Piloting a Smartphone App to Improve Treatment Adherence Among South African Adolescents Living With HIV

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Study Protocol and Statistical Analysis Plan

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Protocol Title: Developing a Smartphone App to Improve Treatment Adherence among South African Adolescents Living with HIV

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Background

Interventions that engage adolescents living with HIV to improve adherence to antiretroviral therapy (ART) are urgently needed. Adolescents repeatedly demonstrate suboptimal levels of ART adherence, which is associated with increased morbidity and mortality. Developing adherence-promoting interventions for adolescents requires an understanding of factors that shape adherence from multiple levels. Developmental theories suggest that adolescents are particularly sensitive to their social networks. Mobile health (mHealth) interventions, those that use mobile technology (e.g., smartphones apps) to transmit health information, hold promise as an effective way to improve ART adherence. These smartphone apps can be used to engage social networks and provide social support. Access to mobile phone technology is rapidly increasing among youth in South Africa, making mHealth interventions feasible and potentially scalable in this setting. This study will adapt HealthMpowerment, a theory-based mHealth intervention developed in the U.S., to improve ART adherence among South African adolescents living with HIV. The adapted intervention is called *MASI (MAsakhane Siphucule Impilo Yethu*; isiXhosa for 'Let's empower each other and improve our health").

Purpose of the study

The purpose of this study is to customize and pilot test an mHealth intervention to promote ART adherence among adolescents and young adults (AYA) living with HIV in Cape Town, South Africa. We will first analyze secondary data collected as part of the *Cape Town Adolescent Antiretroviral Cohort* to identify the relationship between social network-level factors and clinical outcomes (e.g., ART adherence and viral load) in this population. Next, we will conduct formative research, including multiple phases of in-depth interviews (IDIs), to iteratively adapt HealthMpowerment to create *MASI* for adolescents living with HIV in Cape Town. Finally, we will pilot test *MASI* with 50 AYA living with HIV to a) assess its feasibility and acceptability and b) explore preliminary effects on ART adherence and social support. Qualitative data collection will help identify and refine next steps for MASI.

Background on HealthMpowerment and *MASI*

HealthMpowerment is a theory-based intervention developed in the U.S. to engage HIV-positive, negative, and status-unknown youth and to reduce HIV-related risk behaviors. An earlier version of HealthMpowerment resulted in significant reductions in risky sexual behaviors among young men who have sex with men in the U.S. The app includes an anonymous social network. Participants have usernames and avatars, but no identifying information is included for each person. We advise all participants to pick a username that does not include their real name, email address, or their other social media account names. HealthMpowerment has now been updated for delivery via iOS and Android smartphones in a nationwide study in the U.S. that launched in July, 2020. For our study, *MASI* will support the following features:

- Forums - Start or add to existing discussions, upload images, videos; favorite posts and follow others; research staff (including peer mentors) monitor and add to forum posts to encourage dialogue
- Med Tracker -Track ART adherence in calendar; schedule tailored reminders for taking medicine
- Ask an Expert – Post/read questions answered by local doctors/counselors; posted anonymously
- Activities - Engaging activities including quizzes, self-assessments, and goal setting activities
- Resource Center - Multi-media resources and information on various health topics
- Gamification - Sophisticated tracking of app use to trigger tailored rewards; badges awarded

We will customize all of the intervention content so that it is relevant to adolescents in Cape Town.

Overview of the study procedures and participants

The proposed study is nested in larger study titled “Improving Assessment for Neurocognitive Impairment among Perinatally HIV Infected Youth *(NASA study)*” (REF: 215/2018). The proposed research will address the following three specific aims.

Aim 1: Analysis of Secondary Data; previously approved by UCT HREC with IAA between UCT and Duke

The first aim consists of secondary data analysis of data generated from adolescents living with HIV enrolled in the *Cape Town Adolescent Antiretroviral Cohort* (CTAAC; HREC: 051/2013; Amendment: 18

April 2017). After the approval of the of the Protocol Amendment, we established an IRB Authorization Agreement between UCT and Duke University for the analysis of these data (IAA; executed July 13, 2017).

