Research Protocol

LifeSteps for PrEP for young men who have sex with men: adapting a PrEP adherence intervention for high-risk youth

Katie B. Biello, PhD, MPH\(^1,2,3\), Christina Psaros, PhD\(^4,5\), Douglas S. Krakower, MD\(^6,7\), Elliot Marrow, BA\(^3\), Steven A. Safren, PhD\(^8\), Matthew J. Mimiaga, ScD, MPH\(^1,2,3\), Lisa Hightow-Weidman, MD, MPH\(^9\), Patrick Sullivan, DVM, PhD\(^10\), Kenneth H. Mayer, MD\(^3,7,11\)

\(^1\) Departments of Behavioral & Social Sciences and Epidemiology, Brown University School of Public Health, Providence, RI
\(^2\) Center for Health Equity Research (CHER), Brown University, Providence, RI
\(^3\) The Fenway Institute, Fenway Health, Boston, MA
\(^4\) Department of Psychiatry, Massachusetts General Hospital, Boston, MA
\(^5\) Department of Psychology, Harvard Medical School, Boston, MA
\(^6\) Department of Medicine, Harvard Medical School, Boston, MA
\(^7\) Division of Infectious Diseases, Beth Israel Deaconess Medical Center, Boston, MA
\(^8\) Department of Psychology, University of Miami, Coral Gables, FL
\(^9\) Institute for Global Health and Infectious Diseases and Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC.
\(^10\) Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA.
\(^11\) Department of Global Health and Population, Harvard T. H. Chan School of Public Health, Boston, MA

Corresponding Author:
Katie B. Biello, PhD, MPH
Assistant Professor
Departments of Behavioral & Social Sciences and Epidemiology
Center for Health Equity Research (CHER)
Brown University School of Public Health
Box G-S121-8
Providence, RI 02912
Tel: 1 (401) 863-3082
Email: katie_biello@brown.edu
ABSTRACT

**Background:** New HIV infections occur at a disproportionately high rate among young men who have sex with men (YMSM). It is therefore essential that comprehensive HIV prevention strategies, specifically tailored to their needs and perceptions, are developed, tested, and disseminated. Antiretroviral pre-exposure prophylaxis (PrEP) is effective in decreasing HIV transmission among MSM; however, adherence is critical to its efficacy. In open-label studies among YMSM, adherence was suboptimal. Behavioral approaches that address the unique challenges to YMSM PrEP adherence are needed.

**Objective:** To describe the protocol for intervention refinement and a pilot randomized controlled trial (RCT) of a PrEP adherence intervention, LifeSteps for PrEP for YMSM (LSPY).

**Methods:** This study includes two phases: 1) formative qualitative interviews with approximately 20 YMSM and 10 key informants, for the purposes of intervention adaptation and refinement; and 2) a pilot RCT of up to 50 YMSM to assess feasibility, acceptability, and preliminary efficacy of the LifeSteps for PrEP for YMSM, compared to the PrEP standard of care, to improve PrEP adherence. Participants will be recruited at 3 iTech Subject Recruitment Venues in the United States.

**Results:** Phase 1 is expected to begin in late 2017, and enrollment of Phase 2 is anticipated to begin in early 2018.

**Conclusions:** There are few rigorously developed and tested interventions designed to increase PrEP adherence among YMSM in community settings, despite this population’s high HIV incidence. The long-term goal of this intervention is to develop scalable protocols to optimize at-risk YMSM’s PrEP uptake and adherence, in order to decrease HIV incidence.

**Trial Registration:** The study is in the process of being registered on ClinicalTrials.gov.

**Keywords:** Antiretroviral pre-exposure prophylaxis (PrEP), HIV prevention, adolescents, men who have sex with men (MSM), adherence

