HPTN 112
Improving HIV prevention among heterosexual cisgender men seeking STI services in Malawi: examining the benefits, acceptability, and associated costs of a systems-navigator-delivered integrated prevention package

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A Study by the HIV Prevention Trials Network (HPTN)

Sponsored by:

Division of AIDS (DAIDS), United States (US) National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH)

Non-IND Study

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Version 2.0
19 December 2023

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PROTOCOL SIGNATURE PAGE

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I will conduct the study in accordance with the provisions of this protocol and all applicable protocol-related documents. I agree to conduct this study in compliance with United States (US) Health and Human Service regulations (45 CFR 46); applicable US Food and Drug Administration regulations; standards of the International Conference on Harmonization Guideline for Good Clinical Practice (E6); Institutional Review Board/Ethics Committee determinations; all applicable in-country, state, and local laws and regulations; and other applicable requirements (e.g., US National Institutes of Health, Division of AIDS) and institutional policies.

I have read and understand the information in this protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

_____
Name of Investigator of Record (print name)

_____ _____
Signature of Investigator of Record Date (DD/MONTH/YYYY)

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
AIDS	Acquired immunodeficiency syndrome
ARV	Antiretroviral
ART	Antiretroviral Therapy
CAB	Community Advisory Board
CAB-LA	Long-acting injectable formulation of cabotegravir
CBC	Complete blood count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments of 1988
CPQA	Clinical Pharmacology Quality Assurance
CRF	Case Report Form
CRM	(LOC) Clinical Research Manager
CRMS	(DAIDS) Clinical Research Management System
CRS	Clinical Research Site
CTA	Clinical Trials Agreement
CT/NG	Chlamydia trachomatis/Neisseria gonorrhoeae
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DBS	Dried Blood Spot
DHHS	US Department of Health and Human Services
DSMB	Data and Safety Monitoring Board
EQA	External Quality Assurance
EWG	(HPTN) Ethics Working Group
GCLP	Good Clinical Laboratory Practices
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
ICF	Informed Consent Form
IDI	In-depth Interview
IoR	Investigator of Record
IQA	(DAIDS) Immunology Quality Assurance
IRB	Institutional Review Board
LAI	Long-acting Injectable
LC	(HPTN) Laboratory Center

LDMS	Laboratory Data Management System
LL	Local laboratory
LOC	Leadership and Operations Center
LTF	Loss to Follow-Up
MO	Medical Officer
MoH	(Malawi) Ministry of Health
MOP	(HPTN) Manual of Operations
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
PRO	Protocol Registration Office
POC	Point of Care
RSC	Regulatory Support Center
SDMC	(HPTN) Statistical and Data Management Center
SSA	Sub-Saharan Africa
SSP	Study Specific Procedures (Manual)
SMC	Study Monitoring Committee
STI	Sexually Transmitted Infection
SOE	Schedule of Events
SOC	Standard of Care
SOP	Standard Operating Procedures
TLFB	Timeline Follow-back
QA	Quality Assurance
QC	Quality Control
US	United States
WHO	World Health Organization

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Improving HIV prevention among heterosexual cisgender men seeking STI services in Malawi: examining the benefits, acceptability, and associated costs of a systems-navigator-delivered integrated prevention package

SCHEMA

Purpose:	To evaluate the potential benefit(s), acceptability, and associated costs of a systems navigator-delivered HIV prevention intervention in promoting and supporting persistent use of evidence-based HIV pre-exposure prophylaxis (PrEP) among heterosexual cisgender men receiving care for sexually transmitted infections (STIs) in Lilongwe, Malawi.
Design:	Single site pilot effectiveness-implementation hybrid type 1 trial
Population:	The study population will consist of the following participant types: 1. HIV seronegative heterosexual cisgender males seeking STI services who have accepted PrEP services 2. Other key stakeholders relevant to systems navigation program implementation
Study Size:	Approximately 200 heterosexual cisgender males, presenting as HIV-seronegative and initiating PrEP (followed prospectively) and approximately 15 other key stakeholders.
Study Duration:	The proposed study duration is 15 months (65 weeks), including up to 39 weeks for participant recruitment. Seronegative participants will be on study for at least 26 weeks, and up to 52 weeks.
Study Location:	Bwaila STI clinic, Lilongwe, Malawi
Study Regimen:	Systems navigation integrated into PrEP services delivered at an STI clinic in promotion of persistent effective PrEP use - either daily oral, 2-1-1 event driven, or injectable. Navigators will: • conduct brief counseling (and risk-focused) sessions, • POC STI testing, • assess barriers of PrEP use, and contact persons who default from PrEP care to facilitate PrEP re-engagement, offering PrEP "restart" kits as appropriate.
Primary Objective(s):	• To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among heterosexual cisgender men seeking STI clinical services in Lilongwe, Malawi at 26 weeks. • To assess acceptability and barriers of implementing a systems-navigator delivered HIV prevention package among key stakeholders in the clinic and heterosexual cisgender men initiating PrEP at STI clinics.
Secondary Objectives:	• To assess feasibility of a future randomized controlled trial.

Exploratory Objectives:	• To assess prevention-effective PrEP use among heterosexual cisgender men initiating PrEP at STI clinics. • To assess PrEP modality preferences among heterosexual cisgender men initiating PrEP at STI clinics. • To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among heterosexual cisgender men seeking STI clinical services in Lilongwe, Malawi, at 39 and 52 weeks. • To quantify costs and resources necessary to develop and integrate a systems-navigator delivered HIV prevention package into an urban STI clinic, informing future cost-effectiveness model development. • To perform laboratory assessments that may include evaluation of factors related to HIV infection or other STIs; characterization of HIV in participants who acquire HIV; characterization of the host response to antiretroviral drugs; and evaluation of virologic, pharmacologic, or STI-based laboratory assays. • To evaluate event-driven PrEP drug concentrations within the context of TLFB reported PrEP use and sex acts. • To explore the perceived and experienced PrEP related stigma and potential influence of perceived gender norms on PrEP persistence among heterosexual cisgender men initiating PrEP at the STI clinic.

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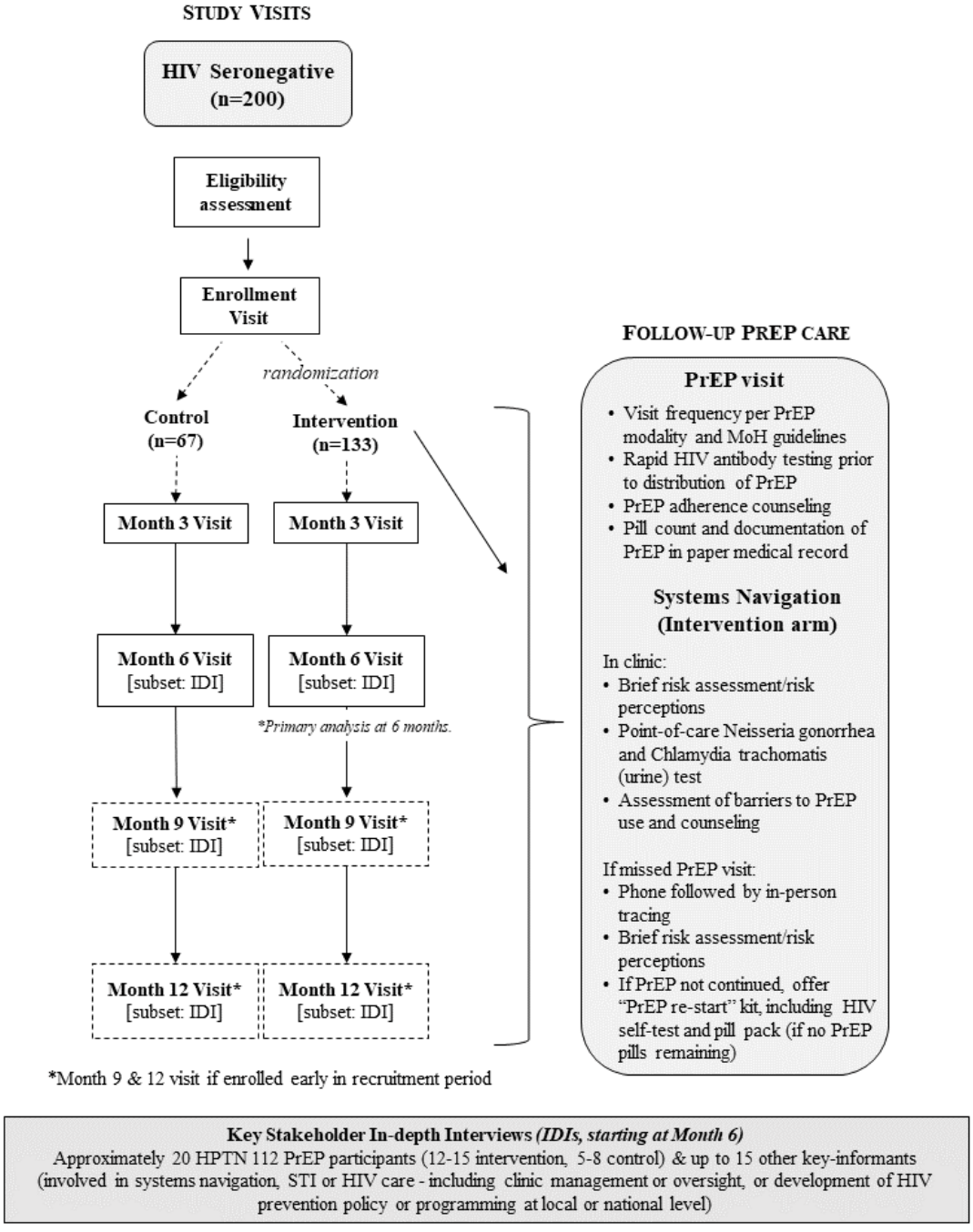
OVERVIEW OF STUDY DESIGN



Key Stakeholder In-depth Interviews *(IDIs, starting at Month 6)*
Approximately 20 HPTN 112 PrEP participants (12-15 intervention, 5-8 control) & up to 15 other key-informants (involved in systems navigation, STI or HIV care - including clinic management or oversight, or development of HIV prevention policy or programming at local or national level)

1.0 INTRODUCTION

Cisgender men who present to a sexually transmitted infection (STI) clinic in Malawi demonstrate risk for transmission and acquisition of HIV infection. Recent evidence suggests a small number of cisgender men will present with new onset or recognized diagnosis of HIV. The majority of cisgender men will not be living with HIV, but still at risk for HIV infection. This protocol is a pilot effectiveness-implementation hybrid-1 study. It describes research to assess the benefits, acceptability, and feasibility of a future larger trial of a systems navigation-delivered intervention, integrated into routine STI care as a strategy to engage heterosexual cisgender men in evidence-based HIV prevention activities, specifically biomedical pre-exposure prophylaxis (PrEP). The overall goal of this pilot study is to inform a future broader implementation science trial, engaging cisgender men from STI clinics to improve uptake and persistent use of PrEP, reducing incident infections among HIV-uninfected heterosexual cisgender men and their cisgender female sexual partners.

1.1 BACKGROUND AND RATIONALE

Despite dramatic reductions in HIV incidence globally, progress towards ending the epidemic have stalled. A vaccine has not yet been generated; evidence-based strategies include integrated biomedical and behavioral strategies. HIV status neutral interventions include effective treatment of HIV infection and provision of PrEP to people who are at high risk of acquiring HIV. The rollout of PrEP has been hampered by inconsistent referral, inadequate uptake, and poor persistence despite ongoing HIV risk.[1-6] It is necessary to identify patients at high risk of acquiring HIV, efficiently link them to appropriate prevention services, while maintaining access to those services throughout the period of HIV risk.

PrEP services were rolled out in 2020 in Malawi. The PrEP services target populations at high risk of HIV acquisition, which include individuals who buy or sell sex, key populations, sero-different couples, cisgender adolescent girls and young women, and STI patients.

Persons seeking STI services are a compelling population on which to focus HIV prevention resources; an incident STI is an objective indicator of unprotected sex and, in high HIV incidence settings, a reasonable proxy for HIV risk. In Malawi, persons with STIs are prioritized for HIV prevention, including PrEP, and PrEP was integrated into a Lilongwe-based STI clinic in November 2021.[7] STIs are managed using a syndromic approach hence STI diagnostic testing is not part of standard of care. Most patients (>80%) present with discharge or genital ulcer syndromes. HIV prevalence among STI patients is around 5-10% and our past research in this clinic demonstrates that about 0.5% of HIV seronegative patients have acute HIV infection, highlighting the importance of engaging this population in effective HIV prevention interventions.[8-10]

Our preliminary work integrating oral PrEP into a Malawi STI clinic suggests acceptability of PrEP provision alongside STI services among heterosexual cisgender men, and enthusiasm for highly effective,[11,12] and now approved for use long-acting injectable (LAI) PrEP. Likewise, published literature encourages an increase in integrated services to reduce the incidence of both HIV and STIs.[13] Although the World Health Organization includes persons with STIs as a priority PrEP population,[7] our ongoing study is one of the first to incorporate PrEP with STI clinics in sub-Saharan Africa (SSA).[14] Reflecting the demographics of persons seeking testing, >60% of the 150 enrolled PrEP users in our cohort are heterosexual cisgender males (unpublished). Through this work, we have identified important gaps in PrEP service delivery including drop-off of referral from clinic staff (only 20% of all PrEP-eligible persons receiving STI services were offered PrEP) and poor PrEP persistence.

Besides demonstrating persistent HIV risk within this population, with nearly one-quarter of cisgender male participants having an incident gonorrhea or chlamydia infection during the 6 months of follow-up, this work has also started to identify important barriers to persistent PrEP use among heterosexual cisgender males who initiate PrEP. Preliminary review of persistence data from an ongoing pilot study of PrEP in Malawi (unpublished) suggests that although 41/115 (35%) of cisgender men remained persistent on PrEP for 6 months after enrollment (adequate doses based on pill count and on-time follow-up consistent with adherence to daily oral PrEP), 17% were lost-to-follow-up immediately after initiating PrEP, and another 11% were lost-to-follow-up following their first (1-month) PrEP follow-up visit. Ongoing analysis of qualitative data from this same cohort suggests challenges with taking a pill every day, barriers in disclosing to friends and family, and changes in relationship status that influence perceived risk.

Fluctuations in HIV risk and perceived HIV risk influence both the initiation of and consistent effective use of PrEP. Historically, these dynamics have been evaluated only in sero-different couples or among heterosexual cisgender women. Tailored counseling may facilitate improved PrEP uptake and use, and even brief risk-reduction counseling sessions may be effective, particularly when delivered in so-called “teachable moments”, which may include the presentation with an STI.

Efficiently and effectively addressing barriers to uptake of PrEP ***and*** persistent use of PrEP is critical to improve HIV prevention outcomes, especially among historically understudied heterosexual cisgender men in SSA, including in Malawi, for whom healthcare engagement is sporadic. Our single-site pilot study is responsive to the HIV Prevention Trials Network (HPTN) call for concepts (fall 2022), which requested small pilot studies that focused on understanding the prevention opportunity for heterosexual cisgender men living in SSA – a population identified as an existing and important gap within network research in this region. We have further focused the population to cisgender men who are at increased risk of acquiring HIV, namely, cisgender men who are presenting to an STI clinic with symptoms consistent with an STI or a recent exposure to a person with an STI.

Our study addresses crucial network priority areas, specifically evaluating integrated strategies that improve sexual health outcomes related to HIV and non-HIV STIs.

1.2 RATIONALE FOR STUDY DESIGN

HPTN 112 is a pilot effectiveness-implementation hybrid type 1 trial designed to assess the feasibility and acceptability of a novel STI-clinic based intervention to facilitate rapid and continued engagement in effective HIV prevention services (PrEP), among heterosexual cisgender men. Although cisgender women in Malawi account for the majority of incident HIV, largely due to effective antenatal HIV screening, cisgender men make up a growing proportion of new infections. Failure to prevent infections among cisgender men, or rapidly diagnose and link cisgender men with prevalent infection to antiretroviral therapy (ART), fuels incident infections among cisgender women and contributes to the stagnating HIV incidence in Malawi. The STI clinic represents a unique clinical setting in which cisgender men with documented HIV risk are rarely directly engaged in effective prevention tools. Given the limited sample size, short recruitment period, and heterogeneity of determinants of persistent PrEP use across different populations, transgender persons and cisgender women are not included in this initial pilot.

Systems navigation and counseling is a theory-derived evidence-based intervention that could improve referral to, uptake of, and persistence of effective HIV prevention interventions including PrEP. Systems navigation includes identifying persons most likely to benefit from HIV prevention tools and helping them navigate complex, dynamic obstacles to uptake and retention. This intervention draws from a combination of social cognitive theory[15] and social identity theory,[16] using counseling and engagement to develop a person's capacity and confidence to remain engaged in PrEP care.

PrEP efficacy is associated with having adequate (effective or target) drug concentrations during periods of potential HIV exposure. Inadequate adherence to daily oral PrEP can lead to lower drug concentrations at anatomic sites of viral exposure, thus compromising PrEP effectiveness; the challenges associated with oral PrEP adherence may be mitigated by longer-acting agents, including LAI PrEP. Although LAI PrEP removes the need for daily dosing, timely injections are necessary to achieve and maintain target drug concentrations. Alternatively, so-called "on-demand" or "event-driven" PrEP, in which PrEP users take pills only around the time they have sex, may be protective against HIV acquisition and, depending on frequency of sex acts, could increase the interval between dosing compared to daily oral PrEP. However, data for use of this strategy has been mixed, and little is known about acceptability and effective use among heterosexual cisgender men. By triangulating timing of self-reported sex acts, self-reported event-driven PrEP use, and PrEP drugs levels collected at quarterly intervals, this study will be able to explore how these measures can be combined to better evaluate prevention-effective event-driven PrEP use among men.

Importantly, although a registered product approved for use in Malawi, and eventually expected to be available to cisgender men, LAI PrEP is not currently available at the time of this writing. It is expected to become an option for cisgender men during the proposed enrollment period. All three types of PrEP available (or to be available) to participants in this study (daily oral, "event-driven", and LAI) are approved for use in Malawi. However, there are no prior studies documenting preference for, uptake of, or adherence to LAI PrEP (compared to daily oral or "event-driven") among heterosexual cisgender men. Our preliminary work in this clinic suggests that between 50-60% of cisgender men may prefer injectable PrEP over pills, but this has only been examined in a hypothetical scenario to-date. This study will provide crucial information regarding preferences for PrEP modalities in this understudied population.

