV-transmission-risk behavior acts with a 95% confidence interval about his term will quantify intervention effect. Generalized estimating equations with person as the cluster will be used to account for within person repeated measure collinearity. As a sensitivity analysis, this will be repeated including all baseline covariates that are statistically associated ($p < 0.05$ to enter and $p \geq 0.10$ to leave in a stepwise selection) with HIV-transmission-risk behavior in negative binomial GEE models with person as the cluster and adjusting for time of visit (i.e. 4-, 8-, and 12 months each vs. baseline).

If there are excess zeros at each post-baseline visit, we will consider using a zero-inflated negative binomial model instead. However, this approach will split the intervention effect

parameter into two models and thus may dampen power to detect statistical significance for an intervention that affects both parts. In this setting, we thus will more likely use the sensitivity analysis approach described below.

Other Sensitivity Analyses: As a sensitivity analysis, averaged HIV-transmission-risk behavior over all 3 post-baseline visits (or 2 post-baseline visits if one visit is missing) will be used as the outcome in an ANCOVA linear regression model that adjusts for baseline HIV-transmission-risk behavior as a predictor and includes treatment arm assignment as a covariate. For those who are missing one post-baseline visit, indicator variables as to which visit is missing will be included. The mean difference in HIV-transmission-risk behavior acts with a 95% confidence interval about his term will quantify intervention effect. This will be repeated including all baseline covariates that are statistically associated ($p < 0.05$) with HIV-transmission-risk behavior in Stepwise selection ($p < 0.05$ to enter and $p \geq 0.10$ to leave) into the above model. Should the negative binomial model described in the first paragraph of section 3. fail to converge, this will become the primary analysis. The statistical significance threshold for the new (vs. control) intervention arm effect will again be a two-sided $p \leq 0.05$.

4 Analysis of Secondary Outcomes

The Secondary Outcomes of interest (all of these taken pre-intervention and at 4-, 8-, and 12-month follow-ups) are:

- Depression as measured by The Center for Epidemiological Studies-Depression Scale (CES-D). CES-D will be examined as a continuous variable and as a binary variable using the cutoff of ≥16 (indicating clinical depression).
- Anxiety as measured by Beck Anxiety Inventory (BAI). BAI will be examined as a continuous variable and using the cutoff of ≥ 16 (indicating potentially concerning levels of anxiety).
- Suicidality as measured by Suicidal Ideation Attributes Scale (SIDAS). SIDAS will be examined as a continuous variable and as a binary outcome using the cutoff of ≥ 21 (indicating high risk of suicidality) as well as any score above 0.
- Alcohol consumption as measured by
    - The Alcohol Use Disorders Identification Test (AUDIT-C). AUDIT-C will be examined as a continuous variable and as a binary outcome using the cutoff of ≥ 4.
    - Percentage of Heavy drinking Days in the past 30 days prior to the visit will be examined as a continuous variable.

Due to multiple comparison issues, these will each be tested individually using a two-sided Type-1 error of 0.01 and quantified using 99% confidence intervals.

Levels of these measures at 4-, 8-, and 12-month follow-up will be compared (adjusting for the level at the baseline visit) between the Comunică intervention and EAC group in repeated measures analyses as described below.

4-A For Continuous Outcomes that are Heavily Skewed to the Right and Without an Excessive Point Mass at 0 for 4-, 8-, and 12-months follow-up

We anticipate that BAI and number of heavy drinking days will fall into this category. A similar approach to that described for the Primary Outcome will be used.

4-B For Continuous Outcomes that are not Heavily Skewed to the Right at 4-, 8-, and 12-months follow-up

We anticipate that CES-D and AUDIT-C will fall into this category. We will fit repeated measure linear regression mixed models for outcomes at baseline and 4-, 8-, and 12-months follow-up with subject intercept as a fixed effect, main effects for 4-, 8-, and 12-months and a single interaction term between treatment arm assignment and the timepoint being post intervention delivery. In sensitivity analyses, this will be repeated including all baseline covariates that are statistically associated ($p < 0.05$) with the outcome in univariate models using stepwise selection ($p < 0.05$ to enter $p \geq 0.10$ to leave) into the above-described models. The mean post intervention difference in the outcome between the treatment arms with 95% confidence intervals about his term will quantify intervention effect.

4-C For Binary Outcomes

We will also look at the following binary outcomes: HIV-transmission-risk behavior > 0, CES-D ≥ 16, SIDAS ≥ 21, SIDAS ≥ 0, AUDIT-C ≥ 4 in repeated measures model using the post-baseline visit and post intervention visits at 4-, 8-, and 12-month follow-ups. Repeated measures generalized estimation equations will be fit about individual as the cluster using a logit link. The visit number (i.e., 4-, 8-, and 12-months vs. vs. baseline) and treatment arm assignment will be included as main effects, as will the baseline preintervention level of the outcome being modeled. In sensitivity analyses, this will be repeated including all baseline covariates that are statistically associated ($p < 0.05$) with the outcome using Stepwise selection ($p < 0.05$ to enter $p \geq 0.10$ to leave) into the above-described models. The intervention effect will be quantified by Odds Ratios with 95% confidence intervals.

We will also use exact tests to compare treatment arms for having been ever diagnosed during the single timepoint 12-month study follow up with HIV, syphilis, chlamydia, and gonorrhea.