INTRODUCTION

In the United States (US), men who have sex with men (MSM) represent over half of all individuals living with HIV (56%) [1,2] and account for the largest number of new HIV infections each year (70%), with rates of new diagnoses at least 44 times greater than rates among heterosexual men.[1,2] While the incidence of new infections has decreased among other groups (e.g., heterosexuals, injection drug users), the annual number of new infections among MSM has consistently increased over the past 20 years.[1] New HIV infections occur at a disproportionately high rate among young MSM (YMSM) in particular.[3,4] As such, it is essential that comprehensive HIV prevention strategies, specifically tailored to the needs and perceptions of YMSM, are developed, tested, and disseminated.
Pre-exposure prophylaxis (PrEP) is currently the only FDA-approved biomedical prevention method for MSM in the US. The iPrEx study,[5] which recruited 2,499 men and transgender women over eleven sites in six countries, represented the first proof of concept that oral chemoprophylaxis is effective in decreasing HIV transmission among MSM. However, adherence is critical to PrEP efficacy. In the iPrEx study, among participants with detectable levels of tenofovir in their blood, the risk of acquiring HIV decreased by over 90%, and the intent-to-treat efficacy was 86% in 2 subsequent TDF/FTC PrEP clinical trials of MSM in the UK and France.[6,7] Pharmacologic analyses corroborated the highly protective effects of TDF/FTC for PrEP among individuals who had detectable medication levels in their blood, highlighting the critical role of adherence in PrEP efficacy. This underscores the need for future PrEP interventions to focus on evidence-based strategies to promote adherence, in order to optimize the benefits that antiretroviral chemoprophylaxis may be able to provide for at-risk MSM.

Although YMSM readily accepted PrEP in several studies, adherence was suboptimal. In an open-label study of PrEP use by 18 - 22 years-old YMSM (ATN 110), only one-third of the study participants had protective drug levels at 1 year despite intensive adherence counseling, and HIV incidence in the sample was 3% per year.[8] Adherence was also suboptimal in a parallel PrEP study of 15 - 17 years-old YMSM, and annualized HIV incidence exceeded 6%.[9] In these studies, adherence tended to decline after 3 months of PrEP use, when the interval between study visits was extended from monthly to every 3 months, despite individualized or group-based behavioral adherence interventions. PrEP adherence might be even lower for YMSM prescribed PrEP in primary care settings, where adherence support may be less intensive than in clinical trials. Thus, tailored interventions to support adherence to PrEP in YMSM are needed.

Interventions to support PrEP adherence have shown promise in adults, but require adaptation to meet unique needs of adolescents. LifeSteps is an evidence-based HIV medication adherence intervention for HIV infected individuals, which was developed by Safren et al.[10-12] It has been adapted for diverse populations,[13-15] including adolescents in the “Positive
Positive STEPS was successful in improving ART adherence relative to a standard of care comparison group in a pilot randomized controlled trial among HIV-infected youth, aged 16 - 24 in the US, and is currently being evaluated in an NIH-funded, two-city efficacy trial (NCT03092531). LifeSteps has also been adapted for PrEP users. In a study of at risk MSM aged 18 or older, a 4-session, nurse-delivered version of LifeSteps adapted for PrEP users resulted in excellent adherence to PrEP and higher drug levels in the intervention condition as compared to a time- and attention-matched control condition. Given the evidence that shows text messages can improve health outcomes when integrated with counseling, especially in adolescents, the use of weekly text messages as motivational and social cues to support adherence was added to LifeSteps.

Many YMSM may be dealing with a variety of unique psychosocial (e.g., sexual identity formation, depression, substance use) and socio-structural (e.g., stigma, bullying, unstable housing, family trauma) concerns, creating potential barriers to PrEP adherence that require additional support, in order for them to optimally adhere to and achieve maximal benefit from PrEP. To determine the extent to which these factors might influence PrEP adherence, LifeSteps for PrEP is being further optimized for YMSM through formative interviews with at risk YMSM and their providers, and with a subsequent pilot study.

Theoretical framework for intervention. The adaptation of LifeSteps for PrEP for YMSM is being guided by the Gelberg-Andersen Behavioral Model for Vulnerable Populations. This model posits that health behaviors are influenced by a complex interplay of environmental and patient factors. For at-risk YMSM, environmental factors that may affect adherence include challenges they face in their external environments (e.g. unstable housing) and those faced in healthcare environments (e.g. relying on parents’ insurance). Patient, or individual, factors that affect adherence to PrEP include predisposing factors (e.g. low health literacy), enabling factors (e.g. copay assistance), and perception of need (e.g. HIV risk perception). The proposed
intervention — through the LifeSteps for PrEP modules and daily text messages — aims to exert its effects on multiple domains of the model to optimize adherence to PrEP.  