Fluctuations in oral PrEP also expose patients to HIV risk.[17] As such, our study design integrates a "return-to-PrEP" kit, including a 14-day supply of oral PrEP and a home HIV test kit for participants who, after counseling sessions, decline interest in additional PrEP. Participants who no longer feel they need PrEP are encouraged to return to the PrEP clinic and are offered this "re-start" kit alongside instructions for self-testing and use of the pill pack to facilitate immediate protection if they are not able to plan far enough to restart PrEP in a timely manner. This "re-start" kit will be provided by systems navigators (see Section 5.4).

Our STI-clinic based recruitment approach capitalizes on the synergistic co-STI/HIV epidemics globally and in the region and population of interest. Findings could inform a multi-site/multi-country implementation science study in which systems navigation is integrated into STI clinics as a strategy to recruit and retain high-risk heterosexual cisgender men in effective HIV prevention tools, including PrEP.

2.0 STUDY OBJECTIVES

The overall goal of this study is to evaluate the benefit(s), acceptability, and associated costs of integrating systems navigation and brief counseling into STI clinic based PrEP provision. The primary, secondary, and exploratory objectives of the study are listed below. Endpoints related to each objective are described in Section 8.2.

2.1 PRIMARY OBJECTIVE(S)

2.1.1 To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among cisgender heterosexual men seeking STI clinical services in Lilongwe, Malawi at 26 weeks.

2.1.2 To assess acceptability and barriers of implementing a systems-navigator delivered HIV prevention package among key stakeholders in the clinic and heterosexual cisgender men initiating PrEP at STI clinics.

2.2 SECONDARY OBJECTIVES

2.2.1 To assess feasibility of a future randomized controlled trial.

2.3 EXPLORATORY OBJECTIVES

2.3.1 To assess prevention-effective PrEP use among heterosexual cisgender men initiating PrEP at STI clinics.

2.3.2 To assess PrEP modality preferences among heterosexual cisgender men initiating PrEP at STI clinics.

2.3.3 To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among heterosexual cisgender men seeking STI clinical services in Lilongwe, Malawi at 39 and 52 weeks.

2.3.4 To quantify costs and resources necessary to develop and integrate a systems-navigator delivered HIV prevention package into an urban STI clinic, informing future cost-effectiveness model development.

2.3.5 To perform laboratory assessments that may include evaluation of factors related to HIV infection or other STIs, characterization of HIV in participants who acquire HIV, characterization of the host response to antiretroviral drugs, and evaluation of virologic, pharmacologic, or STI-based laboratory assays.

2.3.6 To evaluate event-driven PrEP drug concentrations within the context of TLFB reported PrEP use and sex acts.

2.3.7 To explore the perceived and experienced PrEP related stigma and potential influence of perceived gender norms on PrEP persistence among heterosexual cisgender men initiating PrEP at the STI clinic.

3.0 STUDY DESIGN

HPTN 112 is a single site pilot effectiveness-implementation hybrid type 1 trial enrolling heterosexual cisgender men presenting for STI care in Lilongwe, Malawi. HIV seronegative participants will be randomized (1:2) to standard of care PrEP services (SOC) or systems navigator-assisted PrEP care (intervention) as described briefly below.

Standard of care PrEP services include PrEP eligibility assessment, rapid HIV antibody testing prior to provision and/or refill of PrEP, and PrEP follow-up with a PrEP nurse in accordance with contemporary PrEP guidelines. Specifically, SOC services do not generally include POC STI testing (with the exception of rapid syphilis and Hepatitis B antigen testing, if kits are available, at PrEP initiation) nor tracing for missed PrEP visits.

Participants randomized to the SOC condition will receive these standard PrEP services as provided by the Malawi MoH.

The intervention package (intervention arm only) is integrated into PrEP visits and includes evaluation of barriers and facilitators to ongoing PrEP use, POC STI testing to inform counseling regarding ongoing PrEP care engagement, tracing for any missed PrEP visits, and offering a PrEP "restart" kit for cisgender men who choose to discontinue PrEP during the follow-up period. Recognizing increasingly cyclical PrEP use patterns, navigators serve as a direct entry point to retain or re-engage participants in HIV prevention care. Additional details regarding selection of systems navigators and specifics regarding the intervention package are described in Section 5.0.

All PrEP services, including determining PrEP eligibility and monitoring of PrEP use and safety, will be conducted by the Malawi Ministry of Health, per their PrEP management guidelines. No additional safety monitoring will be conducted to inform participant care or safety specific to PrEP through this study. All three types of PrEP available (or to be available) to participants in this study (daily oral, "event-driven", and LAI) are approved for use in Malawi.

Throughout the study design, we distinguish between PrEP visits and study visits. PrEP visits are conducted on a timeline determined by the MoH and should align with the modality of PrEP that a participant has selected. During a PrEP visit, the navigator will meet with the participant, discuss risk and PrEP use, and offer POC STI testing to inform the risk discussion. Navigators will conduct tracing activities for any missed PrEP visit, in accordance to PrEP-user stated preferences for tracing (see Section 5.0). Study visits, on the other hand, occur every 13 weeks regardless of PrEP modality, and are completed by study nurses. These visits include in-depth behavioral surveys and specimen collection. Participants receive a financial incentive to attend and complete the study visits, and these visits continue regardless of a participant's decision to continue or discontinue PrEP use. Tracing for missed study visits will utilize study staff – these staff members are distinct from Systems Navigators, who only trace for missed PrEP visits in the intervention arm. This distinction and separation is crucial to inform our primary outcomes (effect of navigation on PrEP persistence) and avoid contamination of interpreting the PrEP use outcomes in the context of financial incentives that are external to the study intervention.

In-depth qualitative interviews will be conducted with a subset of cisgender men who initiate PrEP (approximately 20 at last study visit) and with other key stakeholders (approximately 15) including persons involved in provision of navigation, STI or HIV care or prevention (including clinic management or oversight), or development of HIV prevention policy or programming at local or national level. The purpose of these interviews is to explore facilitators and barriers to acceptability of the intervention components.

3.1 PARTICIPATING SITE

Bwaila Sexually Transmitted Infection (STI) Clinic is located in Lilongwe, Malawi. Bwaila STI Clinic is an affiliate of UNC Project Malawi. UNC Project Malawi is the official CRS for this study and will be registered to the protocol and responsible for data management and LDMS.

The Bwaila STI clinic is located within the Bwaila Hospital, a free secondary level public facility. The Bwaila hospital is in a busy town area in the center of the Lilongwe city, the capital city of Malawi. It has a catchment population of about 130,000 people. At the Bwaila STI clinic, PrEP services are co-located within the STI clinic, an integrated program launched in November 2021. HIV testing is standard of care and is offered as a routine opt-out service. HIV status ascertainment is around 98%. All STI patients who test HIV negative may be offered PrEP. On average, the STI clinic sees about 50 HIV seronegative patients per day of whom about 45% are cisgender male. Among the seronegative patients, about 5-10% accept to start PrEP daily. Hepatitis B testing before PrEP initiation is standard of care however, clients can start PrEP and be tested later if testing is unavailable at initiation.

The UNC Project Malawi works in collaboration with a Community Advisory Board (CAB). The CAB consists of diverse members that span across all demographics including adolescents and backgrounds. The CAB meets routinely every quarter and when a need arises. Aside from the general CAB, the UNC Project Malawi CAB has an adolescent arm called the Adolescent CAB, which provides guidance on studies that involve adolescents. The protocol team held a consultative meeting with the UNC Project Malawi CAB where the members were briefed about the HPTN 112 protocol. CAB members provided feedback on the general approach of the study and guidance on how to select appropriate system navigators. In addition, the members provided guidance on the best ways for the system navigators to approach participants in their communities. In addition, the Malawi MoH Department of HIV, Viral Hepatitis and STIs provided their support for the study. Finally, the protocol team will brief the Lilongwe District Health Office Research Committee on the HPTN 112 protocol and obtain a letter of support on the same.

3.2 STUDY DURATION

The proposed study duration is approximately 15 months (65 weeks) total, with individual participants being followed on study for at least 26 weeks and up to 52 weeks. We expect accrual to require up to 39 weeks.

4.0 STUDY POPULATION

Cisgender men account for approximately half of all persons seeking STI services at Bwaila STI clinic (approximately 15,000 annual visits) and nearly all identify as only having sex with cisgender women. Given the limited sample size, short recruitment period, and heterogeneity of determinants of persistent PrEP use across different

populations, transgender persons and cisgender women are not included in this initial pilot. Furthermore, our past work in this space suggests that individuals who identify as gender non-binary typically seek sexual health services at other area drop-in centers, rather than the STI clinic where this study will be conducted.

Approximately 200 HIV seronegative cisgender individuals assigned male at birth (here and throughout referred to as cisgender men) who have presented to care for STI management will be included in this study. Participants will be selected for the study according to the criteria in Section 4.1 and 4.2 and the co-enrollment guidelines in Section 4.4. Participants will be recruited, eligibility will be determined, and then enrolled as described in Section 4.3.

Requirements related to participant retention and withdrawal from the study are described in Sections 4.5 and 4.6, respectively. All participants will be recruited from the Bwaila STI clinic (Section 3.1). A subset of HIV seronegative participants will also be interviewed (approximately 20) during study participation.

We will also interview key stakeholders relevant to the adoption and implementation of systems navigation as a strategy to improve HIV prevention integration in the STI clinic.

4.1 INCLUSION CRITERIA

In HPTN 112, there are two populations eligible to participate in the study, 1. Persons initiating PrEP (n=200, 20 of whom will also participate in stakeholder interviews), and 2. Other key stakeholders (approximately 15).

1. Cisgender adult and adolescent cisgender men who meet all of the following criteria are eligible for inclusion in this study as a **participant initiating PrEP**:

1. Age ≥18 years or age 15-17 (with assent and parent/guardian consent)
2. Able to provide informed consent
3. No plans to move outside study area for at least 26 weeks after study enrollment
4. Willing to provide contact/locator information, including phone number, to facilitate tracing
5. Willing to participate in study activities, including specimen collection
6. Willing to participate in study activities, including systems navigation, counseling, and POC STI testing
7. Sought STI clinic services within 7 days of enrollment
8. Initiated on PrEP at STI clinic within 7 days of enrollment*
9. Reports at least one cisgender female sex partner in the 6 months prior to enrollment
10. Self-identifies as heterosexual

***** *Newly initiating PrEP or re-initiating PrEP after at least 13 weeks from last PrEP use or injection.*

All participants will have been prescribed PrEP prior to enrollment. As such, they will have been deemed PrEP eligible according to contemporary Malawi PrEP guidelines. At time of writing, eligibility for oral PrEP includes:

1. HIV seronegative
2. At substantial risk for HIV, with prioritization of persons who:
    - Buy or sell sex
    - STI clients
    - Sero-different couples including HIV-negative people for whom their partner living with HIV is: not on ART, on ART <6 months, has high viral load, or is non-adherent to ART.
3. No concern for acute HIV infection based on provider screening for signs or symptoms consistent with acute HIV.
4. Willingness to attend scheduled PrEP visits
5. No contraindication to use of TDF and 3TC
6. Bodyweight ≥30kg (66lbs.)
7. No known renal diseases
8. No diabetes mellitus

2. Individuals who meet all of the following criteria are eligible for inclusion in this study as **other key stakeholders**:

1. Age ≥18 years at the enrollment visit
2. Able to provide informed consent
3. Involved in provision of clinical service navigation, systems navigation, STI or HIV care or prevention (including clinic management or oversight), or development of HIV prevention policy or programs at local or national level

4.2 EXCLUSION CRITERIA

Exclusion for the two participant groups is as follows:

1. Cisgender adult and adolescent men who meet any of the following criteria are ineligible for inclusion in this study as a **participant initiating PrEP**:

1. Appearance of psychological disturbance or cognitive impairment that would limit the ability to understand study procedures, as determined by the investigators
2. Any other condition that, in the opinion of the investigators, would make participation in the study unsafe, or otherwise interfere with the conduct of the study

3. Current participation in any HIV prevention study or other study considered to interfere the interpretation of study outcomes (see Section 4.4).

2. Individuals who meet any of the following criteria are ineligible for inclusion in this study as **other key stakeholder**:

1. Appearance of psychological disturbance or cognitive impairment that would limit the ability to understand study procedures, as determined by the investigators
2. Any other condition that, in the opinion of the investigators, would make participation in the study unsafe, or otherwise interfere with the study activities

4.3 RECRUITMENT PROCESS

Details of study recruitment flow are specified in Appendix I.

This study includes two types of participants:

1. Approximately 200 HIV seronegative cisgender male PrEP eligible participants will be recruited. This will include heterosexual cisgender men who report to the STI clinic seeking services and are PrEP eligible according to Malawi HIV testing algorithms. PrEP eligible participants enrolling in this study should be initiating PrEP.
2. Approximately 15 other key stakeholders will be recruited using purposive sampling to engage stakeholders with diverse roles, responsibilities, and exposure/experience with the intervention.

We anticipate that recruitment of participants will take place for up to 39 weeks. All participants will be enrolled from the Bwaila STI clinic. The site will use its previously established systems for recruiting participants. As part of the routine system, individuals with a suspected STI are referred to the STI clinic from the outpatient department. Upon arrival at the STI clinic, the patients are registered into the STI clinic electronic medical registration (EMR) system and escorted to the waiting area. At the waiting area, patients receive group health education. During the group health education, clinic staff will introduce the HPTN 112 study in brief through oral and written (study flyer) description to prospective participants and will encourage cisgender men to participate in eligibility determination activities at the study site. Staff will inform cisgender men that those who are interested in the study will receive more information about the study through a one-on-one discussion.

After group health education, which includes introduction to any enrolling study at the clinic, as part of local standard of care, the patients undergo HIV testing using the Malawi HIV Testing and Counselling guidelines, including risk reduction counselling as part of routine services. All HIV seronegative patients are offered a brief discussion of

PrEP services and HIV risk, based on self-reported risk behaviors and assessed for PrEP eligibility as standard of care. Those who are interested are referred to the PrEP nurse for discussion and initiation. After being started on PrEP by the nurse, potential participants will be approached by study staff and receive information regarding the study and undergo eligibility assessment. This form will include all data relevant for determining eligibility; no identifying information will be included on this form. If eligible and interested in participation, potential participants will undergo study consent, enrollment, and randomization procedures (see Section 6.1). Systems navigators will engage cisgender men randomized to the intervention arm at this point.

A sample of the assent and consent forms can be found in Appendices V and VI. If during the eligibility assessment, they are found to be ineligible, recruitment will be discontinued, and participants will be dismissed.

Throughout enrollment procedures, study staff will emphasize that enrollment in the trial does not require a commitment to use of PrEP throughout the follow-up period. Participants will also be reminded that study remuneration is being provided at the designated quarterly study visits, not as part of their scheduled PrEP care.

4.4 CO-ENROLLMENT GUIDELINES

HIV seronegative participants should not be currently participating in any HIV prevention study and may not enroll in any HIV prevention trial during this study; these guidelines are needed to facilitate high levels of retention, and to avoid confounding in the interpretation of the primary and secondary endpoint data. Limitations are made explicit in the informed consent forms.

Participants can participate in this study if they are enrolled in other studies not offering HIV prevention, such as observational studies. Examples of excluded studies including any phase 1 HIV vaccine study, any assessment of novel biological products, and studies with multiple visits, the engagement in which could influence interpretation of HPTN 112 study outcomes. All co-enrollments should be discussed and approved by the principal investigator in coordination with select members of the protocol team. Studies that include any intervention, including behavioral interventions that may influence HIV or STI prevention outcomes, can be assessed on a case-by-case basis.

4.5 PARTICIPANT RETENTION

4.5.1 Retention in PrEP care

As part of the proposed intervention, systems navigators will be tasked with tracing for missed PrEP visits, as described below (section 5.2). Tracing activities are conducted in accordance to the stated preference of the participant, and can include phone and in-person tracing. Notably, these PrEP tracing tasks are distinct from study follow-up visits, which will occur separately from PrEP visits. The separation (see Section 3.0) is designed to avoid conflating PrEP persistence

outcomes with study activities, the latter of which have remuneration provided. PrEP visit reminders (and tracing) will coincide with the PrEP follow-up schedule as dictated by the Malawi Ministry of Health.

4.5.2 Retention in study

Participants do not need to continue PrEP to remain in the study. Once a participant enrolls in this study, the study site will make every effort to retain him for at least 26 weeks of study follow-up to minimize possible bias associated with loss-to-follow-up.

Study staff will remind participants of upcoming visits using phone calls and will trace (phone) participants who miss a visit within 7 days post scheduled visit date. Participants who do not report to the study site within 14 days of a scheduled visit will be traced physically by study staff. All tracing is conducted with attention to confidentiality, through which neither the identity of the participant nor the nature of the study, would be disclosed to any person without the explicit guidance from the participant (or their guardian). All participants provide preferred locator information (including mode of tracing, location at which one could be traced, names or contact information of persons who can be contacted in the event participant is not located) and tracing attempts follow these preferences. Locator information and preferences are updated at each study visit. Specifically, study staff discuss how they should identify themselves when texting, calling, or visiting a participant and staff confirm with the participant whether limited messages can be left with specific contacts. If the participant is aged 15-17, the guardian's preferences for tracing will be recorded and updated at each contact as needed. A basic philosophy of the retention strategy is that follow-up begins at recruitment and is a priority at every visit. Components of such procedures include:

- Thorough explanation of the study visits schedule and procedural requirements during the informed consent process, with re-emphasis at each study visit.
- Collection of detailed locator information at the enrollment visit, with active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other venues that participants frequent.
- Use of appropriate and timely visit reminder mechanisms.
- Visit calendars and flyers or other handouts will be offered at enrollment to assist with retention.

- Immediate and multifaceted follow-up on missed visits, including outreach/locator efforts such as phone calls, text messages, or home contacts, consistent with stated participant (or guardian) preference.
- Mobilization of trained outreach workers or "tracers" to complete in-person contact with participants at their homes and/or other community locations.

- Regular review of follow-up procedures and current status by site leadership and staff.

- Regular communication with the study community at large to build trust and increase awareness about the study and prevention of HIV. Specifically, briefing of CAB, relevant stakeholders working withing catchment from which potential participants may arise, and local Chiefs and other influential gate keepers.