The purpose of this aim is to identify the relationship between social network-level factors (including structural and functional characteristics of their social networks) and HIV-related clinical outcomes including ART adherence and viral suppression among adolescents living with HIV.

Aim 2: Formative research to iteratively customize an mHealth intervention to promote ART adherence among adolescents living with HIV by engaging their social networks

In this aim, we will collect data from adolescents to customize the HealthMpowerment app for this population. We will recruit participants from the larger NASA study. Participants and caregivers in the NASA study are regularly asked for assent/consent to be approached about additional research studies (documented on an ok-to-contact list), which we will use for recruitment into this study. Participants will be eligible to participate if they have daily access to an Android or iOS smartphone meeting minimal requirements (e.g., Operating system is Android version 5.0 or higher or iOS version 10 or higher, phone has at least 200 mb in free storage). Participants will be asked to participate in 1 in-depth interview (IDI), another set of 2 IDIs (before and immediately after beta testing the app), or both.

In the first phase of Aim 2, we will conduct IDIs with approximately 15 adolescents living with HIV (ages 14-20 years). After providing consent/assent, participants will be asked to complete a brief survey about their background; social support; stigma; adherence to treatment; and use of their smartphone for getting health information. The interviews will take about 1.5 hours and will include questions about experiences with HIV treatment; support and challenges related to ART adherence; how COVID-19 has impacted their care and treatment; use of phones generally and how phones are used to search for health information; what they want in a smartphone app designed to support adolescents living with HIV (e.g., what topics should be included in the app). The IDIs will also be an opportunity to explore potential risks and harms related to privacy, confidentiality, and unintended consequences (e.g., stigma and inadvertent disclosure). Interviews will be audiotaped and then translated and transcribed from Xhosa to English.

In the second phase of Aim 2, we will conduct app testing of our customized app. Study activities for this phase of Aim 2 will include a set of 2 IDIs with 12-16 adolescents living with HIV (ages 14-20 years). Prior to the first IDI, participants will be asked to complete a brief survey about information on their background; social support; stigma; adherence to treatment; and use of their smartphone for getting health information. The first IDI will take about 2 hours and will be about opinions about how the app and study logo look, opinions about how the avatars look and how to improve them, opinions about earning points and badges and how to make them more engaging. During the visit for the first IDI, we will install the app on each participant's phone. After the participant registers and creates a private username and password, we will demonstrate how to use the app. Participants will be asked to spend at least 10 minutes a day on the app for 1-3 weeks, until the second IDI is scheduled. We will be able to monitor where participants go within the app, what features/articles are used, and the length of time spent on the app. Participants will be given smartphone data to support their use of the app during this time. The second IDI, will allow participants to provide feedback based on their experience with the app, desired improvements, proposed changes to the community guidelines, and information on facilitators and barriers to uptake and daily engagement as well as any technical difficulties encountered, privacy or confidentiality concerns.

Aim 3: Pilot test the mHealth intervention with 50 adolescents and young adults living with HIV to (a) assess its feasibility and acceptability and (b) explore preliminary effects on ART adherence and social support.

We will conduct a pilot randomized controlled trial (RCT) to test *MASI* with 50 AYA with HIV (25 males and 25 females). We will recruit participants from the larger NASA study using the same procedures used successfully in Aim 2. Additional participants will be recruited outside NASA at public ART clinics linked to Groote Schuur Hospital in Cape Town, South Africa, and through participant referral.