**Aims and objectives.** The long-term goal is to develop scalable protocols to optimize at risk YMSM’s PrEP uptake and adherence in order to decrease HIV incidence. The first step towards this goal is to revise and refine LifeSteps for PrEP for delivery by nurses specializing in adolescent health, so that it is tailored for high risk HIV-uninfected YMSM initiating PrEP. The aim of this paper is to describe the protocol for the refinement of LifeSteps for PrEP for YMSM, and a pilot randomized controlled trial (RCT) to examine the acceptability and feasibility of LifeSteps for PrEP for YMSM. We hypothesize that participants who are randomized to LifeSteps for PrEP will be highly satisfied with the intervention. We also hypothesize that, while not powered to detect significant differences, YMSM randomized to the LifeSteps for PrEP condition will demonstrate better adherence compared to YMSM in the standard of care condition.

**METHODS**

**Phase 1: LifeSteps for PrEP for YMSM Refinement**

To refine the LSPY intervention, we will conduct in-depth, individual qualitative interviews with up to 20 HIV-uninfected, at risk YMSM who present for bacterial sexually transmitted infection (STI) screening or treatment, or those seeking PrEP at Fenway Health, an iTech subject recruitment venue (SRV) and clinical center, which specializes in the care of sexual and gender minority patients.[27] We will also conduct in-depth qualitative interviews with up to 10 key informants, including PrEP providers and staff at community-based organizations that work with YMSM. Youth participants will be HIV-uninfected YMSM between ages 15 and 24 who self-report evidence of high risk for acquiring HIV infection (e.g., recent bacterial STI diagnosis). We will use purposive sampling to recruit a diverse sample of YMSM with respect to
race/ethnicity, age, and prior PrEP experience. We will recruit YMSM at various points in the PrEP continuum of care, including those who have opted not to initiate PrEP despite recommendations from clinicians, those who are using PrEP and report high levels of adherence and those who report adherence challenges.

After informed consent/assent and prior to the interview, participants will complete a brief demographic and behavioral questionnaire in order to contextualize the qualitative data. In the interviews, we will identify potential strategies to optimize adherence to PrEP for YMSM, and we will explore youth perspectives on the use of nurses to deliver the intervention and weekly text messages.

For PrEP-naïve youth, we will also explore youth concerns about adhering to PrEP, how these concerns influence their decisions about whether or not to initiate PrEP, and whether the availability of a structured supportive intervention that was nurse-delivered or regular text messages would influence these decisions.

For PrEP-experienced youth, we will explore their experiences with medication adherence and strategies used to overcome any barriers, and their views on the content of what they might have wanted to discuss with a nurse (e.g. potential side effects, lab monitoring, how to discuss PrEP with friends and family, substance use) and acceptability of text messaging.

Specific topics to be explored are based on the conceptual model described above, and include: 1) Environmental factors affecting access and adherence to PrEP, including structural factors (e.g. housing insecurity, lack of transportation), healthcare factors (e.g. inconvenient scheduling of clinical visits, non-affirming atmosphere for sexual minorities); 2) Patient factors that may influence adherence, including predisposing issues (e.g. substance use, depression), enabling factors (e.g. knowledge of the benefits of PrEP, social supports), and perceived need to use PrEP (e.g. self-perception of HIV risk); and 3) Perspectives regarding the proposed adherence interventions, including the use of text messaging as reminders and motivational cues (e.g. ideal timing, content), and a nurse-led intervention (e.g. reasons they would or would not want to
discuss adherence with a nurse, the preferred content and structure of counseling sessions). An open-ended approach will allow us to elicit potentially unexpected considerations that influence initiation of and adherence to PrEP among YMSM.