4.6 PARTICIPANT WITHDRAWAL

Regardless of the participant retention methods described above, participants may voluntarily withdraw from the study for any reason at any time. The investigators also may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, DAIDS Medical Officer, Statistical and Data Management Center (SDMC) Protocol Statistician, and LOC Clinical Research Manager (CRM). Participant non-adherence to the intervention is not a reason for participant withdrawal from the study. Additionally, seronegative participants must agree to initiate PrEP to enroll in the study, but they do not have to continue to take PrEP to remain on study.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site institutional review boards (IRBs) or ethics committees (ECs) terminate the study prior to its planned end date.

Participants will not be considered withdrawn unless the participant actively withdraws or dies, or the investigators withdraw the participant for the reasons given above. Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study early, and study staff will record the reason(s) for all withdrawals from the study in participants' study records.

5.0 STUDY INTERVENTION PACKAGE

The study intervention components, as described below, are integrated into the PrEP visit for participants randomized to the intervention arm. Timing for PrEP visits will be determined by the MoH PrEP nurse, aligning with contemporary recommendations for PrEP follow-up. According to the Malawi Ministry of Health PrEP program, persons who initiate oral PrEP are scheduled for PrEP follow-up visits at months 1, 3 and every 3 months thereafter. Injectable PrEP guidelines are not yet available but are expected to include a visit at 1-month and then every two months thereafter, aligning with scheduled

injections. The study intervention will not interfere with regular PrEP care – PrEP nurses will still proceed with any PrEP adherence counseling as well as any HIV risk reduction counseling consistent with Malawi PrEP guidelines at each PrEP visit.

The study intervention package includes: 1. Access to a systems navigator, intended to engage with participants at each PrEP visit and who can trace participants who do not attend a scheduled PrEP visit; 2. POC STI testing; and 3. A PrEP re-engagement or "re-start" kit offered to participants who choose to stop PrEP.

Study intervention activities occur primarily at the Bwaila STI clinic, with the notable exception of tracing for missed visits, which fundamentally will occur in the field. PrEP visits, and any associated meetings with systems navigators, will occur at the Bwaila STI clinic, whereas HPTN 112 study visits (conducted by non-navigator study staff), will occur in a separate building. The schedule and content of study visits is further specified in Section 6.3, and occur quarterly regardless of a participants' ongoing PrEP use or PrEP schedule.

5.1 SYSTEMS NAVIGATORS: SELECTION AND TRAINING

Navigators will be cisgender male and will be selected from the community with guidance from the Community Advisory Board (CAB). Navigators must be knowledgeable about the community's dynamics and reflect the demographics of the target population. They will undergo extensive training including but not limited to: basic knowledge of STIs, HIV, and PrEP; PrEP modalities, including potential benefits and expected challenges; motivational interviewing; psychosocial counselling; techniques for active listening and rapport building; and HPTN 112 procedures. Although not required, navigators may themselves have been previously or currently prescribed PrEP. The navigators will also be trained regarding personal safety, discrete tactics for follow-up tracing, and confidentiality. These components and attributes have been developed in coordination with local CAB members. All training materials will be developed in advance of study implementation with a separate Systems Navigation Manual, the content of which will include a series of didactics as well as role playing and direct observation. Navigators will receive periodic refresher training and regular evaluations.

Navigators engage with participants during PrEP visits (and in the field for tracing related to a missed PrEP visit) – although these are activities intentionally distinguished from study visits (see Appendix I). Because this protocol is still considered research, all navigators will receive training related to ethical conduct of clinical research.

5.2 SYSTEMS NAVIGATORS: COUNSELING AND TRACING

Participants meet with a systems navigator after enrollment into the study (and randomization to intervention arm). Navigators help identify motivators for PrEP use and potential barriers to continued consistent use. During meetings with

participants, the navigator will use a standardized list to evaluate progress or barriers to PrEP and persistent effective PrEP use, formulating plans to overcome any identified barriers (i.e., offering reminders for appointments, assistance identifying champions to help support and encourage PrEP use, or adherence strategies to improve use of PrEP as prescribed).

The navigator will meet with the participant only after they are enrolled in the study and then at each subsequent PrEP visit (see Appendix I) to formulate plans and strategies for ongoing PrEP use. Contact between PrEP visits will be tailored to participant needs, with the goal of maintaining regular contact and facilitate PrEP engagement, as informed by the elicited barriers to persistent PrEP use.

Intervention arm participants who miss a scheduled PrEP visit, typically considered 7-calendar days past a scheduled date, may be traced by navigators. Tracing efforts will be conducted in a manner consistent with the participant's stated preferences in terms of mode (phone, text message, in-person), time of day, and location if physical tracing is conducted. As described above, navigators receive training in confidentiality and discretion in any tracing attempts. All tracing is conducted with attention to confidentiality, through which neither the identity of the participant nor the nature of the study or reason for outreach, would be disclosed to any person without the explicit guidance from the participant (or their guardian). Navigators will first attempt phone and text messages, with additional in-person tracing attempts if no response or return to care and stated as an option when locator information is collected. Locator information and preferences are updated at each encounter. Specifically, navigators discuss how they should identify themselves when calling or visiting a participant and whether limited messages can be left with specific contacts. If the participant is aged 15-17, the guardian's preferences for tracing for any missed PrEP visit will be recorded and updated at each contact as needed.

Given the potential field-presence of System Navigators, similar procedures as those outlined in Section 4.5.2 will be conducted for community sensitization, including regular communication with the study community at large, briefing of CAB, engaging relevant stakeholders working withing catchment from which potential participants may arise, and alerting local Chiefs and other influential gate keepers. These procedures help to maintain the safety of field-based navigator tasks, further detailed in Section 10.3.

5.3 RISK ASSESSMENT AND POC STI TESTING

At each PrEP visit or tracing contact for a missed PrEP visit, participants will complete a brief risk assessment, with the assistance of the navigator. This assessment will capture and characterize HIV risk of sexual behaviors of the participant (i.e., new partners, partners with unknown or known HIV infection, condomless sex, sex while intoxicated, etc.), as well as perceived risk of HIV, and self-reported PrEP use. POC urine chlamydia and gonorrhea tests will be done in

addition to STI symptom assessment. *All HIV testing for PrEP care is conducted by Malawi MoH HIV Testing and Counseling – there is not additional HIV testing done by navigators as part of PrEP visits.*

All STI test results obtained through study visits, including POC STI testing, will be returned to HIV seronegative participants. Especially in the event a participant does not receive their results at the clinic, systems navigators will ensure their delivery and accompanying referral for treatment if indicated. The combination of rapid STI test results, self-reported risk, risk perception, and PrEP use will be used to guide structured brief counseling sessions regarding ongoing risk, PrEP use, and identify strategies or barriers to PrEP engagement (as above).

5.4 PrEP RE-ENGAGEMENT AND "RE-START"

For participants who choose to discontinue PrEP, navigators serve as a point of contact for re-engagement and will encourage participants to re-initiate PrEP if or when HIV risk resumes. It is expected that most participants who choose to discontinue PrEP will not attend their scheduled PrEP visit, and thus the decision to discontinue PrEP will often be identified at the point of navigator-initiated tracing (see above). Any participant who discontinues PrEP will be offered a PrEP "re-start" kit, which include a supply of oral PrEP, an HIV-self test, and brief instructions to facilitate safe immediate restart in the event that risk recurs without their first re-engaging in clinic-based PrEP care. Acceptance and use of this kit will be explored in subsequent study visits.

6.0 STUDY PROCEDURES

An overview of the study visits and procedures is presented in Appendix II with expected visit flow for HIV seronegative participants described in Appendix I. Presented below is additional information on visit-specific study procedures. Visit windows can be found in Section 6.8 and visit coding is described in the SSP Manual.

6.1 DETERMINATION OF ELIGIBILITY

For each participant, independent written informed consent will be obtained before any study procedures are initiated. Eligibility determination procedures may occur over one or more visits up to and including the day of Enrollment. Enrollment must occur within 7 days of eligibility determination. For most participants, eligibility determination procedures will occur on the same day as study enrollment.

Eligibility determination includes assessing if a STI clinic patient has been offered PrEP (and thus deemed eligible for PrEP according to local guidelines, Section 4.1), and confirming that additional study eligibility criteria are met. All HIV testing, a necessary component of PrEP eligibility determination, will be conducted by Malawi Ministry of Health staff as part of standard procedures for all patients presenting to care at the Bwaila STI clinic. If any result or interpretation other than negative or non-reactive is obtained

for any HIV test, the person is not eligible for PrEP and thus not eligible for the study. Additional testing to confirm suspected HIV infection will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be referred for appropriate care, as necessary, through standard referral channels.

Those individuals who meet eligibility will be offered enrollment (see Section 6.2). Individuals deemed not eligible will be informed that they do not meet the eligibility criteria for the study and will be referred for appropriate medical care, if necessary.

6.2 ENROLLMENT VISIT

6.2.1 Enrollment for HIV seronegative participants initiating PrEP

Enrollment will occur following determination of study eligibility and after completion of full study consent. This visit may occur up to 7 days following eligibility determination. A participant will be considered enrolled after completing all informed consent activities, including randomization. All enrolled participants initiating PrEP will have undergone HIV antibody testing in accordance with local PrEP eligibility determination processes. As part of study participation, they will be evaluated for acute HIV infection with HIV RNA testing (see Section 9.1). Persons with any detectable HIV RNA from enrollment visit will be linked to appropriate HIV care. They will remain in the study for a maximum of an additional 26 weeks following seroconversion to facilitate additional testing and confirm viral suppression on antiretroviral therapy.

In both control and intervention arms, we will capture in-depth behavioral and health assessments, using validated scales where possible to facilitate exploration of predictors of PrEP persistence and inform specific objectives and strategies to improve psychosocial counseling interventions. To obtain more granular information regarding sexual activity, particularly relevant for cisgender men who choose event-driven oral PrEP, we will use a timeline follow-back (TLFB) in which self-reported sex acts over the past 30-days are captured in a calendar format.

Administrative, Behavioral, and Regulatory Procedures:

- Informed consent
- Locator information
- Behavioral risk, risk perceptions, and 30-day health assessment
    - timeline follow-back (TLFB; sex acts)
    - substance use
    - mental health
    - anticipated and experienced PrEP-related stigma
    - anticipated and experienced HIV-related stigma
    - gender norms
- PrEP use assessment*
- HIV risk reduction counseling

**The PrEP use assessment is a basic assessment of if the individual is using PrEP, self-reported adherence, and other related factors.*

Clinical Procedures:

- Symptom-driven physical examination
- Blood collection
- Urine collection

Laboratory Procedures:

- HIV rapid antibody testing
- HIV RNA
- Chlamydia trachomatis/Neisseria gonorrhoeae (CT/NG)
- Syphilis testing (RPR & reflex TPPA if appropriate)
- Plasma storage
- Urine storage
- Dried blood spot (DBS) storage

6.3 FOLLOW-UP VISITS

Study specific assessments will be conducted separately from STI-clinic based PrEP visits. The proposed study duration is approximately 15 months (65 weeks) total, with individual participants being followed on study for at least 26 weeks and up to 52 weeks, depending on the time at enrollment. Recruitment will be conducted within approximately 39 weeks.

Any participant who has had a reactive/positive HIV test during PrEP follow-up will have further testing to confirm infection. In all cases, confirmation of infection requires testing samples collected on two different dates.

In both control and intervention arms, study specific visits will be conducted as follows:

6.3.1 Quarterly visits (Weeks 13, 26, 39* and 52*)

The following procedures will be conducted at each quarterly visit:

Administrative and Behavioral Procedures:

- Locator information (if location has changed)
- Behavioral risk, risk perceptions, and health assessment
    - 30-day timeline follow-back [TLFB] (sex acts and PrEP use)
    - substance use
    - mental health
    - anticipated and experienced PrEP-related stigma
    - anticipated and experienced HIV-related stigma

    - gender norms
- PrEP use assessment
- HIV risk reduction counseling

Clinical Procedures:

- Symptom-driven physical examination
- Blood collection
- Urine collection

Laboratory Procedures:

- HIV rapid antibody testing
- Syphilis RPR & reflex TPPA if appropriate
- CT/NG (if >2 weeks since testing conducted at PrEP visit)
- Plasma storage
- Urine storage
- DBS storage

**A subset of participants will also have a visit at Weeks 39 and 52, if the window of study follow-up allows. Participants enrolled in the first 13 weeks of recruitment will be followed for 52 weeks and those enrolled during the first 26 weeks of recruitment will be followed for 39 weeks. The remaining participants will be followed for 26 weeks total follow-up.*

Identical procedures will occur at Weeks 13, 26, 39, and 52, with the notable exception that a subset of participants will be asked to engage in an in-depth interview during their final visit (Week 26, 39, or 52).

6.4 PROCEDURES FOR PARTICIPANTS WITH SUSPECTED OR CONFIRMED HIV INFECTION

The following sections relate specifically to HIV seronegative participants initiating PrEP.

6.4.1 Enrollment

HIV testing will be performed to identify persons with HIV infection prior to enrollment, in line with Malawi PrEP eligibility and HIV testing guidelines (Section 4.3). Individuals who have one or more reactive/positive HIV tests at eligibility assessment (prior to enrollment) are not eligible to participate in this study as PrEP participants. Per current Malawi PrEP eligibility criteria (Section 4.1), PrEP should not be offered to persons with signs or symptoms consistent with acute (pre-seroconversion) HIV infection. All enrolled HIV-seronegative participants will be screened for acute HIV infection with HIV RNA testing (Section 9.1), regardless of signs or symptoms, as part of study procedures. Persons with detectable HIV RNA from enrollment visit will be linked to appropriate HIV care and followed as described in Section 6.1.

6.4.2 After study enrollment

Participants will be tested for HIV at all follow-up PrEP visits prior to distribution of PrEP medication, per Malawi standards. Participants will be tested for HIV at all study visits, regardless of HIV testing results from PrEP visits. Participants who have any reactive/positive HIV test result during follow-up visits will be referred for care. These participants will have further testing to confirm infection and will be followed quarterly up to approximately 26 weeks to assess viral suppression. In all cases, confirmation of infection requires testing samples collected on two different dates.

6.5 OTHER STUDY PROCEDURES

6.5.1 Sexually transmitted infections

Testing for CT/NG and syphilis will occur throughout the study. Testing will be performed at LL. Intervention arm participants who have been tested within the two weeks prior to a study visit as part of their PrEP care will not be re-tested for CT/NG. Syphilis testing may be repeated as the PrEP clinic uses POC tests that are not entered into Laboratory information systems and thus cannot be captured other than self-report/paper medical record. POC test results documented in participant records may be extracted using case report forms, however, all CT/NG and syphilis results performed at LL will be entered into appropriate study databases, extracted from existing laboratory information systems. Results will not be returned same day, however, participants who test positive for an STI at study visits will be informed of their result and be referred for treatment as per local guidelines.

6.5.2 HIV and risk reduction counseling

PrEP visits: Participants randomized to the standard of care arm who remain engaged in PrEP care will receive HIV testing and counseling, as well as any risk reduction counseling, from MoH staff and PrEP nurses (respectively) in accordance with local policy and guidelines. Participants randomized to the intervention arm will similarly receive HIV testing and counseling and PrEP counseling from MoH staff, as well as relevant counseling through systems navigation.

Study visits: Standard pre- and post-test counseling will be provided as part of HIV testing conducted at each study visit (see Section 6.3). All participants will be offered condoms.

6.6 QUALITATIVE DATA COLLECTION

To assess the acceptability of the intervention, individual semi-structured interviews will be conducted with stakeholders, including enrolled participants (during final study visit), and other clinic-based key stakeholders who will be engaged during the final stages of intervention follow-up. Stakeholders include key personnel as described in Section 4.1.

Participation of all stakeholders will be entirely voluntary. The subset of PrEP user participants will assent and/or consent to participate in their enrollment consent, but can

opt out upon being approached for an interview. If other stakeholders choose not to participate, he/she will experience no penalty or loss of employment or benefits. Procedures will be undertaken to ensure that no penalties are incurred nor pressure exerted by supervisors. The informed consent process for interviews will be conducted in a location that assures adequate privacy and confidentiality.

All interview transcripts will be stripped of personal identifiers. Reports and publications will be thoroughly redacted to confirm that no identities can be discerned.

Semi-structured interviews will follow a standard guide that includes probes and queries specific to stakeholders. They will explore experiences with the intervention, perceived barriers to persistent PrEP engagement among the target population, and potential barriers or facilitators to scaling or sustaining the intervention. Specifically, interviews will explore how the intervention successfully or unsuccessfully addresses barriers or enhances facilitators of PrEP uptake and persistent effective use. Barriers will be also assessed through the barrier questionnaire with the participant systems navigators' data forms/log books, and interviews with additional stakeholders.

All interviews will be audio-taped, translated, and transcribed by qualified personnel, with any identifiable information redacted from transcripts prior to dissemination for analysis.

6.7 COST AND RESOURCE DATA COLLECTION

We will embed empirical costing into study procedures. Costs will be collected prospectively in two ways: micro costing and time-and-motion logs. Micro-costing involves "direct enumeration" for consumed inputs, an ingredients-based approach. We will quantify resources associated with the development and implementation of our intervention. We will also extract data from project expenditure and management records, including purchase logs and human resource records. Time-and-motion assessments record how involved parties (navigators) divide time among navigation-related tasks, reliably apportioning effort relevant to implementing the intervention. This includes time for trainings, counseling, tracing, and other related tasks. No formal modeling is proposed as part of this protocol.

6.8 VISIT WINDOWS

For each required study visit, there is an allowable visit window specifying on which study days (post-enrollment) the visit is "allowed" to be completed. The allowable visit windows are contiguous from visit to visit, and do not overlap. Within each allowable visit window, there is a target visit window and study visits should ideally be conducted within this window. These windows are outlined in the table below. If more than one visit is necessary to complete all visit procedures, these could be completed during multiple days within the allowable visit window.

Table 1. Visit Window Schedule

Visit	Target Visit Day	Target Visit Window	Target Visit Window Days	Allowable Visit Window
Eligibility Determination	--	--	Up to 7 days before enrollment	--
Enrollment	Day 0	--	0	0
Week 13	Day 91	-21/+21	Day 70 – 112	Day 70 - 153
Week 26	Day 182	-21/+21	Day 161 - 203	Day 154 - 244
Week 39 (optional)	Day 273	-21/+21	Day 252 - 294	Day 245 - 336
Week 52 (optional)	Day 365	-21/+21	Day 344 - 386	Day 337 – 427

6.9 INTERIM CONTACTS AND VISITS

Interim contacts and visits (those between regularly scheduled follow up visits) may be performed at participant request or as deemed necessary by the IoR or designee at any time during the study. All interim contacts and visits will be documented in participants' study records and on applicable CRFs.

