

Preparing for Pre-exposure Prophylaxis Implementation  
in Central-Eastern European Countries With Low Access  
to Biomedical Prevention

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## BACKGROUND

### Abstract

Despite the effectiveness of pre-exposure prophylaxis (PrEP) in preventing HIV acquisition, PrEP is not currently medically prescribed in Romania, although demand is rapidly growing. Evidence-based knowledge is urgently needed to guide PrEP's effective rollout in Romania. First, Romania has the 2nd highest increasing HIV incidence of 15 Central-Eastern European (CEE) countries, with gay and bisexual men (GBM) being one of the few epidemic-driving groups; however, there is no national HIV programming for GBM. Second, in a large 2019 GBM report, Romania was the 8th of 44 European countries with the largest gap between PrEP use (1%) and demand (70%). Third, Romania displays some of the highest homophobic attitudes in CEE, keeping GBM in hiding and underutilizing healthcare. Consequently, many Romanian GBM obtain PrEP on their own and use it without medical guidance, thereby increasing their HIV and other health risks. To address the unmet HIV-prevention needs of Romanian GBM, the US-Romanian research team proposes to introduce a culturally-responsive pre-exposure prophylaxis (PrEP) program in Romania. The intervention consists of two tools that the team developed and tested in the US and adapted for Romania in a prior study: 1) SPARK, an in-person motivational intervention for uptake of and adherence to PrEP using an empowering sexual health approach; and 2) P3 (Prepared, Protected, emPowered), a PrEP adherence support app that utilizes engaging social networking and game-based elements, with an in-app portal for individualized live adherence counseling. PrEP Romania's feasibility, acceptability and early efficacy will be tested across two aims.

Aim 1. Any necessary adjustments to PrEP Romania based on a prior trial will be made. Then, 120 PrEP-eligible gay and bisexual men in two Romanian cities (Bucharest and Cluj) will be randomized to receive either 1) PrEP Romania or 2) a PrEP education condition. Differences across arms in PrEP uptake, adherence, persistence (self-reported and biomarker verified) at 3- and 6-mos post-PrEP initiation will be examined.

Aim 2. Individual and institutional barriers and facilitators of implementing PrEP Romania will be investigated by examining Aim 2 feasibility and acceptability data, and via research staff, and GBM interviews to inform a future hybrid effectiveness-implementation trial.

## Study Purpose and Rationale

Despite evidence of the effectiveness of pre-exposure prophylaxis (PrEP) in preventing HIV acquisition, PrEP is often hardest to access in global regions and populations most at risk. In Romania, for instance, PrEP is not currently medically prescribed, yet there is urgency around its rollout. First, Romania has the 2nd highest increasing HIV incidence of 15 Central-Eastern European (CEE) countries, with gay and bisexual men (GBM) being one of the few epidemic-driving groups; yet, there is no national HIV programming for GBM. Second, in a large 2019 GBM report, Romania was the 8th of 44 European countries with the largest gap between PrEP use (1%) and demand (70%). Third, Romania displays some of the highest homophobic attitudes in CEE, keeping GBM in hiding and underutilizing healthcare. Consequently, many Romanian GBM obtain PrEP on their own and use it without medical guidance, thereby increasing their HIV and other health risks. To address the unmet HIV-prevention needs of Romanian GBM, this study proposes to introduce a culturally-responsive PrEP program to the country of Romania.

Specifically, PrEP Romania is a hybrid in-person + mobile health (mHealth) program that facilitates PrEP uptake and adherence by providing knowledge, motivation, and support. mHealth is an ideal HIV-prevention strategy for Romanian GBM given its private accessibility in stigmatizing locales. The study will integrate and adapt for Romania two tools we developed and tested in the US 1) SPARK, an in-person intervention for uptake of and adherence to PrEP using brief sex-positive motivational counseling; and 2) P3 (Prepared, Protected, emPowered), a PrEP adherence support app that utilizes engaging social networking and game-based elements, while an in-app portal allows for individualized live text-based adherence counseling to heighten GBM's sense of accountability, enhance their motivation, and address specific adherence needs. These goals will be accomplished in collaboration with a Romanian Partner Consortium of GBM-competent health providers, including: infectious disease physicians (IDPs), whom we trained in GBM-affirmative practice; community-based organizations (CBOs); and the National Institute of Infectious Diseases (NIID) and Romanian Association against AIDS (ARAS), prominent HIV-focused medical institutions. This study has two aims.

