Evaluation of Life-Steps to Enhance Adherence and Engagement in PrEP Care

Principal Investigator Name: Steven A. Safren

NCT Number: NCT04316715

Documents:
Statistical Analysis Plan

DATA ANALYSIS

Power and Sample Size Considerations. The primary power analysis is based on longitudinal, mixed effects models comparing the primary outcome— DBS TFV-DP concentrations—between the "Life-Steps for PrEP" intervention and SOC conditions with repeated measures at 3, 6, 9, 12, 15 and 18 months of follow-up. Careful consideration was given to the effect size used in the power analysis, and, in part, was estimated using data from our NIMH-funded R34 pilot RCT of the Life-Steps for PrEP intervention. In the present study, participants randomized to the control arm will receive SOC PrEP adherence information and HIV prevention services referrals at baseline and at 3, 6, 9, 12, 15 and 18-month follow-up assessment visits. We powered the current study using true-scenario effect size data from a prior study examining the utility of 2-way daily text messaging to optimize PrEP uptake among a sample of high risk MSM (at the acute assessment, 34% of intervention participants were adherent measured by DBS TFV-DP concentrations of >1246 fmol/punch vs. 24% in the control arm) (3), as well as data from our pilot RCT showing a mean difference of 56.8 ng/ml blood-drug levels between the intervention vs. control condition [157.8 ng/ml (131.6) vs. 101.0 ng/ml (84.1); p<.03] (23). Although our R34 pilot RCT of the "Life-Steps for PrEP" intervention showed promising adherence levels at 6 months, effect sizes from pilot trials with small sample sizes such as this one are less reliable and typically overestimated. As such we took a conservative approach and reduced the effect size by 20% of what we observed, which is consistent with a clinically meaningful change in PrEP adherence. With a two-tailed p-value of 0.05, group sample sizes of 100 participants per arm (200 completers), assuming a correlation of 0.80 between repeated adherence measures there will greater than 84% power to detect in excess of a medium effect size difference (approximately 10% in the slope) between the Life-Steps for PrEP and SOC arms. For categorical outcomes (e.g. percent of patients in each condition achieving adherence of blood drug levels consistent with taking at least 4 pills per week, resulting in at least a 96% reduction in HIV acquisition (104)), with a two-tailed p-value of 0.05, the seven repeated measures, and 120 patients per arm, we would need at least a 10 percentage point difference across the two conditions (e.g., 90% of those in the Life-Steps for PrEP arm and 80% of those in the SOC arm) to achieve 85% power. To account for 20% attrition at 18-months, we plan to enroll a baseline sample size of 250 participants who will be randomized equally across the two study arms (n = 125 per arm) and half of which will be recruited in Boston and the other half in Miami.

Initial analyses. The distribution of all variables will be assessed, as will the correlations between all variables and the primary/secondary outcomes. We will assess for patterns of missing data, which are expected to be low as the study partially utilizes ACASI (iPads), which reduces participant nonresponse. If these issues do arise, we will consider utilizing multiple imputation methods for missing data. Attrition effects will be evaluated by testing whether systematic differences exist between those participants who complete the research versus those who drop out. In the preliminary analyses we will examine the equivalence of the random assignment of groups with regard to key baseline characteristics. This will involve assessment of the treatment groups on socio-demographics, sexual risk and psychosocial syndemic variables. In the unlikely event randomization does not work to balance these at baseline, we will run analyses both with and without these variables as covariates to see whether baseline differences may account for differences in outcomes.