Some interim visits may occur for administrative reasons. For example, the participant may have questions for study staff. Interim visits at which no data are collected are not documented on CRFs. Other interim contacts and visits may occur in response to social harms experienced by study participants. When interim contacts or visits are completed in response to participant reports of social harms, study staff will assess the reported event, record the event on the CRF, and provide or refer the participant to appropriate medical care.

7.0 MONITORING AND ADVERSE EVENT REPORTING

7.1 ADVERSE EVENT REPORTING

As this study only involves low-risk activities (recruitment activities; testing for HIV and STIs; questionnaires; support for linkage-to-PrEP, PrEP engagement, and PrEP adherence) and contains no biomedical intervention or clinical care (PrEP prescription or other medical treatment), standard adverse event reporting and monitoring will not be undertaken. Any product related to this study (i.e. PrEP) is not being offered or administered directly by the study staff. All drugs used by participants in this study (i.e., PrEP, STI treatment) for the prevention of HIV or management of STIs, have regulatory approval for this purpose in Malawi and have well-established safety profiles. All safety monitoring of these approved drugs will be at the discretion of Malawi Ministry of Health.

Confidential HIV and STI surveillance reporting will be done according to local regulations. Participants will be reminded of these requirements via the Informed Consent Form.

7.2 MONITORING AND CLINICAL DATA REVIEW

The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the protocol team if unexpected concerns arise. Sites are required to have detailed SOPs describing methods for social harms reporting to ensure that social harms are reported and managed in accordance with the protocol and for alerting the Protocol Team if unexpected concerns arise. Study participants will be provided a 24-hour telephone number and contact information and instructed to contact the study clinician to report any social harms they may experience. For life-threatening events, they will also be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation where the study clinician is based, and to request that the clinician be contacted upon their arrival.

The SDMC will prepare routine study conduct and social harms reports for the Study Monitoring Committee (SMC), which will meet by conference call approximately every 6 months. More frequent or *ad hoc* reviews may be conducted by the SMC as needed. A recommendation to stop the trial may be made by the SMC, if warranted.

7.3 SOCIAL IMPACT REPORTING

It is possible that participants' involvement in the study could become known to others, and that a social harm may result (i.e., because participants could be perceived as having HIV or at increased likelihood for HIV acquisition). For example, participants could be treated unfairly, or could have problems being accepted by their families and/or communities. Although self-identification as heterosexual is an inclusion criterion, it is possible that cisgender male participants may disclose having sex with other men or transgender individuals, including naming men as recent partners. Given the fact that homosexuality is illegal in Malawi, extensive care will be taken to preserve confidentiality and safety of all participants. All staff, including systems navigators, will be informed of the sensitive nature of all disclosed sexual activities and will be trained in the appropriate conduct of clinical research to treat all participants fairly and professionally. Reporting of any participant-reported homosexual activity is not required of research studies.

Research staff will be trained to recognize, collect, and report social impacts, and provide referrals for counseling and social service support, if necessary. Any social harm that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the site's IRBs at least annually, or according to their individual requirements. Participants could also benefit from the study in various ways. Therefore,

both social harms and benefits due to participation in the study will be collected and reported on CRFs during regular visits. In the event that a participant reports a social harm, every effort will be made by study staff to provide appropriate care and counseling to the participant as necessary, and/or referral to appropriate resources for the safety of the participant. The site will provide such care and counseling in accordance with locally-available resources. While maintaining participant confidentiality, study staff may engage the CAB in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

8.0 STATISTICAL CONSIDERATIONS

8.1 REVIEW OF STUDY DESIGN

This is a single site, two-arm, randomized pilot study. Two-hundred eligible participants will be randomized to the intervention or standard of care arms in a 2:1 ratio. Randomization will be stratified by age (15-25, >25), and a permuted blocks design will be used to ensure balanced treatment assignments within each stratum. Age-based stratification was selected due to expected differences in effect of intervention and base-case PrEP persistence among younger compared to older cisgender men. We have opted for a 2:1 randomization to facilitate evaluation of our acceptability outcomes, which are only examined among persons randomized to the intervention arm.

8.2 OBJECTIVES AND ENDPOINTS

Further details on how these endpoints are defined and measured are included in the statistical analysis plan (SAP). Of note, we aim to use validated instruments whenever feasible.

8.2.1 Primary Objective(s) and Endpoints

8.2.1.1 To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among heterosexual cisgender men seeking STI clinical services in Lilongwe, Malawi at 26 weeks.

Consistent with this primary study objective, the following endpoint(s) will be assessed: Persistent PrEP use across all three modalities (LAI, daily oral, or event-driven PrEP), where persistence is defined as adherence to any PrEP modality through 26 weeks, comparing proportions in intervention and control arm participants.

- (LAI) receive on-time injections (+/- 7-day window for the first injection and 14-day window thereafter)
- (Daily Oral) have protective PrEP concentration detected at designated study follow-up visits, based on intraerythrocytic TFV-DP collected as DBS; TFV-DP concentrations associated with ≥4 doses/week will be classified as adherent.

- (Event-driven) self-reported PrEP adherence (2+1+1), in the past 30 days, assessed through self-report of PrEP use and sex acts at study follow-up visits, and intraerythrocytic TFV-DP concentrations.

8.2.1.2 To assess acceptability and barriers of implementing a systems-navigator delivered HIV prevention package among key stakeholders in the clinic and heterosexual cisgender men initiating PrEP at STI clinics.

Consistent with this primary study objective, the following endpoint(s) will be assessed among participants in the intervention arm only:

- Engagement with system navigators:
  - Overall: Proportion of intervention arm participants engaged by systems navigator within 7-days of enrollment visit (defined as any contact, i.e. text exchange, in-person communication)
  - Overall: Proportion of intervention arm participants engaged by systems navigators at least once after the initial engagement during the first 26 weeks following initiation of PrEP.
  - Overall: Proportion of intervention arm participants with attempted engagement by systems navigators at least once after the initial engagement during the first 26 weeks following initiation of PrEP.
  - Overall: Mean (standard error) number of contacts (text, telephone call, home visit, other) with intervention arm participants made with systems navigators (mean contacts per participant) during first 26 weeks following initiation of PrEP.
- Uptake of self-test/pill pack ("re-start" kit) among those to whom it is distributed (through end of study participation):
  - Proportion who self-report use of HIV self-test
  - Proportion who self-report use of PrEP pill pack
  - Proportion who self-report use of HIV self-test in conjunction with/prior to initiation of PrEP pill pack
- Acceptability and barriers among key stakeholders, including participants enrolled as seronegative PrEP initiators and other key stakeholders:
  - Acceptability based on quantitative surveys (participants enrolled as seronegative PrEP initiators only)
  - Perceived facilitators and barriers to implementation of the intervention will be assessed through individual semi-structured interviews.

8.2.2 Secondary Objective(s) and Endpoints

8.2.2.1 To assess the feasibility of a future randomized controlled trial.

Consistent with this secondary study objective, the following endpoint(s) will be assessed, considering all enrolled HIV seronegative participants:

- Calendar time to enroll 200 participants
- Proportion of participants retained at each [eligible] study visit
- Complete all study visits through 26 weeks, 39 weeks, and 52 weeks (among participants eligible for longer follow-up)
- Proportion of PrEP visits on the same day as study visits, by PrEP modality
- Proportion of participants completing 30-day TLFB at quarterly study visits
- Time to complete each study visit
- Additional time (at PrEP visits) engaging with systems navigators

8.2.3 Exploratory Objectives and Endpoints

8.2.3.1 To assess prevention-effective PrEP use among heterosexual cisgender men initiating PrEP at STI clinics

Prevention-effective PrEP use evaluates PrEP use in the context of ongoing HIV risk, exploring the alignment between periods with evidence of ongoing HIV risk and protective PrEP levels. This will be assessed for participants by evaluating self-reported HIV risk behaviors, observed incident STI or HIV, and PrEP use during quarterly study follow-up visits:

- Proportion of PrEP initiators with incident STI/HIV
- Proportion of PrEP initiators who report HIV risk during study follow-up, including self-reported sexual behaviors, and HIV status of partners
- Proportion of PrEP initiators who have target PrEP concentrations (oral) or on-time receipt (LAI) during periods of potential HIV risk based on incident HIV/STI, self-reported sexual behaviors, and HIV status of partners.
- Proportion of PrEP initiators who discontinue PrEP (based on self-report or medical record review)
- Proportion of sex acts with appropriate PrEP dosing (before and after each act) in 14- and 30-day recall periods, among PrEP initiators endorsing event-driven PrEP use

8.2.3.2 To assess PrEP modality preferences among heterosexual cisgender men initiating PrEP at STI clinics.

We will assess proportion of cisgender men selecting each of the available PrEP options at enrollment, and examine any changes in PrEP modality selection during study follow-up.

8.2.3.3 To assess the effect of a systems-navigator facilitated HIV prevention package on PrEP persistence among heterosexual cisgender men seeking STI clinical services in Lilongwe, Malawi, at 39 and 52 weeks.

Consistent with this exploratory objective, we will assess all PrEP use outcomes described in Section 8.2.2 for subset of participants who are eligible for extended follow-up based on enrollment date, extending to 39 weeks or 52 weeks.

8.2.3.4 To quantify costs and resources necessary to develop and integrate a systems-navigator delivered HIV prevention package into an urban STI clinic, informing future cost-effectiveness model development.

Consistent with this exploratory study objective, the following endpoint(s) will be assessed:

- cost quantification following an ingredients-based micro-costing approach, including costs associated with training and time-and-motion evaluation of systems navigation activities including counseling and tracing.

8.2.3.5 To perform laboratory assessments that may include evaluation of factors related to HIV infection or other STIs; characterization of HIV in participants who acquire HIV; characterization of the host response to antiretroviral drugs; and evaluation of virologic, pharmacologic, or STI-based laboratory assays.

8.2.3.6 To evaluate event-driven PrEP drug concentrations within the context of TLFB reported PrEP use and sex acts.

8.2.3.7 To explore the perceived and experienced PrEP related stigma and potential influence of perceived gender norms on PrEP persistence among heterosexual cisgender men initiating PrEP at the STI clinic.

This exploratory objective will be assessed using a combination of quantitative surveys as well as the qualitative interviews with cisgender male participants.

8.3 SAMPLE SIZE

For our HIV seronegative PrEP initiation participant population, we expect to enroll approximately 200 heterosexual cisgender males. We assume 10% loss to follow-up through 26 weeks. As a pilot study, the sample size is chosen to provide reasonable precision for assessing the primary endpoints and informing future studies. We chose a

2:1 randomization to intervention and SOC to maximize our ability to assess acceptability of the intervention.

Based on previous studies, we expect persistent PrEP use under standard of care (SOC) is 40% at 26 weeks. The targeted difference in persistent PrEP use at 26 weeks between the intervention and the standard of care arm is 15%-35%. Table 1 gives the two-sided 95% confidence intervals for the true proportions of persistent PrEP use (a binary endpoint) separately for two arms. This is a pilot study seeking to rapidly evaluate indication of an effect signal that would suggest potential benefit of systems navigation to inform a future larger study. Our sample size, selected to quickly enroll and answer this important and timely knowledge gap, will be sufficient to identify a minimum detectable RD of 0.22 assuming 80% power and 5% alpha level, and RD of 0.25 assuming 90% power and 5% alpha level.

Table 2: 95% confidence intervals for the true proportions of persistent PrEP use at 26 weeks separately for two arms, given the total sample size of 200 and assuming 10% loss to follow-up (a working sample size of 180)

Proportion of persistent PrEP use under SOC	Proportion of persistent PrEP use under intervention with varying risk difference (RD)				
	RD=0.15	RD=0.2	RD=0.25	RD=0.3	RD=0.35
(0.28, 0.52)	(0.46, 0.64)	(0.51, 0.69)	(0.56, 0.74)	(0.62, 0.78)	(0.67, 0.83)

8.4 ACCRUAL AND RETENTION

A total of approximately 200 HIV seronegative PrEP initiating participants will be enrolled in approximately 39 weeks and followed for at least 26 weeks but up to 52 weeks. An overall retention rate of 90% will be targeted.

8.5 STATISTICAL ANALYSIS

8.5.1 Primary Analyses

Effect of intervention on persistent PrEP use

Comparison of persistent PrEP use will be performed on all enrolled participants during the first 26 weeks of study follow-up. Participants may choose to switch PrEP modalities during study follow-up; persistence to each modality will be assessed during the follow-up time when the participant reports using that modality, using a combination of self-report and clinic records. Only those who are retained on study at the end of 26 weeks will be considered to have reached the persistence endpoint. Data will be presented in a two-by-two table in which each participant is classified as persistent/non-persistent to PrEP. A Z-test based on asymptotic normality will be used to compare persistent PrEP between the intervention and the SOC arm.

Acceptability and barriers

For binary endpoints, the number will be tabulated, its specified proportion will be calculated, with variance calculated under binomial distribution. For continuous endpoints, its mean, median, standard deviation, quantiles and range will be calculated. Qualitative analyses are described separately (Section 8.6)

8.5.2 Secondary Analyses

Feasibility of a future randomized controlled trial

Secondary data analysis will tabulate the number of each endpoint observed during the study. For binary endpoints, its percentage of the total enrolled participants will be calculated, with variance calculated under binomial distribution. For continuous endpoints, its mean, median, standard deviation, quantiles and range will be calculated. Z-tests will be used to compare endpoints between arms.

8.6 QUALITATIVE ANALYSES

Acceptability and feasibility of the systems navigation component will also be assessed through administration of brief behavioral surveys and qualitative interviews with approximately 20 study participants. The surveys will include, but not be limited to, questions about participants' attitudes/beliefs towards their interactions with the systems navigator, as well as other related topics such as their perceived risk for HIV. Approximately 15 other key stakeholders will also be interviewed regarding the adoption and implementation of systems navigation as a strategy to improve HIV prevention integration in the STI clinic.

Participant in-depth interviews (IDI) will be scheduled to attempt to correspond with their final study visit (week 26, 39, or 52). When conducting a qualitative exploration, the sampling method should be designed to include a range of possible perspectives on the phenomenon under study, thus ideal qualitative samples are purposive in nature. For this study, we will utilize a purposive sampling strategy, which will allow for consideration of the concepts of range, saturation/redundancy, and stratification in the sampling frame. We will ask site staff to identify potential participants who would be interested in and comfortable with sharing their experiences in the study. Data on acceptability and factors affecting adherence will be collected during the IDI, including questions that explore the use and the acceptability of the systems navigation component. Additional interview topics will include challenges to study participation as well as risk perception. These interviews will be conducted by a trained study interviewer and will follow a semi-structured questionnaire guide. They will be approximately 60 minutes in duration and will be conducted in an area that maximizes participant privacy and confidentiality. Participants may be compensated for the completion of the in-depth interview. These interviews will be recorded for analysis and transcribed. Recording storage, tracking, and

management details will be described in the site's SOPs. These recordings will be stored in accordance with the longest requirement of any applicable regulations.

After transcription, all qualitative interviews will be translated into English (as needed), and then uploaded into a qualitative software analysis program (such as NVivo 12). The HPTN 112 Qualitative Team will follow a process of reading, coding, data display and data reduction in order to explore in greater depth participants' attitudes towards and experiences with the intervention. Data coding and analysis will be both iterative and interactive processes. The team will first read all interview transcripts in order to increase familiarity with the data. Next, the team will assign a priori codes and create emergent codes. Transcripts will then be re-read to create pattern codes that connect subsequent concepts under larger headings. Consistent patterns in meaning, concepts, and themes across all interviews will be identified, and detailed memos/data matrices will be developed to examine how participants' perceptions related to the intervention (i.e., ease of use, interactions with systems navigators, perceived efficacy) and to risk perception (i.e., motivations for participation, impact on partner or other social relationships) influence acceptability and interest in future use of a systems navigation component embedded in the clinic. Comparative analyses will be conducted to clarify differences that may exist for any subgroups of participants. Coding and analytic activities will be discussed during qualitative data analysis meetings, and discrepancies in coding and interpretation will be resolved through consensus.

See Appendix II for timing of interviews.

9.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described below and in Appendix II and Section 6.2.1; tests to be performed at a subsequent visit for participants who have a reactive or positive HIV test interpretation are described in Appendix III.

9.1 LOCAL LABORATORY SPECIMENS

As described in Section 6, the following types of specimens will be collected at the local laboratory (LL):

- Blood
- Urine

As described in Section 6, the following types of testing will be performed at the local laboratory (LL):

- HIV rapid antibody testing
- HIV RNA (Enrollment)
- STI testing for syphilis (RPR and reflex to TPPA, if appropriate)
- STI testing for CT/NG

LLs will perform HIV and STI testing as indicated in Appendices II-IV. All STI test results obtained through study visits, including POC STI testing through systems navigators, will be returned to HIV seronegative participants. Some results will not be returned same day, however, participants who test positive for an STI at study visits will be informed of their result and be referred for treatment as per local guidelines. For HIV seronegative participants, HIV RNA testing will typically be tested within 7-10 days of enrollment. Participants will be informed if this result is consistent with HIV infection, despite negative rapid antibody testing at enrollment.

The study site must adhere to the HPTN Manual of Operations (MOP), the SSP Manual, and local SOPs, for proper collection, processing, labeling, transport, and storage of specimens to the LL. Non-US laboratories performing these tests will be monitored by an External Quality Assurance (EQA) provider or specified quality assurance contractor. In addition, each study site must adhere to the Requirements for Laboratories in Performing Testing for DAIDS-Supported and/or Sponsored Clinical Trials policy (DAIDS-OD-A-POL-00002) as outlined in the DAIDS SCORE Manual and the DAIDS Good Clinical Laboratory Practice (GCLP) as appropriate. Laboratories must also follow the DAIDS Clinical Research Laboratory and Specimens Management policies at https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management. Specimen collection and storage at the local laboratory will be documented using the Laboratory Center Specimens Management System (LDMS) as described in the SSP Manual.