**Aim 1. Conduct a randomized controlled trial (RCT)** to test the early efficacy of PrEP Romania. The US team will make necessary adjustments to PrEP Romania with the Romanian Partner Consortium. These adjustments are based on a pilot study conducted prior to the award of the current study by NIH, between September 2020 and March 2022. Then, 120 PrEP-eligible

GBM in two cities (Bucharest and Cluj-Napoca) will be randomized to receive either 1) PrEP Romania (counseling, self-directed app use, and in-app text-based adherence support for 6 months) or 2) a PrEP education condition. We will examine differences across arms in PrEP uptake, adherence, persistence (self-reported and via dried blood sample biomarkers), and mediators (self-efficacy, mental health) at 3- and 6-months post-PrEP initiation.

**Aim 2. Explore implementation outcomes** to prepare for a future multi-city effectiveness trial. The team will identify individual and institutional barriers to and facilitators of implementing PrEP Romania by applying Proctor et al.'s implementation framework to the analysis of RCT's feasibility and acceptability data, and PrEP counselor, IDP, clinic administrator, and GBM interviews. Results will inform a future effectiveness-implementation hybrid trial of a scaled-up PrEP Romania across several cities.

## Research Aims & Abstracts

Hypotheses: Compared to control arm (education only), PrEP Romania participants (counseling, self-directed app use, and in-app text-based adherence support for 6-mos) will be more likely to accept PrEP (H<sub>1</sub>); evince better adherence (H<sub>2</sub>); and sustain PrEP use across 6-mos (H<sub>3</sub>).

<b>STUDY DESIGN</b>
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One hundred and twenty GBM will enroll in a 2-arm pilot to test PrEP Romania's (a) feasibility (medical visit attendance), (b) acceptability (intervention staff and GBM interviews about counseling and app usability), and (c) PrEP uptake (filled prescriptions), adherence (self-reported and DBS) and persistence (still on PrEP) at 3- and 6-month follow-ups.

*Study Sites:* Two of Romania's primary infectious disease (ID) centers in Bucharest and Cluj-Napoca will serve as the study sites. Their IDPs are involved in our ongoing research and treat GBM who test positive for HIV/STIs through our study. They, together with their site psychologists, were part of the team's pilot study for the current RCT, which ended in March 2022.

*The National Institute of Infectious Diseases (NIID) Bucharest Clinic.* The largest ID university hospital in Romania, NIID is one of 9 regional centers monitoring HIV. NIID monitors all HIV/AIDS cases in Romania, and oversees the other 8 regional centers.

*The Cluj-Napoca Clinic.* The Regional Center of Evidence and Monitoring of HIV Infection Cluj-Napoca (CREM Cluj) covers 5 jurisdictions in northern Romania. A total of 706 HIV/AIDS patients are registered in CREM Cluj, with 668 being on ART.

Inclusion Criteria. Men will be eligible based on criteria for GBM PrEP candidates: 1) male sex at birth and current male identity; 2) age 18 years old; 3) 1 acts of condomless anal sex with an HIV-positive or status-unknown male partner or diagnosis of bacterial STI in past 6 mos; 4) confirmed to be HIV-negative upon study testing; 5) own a mobile device (smartphone, tablet, laptop); 6) will reside in Romania for the following 6 months; and 7) are not currently participating in other research studies or related projects.

Exclusion Criteria. Children <18 years old will be excluded as Romanian law that prohibits prescribing medication to minors without parental consent, which may jeopardize wellbeing if youth are “outed” to unsupportive families.

## **Study procedures**

Recruitment: We will enroll a total of 120 men meeting the above criteria. GBM living in or within 40 miles of Bucharest (n=60) and Cluj (n=60), will be recruited and enrolled if eligible.

Rationale: We have existing collaborations with clinics in these 2 cities, which are major Romanian medical infectious disease centers with a sufficiently large GBM patient load and high HIV risk (given their urbanicity and being international travel hubs). It is normative for Romanians from surrounding small urban and rural settlements to travel to these cities for medical and social reasons (especially GBM for whom resources are scant and urban migration is normative). Thus, participating from within a 40-mile radius around each city will not represent an unusual demand.