Screening and participant eligibility: Participants will be screened by phone to see if they meet the following eligibility criteria:

- Age >= 15 years and <= 21 years
- Knows HIV status (Screened AYA who do not know their HIV status will receive information on free voluntary HIV counseling and testing services)
- Living with HIV
- Has been prescribed medication to treat HIV
- Not attending school for learners with special needs (e.g., School of Skills)
- Has not repeated a grade in school more than once
- Have a smartphone that can download apps
- Feels comfortable using an app with content in English
- No plan to move outside of Cape Town in the next six months

- Have not previously participated in the MASI app testing phase of our study

Participants who meet these criteria will be invited for an in-person appointment. After completing the informed consent/assent process (including consent from an adult, if applicable), we will confirm the final eligibility criteria:

- Able to successfully install the MASI app on their smartphone

Eligible participants will complete a baseline assessment, which will be an interviewer-administered survey with data entered electronically by the interviewer using REDCap data collection software. Paper surveys will be available in the event online data entry is not possible. For survey questions with a higher potential for social desirability bias (e.g., sexual behavior and study feedback), we may offer participants the opportunity to self-enter data into REDCap.

Following the baseline assessment, the interviewer will use REDCap's randomization tool to assign participants to condition. Using this process, participants will be randomized to the intervention or control condition (1:1), with randomization stratified by gender. The intervention condition will include all features of *MASI* while the control condition will be an information-only version of *MASI* which will include the Resources feature and homepage. Study participants will be asked to engage with the app for 6 months. All participants will receive 1G in monthly cellphone data packages for 6 months; research staff will touch base with participants each month to ensure the participant still has access to a working device before sending data.

Participants will complete follow-up assessments as well as 3- and 6-months follow-up. Assessments will take approximately 60 minutes and will be conducted in a private room so that participants can speak without being overheard. Phone assessments may be conducted in the event it is not possible to conduct in-person data collection. Assessments will include questions about assessing demographics, HIV-related knowledge, social support, loneliness, resilience, anxiety, depression, stigma, disclosure concerns, disclosure intentions, treatment adherence, sexual activity, perceived usability of MASI, and participant feedback about the study overall.

Risk and Benefits

Potential risks

We believe there is low risk associated with this study. This study does not involve any medical procedures and we believe the probability of experiencing social harms to be low. That being said, we have carefully considered all possible risks to participants (regardless of their probability) in the various phases of the study. Potential risks to participants in this study include: 1) COVID-19 related risks during in-person study activities, 2) emotional discomfort and distress resulting from the topics covered in the IDIs or during assessments for the pilot study, 3) emotional discomfort or distress when reading content on the app, 4) unintended disclosure, 5) violations of privacy and confidentiality concerns, and 6) risks of coercion. We believe that the steps described below will minimize or prevent these potential risks.

Protection against risks

COVID-19 related risks. COVID-19 related risks may be possible during in-person study activities. To reduce the spread of COVID-19, and to limit the exposure among participants and staff, we will implement all UCT-approved COVID-19 guidelines and recommendations to keep our participants and staff safe. Our staff will continue to follow all active FHS SOPs before, during, and after all study visits.

Emotional discomfort and distress. The topics covered in the IDIs or during assessments for the pilot study will involve sensitive topics (e.g., challenges with adherence, stigma) that may lead to distress and emotional reactions. To protect against emotional distress, each interview will begin with an explanation that participants are free to refuse to answer any question and may terminate the interview at any time. Interviewers will be trained to identify and respond to signs of discomfort and distress

Participants may also experience *emotional discomfort or distress* when reading content on the app. We will strive to create a safe and comfortable app environment for all study participants. However, it is possible that participants in the intervention arm may experience emotional discomfort or distress due to things other participants post through the app's forums. We will provide participants with information to allow them to contact the study team at any time if they experience emotional distress related to participation in the study. We will also include "community guidelines" as part of the intervention app's on-boarding process. This information will also be included within the app. During the formative phase of this research, we will review these guidelines to ensure they are comprehensive given the regular evolution of online environments and social media tools. The guidelines will continue to include language around non-discrimination, non-offensive language, openness and confidentiality.