9.1.1 Specimen Storage at Study Site

Sites will provide short-term storage of blood (plasma, DBS) and urine to facilitate batched testing. Stored samples will be shipped to the HPTN LC (located in the US) for Quality Assurance (QA), as well as measurement of antiretroviral drugs from DBS or plasma. Stored samples may also be used for characterization of HIV in participants who acquire HIV, additional testing of STI pathogens, and evaluation of laboratory assays related to the study objectives. Specifically, these tests are conducted to characterize factors associated with HIV and STI infection, and virologic, pharmacologic and immunologic responses among men initiating PrEP at Bwaila STI clinic. Testing on stored samples will be performed by the HPTN LC or another laboratory selected and approved by the HPTN LC. Samples stored at study sites may not be used for LL testing not otherwise specified in the protocol without written approval by the HPTN LC and appropriate regulatory body prior to use.

Stored samples may be maintained at the site until the study is complete. The HPTN LC will communicate with sites when samples can be destroyed; sites will follow LL policies for sample destruction. A list of samples to be destroyed will be provided by the SDMC, which will be reviewed and reconciled by the site as part of the sample destruction process.

9.1.2 Virology

HIV testing will be performed by local laboratories and will follow Malawi Ministry of Health algorithms.

Additional virologic assays may be performed to address study objective 2.3.5 at the HPTN LC or a laboratory designated by the HPTN LC. This testing may include the following tests for participants who acquire HIV infection: HIV viral load, HIV resistance testing, HIV subtyping, and other tests to characterize HIV viruses and/or the host response to HIV infection. Further, the HPTN LC may perform HIV RNA testing at study visits with stored samples from individuals who do not acquire HIV during the study. Results will not be returned to the sites or study participants, except for HIV diagnostic testing (if results obtained at the HPTN LC do not agree with site results).

Resistance testing may be performed at the HPTN LC or a laboratory selected by the HPTN LC. Results of this testing will not be returned to study sites.

9.1.3 Pharmacology

To address study objective 2.3.5, plasma and DBS samples for pharmacology testing will be collected throughout the study from all participants. Pharmacology testing will be performed at the HPTN LC or a laboratory designated by the HPTN LC. The primary pharmacologic assessments will be performed using assays that have been appropriately validated and approved. Results will not be returned to the study participants. Interpretation of pharmacologic results, including pharmacokinetic modeling, will be led by the HPTN LC Pharmacology Core, in collaboration with other groups, as needed.

Stored plasma may also be tested for the presence of other antiretroviral drugs or other concomitant medications.

9.1.4 Other HPTN LC testing

STI testing (syphilis, CT/NG) will be performed at the LL. Stored urine may be used for the following to inform objective 2.3.5: additional characterization of STIs, including CT/NG, M. genitalium, T. vaginalis; evaluation of laboratory assays for identification of STIs. Deidentified samples may also be used to evaluate incidence and prevalence of other STIs.

9.2 QUALITY CONTROL AND QUALITY ASSURANCE PROCEDURES

HPTN LC staff will conduct periodic visits to the study site to review the implementation of on-site laboratory quality control (QC) procedures, including proper maintenance of laboratory equipment and use of appropriate supplies and reagents. HPTN LC staff will follow up directly with site staff to resolve any QC or QA problems identified through proficiency testing or on-site visit reviews. Throughout the course of the study, the HPTN

LC will perform QA testing for HIV infection on stored samples. HPTN LC staff will follow-up directly with site staff to resolve any QA problems identified through this process.

Samples will be shipped to the HPTN LC on a routine basis throughout the study. Site staff will be informed by the HPTN LC on when to ship stored samples.

9.3 HIV DIAGNOSTIC TESTING

Eligibility HIV testing (to determine PrEP eligibility) will be conducted per Malawi Ministry of Health guidelines.

Additional testing at scheduled study visits will be conducted by LL. HIV infection status will be confirmed at study sites using local HIV testing guidelines or following the advice of the HPTN LC. In addition, if a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, testing will be performed following in-country recommendations. The HPTN LC may characterize seroconversion events using additional HIV testing approaches.

9.4 HIV RNA TESTING

Quantitative HIV RNA (viral load) testing will be performed at LLs at enrollment for HIV seronegative participants. For HIV seronegative participants who acquire HIV infection during study follow-up, viral load testing will be performed at the visit when HIV infection is confirmed and at subsequent study visits. LLs must participate in a DAIDS-contracted EQA program, with results that are deemed satisfactory by the HPTN LC.

9.5 BIOHAZARD CONTAINMENT

As the transmission of HIV and other blood-borne pathogens can occur through contact with used needles, blood, and blood products containing HIV, appropriate blood and secretion precautions will be employed by all personnel in the drawing of blood and shipping and handling of all specimens for this study, as currently recommended by the United States Centers for Disease Control and Prevention. All specimens will be shipped using packaging that meets requirements specified by the International Air Transport Association Dangerous Goods Regulations for UN 3373, Biological Substance, Category B, and Packing Instruction 650.

10.0 HUMAN SUBJECTS CONSIDERATIONS

10.1 ETHICAL REVIEW

The HPTN Ethics Working Group developed the HPTN Ethics Guidance for Research, a network-wide ethical principles document, which is suitable for further elaboration and tailoring for each study.

This protocol and the template informed consent forms (ICFs) contained in Appendices III and IV were reviewed and approved by the HPTN Scientific Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, ICFs, participant education and recruitment materials, other requested documents, and any subsequent modifications will also be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

Subsequent to initial review and approval, the responsible IRBs/ECs will review the protocol at least annually. The Investigator will make safety and progress reports to the IRBs/ECs at least annually, and within three months of study termination or completion. These reports will include the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. The study site will submit documentation of continuing review to the DAIDS Protocol Registration Office (PRO), in accordance with the current DAIDS Protocol Registration Policy and Procedures Manual.

10.2 INFORMED CONSENT

Written informed consent will be obtained from each study participant. Study ICF(s), based on the template in Appendices III and IV, describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. ICFs will be translated into local language and the accuracy of the translation verified by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their ICF(s). Non-literate participants will be asked to document their informed consent by marking their ICF(s) (e.g., with an X, thumbprint, or other mark) in the presence of a literate third-party witness. Further details regarding DAIDS requirements for documenting the informed consent process with both literate and non-literate participants are provided in the DAIDS SCORE Manual. Any other local IRB/EC requirements for obtaining informed consent from non-literate persons also will be followed.

Participants will be provided with a copy of their ICF if they are willing to receive it.

Consistent with prior PrEP research at the Bwaila STI clinic as conducted by HPTN 112 investigators, this study proposes to enroll adolescents aged 15 to 17 years old.[15] All minors (under the age of 18) will be required to provide assent with parental consent. Malawi guidelines allow those aged 15 and above to initiate PrEP if they meet other

eligibility requirements. Adolescents are often excluded from research studies largely because of confusion about whether they should be regarded as children or as adults, and because of uncertainty regarding who has the right and ability to give consent for adolescents to participate in research. However, such exclusion potentially deprives research of the important and unique perspective of the adolescent to which the adolescent may themselves benefit.[22] As such, this trial will enroll adolescents using the above procedures.

We will provide adequate protection in the confidentiality of all study activities, including receipt of care, participation in interviews, tracing, and referrals for services if needed (see Section 10.6).

10.3 RISKS

It is not expected that this trial will expose participants to unreasonable risk. Blood draws may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection. Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving risk reduction and PrEP counseling. They also may become worried or anxious while waiting for their HIV test results. Trained counselors will be available to help participants deal with these feelings. Although the site will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could be thought of as vulnerable for HIV infection because of their participation in a PrEP study).

Study procedures also address the potential risk of field-based tracing for missed study or PrEP visits (by study staff and systems navigators, respectively). All tracing efforts are conducted consistent with the stated preferences and locator information provided and updated regularly by participants or their parent/guardians. Community sensitization and CAB involvement are cornerstones in maintaining the safety of participants and those conducting tracing activities. Additional measures to mitigate risk to persons conducting tracing activities include working in pairs or teams, bringing phones to facilitate communication, using flexible transportation (i.e. not relying on availability of public transport), and extensive training regarding immediate departure if any hostility is perceived. Any such event is generally reported back to the community representative.

10.4 BENEFITS

There may be no direct benefits to participants in this study, however, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to improved HIV prevention services for heterosexual cisgender men. In addition, participants will receive HIV and STI counseling and testing as part of the study process. Participants also will be referred for treatment if applicable. Participants may benefit from the potentially improved use of

PrEP agents, as facilitated through systems navigation, which are known to protect against getting HIV if taken as directed.

10.5 INCENTIVES

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Site-specific reimbursement amounts will be specified in the study ICF(s).

10.6 CONFIDENTIALITY

All study-related information will be stored securely at the study site. All participant information will be stored in locked file cabinets in areas with access limited to study staff. All laboratory specimens, reports, study data collection, process, and administrative forms will be identified by a coded number only to maintain participant confidentiality. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the NIAID and/or its contractors; representatives of the HPTN LOC, SDMC, and/or LC; other government and regulatory authorities, and/or site IRBs/ECs.

10.6.1 Certificate of Confidentiality

Research participants in Network protocols are protected by a Certificate of Confidentiality (CoC) from the US NIH, which can prevent disclosure of study participation even when that information is requested by subpoena. However, CoCs may not be effective for data held outside of the US.

10.7 COMMUNICABLE DISEASE REPORTING REQUIREMENTS

Study staff will comply with all applicable local requirements to report communicable diseases identified among study participants to local health authorities. Participants will be made aware of all reporting requirements during the study informed consent process.

10.8 STUDY DISCONTINUATION

The study also may be discontinued at any time by NIAID, the HPTN, and/or site IRBs/ECs.

11.0 ADMINISTRATIVE PROCEDURES

11.1 PROTOCOL REGISTRATION

Initial Registration of the protocol by the DAIDS PRO is required prior to the implementation of this protocol. As part of this process, each site must have the protocol and protocol ICF(s) approved, as appropriate, by their IRB/EC and any other applicable regulatory entity (RE). Upon receiving final approval, sites will submit all required protocol registration documents to the DAIDS PRO at the Regulatory Support Center (RSC). The DAIDS PRO will review the submitted protocol registration packet to ensure that all of the required documents have been received. In the case of Initial Registration, site-specific ICFs WILL be reviewed and approved by the DAIDS PRO. Sites will receive an Initial Registration Notification from the DAIDS PRO that indicates successful completion of the protocol registration process. A copy of the Initial Registration Notification should be retained in the site's regulatory files.

Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites are required to submit an amendment registration packet to the DAIDS PRO at the RSC. The DAIDS PRO will review the submitted protocol registration packet to ensure that all the required documents have been received. Site-specific ICF(s) WILL NOT be reviewed and approved by the DAIDS PRO.

For additional information on the protocol registration process and specific documents required for initial and amendment registrations, refer to the current version of the DAIDS Protocol Registration Manual, which can be found at: https://www.niaid.nih.gov/sites/default/files/prmanual.pdf.

11.2 STUDY ACTIVATION

Pending successful protocol registration and submission of all required documents, the HPTN LOC staff will "activate" the site. Study implementation may not be initiated until a study activation notice is provided to the site by the HPTN LOC. In addition, if study activation is determined to be necessary for any subsequent amendments, study implementation may not be initiated until a study activation notice is provided to the site by the HPTN LOC.

11.3 STUDY COORDINATION

Study implementation will be directed by this protocol as well as the SSP Manual. The DAIDS SCORE Manual will outline procedures for conducting study visits; data and forms processing; and other study operations.

Study CRFs and other study instruments will be developed by key members of the protocol team and HPTN SDMC. Data will be submitted to the HPTN SDMC for data cleaning, reporting and analysis. Data management and coding queries will be generated

and applied to the data by HPTN SDMC staff on a routine basis for verification and resolution by site staff.

Close coordination between protocol team members will be necessary to track study progress, respond to queries about proper study implementation, and address other issues in a timely manner. Rates of accrual, adherence, follow-up, and visit completion rates will be monitored closely by the team as well as the HPTN SMC. Select members of the Protocol Team will address issues related to individual study eligibility and any other issues as needed to assure participant safety, consistent case management, documentation, and information-sharing across sites.

11.4 STUDY MONITORING

Study monitoring will be performed in accordance with DAIDS policies. Study monitors will:

- Verify compliance with human subjects and other research regulations and guidelines.
- Assess adherence to the study protocol, study-specific procedures manual, and local counseling practices.
- Confirm the quality and accuracy of information collected at the study site and entered into the study database.
- Verify compliance with GCLP

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of or in addition to onsite visits to ensure the safety of study participants and data integrity.[18] The site will make available study documents for study monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Potential platform options include: Veeva SiteVault, site-controlled SharePoint or cloud-based portal, direct access to Electronic Medical Record (EMR), and Medidata Rave Imaging Solution. Other secure platforms that are 21 CFR Part 11 compliant may be utilized, as allowed by the DAIDS Office of Clinical Site Oversight (OCSO).

For on-site visits, site investigators will also allow study monitors to inspect study facilities and documentation (e.g., ICFs, clinic and laboratory records, other source documents, paper or electronic CRFs), as well as observe the performance of study procedures. Investigators also will allow inspection of all study-related documentation by authorized representatives of the HPTN LOC, HPTN SDMC, HPTN LC, NIAID, site IRBs/ECs, and US regulatory authorities (Office for Human Research Protections (OHRP) and US FDA or other regulatory agencies). A site visit log will be maintained at each study site to document all visits.

11.5 PROTOCOL COMPLIANCE

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) and the RSC prior to implementing the amendment.

11.6 INVESTIGATOR'S RECORDS

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. Under the US Department of Health and Human Services (DHHS) regulations, the Investigator is required to retain all study records relating to research for at least three [3] years after completion of the research, or longer if needed to comply with local regulations.

Completion of a clinical research study occurs when the following activities have been completed:

- All research-related interventions or interactions with human subjects (e.g., when all subjects are off study);
- All protocol-required data collection of identifiable private information described in the IRB/EC-approved research plan;
- All analysis of identifiable private information described in the IRB/EC-approved research plan;
- Primary analysis of either identifiable private or de-identified information.

Study records include administrative documentation including protocol registration documents and all reports and correspondence relating to the study; as well as documentation related to each participant enrolled in the study, including ICFs, locator forms, CRFs, and notations of all contacts with the participant; and all other source documents.

11.7 USE OF INFORMATION AND PUBLICATIONS

Publication of the results of this study will be governed by the HPTN Manual of Operations. Any presentation, abstract, or manuscript will undergo review by the HPTN Manuscript Review Committee, and DAIDS prior to submission.

11.8 CLINICALTRIALS.GOV

This protocol is not an FDAAA "applicable clinical trial." However, this study is subject to the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information. A description of this clinical trial will be available on http://www.ClinicalTrials.gov.

12.0 REFERENCES

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13.0 APPENDICES I-VII

13.1 APPENDIX I: CLINIC FLOW

Figure 1a: Recruitment to first study visit

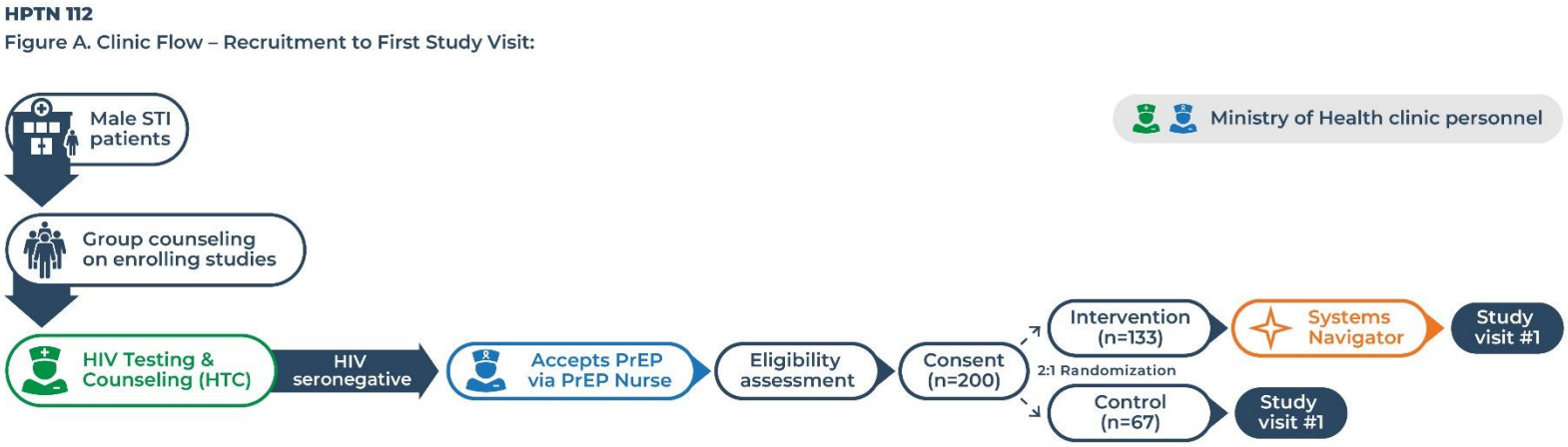
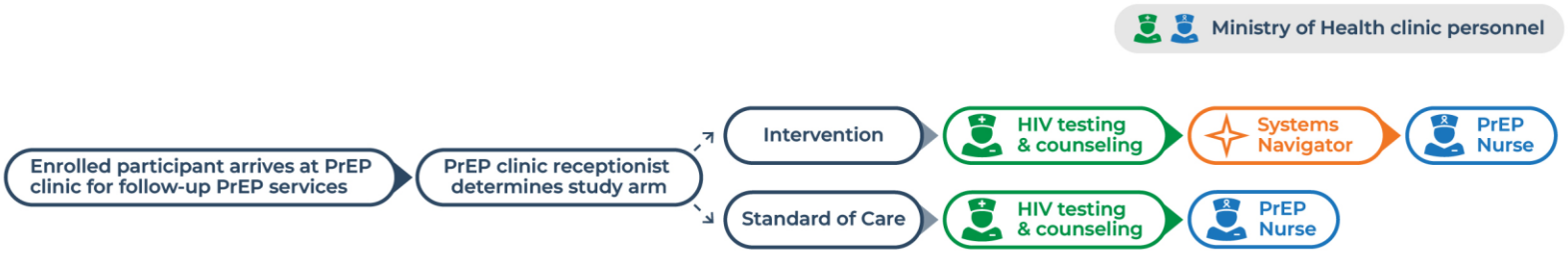


Figure 1b: Follow-up PrEP visits, as determined by Ministry of Health guidelines.