Venues: We will follow our successful recruitment procedures from our previous studies in Romania with this population. First, our partner, ARAS, provides weekly free confidential HIV/STI testing in Bucharest and Cluj’s gay clubs at its so-called “Checkpoints.” Second, we will post study ads on websites of MozaiQ (NGO partner with extra outreach to the Roma community), ACCEPT (LGBT advocacy organization since 1996), study recruiter networks, subscriber lists, and key virtual venues (e.g., Facebook, Planet Romeo). In previous studies, 45% and 24% of participants were recruited on GBM sex-seeking apps, respectively, and 41% and 59% on Facebook/Instagram, respectively. Finally, enrolled participants will be encouraged to spread the word.

Screening: Within the study ad, potential participants will click on a link to complete a 5-min eligibility screener on Qualtrics, a HIPAA-compliant secure web application. The first page in the screener consists of the informed consent form for screening eligibility. This form is self-administered and contains the researchers' contacts that can be used for clarification purposes. Once potential participants have read through the electronic consent form and agree to screen for eligibility, they will click "Yes" on the consent form, if still interested in taking the screener (or "No" otherwise, and exit). Should the consent to screen, the next screen will take them to the first questions of the screener. Eligible GBM will have the option to provide contact information at the end of the screener, in a separate survey, to be contacted for consent.

Consent: Eligible participants will be contacted within days of screening to undergo the phone consent process we used successfully in other studies. Specifically, ARAS staff will send potential participants a link to an electronic Qualtrics-based consent form. ARAS staff and participants will read the electronic consent document together while on the phone (15 minutes). Points of confusion will be clarified and interested participants will submit the electronic consent. The consenting ARAS staff will submit their own version of the Qualtrics-based electronic consent form.

Assessments: Upon consent, participants will be sent their unique study ID an electronic link to a Qualtrics-based baseline survey (30 minutes). They will complete similar 3- and 6-month surveys, and 20% will complete exit interviews with the PI about their intervention experiences to inform future PrEP Romania iterations.

Procedures: After the baseline survey is completed, participants will be randomized 1:1 to receive PrEP Romania (n=60) or an Education Condition (n=60). Next, research staff will help participants schedule their first visit with the clinic for PrEP counseling, biological testing and PrEP prescription pick-up. All participants will be tested at the clinic for HIV at each visit, and, if positive, treated immediately.

**Intervention Arm (PrEP Romania):** The intervention, named PrEP Romania, is based on the team's previously tested PrEP Adherence and Counseling Protocols, delivered in-person. PrEP adherence is supported via an app previously tested by the team, including in Romania. To facilitate uptake, the Sexual Health Counseling Intervention seeks to "normalize" PrEP as part of a comprehensive HIV prevention/sexual health strategy chosen by the PrEP candidate. The intervention's "sex-positive" approach is ideal for Romania given its focus on de-stigmatizing both

sexual behavior and potential PrEP stigma, two drivers of negative attitudes of sexual behavior among men. PrEP Romania defines sexual health as physical, mental, emotional, and social wellbeing in the context of sexuality. Consistent with research on message framing, this intervention presents PrEP – and other sexual health promotion strategies– in a gain frame, emphasizing the positive impact of health promotion behavior, rather than the potential hazards of risk-taking. This is salient for Romanian GBM by allowing them to view their sexuality as natural and pleasurable, while minimizing stigmatizing societal discourses. PrEP Romania helps GBM consider PrEP as a means of sexual agency and fulfillment by asking them to reflect on their ideal sex life and identify sexual health priorities. SPARK is delivered in a clinic setting by a counselor using motivational interviewing techniques (e.g., open-ended questions, affirmations). The PrEP Adherence component provides behavioral support for PrEP adherence across five steps: 1) provision of rationale for daily dosing (e.g. blood drug concentrations); 2) creation of plans to integrate PrEP into daily routines (e.g., when, where, how); 3) managing side effects (e.g., over-the-counter remedies); 4) navigating PrEP use disclosure to avoid stigma (e.g., when and whom to tell); and 5) anticipating circumstantial changes that can affect PrEP use (e.g., traveling). PrEP Romania uses US CDC guidelines for PrEP daily use.