Study visits will last approximately 60-90 minutes. All interviews will be digitally-recorded and interviewers will take detailed notes using debriefing forms. Recordings will be transcribed by members of the iTech Analytic Core (AC) who are trained in qualitative methods. The qualitative team will apply rapid qualitative analysis techniques to the analysis of interview data.[28] This approach involves initial identification of themes and tabulation of frequencies regarding endorsement of themes across participants. Immediately following each of the interviews, the facilitator team will record observational insights, content, and key themes from the interview. This approach will result in an ongoing set of memos created by the team that rapidly describes and elucidates salient themes. The memos will guide the codebook creation and coding scheme for a more formal content analysis of transcripts.[29,30] These data will inform the design of the youth-tailored LSPY that we will test in the RCT pilot.

**Phase 2: Pilot Randomized Controlled Trial.**

**Trial Registration, Ethics, Consent and Institutional Board Approval**

The research and ethics presented in this study has been reviewed and approved by the University of North Carolina at Chapel Hill Institutional Review Board (17-2513). A Certificate of Confidentiality has been obtained from the National Institute of Child Health and Human Development and a waiver of parental consent/assent will be obtained for participants who are 15-17 years old. The study is also in the process of being registered on ClinicalTrials.gov.

All participants will undergo screening in a private room at the clinical research site. If eligible (see below), informed consent will be conducted at this time. The informed consent/assent documents will include detailed information on all study procedures and answer questions concerning the study and assent/consent process.
Study Design

A three-site, two-arm pilot randomized controlled trial will be conducted to assess feasibility and acceptability of the LSPY intervention and preliminary efficacy of the intervention to improve PrEP adherence and retention in PrEP care, compared to a standard of PrEP care control group. We will enroll up to 50 YMSM in the RCT (randomized 1:1 to the 2 arms) from iTech SRVs in Atlanta, GA, Boston, MA, and Chicago, IL. Participants will be followed for 6 months and will complete biological (i.e., renal safety, STI screening, and drug levels) and behavioral assessments every 3 months, including self-reported PrEP adherence, sexual behaviors, and psychosocial health. We will also conduct a brief, 15-minute semi-structured exit interview with participants in the LSPY intervention arm to provide an opportunity for more in-depth and open-ended feedback on intervention satisfaction and acceptability. These data will be used to finalize the intervention manual to enhance participant acceptability. See figure 1 for the pilot RCT schema.

Figure 1. Pilot RCT study schema
Participants

Study participants (n=50) will be assessed for eligibility by completing a brief screener. Inclusion criteria include: (1) age 15 - 24 years; (2) assigned male sex at birth; (3) identify as male; (4) identified as PrEP candidates by local clinicians because of self-reported risk and/or presentation with a new bacterial STI. Participants will also be able to understand, read, and speak English.

Recruitment

Active recruitment will be carried out by study staff at each SRV by recruiting men at the clinical sites and at local organizations and venues where YMSM attend. This may include community-based organizations for LGBT youth, Youth Pride events, etc. At recruitment venues, trained staff will approach youth and offer them information about the study (either verbally or by
offering them a business card or advertisement flyer), including brief descriptions of the study design and contact information (i.e., study email and phone number).

Additionally, passive approaches for recruitment will include posting study information via flyers, posters, and palm cards describing the study at these venues. Moreover, online recruitment will be conducted by placing banner advertisements on popular online social media outlets for YMSM (e.g., Facebook, Grindr, etc.).

**Randomization**

Only participants who express interest in LSPY to increase PrEP adherence, meet eligibility criteria, and provide informed consent/assent will be eligible for randomization. Fifty YMSM who are PrEP-naïve, and appropriate candidates for antiretroviral PrEP at the 3 iTech SRVs (15-20 per site) will be randomized 1:1. Randomization will be stratified by SRV,[31] and will be based on a pre-generated list created by iTech AC statisticians and accessed by a web portal.

**Incentives**

Participants in the pilot RCT will receive $50 USD compensation for the in-person screening/baseline assessment and $50 USD compensation for each completed follow up assessment and the exit interview.

**Intervention**

**Standard of Care Condition:** Following completion of baseline assessments, participants in both conditions will receive standard of care for PrEP initiation and adherence. Each participating SRV will document standard of care procedures at their site prior to protocol initiation.