During the pilot study, study staff, including Peer Mentors (who will be hired to engage with participants within the app) will review and help monitor forum posts. Study staff will monitor posts made during business hours with posts made outside of business hours reviewed in the morning of the next business

day. If a participant posts something that could be considered in breach of the guidelines, study staff will remove the post and contact the participant to notify them and explain why the post was removed. Our protocol describes additional action steps should a participant accumulate three violations of this nature. Study staff will also monitor posts for content that indicates a need to implement the SOP for Various Scenarios, including concerns about harm to the participant or others.

Unintended disclosure. Unintended disclosure is also a potential risk. Study staff will be trained (or re-trained) on confidentiality standards and proper interviewing techniques to minimize this risk. Participant names will not be included in any data collection instruments or intervention forum posts. The only numbers used to label and identify data from the participant will be the Study ID or their username (app handle) for the intervention. Questionnaires and audio files will be linked using the Study ID and the interview date. We also have extensive data procedures already in place to ensure security of the data and information provided by participants. Data will not be released to non-study staff at any time. All electronic data sharing between sites will be done only on the secure server (e.g., via Duke Box.com).

Privacy and confidentiality concerns. Participants may have privacy and confidentiality concerns**.** Participants will be reminded to consider their surroundings and the privacy of their device before engaging with the intervention app. No communication between study staff and participants will include sensitive information about HIV or anything that could reveal their participation in a study. To protect their privacy, participants will be required to enter a PIN to gain access to the app if it has been 5 minutes since the app was open on their device, or 15 minutes if the app was open but inactive as a fail-safe to avoid unintended disclosure. Participants will also be encouraged to interact with the study application when in private. Participants in focus group discussions will be asked to respect confidentiality and not share the identities of other participants or content shared in the discussions. Finally, participants will be notified of these risks in the consent process.

Risks of coercion. There may also be risks of coercion. We are aware of the ethical considerations in providing compensation to people living in impoverished conditions because providing compensation may unintentionally coerce participation in research. Thus, we will limit the compensation amount to no more than R250 per study visit. Additionally, participants will be reminded that the study participation is voluntary and that refusing to participate in the study or withdrawing from the study is an option at any time.

Potential Benefits

There are no direct benefits to adolescents who participate in this study. Participants may benefit from knowing that the information learned from this study will help to improve the situation of youth like themselves. If the pilot RCT is successful there are potential social benefits that can be gained from the study. The proposed research may identify new insights into how to best support adolescents living with HIV using mobile technology. The risks to participants are reasonable in relation to the anticipated benefits of the research.

Confidentiality

Confidentiality is of critical importance, and we will take precautions to protect against the possibility of a confidentiality breach. We will conduct study visits in a private area so that participants can speak without being overheard. Minimal identifying information will be collected during the IDIs. When the digitally recorded interview is transcribed, only nick names or fictional names will be used. Study documents will only be identified only by a study ID number, not by name. The research team will maintain a separate list that links the study ID number with the personally identifying information. This list will be kept in a locked filing cabinet at UCT and/or in password protected files on password protected computers and secure servers. Other paper study documents (e.g., written informed consent forms and hard copies of data) will be kept in a locked filing cabinet at UCT. All electronic data collected in this study will be stored on a secure and confidential server housed at the University of Cape Town, Duke University, and Florida State University. Participants' names will never appear in any report resulting from the project.

Any content that participants share on the app will only appear with their username. To protect their privacy, we will encourage participants to choose a unique username that is different from their real name, email address, and their social media accounts. We will strongly discourage participants from sharing personal information in the app that could reveal their identity. If a participant chooses to share identifiable information about themselves in the app, it may result in the breach of their confidentiality to other participants. We reserve the right to remove it from the app if it violates our app guidelines. Any study-related messages that are sent to participants will not disclose the fact that they are in a research study. All messages will be free of any identifying information and will not have any personal health information. To further ensure participant privacy, we will encourage participants to change the settings on their phone to keep the body of text messages from appearing on the main screen when they receive a message.