Specific Aim 1: Data analysis will follow a sequence that is designed to answer the outcome question: Does the Life-Steps for PrEP intervention maintain PrEP adherence (TFV-DP in DBS = 700+ fmol/punch – corresponding to levels that are consistent with taking 4+ pills per week) relative to the SOC condition? The emphasis of this study is on establishing the efficacy of the intervention. The primary analysis will compare maintenance of PrEP adherence levels at 3, 6, 9, 12, 15 and 18-month follow-up assessment visits between the randomized conditions. We will then examine self-report adherence data. For all analyses, if there are not violations of assumptions, we will use generalized linear models (GLM) with properly chosen (based on the distribution of dependent variable) link functions to analyze longitudinal data for each major study aim. The GLMs will be estimated using generalized estimating equations with robust standard error estimates to account for repeated measures of the outcome (103,105). If the assumptions underlying these methods are not met, alternate analyses will be performed, such as Bayesian or negative binomial techniques. We will test the effects of the Life-Steps for PrEP intervention, compared to the SOC condition, at 3, 6, 9, 12, 15 and 18-months. All statistical tests will determine significance with alpha = 0.05. To reduce the threat of bias, the intent-to-treat principle will be utilized for all analyses, where individuals will be analyzed according to the condition that they were randomized, regardless of their fidelity to that condition. Participants who miss 2 or more sessions will be categorized as "non-completers" and analyzed in sensitivity analyses. As a secondary outcome, we will compare changes in sexual behaviors (i.e., condomless anal sex) in relation to PrEP effective adherence between the intervention vs the control condition. If on demand PrEP is approved, we will include "prevention adherence" as an outcome in the primary paper; for this analysis, participants will only be coded as non-adherent if they are having condomless anal sex with casual or HIV positive status partners when not "on PrEP" (per any forthcoming CDC guidelines).

Specific Aim 2: To examine hypothesized mediators of the intervention, we will employ *MEDIATE procedures*. *MEDIATE* estimates the total, direct, and indirect effects of causal variable(s) (*xlist)* on the outcome variable (*yvar)* through a proposed mediator variable or set of mediator variables (*mlist)*, controlling

for (optional) one of more variables (*covlist*). *MEDIATE* is similar to *INDIRECT* (106-108), but allows multiple *X* variables, and also offers features for handling and coding a single multicategorical *X* variable. Inferences for indirect effects can be based on percentile bootstrap confidence intervals or Monte Carlo confidence intervals. To examine potential moderators of the intervention, will add interaction terms one-by-one for the intervention condition and the potential moderators (e.g., age, sexual compulsivity). Significant or large interaction terms suggest that the effects of the intervention differ for different subgroups.

Specific Aim 3: The assessment of total and incremental costs of the intervention and SOC begins with a careful accounting of the resources invested in each condition. The intervention includes start-up costs associated with trainings, which are not factored into the evaluation of incremental costs, but are important for documenting the feasibility, scalability, and long-term sustainability from provider and third party payer perspectives. A key advantage of collecting cost data alongside the trial is that we can use an activity-based micro-costing approach to identify, measure, and value all resources invested by participating providers, and ultimately link costs to the key clinical outcomes being measured in the main trial. This micro-costing approach is recommended by the Panel on Cost-Effectiveness in Health and Medicine[55] as it provides the most detailed accounting of program inputs (i.e., resources) and provides practical information regarding the feasibility of program adoption in other sites/settings with their own unique pool of resources. The analysis will be framed from the provider perspective. We have added Dr. McCollister to the study team to provide guidance to Dr. Mimiaga to lead this analysis. See Drs. McCollister and Mimiaga's biosketches for prior experience.

We will estimate the costs of providing this intervention relative to the SOC based on detailed records of all participant contacts (in-person/telephone), salary & benefit costs of interventionists, overhead costs, the cost of clinical supervision, the cost of providing intervention materials ("homework" materials) to participants and participant costs (see "resource utilization" in assessment section). Additional cost data associated with health services utilization will be collected to look at potential cost-offsets to the healthcare system. Costs will be summarized in terms of total intervention costs, incremental cost of the intervention relative to the SOC, and the average per-person cost of Lifesteps for PrEP and SOC. Average cost per person can be paired with clinical outcome data from the main trial to examine cost effectiveness (e.g., cost per increased rate of adherence). Basic cost-outcome comparisons will be explored in the proposed work, with the ultimate goal of collecting all necessary data inputs for a formal cost-effectiveness analysis simulation model to evaluate the impact of the intervention overtime on HIV transmission. Economic modeling can estimate long-term clinical outcomes, costs, and cost effectiveness of an intervention and employ probabilistic sensitivity analyses to evaluate the uncertainty in the simulation outcomes, accounting for variation in disease epidemiology, population characteristics, organizational factors, and other sources of heterogeneity across intervention sites. CEA modeling will be pursued under a separate funding mechanism, but will build directly from the economic and clinical data collected in this study.

The statistical analysis plan was specified prior to initiating data analysis procedures. If assumptions are violated, revisions to the analytic plan may be necessary. Modifications will be methodologically justified, documented, and implemented to support valid interpretation of study findings