**“LifeSteps for PrEP for YMSM” Condition:** The experimental intervention was derived from our prior PrEP work, and will be finalized following Phase 1 focus groups. Currently, the LSPY intervention consists of four weekly sessions at the time of PrEP initiation and two booster
sessions, which occur two and three months after PrEP initiation. Overall, the core components of the intervention will focus on medication adherence, sexual behavior, and problem solving to overcome barriers to adherence, using motivational interviewing techniques when needed. The first session will include education about PrEP, a discussion involving the psychosocial context in which PrEP use occurs, a brief motivational interviewing exercise, and discussion of establishing a dosing schedule. Session content after session one is designed to be flexible, allowing patients to identify their adherence support needs. Session two will begin with an adherence “check-in,” and then will focus on understanding the clients’ experiences taking PrEP, and engaging in problem solving to address any reported barriers to adherence. Session three will also begin with an adherence check-in and then will introduce sexual risk behavior education, identifying high-risk activities, and factors that could increase and decrease personal risk for HIV as well as other STIs. The session will involve a discussion about biological factors associated with HIV transmission (e.g., partners’ level of infectiousness, measured by plasma HIV RNA), as well as other STIs, and will discuss ways to reduce their risk in the context of taking PrEP. In the final weekly session, the nurse-counselor will discuss PrEP adherence goals and prior session content, and patients’ plans for continued PrEP use upon intervention completion. Optional modules will provide a framework to help interventionists work with participants who were experiencing substance abuse or mental health concerns that were adversely impacting PrEP adherence. 

Booster sessions at months two and three are designed to offer an opportunity for the trained study nurse to assess PrEP adherence in the absence of weekly support. Study nurses can use booster sessions to review PrEP adherence over a longer time-span and to address barriers to adherence using problem-solving skills learned during the earlier sessions. For participants who identified no challenges to adherence, the study nurse can use the booster session to review and refine the existing adherence plan and help them identify potential future barriers to adherence.

As part of the LSPY intervention, weekly text messaging will be used to support adherence, as well as to understand participants’ patterns of behavior. Participants will receive
weekly text messages to 1) motivate them to take their medications and 2) assess whether or not they took their medication and whether or not they had condomless sex. The weekly texts will continue throughout the follow-up period for each participant in the intervention group.

**Data Collection**

Baseline assessments will be conducted in person, with follow up assessments at 3 and 6 months. At each major assessment, participants will complete an assessment battery via a secure web-based data entry system. As mentioned previously, participants in the LSPY intervention arm will receive a weekly, brief SMS-based survey to assess whether or not they took their medication, and whether or not they had condomless sex in the past week. By obtaining data on the weekly patterns of medication adherence and HIV risk, the study team will be able to assess whether changes in adherence were associated with increased, unchanged, or decreased HIV risk.

**Primary Outcome Measures**

To measure acceptability of the LSPY intervention, participants will self-report the degree to which they find the intervention appropriate and useful using Likert-type agreement scales on factors such as the content of the intervention, length of the intervention, and delivery of the intervention. We will use the System Usability Scale (SUS), a validated 10-item measure, which is scored from 0 to 100.[32] A score of 50 or greater indicates that the app is acceptable.[33]

In order to assess feasibility, we will track the number of potential participants we screen, the number of potential participants who meet study inclusion criteria, the number of participants who meet study criteria and then enroll, and the number of treatment and assessment sessions completed by all enrolled participants (across conditions). We will also track the duration of assessments, and reasons for declining enrollment and for prematurely leaving the trial.

Although this pilot study is not powered to examine efficacy of biological and behavioral outcomes, at each major assessment, dried blood spot (DBS) drug levels of tenofovir-diphosphate and emtricitabine-triphosphate will serve as biological correlates of adherence.[34] Self-reported
adherence to PrEP will also be assessed using timeline follow-back.[35] We will also obtain medical record release forms from participants in order to determine medical appointment adherence, measured as the proportion of scheduled clinic visits attended by each patient over their study observation period.

**Secondary Outcome Measures**

In order to assess the impact of the intervention on potential mediators of adherence, we will also assess readiness to use PrEP and adherence problem solving scales. Behavioral skills for PrEP use will be assessed with 12 items that ask how “hard” or “easy” it was for participants to implement a variety of skills, including discussing side effects with medical providers, remembering to take pills on time. PrEP taking self-efficacy will be adapted from the HIV Treatment Adherence Self-Efficacy Scale,[36] which assesses confidence to take medications in various situations. Finally, we will also assess individual (e.g., sexual behavior, mental health) and environmental (e.g., incarceration, stigma, healthcare access) covariates that could impact adherence.