In instances where something a participant says or does indicates potential harm to the participant or

others, we are legally required to report the concern. We have created an SOP for various scenarios (see Research Protocol appendix) that outlines the conditions and procedures for reporting in accordance with the South Africa's Children's Act.

Thus, while we acknowledge that a breach of confidentiality is possible, the likelihood is very low.

Compensation, Transportation, and Refreshments

We will provide participants R250 per study activity for time and travel. This is consistent with the compensation provided to participants in the larger/main NASA study. Additionally, participants who participate in the second set of IDIs for beta-testing the app will be given smartphone data to support their use of the app during that period. Participants in the pilot study will be given smartphone data to support their use of the app for 6 months.

We will arrange for a registered and reliable transport company to collect the participants (and their parent/ legal guardian / caregiver) in their area of residence and bring them to the Department of Psychiatry and Mental Health, University of Cape Town for the assessments. Having participants picked up and dropped off for their study visits ensures that they arrive on time and at the correct location. Providing reliable transport for participants to the study sites also significantly decreases the rate of no-shows and losses to follow-up. We will also provide participants with light refreshments after their participation in these study activities.

Informed consent

Prior to participating in this study, participants/caregivers will provide informed consent (and assent, if applicable). All adolescents under 18 years of age will be required to have parental/ legal guardian / caregiver consent. For these adolescents, we will seek parental/ legal guardian/ caregiver consent and the adolescent will be asked to provide assent to participate. As is done in the larger/main NASA study, informed consent forms will be provided in English and the study staff will be bilingual and able to ensure full comprehension. A study staff member will describe the study in detail to the participants, allow them ample time to read the consent form thoroughly (or have it read to them) and ask questions, and ensure that they understand the study purpose, procedures involved, and potential risks. Participants will be told that their decision to participate will not affect their current or future health care at the HIV clinic. Participants will have the opportunity to ask questions regarding the consent. Verification of comprehension of the consent form will be accomplished by asking participants to recall central points in the consent process, including the purpose of the study, procedures involved, and potential risks. This verification will also provide an opportunity to clarify any points of confusion. Participants (or their parent/ legal guardian/ caregiver, if applicable) will sign two copies of the informed consent form, one for the study records and one to take for their personal documentation.

Statistical Analysis Plan

The study will enroll 50 adolescents and young adults with HIV into the study (25 males and 25 females based on self-reported sex assigned at birth). The study's sample size (n = 50) was selected to be large enough to reasonably evaluate the feasibility and acceptability of MASI while balancing budgetary constraints.

Descriptive summaries will be computed for all study outcomes with continuous variables summarized with means and standard deviations (or medians with interquartile range in the case of skewed distribution) and categorical variables summarized with counts and proportions. Outcomes will be summarized, stratified by treatment group, at each available study time point.

As a pilot study with a primary focus on feasibility and acceptability, the examination of MASI's preliminary efficacy will be exploratory. To explore MASI's preliminary efficacy on ART adherence and social support at 3- and 6-months, we will use linear mixed models to compare outcomes among participants randomized to MASI compared vs. the information-only control at each time point. Log transformed outcomes and alternative modeling approaches such as Poisson and negative binomial will be considered in the event that assumptions for the linear model are violated. All models will include a fixed effect for sex assigned at birth (stratification variable) and a random intercept term to account for correlation in the response due to repeated measures within study participants over time. A random slope for participant will also be considered, as will the covariance structure of the errors (e.g., exchangeable, autoregressive). Distribution of residuals will be examined to confirm that modeling assumptions are met. Because sample size is small (this study is not powered to detect clinically meaningful effect sizes) and the regression analyses are exploratory in nature, inference will focus on the size and direction of the total treatment effects rather than statistical significance.

Additional exploratory analyses will examine MASI's effects over time on HIV/AIDS knowledge and stigma using methods similar to those employed for adherence and social support outcomes. We will also conduct descriptive analyses examining trends and patterns in user engagement with various components of the MASI interface over time.