13.2 APPENDIX II: SCHEDULE OF EVALUATIONS FOR HIV-UNINFECTED PARTICIPANTS

	Eligibility Determination	Enrollment	Weeks 13	26	39[1]	52[1]	Early termination[2]
Administrative and Behavioral Evaluations/Procedures[3]							
Informed consent		X					
Randomization		X					
Demographics	X	X					
HIV risk factors	X	X					X
Locator information		X	X	X	X	X	
Behavioral risk assessment		X	X	X	X	X	X
PrEP use assessment		X	X	X	X	X	X
Mental health status		X	X	X	X	X	X
Substance use		X	X	X	X	X	X
Perceived HIV & PrEP Stigma		X	X	X	X	X	X
Gender norms		X	X	X	X	X	X
HIV risk reduction counseling		X	X	X	X	X	X
In-depth interviews[5]				X	X	X	
Clinical Evaluations/Procedures							
Symptom-driven physical exam		X	X	X	X	X	
Venous blood draw		X	X	X	X	X	X
Urine collection		X	X	X	X	X	X
STI management referral[4]		X	X	X	X	X	X
Laboratory Evaluations/Procedures							
Rapid HIV testing	X[6]	X[6]	X	X	X	X	X
HIV RNA[7]		X					
STI testing[8]		X	X	X	X	X	X
Plasma (storage)		X	X	X	X	X	X
DBS (storage)		X	X	X	X	X	X
Urine (storage)		X	X	X	X	X	X

[1] all participants will be followed at least 26 weeks; persons enrolled in the first 13 weeks will be followed up to 52 weeks;

[2] extent of procedures, including surveys and specimen collection, at early termination visit will be determined depending on reasons for termination and ongoing safety/ability to obtain consent of the participant;

[3] Systems navigation occurs at the participant's clinic PrEP visits, and not the study visits for this study. Therefore, systems navigation provided by the study is not included in this Schedule of Evaluations;

[4] referral for management in the event of new or persistent STI symptoms/complaints;

[5] in-depth interviews will be conducted with a subset of participants at their final visit (week 26, week 39, or week 52);

[6] HIV testing for PrEP eligibility determination will be conducted by Malawi Ministry of Health personnel

[7] HIV RNA will be tested at LL on enrollment; HIV RNA testing may be performed on stored plasma collected at follow-up visits at the HPTN LC;

[8] STI testing, including *Neisseria gonorrhea* (NAAT), *Chlamydia trachomatis* (NAAT), and syphilis (RPR) will be collected at study visits *unless* results of these tests are documented within 2-weeks in review of record.

13.3 APPENDIX III: SCHEDULE OF EVALUATIONS FOR PARTICIPANTS WHO SEROCONVERT ON STUDY

	Weeks post seroconversion		Early termination
	13 Weeks	26 Weeks	
Administrative and Behavioral Evaluations/Procedures			
Locator information	X	X	
Clinical Evaluations/Procedures			
Venous blood draw	X	X	X
HIV management referral[1]	X	X	X
Laboratory Evaluations/Procedures			
HIV RNA	X	X	X
Plasma (storage)	X	X	X
DBS (storage)	X	X	X

[1] HIV management referral will only occur if participant is not already in care.

13.4 APPENDIX IV: SAMPLE ENROLLMENT INFORMED CONSENT

HPTN 112: Improving HIV prevention among heterosexual cisgender men seeking STI services in Malawi: examining the benefits, acceptability, and associated costs of a systems-navigator- delivered integrated prevention package

SAMPLE ENROLLMENT ICF
Version 2.0
19 December 2023
DAIDS Document ID: 39057

Sponsored by: Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID), US National Institutes of Health (NIH).

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CONCISE SUMMARY: This is a research study. Taking part in this research study is voluntary (your choice). You do not have to participate, and you can leave the study at any time. No matter what you decide, any other care that you get at this site will not change.

This study is testing whether adding a systems navigator (similar to a coach or guide) to pre-exposure prophylaxis (PrEP) care, a medicine that can help prevent HIV, improves PrEP use among heterosexual men, compared to the current standard PrEP care.

The study will take about 15-months total. If you choose to enroll in the study, you will be followed on the study for at least 6 months and up to 12 months. You will be asked to give blood and urine specimens for HIV, STI, and other tests. You do not need to remain on PrEP to continue participation in this study.

There are very limited risks involved with this study, including (but not limited to) risk of discomfort, dizziness/faintness, and/or bruising, swelling and/or infection from your blood being taken. You may also feel feelings of embarrassment or worry when answering questions about your own behaviors and/or receiving HIV counseling, or become worried while waiting for your HIV test results. Finally, there is the potential that some of your information may become known to others, even though the study will do everything possible to prevent that.

There may be no direct benefits to you for being in this study, but others may benefit in the future from information learned from this study. Specifically, information on how to improve HIV prevention services for heterosexual men. In addition, you will receive HIV and STI counseling and testing as part of the study process and will be referred for treatment as needed.

More information about this study is described in the rest of this form. We will help you understand the information and answer all your questions. You should feel that you understand the study before deciding whether you will participate. If you agree to join the study, you will be asked

to sign your name or make your mark on this form. We will offer you a copy of this form to keep.

What are some general things you should know about research studies?
You are being asked to take part in a research study. To join the study is voluntary. You may choose not to participate, or you may withdraw your consent to be in the study, for any reason, without penalty.

Research studies are designed to obtain new knowledge. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher or the health care provider. If you are a patient with an illness, you do not have to be in the research study in order to receive health care. Details about this study are discussed below. It is important that you understand this information so that you can make an informed choice about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The main purpose of this research study is to understand if it is helpful to use a systems navigator (coach or guide) to support the use of PrEP to prevent HIV. The overall goal of this study is to collect data that will inform future research, helping men from STI clinics reduce risk of getting HIV by taking PrEP.

This study is for adult and adolescent cisgender men who:

- are age 15 years or older,
- are seeking services at Bwaila STI Clinic, and
- have tested HIV negative

Are there any reasons you should not be in this study?
You should not be in this study if you are taking part in another study of drugs or medical devices. You are asked to tell the study staff about any other studies you are taking part in or thinking of taking part in. This is very important for your safety.

How many people will take part in this study?
About 200 HIV-seronegative heterosexual men will participate in this study from Lilongwe, Malawi.

How long will your part in this study last?
Participants who choose to join the study will be in the study for at least 6 months and up to 12 months total.

What will happen if you take part in the study?

During this study, you will be in one of 2 study groups. Researchers will "randomize" you into one of the study groups described here. 2 out of every 3 persons enrolled will be assigned to the intervention group and 1 out of every 3 persons enrolled will be assigned to the standard of care group. Random assignment means that you are put into a study group by chance, like flipping a coin. Neither you nor the study staff can choose your study group. The table below indicates what services each group will receive.

Standard of Care Group	Standard PrEP services, including HIV testing and risk reduction counseling
Intervention Group	Standard PrEP services, including HIV testing and risk reduction counseling. You will also be assigned a systems navigator (coach), respond to a brief questionnaire about your sexual activities, and be tested for STIs at any PrEP visit you attend. This coach may also attempt to contact or trace you for any missed PrEP visit (~7 days late), using information you provide regarding your preferred tracing time, method (phone or in-person), and location.

PrEP visits: If you continue on PrEP, the timing of PrEP visits will be decided by the PrEP nurse at the clinic, according to the Malawi guidelines for PrEP. These visits typically occur every 2-3 months, depending on the kind of PrEP you are taking.

This study is using a Standard of Care Group (also known as a "Control Group") because we do not yet know whether the intervention being tested in this study improves PrEP use. This kind of intervention has not previously been tested in PrEP care among men in Malawi. Using a Standard of Care Group will allow researchers to assess whether providing the additional intervention resources improves PrEP use. That information can be used to make recommendations to health care providers and leaders about what services should be offered in the future.

All participants will complete the study visit procedures outlined below, regardless of which group they are assigned.

Study visits: The study has at least 3 visits (including the enrollment visit today). Besides this first visit, you will be asked to come back for a visit ~3 months and ~6 months from now. If you enroll early in the study, you may also be asked to come back for study visits ~9 months and ~12 months from now. At each visit, you will be asked a series of questions about your behaviors and be tested for HIV and other STIs. You may also be asked to participate in a one-on-one interview. You should attend these study visits even if you have decided to stop taking PrEP.

Enrolling in the Study

If you decide to take part in the study, the Enrollment visit will last about 1-2 hours. During the Enrollment Visit, we will:

- Obtain full written informed consent for the study
- Ask you where you live and how to contact you
- Ask you to answer questions in a survey about your sexual activities and overall health

- Ask you about your previous and current PrEP use
- Provide brief HIV risk reduction counseling
- Conduct a symptom-driven physical exam
- Collect ~10 to 20 mL (about 2 to 4 teaspoons) of blood to make sure you do not have a very early infection with HIV that may not be detected by the standard HIV tests you've received in clinic. If you have not been tested for syphilis (another STI) at any recent PrEP visits, this blood will also be used to test you for syphilis.
- Collect ~ 10mL of your urine to test for STI testing (Chlamydia and Gonorrhea)
- Store blood (plasma, dried blood spots) and urine samples for study-related testing
- If you are assigned to the intervention group, study staff will connect you to your coach to discuss next steps in your PrEP care

Additional Visits: 2 to 4 additional visits over the next 6 to 12 months.
If you decide to join the study, after your Enrollment Visit, you will be asked to come to this location for follow up visits. Participants will be followed for at least 6 months and up to 12 months depending on the time of enrollment.

Each visit will last about 1 hour.

During these follow-up visit(s), we will:

- Ask you where you live and how to contact you, only if the information you gave before has changed.
- Ask you to answer questions in a survey about your sexual activities and overall health
- Ask you questions about if you are still using PrEP, why, or why not
- Provide HIV risk education counseling
- Conduct a symptom-driven physical exam
- Collect ~10 to 20 mL (about 2 to 4 teaspoons) of blood. Your blood will be used to test you for HIV. If you have not been tested for syphilis at any recent PrEP visits, this blood will also be used to test you for syphilis
- Collect ~ 10mL of your urine to test for STI testing (Chlamydia and Gonorrhea) if you have not been tested for these infections at any recent PrEP visits
- Store blood (plasma, dried blood spots) and urine samples for study-related testing

At your final study visit, we will talk with you about the end of the study and when the results of the study will be available. You may also be asked to participate in a one-on-one interview around the time of your final study visit. Approximately 20 participants will be asked to participate in this type of interview. This would add 30-60 minutes to your visit time, and you would be reimbursed for this additional time. The interviewer will ask you questions about your understanding about

HIV prevention, including PrEP, your experience being part of this study, and any challenges you experienced engaging in HIV prevention. If you are assigned to the intervention group, you will also be asked about your experience working with the PrEP coach. The interview will be audiotaped so that your responses can be transcribed for analysis. During transcription, any identifying names or places in the interview will be removed from the transcript. After transcription, the recording of the interview will be destroyed. Analysis will be conducted to look for common themes in all interviews conducted. You can decline participation in this interview.

If you test positive for HIV at any point in the study, you will be referred for HIV care and encouraged to start treatment for HIV immediately and you will have an additional approximately 6-months of study follow-up time from the time you test positive. During this time, you will have blood collected twice – once at 3 months and once at 6 months – to make sure that your body is responding appropriately to HIV treatment. During these visits, we will draw 10-20 mL (about 2-4 teaspoons) of blood to check the amount of HIV in your body. We will ask you about any medications you are taking. If you have not started HIV treatment yet, we will encourage you to start. We will also update your contact information. This could happen at a final visit if you want to stop the study early.

If you stop taking PrEP, we will ask you to stay in the study.
If you permanently stop taking PrEP during the study for any reason, we will ask you to continue to come for your regular study visits, but you will no longer have to undergo certain procedures, like answering questions about taking PrEP, etc. Similarly, if you or miss doses of PrEP or miss PrEP visits, we will ask you to continue to come for your regular study visits as scheduled.

If you get HIV during the study, we will help you get care and support.
We will test your blood for HIV during this study. If you get HIV while you are in the study, you will stop taking PrEP, and we will help you find the care and support you need.

Use of stored samples
In addition to the laboratory testing performed at each study visit, further study-related testing may be performed on blood and urine samples. This will include testing related to HIV and other infections, including testing for anti-HIV medications and for quality control testing (to confirm results obtained in laboratories). If you are found to have a very early phase of HIV or get infected with HIV during the study, some blood may also be used to learn more about HIV viruses, the body's response to HIV infection, and how HIV is spread in the community. The samples used for this testing will be labeled with your study number and will be tested at special laboratory facilities that may be located in the US and other countries outside of Malawi. The laboratory doing the testing will not know who you are. Only approved researchers will have access to your samples. Results of this specialized testing will not be returned to the study site or you. Your samples will not be sold or directly used to produce commercial products or for commercial gain. No host genetic testing will be tested from these samples. Host testing means genetic testing derived from you.

What are the possible benefits from being in this study?
There may be no direct benefits to participants in this study, however, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to improved HIV prevention services for heterosexual men in Malawi and the

African region. In addition, participants will receive HIV and STI counseling and testing as part of the study process. Participants also will be referred for treatment if needed. Participants who choose to continue PrEP may benefit from the use of PrEP medicines which are known to protect against getting HIV if taken as directed.

If you choose not to be in the study, what other treatment options do you have?
Your participation is voluntary. You do not have to take part in any of the tests or procedures in the study. You should also know that:

- If you decide not to join the study, you will not lose your regular medical care.
- If you join this study and later decide to leave, you will not lose your regular medical care.
- You do not have to join the study to receive HIV prevention medications.
- If you decide not to join the study, you will still be able to join another study at a later time if there is one available and you qualify.

Can I change my mind about participating in this study?
Yes, you can change your mind at any time. Your participation in this study is completely up to you (voluntary). Your decision to leave the study will not lead to any penalty, or loss of benefits or rights that you would normally have otherwise.

What are the possible risks or discomforts involved from being in this study?
It is not expected that this study will expose you to unreasonable risk. Blood draws may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling, and/or infection. You may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. You also may become worried or anxious while waiting for their HIV test results. Trained counselors will be available to help you deal with these feelings. Although the site will make every effort to protect your privacy and confidentiality, it is possible that your involvement in the study could become known to others, and that social harms may result. Social harms could occur if you are perceived as having HIV or at increased likelihood of getting HIV. Examples of social harms are when you are treated unfairly or have problems being accepted by your families and/or communities (i.e., because you could become known as vulnerable to HIV).

What if we learn about new findings or information during the study?
You will be told any new information learned during this study that might affect your willingness to stay in the study. For example, if information becomes available that shows that the PrEP coach may have bad effects, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

How will information about you be protected?
Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. To keep your information private, your samples will be labeled with a code that can only be traced back to the study clinic. The results of any tests done on these samples will not be included in your health records. Your name, where you live, and other personal information will be protected by the study clinic. You will be identified by a code, and personal information from your records will not be released without your written permission. Any

publication of this study will not use your name or identify you personally. Your personal information may be disclosed if required by law.

Clinic staff will have access to your study records. Your records may also be reviewed, under guidelines of the US Federal Privacy Act, by:

The Malawi National Health Science Research Committee (NHSRC)
The University of North Carolina at Chapel Hill (UNC) Institutional Review Board (IRB)
The sponsor of the study (US National Institutes of Health [NIH]), its contractors, and its study monitors
The US Office for Human Research Protections (OHRP)
Other local, US, or international regulatory authorities/entities
The HPTN (HIV Prevention Trials Network) that is conducting this study

The study staff will also use your personal information, if needed, to verify that you are not taking part in any other research studies. This includes other studies conducted by Bwaila STI Clinic and studies conducted by other researchers that study staff know about.

Malawi regulations require study staff to report the names of people who get HIV to the local health authority. Outreach workers from the health authority may then contact you about informing your partners, since they also should be tested. If you do not want to inform your partners yourself, the outreach workers will offer to contact them, according to the confidentiality guidelines of the Malawi Ministry of Health.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the study results. You can search this Web site at any time.

What will happen if you are injured by this research?
If you get sick or injured during the study, contact us immediately.

It is unlikely that you will be injured as a result of study participation. If you are injured, the Bwaila STI Clinic will give you immediate necessary treatment for your injuries. You will not have to pay for this treatment. You will be told where you can get additional treatment for your injuries. There is no program to pay money or give other forms of compensation for such injuries either through this institution or the US NIH. You do not give up any legal rights by signing this consent form.

If you think you have been injured from taking part in this study, call the Principal Investigator at the phone number provided on this consent form. They will let you know what you should do.

What if you want to stop before your part in the study is complete?
You can withdraw from this study at any time, without penalty. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped. If you decide to withdraw, we will ask you to come in for a final visit for collection and storage of blood and urine and STI testing and referral

Will you receive anything for being in this study?
You will receive the equivalent of approximately 12USD for your time, effort, and travel to and from the clinic at each scheduled study visit.

Will it cost you anything to be in this study?
There will be no cost to you for study related visits, physical examinations, laboratory tests, or other procedures.

Who is sponsoring this study?
This research is funded by Family Health International (FHI 360) through a grant from the US National Institutes of Health (NIH). This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you have questions about this study?
If you ever have any questions about the study, want to report a social harm, or if you have a research- related injury, you should contact Dr. Mitch Matoga at +265 999 511 726.

If you have questions about your rights as a research participant, you should contact the Head of Secretariat at the National Health Science Research Committee, Dr Collins Mitambo, at +265 999 397 913.

By mail:
The Head of Secretariat
Malawi National Health Science Research Committee (NHSRC)
Ministry of Health
Phone: +265 726 422
or by email: mohdoccentre@gmail.com

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

SAMPLE ENROLLMENT CONSENT SIGNATURE PAGE

If you have read this consent form, or had it read and explained to you, you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

____ I agree to take part in this study.

____ I do not agree to take part in this study

If selected for an interview:

____ If selected, I agree to participate in an interview where I will be asked questions about this research, and the interview will be recorded.

____ If selected, I do not agree to participate in an interview where I will be asked questions about this research.

_____	_____
Participant Name (print)	Participant Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date

13.5 APPENDIX V: SAMPLE KEY STAKEHOLDER INFORMED CONSENT FOR SELECTED SYSTEM NAVIGATORS AND CLINIC STAFF AT BWAILA STI CLINIC, OR OTHER STAKEHOLDERS

HPTN 112: Improving HIV prevention among heterosexual cisgender men seeking STI services in Malawi: examining the benefits, acceptability, and associated costs of a systems-navigator- delivered integrated prevention package

SAMPLE KEY STAKEHOLDER INTERVIEW INFORMED CONSENT
Version 2.0
19 December 2023
DAIDS Document ID: 39057

Sponsored by: Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID), US National Institute of Health (NIH).