Prepared, Protected, emPowered (P3) App Overview: P3 is the app component that accompanies PrEP Romania, to support PrEP adherence and persistence. P3 is a theory-based, smartphone app that utilizes social networking, game-based mechanics, and evidence-based features to improve adherence. It was co-created by researchers, health game developers and GBM. P3 is versatile, allowing for customization and adaptations for diverse cultural and linguistic contexts, and technological advances. Within the app, users can receive information and social support, experience health-promoting social norms and reflective appraisals, and connectedness to peers, read informational articles about reducing alcohol use, achieving a healthy sex life, coming out, or building a supportive community. Relatedly, P3 is built for and has reduced users' PrEP stigma-related concerns, which pose barriers to PrEP uptake and adherence if unaddressed. The gaming features of P3, such as answering short quizzes on how to use condoms, are intended to increase health promotion knowledge. P3 is ideal for engaging GBM in sustained behavior change by maintaining attention, and reducing boredom and attrition. P3 has an extensive library of facts on PrEP, sexual health, and relationships, from which Romanian GBM can benefit from accessing. Adherence counseling will be delivered via live text-based chat through the app, 2 weeks after

PrEP initiation, and then every 6 weeks. Participants can ask questions about PrEP and health through the app, which will be answered by the trained research team. The entire follow-up period will be 6 months. At the first 1-hr visit, the PrEP counselor will deliver the in-person component PrEP Romania regarding motivation for PrEP uptake, and if applicable, adherence. The counselor will help GBM download the app, and demonstrate each feature, answer all questions and provide a guided tour. Participants will be encouraged to explore all app components routinely and be told that the counselors will contact them periodically through the app messaging system to discuss adherence facilitators and barriers. Next, participants will meet for 1-hr with the IDP, who will discuss requisite lab results and reinforce PrEP-related facts. The IDP will next provide a prescription to all GBM interested in starting PrEP, to be filled at the co-located clinic pharmacy, provided for free through the study. A follow-up clinic visit will occur 3- and 6-months after initial visit. Reported PrEP side-effects will be carefully monitored and, if necessary, PrEP use will be discontinued. In a pilot study for this RCT by this team, no participants reported side-effects. App-based Support. GBM will be encouraged to use the app daily for adherence reminders, information, and socialization. The PrEP counselor will contact GBM via the app two weeks post-PrEP initiation for a 15-min adherence coaching session using adapted SPARK language to reinforce daily adherence and trouble-shoot barriers. Participants may message their counselor with questions, including for technical assistance, to be answered within 24 hrs.

**Control Arm (PrEP Education Condition):** Participants randomized to the control arm will not meet with the PrEP counselor or have access to the app. They will only meet with the study IDP, who will deliver PrEP education. This education content is based on previously tested PrEP messaging education protocol. The low PrEP knowledge among Romanian GBM suggests the utility of a comprehensive PrEP education intervention. The IDPs (not PrEP counselors) will deliver this condition and be instructed to follow it as scripted using check-lists, as to avoid cross-arm contamination. The IDP will first review lab test results and then provide basic PrEP information: what it is (e.g., definition), how it works (e.g., prevents virus replication), efficacy (e.g., clinical trials evidence), side effects (e.g., type, duration), and importance of daily use (e.g., to build and sustain protective levels), and continued condom use (e.g., PrEP as an added layer of protection against HIV, but not STIs, unless condoms are used). IDPs will answer questions and provide PrEP brochures. Participants will return 3 and 6 months after the first visit, as described below. Follow-up Visits. Participants in both arms will receive a PrEP prescription to be filled at



the co-located pharmacy and schedule a follow-up visit 3 months later. At that visit, participants will meet with their counselor and/or IDP to review past-3-month PrEP use, side effects, clarify questions, conduct biological testing as above, and receive a PrEP refill if desired. The same procedures will be used at the 6-month follow-up. Retention. For high app-based engagement and retention follow-up, we will apply strategies we have utilized across our NIH-funded interventions, two of which entailed 8 mHealth counseling sessions with >82% completion and 86% and 93% retention at 3- & 24-months. Study engagement will be bolstered by our GBM-affirmative research staff who will routinely verify and use participants' multiple means of communication (phone calls, SMS, multiple social media messaging, alternate contacts). PrEP counselors will contact unresponsive participants. Participants will be compensated \$30, \$35 & \$40 for BL, 3M, and 6M surveys, and \$30 for exit interviews (20% randomly selected).