**Statistical Analyses**

We will use descriptive statistics to characterize the distribution of all study variables. The primary analysis will measure feasibility of the intervention by the proportion of participants retained in the study at the end of the study period, and we will measure acceptability by the percentage of participants who rate each intervention as acceptable on their final follow-up survey. Point estimates of ≥0.50 for feasibility and acceptability will be considered the minimum criteria for acceptability and feasibility, consistent with standards employed in similar behavioral health studies.

The primary biological outcome analysis will compare adherence (defined by percentage of participants with DBS drug levels above 700 fmol/punch, a level correlated with high protection from HIV acquisition [35,37]) at the 3 and 6 month visits between the study arms. Group differences in the proportion of PrEP clinic appointments kept will also be compared.
All analyses will use two-tailed tests of significance, with significance at alpha = 0.05. We will follow an intent-to-treat model, analyzing participants in the study arm to which they were assigned. We will examine the equivalence of random assignment to groups with regards to key baseline characteristics, including socio-demographics, prior HIV testing patterns, and sexual risk-related variables. In the event that randomization does not work to balance these characteristics, we will assess whether baseline differences may account for differences in outcomes.

RESULTS

Qualitative interviews are anticipated to begin in late 2017, and recruitment for the pilot randomized controlled trial is anticipated to begin in early 2018, with study follow up complete in September 2018.

DISCUSSION

Oral PrEP has the potential to change the HIV prevention landscape and curtail the HIV epidemic dramatically. When adherence levels are adequate, it can reduce HIV acquisition among MSM by over 90%,\[5,6,37,38\] and increasing the effective use of PrEP among YMSM—one of the highest risk groups for new infections—is one of the leading priorities for HIV prevention. However, YMSM face multiple challenges to initiating and adhering to PrEP,\[39\] and, in two open-label studies of PrEP use by 15-17 and 18-22 year old YMSM (ATN 113 and 110),\[8,9\] adherence was suboptimal after 3 monthly visits and HIV incidence was high (6% and 3%, respectively).

At this time, there are few rigorously developed and tested interventions for increasing PrEP adherence among YMSM in community settings. Our long-term goal is to develop scalable protocols to optimize at risk YMSM’s PrEP uptake and adherence in order to decrease HIV incidence. In a pilot RCT, LifeSteps for PrEP — a 4-session, nurse-delivered cognitive behavioral therapy (CBT)-based counseling intervention — improved adherence to PrEP compared to a time- and attention-matched controls among at risk MSM aged 18 or older.\[17\]
The adaptation for LifeSteps for PrEP for YMSM will be informed, developed, and refined through formative research that involves YMSM at all levels. HIV uninfected YMSM will inform the intervention and curricular materials through formative qualitative interviews and exit interviews after participating in the pilot RCT. By incorporating information and feedback on the content of the intervention from YMSM, we will ensure content is tailored to their contextual realities in a manner that promotes PrEP adherence skills building and problem solving.

Anticipated limitations of this protocol include potential limits of generalizability of the results of the formative, qualitative interviews given that they will take place in one urban city. While preparing for the pilot RCT, we will present the intervention at iTech supported Youth Community Advisory Boards at participating SRVs to obtain additional feedback from geographically diverse populations.

If LSPY demonstrates acceptability and feasibility in this pilot RCT, we plan to test its efficacy in a full-scale, multi-city randomized controlled efficacy trial. If shown to be efficacious, this in-person nurse-delivered counseling intervention with text messaging for ongoing support will allow for a youth-informed, targeted PrEP adherence intervention for YMSM.

Acknowledgements

The authors would like to thank Adi Ferrara, MS, ELS, for help in the preparation of this manuscript.
References


young adult transgender men who have sex with men. Journal of Urban Health 2016;93(1):189-205. PMID: 26753882


26) LSPY P3 PAPER CITATION- UNC ENTER HERE