PRINCIPAL INVESTIGATOR (US): Sarah Rutstein, MD, PhD
PRINCIPAL INVESTIGATOR (MALAWI): Mitch Matoga, MBBS, MSc
Study contact phone: +265 1 755 056
Study contact email: mmatoga@unclilongwe.org

CONCISE SUMMARY
Things you should know about:

- This interview is part of a larger research study.
- Taking part in this research study is voluntary (your choice). You do not have to participate, and you can leave the study at any time.
- The larger study is testing whether adding a systems navigator (similar to a coach or guide) to pre-exposure prophylaxis (PrEP) care, a medicine that can help prevent HIV, improves PrEP use among heterosexual men, compared to the current standard PrEP care.
- You are being asked to be a part of this interview because we would like to talk with you about your experiences as someone working in areas related to the study, like as a systems navigator, a care provider, a clinic manager, or a policy or program developer.
- There will only be one interview and it will take about an hour.
- There are very limited risks involved with this study, including (but not limited to) risk of discomfort, embarrassment, or worry when answering questions. There is the potential that some of your information may become known to others, even though the study will do everything possible to prevent that.
- There may be no direct benefits to you for being part of this interview, but others may benefit in the future from information learned as part of this interview, specifically, information on how to improve HIV prevention services for heterosexual men.

More information about this interview is described in the rest of this form. We will help you understand the information and answer all your questions. You should feel that you understand the

study before deciding whether you will participate. If you agree to join the study, you will be asked to sign your name or make your mark on this form. We will offer you a copy of this form to keep.

INTRODUCTION TO PARTICIPATE

What is the key information I should know about this study?
You have been invited to participate in a research study which includes an interview to discuss your perceptions of and experience with the intervention exploring use of a systems navigator to improve PrEP care for heterosexual men. You are being invited because you are: 1) a provider or supervisor of providers offering STI or HIV care or prevention services; 2) a systems navigator for participants in the study; or 3) involved in the development or implementation of HIV prevention policy or programming at the local or national level in Malawi. This "Key Stakeholder Interview" is an individual discussion about a specific set of topics.

Why is the study being done?
We would like to learn about perceived barriers to persistent pre-exposure prophylaxis (PrEP) use among heterosexual cisgender male STI clinic patients, and potential barriers or facilitators to scaling or sustaining the systems navigation intervention studied during this trial.

What will happen during the study?
The interview will be led by an individual that is not directly a member of our research team here at Bwaila clinic but is affiliated with our overall research organization. The individual will not be someone who has a supervisory role for your position.

How many participants will be in this study?
Approximately 15 participants will participate in these interviews, conducted approximately 6-12 months after the intervention has first been implemented at the clinic. The information from these interviews will help us better understand how the intervention successfully or unsuccessfully addresses barriers or enhances facilitators of PrEP uptake and persistent PrEP use for men accessing care through the STI clinic. We hope the information we learn will help us promote PrEP use among men from STI clinics, reducing the risk of HIV. The information obtained from these interviews will be combined with the rest of the information that is collected during this research study. Approximately 20 participants from the main study will also be interviewed.

What other choices do I have?
Your participation is voluntary. You do not have to take part in this interview. You should also know that:

- If you decide not to join the study, you will not lose your employment or any benefits.
- Your decision to participate or not participate in this study is confidential and we will not inform other people about whether or not you participated.
- If you join this study, you may refuse to answer any of the questions, or stop your participation completely, at any time, for any reason.

Can I change my mind about participating in this study?

Yes, you can change your mind at any time. Your participation in this study is completely up to you (voluntary). Your decision to leave the study will not lead to any penalty, or loss of benefits or rights that you would normally have otherwise.

BEING IN THE STUDY

Enrolling in the study.
If you decide to take part in the study, the interview will last about 1 hour.

During the interview:

- We will obtain full written informed consent for the study.
- The interview will be conducted in a location that assures adequate privacy and confidentiality. The study team will talk with you about this so you know where to go for the interview.
- We will ask you questions that will help us better understand how the intervention successfully or unsuccessfully addresses barriers or enhances facilitators of PrEP uptake and persistent effective use for men accessing care through the STI clinic.

To help assure that we get the best understanding possible from the interview, your answers will be recorded. After the interview is finished, the recording will be typed (called a transcript) and translated by qualified personnel. All identifying information will be removed from the transcript. Your name will not be included on the transcript. The recording will be destroyed after all analysis is completed.

RISKS OF THE STUDY

There may be risks to being in this study.
As noted, to minimize discomfort and to protect your privacy, the interview will be conducted in a private area that will allow you to speak comfortably without being overheard. The greatest risk may involve your privacy and confidentiality. The steps that the study team has taken to protect your privacy are described below.

BENEFITS OF THE STUDY

There may be no direct benefit to you by participating in the study.
You may not receive any other direct benefit from participating in this interview; however, the information gathered during this study may help to provide better access to effective PrEP for heterosexual men in Malawi and the African region.

OTHER INFORMATION ABOUT THE STUDY

There is no cost to you to be in this study.
There will be no cost to you for your participation.

We will give you about 12USD equivalent for each study visit.
You will receive the equivalent of approximately 12USD for your time, effort, and any associated travel for this interview.

We will do our best to protect your private information.
Every effort will be made to keep your personal information confidential. Your personal information (name, position) will be protected by the study team. Your name, or anything else that might identify you personally, will not be used in any publication of information about this study. Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. Because there are only a few staff at your site working on this study, researchers may know your identity and the information you share.

To keep your information private, your interview will be labeled with a code that can only be traced back to the study clinic. Your name, where you live, and other personal information will be protected by the study clinic. Any publication of this study will not use your name or identify you personally. Your personal information may be disclosed if required by law.

People who may have access to your interview, under guidelines of the US Federal Privacy Act, include:

The Malawi National Health Science Research Committee (NHSRC)
The University of North Carolina at Chapel Hill (UNC) Institutional Review Board (IRB)
The sponsor of the study (US National Institutes of Health [NIH]), its contractors, and its study monitors
The US Office for Human Research Protections (OHRP)
Other local, US, or international regulatory authorities/entities
The HPTN (HIV Prevention Trials Network) that is conducting this study
Study team members working on this interview portion of the study

A description of the larger clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of the study results. You can search this Web site at any time.

Contact us at any time if you have questions or problems.
If you ever have any questions about the study, want to report a social harm, or if you have a research-related injury, you should contact Dr. Mitch Matoga at +265 999 511 726.

If you have questions about your rights as a research participant, you should contact the Head of Secretariat at the National Health Science Research Committee, Dr Collins Mitambo at +265 999 397 913.

By mail (site to complete):
The Head of Secretariat
Malawi National Health Science Research Committee (NHSRC)
Ministry of Health
Phone: +265 726 422
or by email: mohdoccentre@gmail.com

SIGNATURE PAGE: Sample Key Stakeholder Interview Informed Consent for Selected System Navigators and Clinic Staff at Bwaila STI clinic, or Other Stakeholders

HPTN 112: Improving HIV prevention among heterosexual cisgender men seeking STI services in Malawi: examining the benefits, acceptability, and associated costs of a systems-navigator- delivered integrated prevention package

Version 2.0
19 December 2023

SAMPLE ENROLLMENT CONSENT SIGNATURE PAGE

If you have read this consent form, or had it read and explained to you, you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

____ I agree to take part in this interview, where I will be asked questions about this research, and the interview will be recorded.

_____	_____
Participant Name (print)	Participant Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date

13.6 APPENDIX VI: SAMPLE ADOLESCENT (AGE 15-17) ASSENT

HPTN 112: Improving HIV prevention among heterosexual cisgender men seeking STI services in Malawi: examining the benefits, acceptability, and associated costs of a systems-navigator- delivered integrated prevention package

SAMPLE ADOLESCENT (AGE 15-17) ASSENT
Version 2.0
19 December 2023
DAIDS Document ID: 39057

Sponsored by: Division of AIDS (DAIDS), US National Institute of Allergy and Infectious Diseases (NIAID), US National Institute of Health (NIH).

PRINCIPAL INVESTIGATOR (US): Sarah Rutstein, MD, PhD
PRINCIPAL INVESTIGATOR (MALAWI): Mitch Matoga, MBBS, MSc
Study contact phone: +265 1 755 056
Study contact email: mmatoga@unclilongwe.org

CONCISE SUMMARY: This is a research study. Taking part in this research study is voluntary (your choice). You do not have to be in the study, and you can leave the study at any time. No matter what you decide, any other care that you get here will not change.

This study is about systems navigators for PrEP for HIV (Human Immunodeficiency Virus).

- PrEP is short for Pre-Exposure Prophylaxis.
- Pre-exposure means before coming into contact with HIV. Prophylaxis is the way people prevent a disease from infecting them.
- A Systems Navigator is like a coach or guide to help with access and use of PrEP.
- With PrEP for HIV, medications are used to prevent people from getting HIV if they are exposed to it.

The study will take about 15 months total. If you choose to be in the study, you will be followed on the study for at least 6 months and up to 12 months. You will be asked to give blood and urine specimens for HIV, sexually transmitted infections (STI), and other tests. You do not need to remain on PrEP to continue being in this study.

There are very few risks with this study, including (but not limited to) risk of feeling uncomfortable, dizziness/faintness, and/or bruising, swelling and/or infection from your blood being taken. You may also feel feelings of embarrassment or worry when answering questions about your own behaviors and/or getting HIV counseling, or become worried while waiting for your HIV test results. Finally, it is possible that some of your information may become known to others, even though the study will do everything possible to prevent that.

There may be no direct benefits to you for being in this study, but others may benefit in the future from information learned from this study. Information on how to improve HIV prevention services for men. In addition, you will receive HIV and STI counseling and testing as part of the study process and will be referred for care as needed.

More information about this study is found in the rest of this form. We will help you understand the information and answer all your questions. You should feel that you understand the study before deciding whether you will participate. If you agree to join the study, you will be asked to sign your name or make your mark on this form. Your parent or guardian will also need to sign a form saying that it is ok for you to join the study. We will offer you a copy of this form to keep.

What are some basic things you should know about research studies?
You are being asked to take part in a research study. To join the study is your choice. You may choose not to be in the study, or you may leave the study at any time, for any reason, without punishment.

Research studies are designed to obtain new information. This new information may help people in the future. You may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your relationship with the researcher or the health care provider. If you are a patient with an illness, you do not have to be in the research study in order to receive health care.

More information about this study is discussed below. It is important that you understand this information so that you can make the best choice for you about being in this research study.

You will be given a copy of this consent form. You should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

Why are we doing this study?
The main reason for this research study is to understand if it is helpful to use a systems navigator (coach or guide) to help in the use of PrEP to keep someone from getting HIV. The overall goal of this study is to gather information that will help us in future research, helping men from STI clinics lower their chances of getting HIV by taking PrEP.

This study is for adult and adolescent men who:

- are age 15 years or older,
- are seeking services at Bwaila STI Clinic, and
- have tested HIV negative

Are there any reasons you should not be in this study?
You should not be in this study if you are taking part in another study of drugs or medical medical tools or equipment. You are asked to tell the study staff about any other studies you are in or thinking of being in. This is very important for your safety.

How many people will take part in this study?
About 200 men who do not have HIV will participate in this study from Lilongwe, Malawi.

How long will your part in this study last?
Men who choose to join the study will be in the study for at least 6 months and up to 12 months total.

What will happen if you take part in the study?

During this study, you will be in one of 2 study groups. Researchers will "randomize" you into one of the study groups described below. 2 out of every 3 persons in the study will be part of the group with the coach/guide (intervention group) and 1 out of every 3 persons in the study will be part of the regular care (standard of care group). Random assignment means that you are put into a study group by chance, like flipping a coin. Neither you nor the study staff can choose your study group. The table below indicates what services each group will receive.

Standard of Care Group	Regular PrEP services, including HIV testing and counseling to help you lower your chance of getting HIV
Intervention Group	Regular PrEP services, including HIV testing and counseling to help you lower your chance of getting HIV. You will also be assigned a systems navigator (coach), answer a brief questionnaire about your sexual activities, and be tested for STIs at any PrEP visit you attend. This coach may also attempt to contact or trace you for any missed PrEP visit (~7 days late), using information you provide regarding your desired tracing time, type (phone or in-person), and location.

PrEP visits: If you stay on PrEP, the timing of PrEP visits will be decided by the PrEP nurse at the clinic, according to the Malawi directions for PrEP. These visits usually occur every 2-3 months, depending on the kind of PrEP you are taking.

This study is using a Standard of Care Group (also known as a "Control Group") because we do not yet know whether adding the coach for PrEP care, which is the intervention in this study, improves PrEP use. This kind of intervention has not been tested in PrEP care among men in Malawi before. Using a Standard of Care Group will allow researchers to tell whether providing the extra intervention resources improves PrEP use. That information can be used to improve instructions for health care providers and leaders about what services should be offered in the future.

All people in this study will finish the study visit activities given below, no matter which group they are in.

Study visits: The study has at least 3 visits (including this enrollment or first visit today). Besides this first visit, you will be asked to come back for a visit ~3 months and ~6 months from now. If you enroll early in the study, you may also be asked to come back for study visits ~9 months and ~12 months from now. At each visit, you will be asked a series of questions about your behaviors and be tested for HIV and other STIs. You may also be asked to participate in an interview with one other person asking you questions. You should come to these study visits even if you have decided to stop taking PrEP.

Enrolling in the Study

If you decide to be in the study, the Enrollment (first) visit will last about 1-2 hours. During the Enrollment Visit, we will:

- Ask you if you agree to be in the study and ask you to sign this form
- Ask you where you live and how to contact you

- Ask you to answer questions in a survey about your sexual activities and overall health
- Ask you about your PrEP use now and in the past
- Provide short counseling to help keep you from getting HIV
- Conduct an exam of your body if you have any issues
- Collect ~10 to 20 mL (about 2 to 4 teaspoons) of blood to make sure you do not have a very early infection with HIV that we might not see with the regular HIV tests you've gotten in clinic. If you have not been tested for syphilis (another STI) at any recent PrEP visits, this blood will also be used to test you for syphilis.
- Collect ~ 10mL (about 2 teaspoons) of your urine to test for STI testing (Chlamydia and Gonorrhea)
- Store blood (plasma, which is part of your blood, and dried blood spots) and urine for study testing
- If you are in the intervention (coach) group, study staff will connect you to your coach to talk about next steps in your PrEP care

Additional Visits: 2 to 4 more visits over the next 6 to 12 months.
If you decide to join the study, after your Enrollment Visit, you will be asked to come to this location for more visits (called follow-up visits). You will be followed for at least 6 months and up to 12 months depending on when you join the study.

Each visit will last about 1 hour.

During these follow-up visit(s), we will:

- Ask you where you live and how to contact you, only if the information you gave before has changed
- Ask you to answer questions in a survey about your sexual activities and overall health
- Ask you questions about if you are still using PrEP, why, or why not
- Provide counseling to help keep you from getting HIV
- Conduct an exam of your body if you have any issues
- Collect ~10 to 20 mL (about 2 to 4 teaspoons) of blood. Your blood will be used to test you for HIV. If you have not been tested for syphilis (another STI) at any recent PrEP visits, this blood will also be used to test you for syphilis
- Collect ~ 10mL (about 2 teaspoons) of your urine to test for STI testing (Chlamydia and Gonorrhea) if you have not been tested for these infections at any recent PrEP visits
- Store blood (plasma, which is part of your blood, and dried blood spots) and urine samples for study testing

At your final study visit, we will talk with you about the end of the study and when the results of the study will be known. You may also be asked to be in an interview with one other person asking you questions around the time of your final study visit. About 20 people in this study will be asked to be in this type of interview. This would add 30-60 minutes to your visit time, and you would be given money for this additional time. The interviewer will ask you questions about your understanding about HIV prevention, including PrEP, your experience being part of this study, and any problems you had with HIV prevention. If you are assigned to the intervention (coach) group, you will also be asked about your experience working with the PrEP coach. The interview will be audiotaped (recorded) so that your answers can be written down in a report for review later. When we write down your answers, any names or places that you say in the interview will be taken out of the written report. After the written report is done, the recording of the interview will be deleted and removed from all storage. A full understanding of the written report will take place to look for common ideas in all interviews we have for this study. You can say no to doing this interview.

If you test positive for HIV at any point in the study, you will be referred for HIV care and encouraged to start treatment for HIV immediately and you will have about 6-months more of study follow-up time from the time you test positive. During this time, you will have blood collected twice – once at 3 months and once at 6 months – to make sure that your HIV treatment is working. During these visits, we will draw 10-20 mL (about 2-4 teaspoons) of blood to check the amount of HIV in your body. We will ask you about any medicines you are taking. If you have not started HIV treatment yet, we will encourage you to start. We will also update your contact information. This could happen at a final visit if you want to stop the study early.

If you stop taking PrEP, we will ask you to stay in the study.
If you stop taking PrEP for good during the study for any reason, we will ask you to continue to come for your regular study visits, but you will no longer have to do certain tasks, like answering questions about taking PrEP. Also, if you miss doses of PrEP or miss PrEP visits, we will ask you to continue to come for your regular study visits as scheduled.

If you get HIV during the study, we will help you get care and support.
We will test your blood for HIV during this study. If you get HIV while you are in the study, you will stop taking PrEP, and we will help you find the care and support you need.

Use of stored (kept) samples
In addition to the laboratory testing done at each study visit, more study testing may be performed on your blood and urine samples. This will include testing related to HIV and other infections, including testing for anti-HIV medicines and for testing to confirm answers found from your blood in the laboratory). If you are found to have the very beginning of HIV or get infected with HIV during the study, some blood may also be used to learn more about HIV viruses, how the body reacts to HIV infection, and how HIV is spread in the community. The samples used for this testing will be labeled with your study number and will be tested at special laboratories that may be located in the US and other countries outside of Malawi. The laboratory doing the testing will not know who you are. Only approved scientists will have access to your samples. Results of this special testing will not be returned to this clinic or you. Your samples will not be sold or directly used to make products for money or used to make money in general. No host genetic testing will be tested from these samples. Host testing means genetic testing derived from you. Genetic testing is when scientists look closely at your DNA (genes).

What are the possible benefits from being in this study?
There may be no direct benefits to participants in this study, however, participants and others may benefit in the future from information learned from this study. Information learned in this study may lead to better HIV prevention services for men in Malawi and Africa. In addition, participants will receive HIV and STI counseling and testing as part of the study. Participants also will be sent for treatment if needed. Participants who choose to stay on PrEP may benefit from the use of PrEP medicines which are known to protect against getting HIV if taken the right way.

If you choose not to be in the study, what other treatment options do you have?
Your participation is your choice. You do not have to take part in any of the tests or activities in the study. You should also know that:

- If you decide not to join the study, you will not lose your regular medical care.
- If you join this study and later decide to leave, you will not lose your regular medical care.
- You do not have to join the study to receive HIV prevention medications like PrEP.
- If you decide not to join the study, you will still be able to join another study at a later time if there is one available and you qualify.

Can I change my mind about participating in this study?
Yes, you can change your mind at any time. Your participation in this study is completely up to you (voluntary). Your decision to leave the study will not lead to any punishment or loss of benefits or rights that you would normally have otherwise.

What are the possible risks or discomforts involved from being in this study?
We do not think that this study will expose you to too much risk. Blood being taken may lead to feeling uncomfortable, feelings of dizziness or faintness, and/or bruising, swelling, and/or infection. You may become embarrassed, worried, or nervous when answering questions about your chances of getting HIV and/or getting HIV counseling. You also may become worried or nervous while waiting for your HIV test results. Trained counselors will be available to help you deal with these feelings. Although the site will make every effort to keep your information safe, it is possible that your being in the study could become known to others, and that social harms may result. Social harms could occur if you are thought to have HIV or thought to have more of a chance of getting HIV. Examples of social harms are when you are treated unfairly or have problems being accepted by your families and/or communities (i.e., because you could be thought to have more of a chance to get HIV).

What if we learn about new findings or information during the study?
You will be told any new information learned during this study that might change whether you stay in the study or not. For example, if information becomes available that shows that the PrEP coach may have bad effects, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

How will information about you be kept safe?
We won't tell anyone else that you are in the study. We won't share anything we find out about you with anyone, even your parent or guardian, without talking to you first. We will keep your

personal information safe, but we cannot be absolutely sure it will be kept safe. We use a code number instead of your name on all the study forms. The results of any tests done on your samples will not be included in your health records. Your name, where you live, and other personal information will be protected by the study clinic. Any written report from this study will not use your name or say who you are. Your personal information may be given to others if needed by law.

Clinic staff will have access to your study records. Your records may also be reviewed, under rules of the US Federal Privacy Act, by:

The Malawi National Health Science Research Committee (NHSRC)
The University of North Carolina at Chapel Hill (UNC) Institutional Review Board (IRB)
The sponsor of the study (US National Institutes of Health [NIH]) and its workers
The US Office for Human Research Protections (OHRP)
Other local, US, or international regulatory authorities/entities
The HPTN (HIV Prevention Trials Network) that is conducting this study

The study staff will also use your personal information, if needed, to make sure that you are not taking part in any other research studies. This includes other studies run by Bwaila STI Clinic and studies run by other scientists that study staff know about.

Malawi rules make sure that study staff report the names of people who get HIV to the local health authority. If you get HIV, outreach workers from the health authority may then contact you about telling your partners you have HIV, since they also should be tested. If you do not want to tell your partners yourself, the outreach workers will offer to contact them, according to the privacy rules of the Malawi Ministry of Health.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information about you. At most, the Web site will include an overall view of the study results. You can search this Web site at any time.

What will happen if you are injured by this research?
If you get sick or injured during the study, contact us immediately.

It is not likely that you will be injured because of study participation. If you are injured, the Bwaila STI Clinic will give you immediate needed treatment for your injuries. You will not have to pay for this treatment. You will be told where you can get more treatment for your injuries.

There is no program to pay money or give other forms of payment for such injuries either through this clinic or the US NIH. You do not give up any legal rights by signing this consent form.

If you think you have been injured from taking part in this study, call the Principal Investigator at the phone number provided on this consent form. They will let you know what you should do.

What if you want to stop before your part in the study is complete?
You can leave this study at any time, without punishment. The scientists also have the right to stop your participation at any time. This could be because you have had a surprising reaction, or have not followed instructions, or because the whole study has been stopped. If you decide to leave the

study, we will ask you to come in for a final visit for collection and storage of blood and urine and STI testing and referral.

Will you receive anything for being in this study?
You will receive the money that is the same as about 12 US dollars for your time, effort, and travel to and from the clinic at each study visit.

Will it cost you anything to be in this study?
There will be no cost to you for study related visits, physical tests, laboratory tests, or other tasks.

Who is sponsoring this study?
This research is funded by Family Health International (FHI 360) through a grant from the US National Institutes of Health (NIH). This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct money-related interest with the sponsor or in the final results of the study.

What if you have questions about this study?
If you ever have any questions about the study, want to report a social harm, or if you have a research- related injury, you should contact Dr. Mitch Matoga at +265 999 511 726.

If you have questions about your rights as a research participant, you should contact the Head of Secretariat at the National Health Science Research Committee, Dr Collins Mitambo, at +265 999 397 913.

By mail:
The Head of Secretariat
Malawi National Health Science Research Committee (NHSRC)
Ministry of Health
Phone: +265 726 422
or by email: mohdoccentre@gmail.com

What if you have questions about your rights as a research participant?
All research on human volunteers is reviewed by a group of people who work to protect your rights and safety. If you have questions or concerns about your rights as a research subject, or if you would like to get or offer information, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

SAMPLE ENROLLMENT CONSENT SIGNATURE PAGE

If you have read this consent form, or had it read and explained to you, you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

____ I agree to take part in this study.

____ I do not agree to take part in this study.

If selected for an interview:

____ If selected, I agree to participate in an interview where I will be asked questions about this research, and the interview will be audiotaped.

____ If selected, I do not agree to participate in an interview where I will be asked questions about this research.

_____	_____
Participant Name (print)	Participant Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date

13.7 APPENDIX VII: SAMPLE PARENTAL CONSENT FOR PARTICIPANTS AGE 15-17

HPTN 112: Improving HIV prevention among heterosexual cisgender men seeking STI services in Malawi: examining the benefits, acceptability, and associated costs of a systems-navigator- delivered integrated prevention package

SAMPLE PARENTAL CONSENT FOR PARTICIPANTS AGE 15-17
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CONCISE SUMMARY: This is a research study. Your child taking part in this research study is voluntary. You and your child do not have to participate, and can leave the study at any time. No matter what you and your child decide, any other care that your child gets at this site will not change.

This study is testing whether adding a systems navigator (similar to a coach or guide) to pre-exposure prophylaxis (PrEP) care, a medicine that can help prevent HIV, improves PrEP use among heterosexual men, compared to the current standard PrEP care.

The study will take about 15-months total. If you and your child choose to enroll in the study, your child will be followed on the study for at least 6 months and up to 12 months. Your child will be asked to give blood and urine specimens for HIV, STI, and other tests. Your child does not need to remain on PrEP to continue participation in this study.

There are very limited risks involved with this study, including (but not limited to) risk of discomfort, dizziness/faintness, and/or bruising, swelling and/or infection from your child's blood being taken. Your child may also feel feelings of embarrassment or worry when answering questions about their own behaviors and/or receiving HIV counseling or become worried while waiting for their HIV test results. Finally, there is the potential that some of your child's information may become known to others, even though the study will do everything possible to prevent that.

There may be no direct benefits to your child for being in this study, but others may benefit in the future from information learned from this study. Specifically, information on how to improve HIV prevention services for heterosexual men. In addition, your child will receive HIV and STI counseling and testing as part of the study process and will be referred for treatment as needed.

More information about this study is described in the rest of this form. We will help you understand the information and answer all your questions. You should feel that you understand the

study before deciding whether your child will participate. If you agree to your child joining the study, you will be asked to sign your name or make your mark on this form. We will offer you a copy of this form to keep.

What are some general things you and your child should know about research studies?
You are being asked to allow your child to take part in a research study. To join the study is voluntary. You may decide to not allow your child to participate, or you may withdraw your permission for your child to be in the study, for any reasons, without penalty. Even if you give your permission, your child can decide not to be in the study or to leave the study early.

Research studies are designed to obtain new knowledge. This new information may help people in the future. Your child may not receive any direct benefit from being in the research study. There also may be risks to being in research studies. Deciding not to be in the study or leaving the study before it is done will not affect your or your child's relationship with the researcher or the health care provider. If your child is a patient with an illness, your child does not have to be in the research study in order to receive health care.

Details about this study are discussed below. It is important that you and your child understand this information so that you and your child can make an informed choice about being in this research study.

You will be given a copy of this consent form. You and your child should ask the researchers named above, or staff members who may assist them, any questions you have about this study at any time.

What is the purpose of this study?
The main purpose of this research study is to understand if it is helpful to use a systems navigator (coach or guide) to support the use of PrEP to prevent HIV. The overall goal of this study is to collect data that will inform future research, helping men from STI clinics reduce risk of getting HIV by taking PrEP.

This study is for adult and adolescent cisgender men who:

- are age 15 years or older,
- are seeking services at Bwaila STI Clinic, and
- have tested HIV negative

Are there any reasons your child should not be in this study?
Your child should not be in this study if they are taking part in another study of drugs or medical devices. Your child will be asked to tell the study staff about any other studies they are taking part in or thinking of taking part in. This is very important for their safety.

How many people will take part in this study?
About 200 HIV-seronegative heterosexual men will participate in this study from Lilongwe, Malawi.

How long will your child's part in this study last?
Participants who choose to join the study will be in the study for at least 6 months and up to 12

months total.

What will happen if your child take part in the study?
During this study, your child will be in one of 2 study groups. Researchers will "randomize" your child into one of the study groups described here. 2 out of every 3 persons enrolled will be assigned to the intervention group and 1 out of every 3 persons enrolled will be assigned to the standard of care group. Random assignment means that your child is put into a study group by chance, like flipping a coin. Neither your child nor the study staff can choose your child's study group. The table below indicates what services each group will receive.

Standard of Care Group	Standard PrEP services, including HIV testing and risk reduction counseling
Intervention Group	Standard PrEP services, including HIV testing and risk reduction counseling. Your child will also be assigned a systems navigator (coach), respond to a brief questionnaire about your sexual activities, and be tested for STIs at any PrEP visit you attend. This coach may also attempt to contact or trace your child for any missed PrEP visit (~7 days late), using information your child provides regarding their preferred tracing time, method (phone or in-person), and location.

PrEP visits: If your child continues on PrEP, the timing of PrEP visits will be decided by the PrEP nurse at the clinic, according to the Malawi guidelines for PrEP. These visits typically occur every 2-3 months, depending on the kind of PrEP they are taking.

This study is using a Standard of Care Group (also known as a "Control Group") because we do not yet know whether the intervention being tested in this study improves PrEP use. This kind of intervention has not previously been tested in PrEP care among men in Malawi. Using a Standard of Care Group will allow researchers to assess whether providing the additional intervention resources improves PrEP use. That information can be used to make recommendations to health care providers and leaders about what services should be offered in the future.

All participants will complete the study visit procedures outlined below, regardless of which group they are assigned.

Study visits: The study has at least 3 visits (including the enrollment visit today). Besides this first visit, your child will be asked to come back for a visit ~3 months and ~6 months from now. If your child enrolls early in the study, your child may also be asked to come back for study visits ~9 months and ~12 months from now. At each visit, your child will be asked a series of questions about their behaviors and be tested for HIV and other STIs. Your child may also be asked to participate in a one-on-one interview. Your child should attend these study visits even if they have decided to stop taking PrEP.

Enrolling in the Study
If you and your child decide to take part in the study, the Enrollment visit will last about 1-2 hours. During the Enrollment Visit, we will:

- Obtain full written informed consent for the study
- Ask your child where they live and how to contact them

- Ask your child to answer questions in a survey about their sexual activities and overall health
- Ask your child about their previous and current PrEP use
- Provide brief HIV risk reduction counseling
- Conduct a symptom-driven physical exam
- Collect ~10 to 20 mL (about 2 to 4 teaspoons) of blood to make sure your child does have a very early infection with HIV that may not be detected by the standard HIV tests they have received in clinic. If your child has not been tested for syphilis (another STI) at any recent PrEP visits, this blood will also be used to test you for syphilis.
- Collect ~ 10mL of your child's urine to test for STI testing (Chlamydia and Gonorrhea)
- Store blood (plasma, dried blood spots) and urine samples for study-related testing
- If your child is assigned to the intervention group, study staff will connect your child to their coach to discuss next steps in their PrEP care

Additional Visits: 2 to 4 additional visits over the next 6 to 12 months.
If you and you child decide to join the study, after their Enrollment Visit, your child will be asked to come to this location for follow up visits. Participants will be followed for at least 6 months and up to 12 months depending on the time of enrollment.

Each visit will last about 1 hour.

During these follow-up visit(s), we will:

- Ask your child where they live and how to contact them, only if the information your child gave before has changed.
- Ask your child to answer questions in a survey about their sexual activities and overall health
- Ask your child questions about if they are still using PrEP, why, or why not
- Provide HIV risk education counseling
- Conduct a symptom-driven physical exam
- Collect ~10 to 20 mL (about 2 to 4 teaspoons) of blood. Your child's blood will be used to test them for HIV. If your child has not been tested for syphilis at any recent PrEP visits, this blood will also be used to test your child for syphilis
- Collect ~ 10mL of your child's urine to test for STI testing (Chlamydia and Gonorrhea) if your child has not been tested for these infections at any recent PrEP visits
- Store blood (plasma, dried blood spots) and urine samples for study-related testing

At your child's final study visit, we will talk with your child about the end of the study and when the results of the study will be available. Your child may also be asked to participate in a one-on-

one interview around the time of their final study visit. Approximately 20 participants will be asked to participate in this type of interview. This would add 30-60 minutes to your child's visit time, and your child would be reimbursed for this additional time. The interviewer will ask questions about your child's understanding about HIV prevention, including PrEP, their experience being part of this study, and any challenges they experienced engaging in HIV prevention. If your child is assigned to the intervention group, your child will also be asked about their experience working with the PrEP coach. The interview will be audiotaped so that your child's responses can be transcribed for analysis. During transcription, any identifying names or places in the interview will be removed from the transcript. After transcription, the recording of the interview will be destroyed. Analysis will be conducted to look for common themes in all interviews conducted. You and your child can decline participation in this interview.

If your child tests positive for HIV at any point in the study, your child will be referred for HIV care and encouraged to start treatment for HIV immediately and your child will have an additional approximately 6-months of study follow-up time from the time your child tests positive. During this time, your child will have blood collected twice – once at 3 months and once at 6 months – to make sure that your child's body is responding appropriately to HIV treatment. During these visits, we will draw 10-20 mL (about 2-4 teaspoons) of blood to check the amount of HIV in your child's body. We will ask your child about any medications they are taking. If your child has not started HIV treatment yet, we will encourage them to start. We will also update your child's contact information. This could happen at a final visit if your child wants to stop the study early.

If your child stops taking PrEP, we will ask your child to stay in the study.
If your child permanently stops taking PrEP during the study for any reason, we will ask your child to continue to come for their regular study visits, but your child will no longer have to undergo certain procedures, like answering questions about taking PrEP, etc. Similarly, if your child miss doses of PrEP or miss PrEP visits, we will ask your child to continue to come for their regular study visits as scheduled.

If your child gets HIV during the study, we will help your child get care and support.
We will test your child's blood for HIV during this study. If your child gets HIV while they are in the study, your child will stop taking PrEP, and we will help your child find the care and support they need.

Use of stored samples
In addition to the laboratory testing performed at each study visit, further study-related testing may be performed on blood and urine samples. This will include testing related to HIV and other infections, including testing for anti-HIV medications and for quality control testing (to confirm results obtained in laboratories). If your child is found to have a very early phase of HIV or gets infected with HIV during the study, some blood may also be used to learn more about HIV viruses, the body's response to HIV infection, and how HIV is spread in the community. The samples used for this testing will be labeled with your child's study number and will be tested at special laboratory facilities that may be located in the US and other countries outside of Malawi. The laboratory doing the testing will not know who your child is. Only approved researchers will have access to their samples. Results of this specialized testing will not be returned to the study site or your child. Your child's samples will not be sold or directly used to produce commercial products or for commercial gain. No host genetic testing will be tested from these samples. Host testing means genetic testing derived from your child.

What are the possible benefits from being in this study?
There may be no direct benefits to participants in this study, however, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to improved HIV prevention services for heterosexual men in Malawi and the African region. In addition, participants will receive HIV and STI counseling and testing as part of the study process. Participants also will be referred for treatment if needed. Participants who choose to continue PrEP may benefit from the use of PrEP medicines which are known to protect against getting HIV if taken as directed.

If your child chooses not to be in the study, what other treatment options does your child have?
Your child's participation is voluntary. Your child does not have to take part in any of the tests or procedures in the study. Your child should also know that:

- If they decide not to join the study, they will not lose their regular medical care.
- If they join this study and later decide to leave, they will not lose theirregular medical care.
- Your child does not have to join the study to receive HIV prevention medications.
- If you and your child decide not to join the study, your child will still be able to join another study at a later time if there is one available and your child qualifies.

Can I change my mind about my child participating in this study?
Yes, you and your child can change your minds at any time. Your child's participation in this study is completely voluntary. You and your child's decision to leave the study will not lead to any penalty, or loss of benefits or rights that you and your child would normally have otherwise.

What are the possible risks or discomforts involved from being in this study?
It is not expected that this study will expose your child to unreasonable risk. Blood draws may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling, and/or infection. Your child may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. Your child also may become worried or anxious while waiting for their HIV test results. Trained counselors will be available to help your child deal with these feelings. Although the site will make every effort to protect your child's privacy and confidentiality, it is possible that your child's involvement in the study could become known to others, and that social harms may result. Social harms could occur if your child is perceived as having HIV or at increased likelihood of getting HIV. Examples of social harms are when your child are treated unfairly or have problems being accepted by their families and/or communities (i.e., because your child could become known as vulnerable to HIV).

What if we learn about new findings or information during the study?
You and your child will be told any new information learned during this study that might affect your child's willingness to stay in the study. For example, if information becomes available that shows that the PrEP coach may have bad effects, you and your child will be told about this. You and your child will also be told when the results of the study may be available, and how to learn about them.

How will information about your child be protected?

Every effort will be made to keep your child's personal information confidential, but we cannot guarantee absolute confidentiality. To keep your child's information private, their samples will be labeled with a code that can only be traced back to the study clinic. The results of any tests done on these samples will not be included in your child's health records. Your child's name, where they live, and other personal information will be protected by the study clinic. Any tracing activities will be done according to you and your child's stated preferences and will not discuss any information related to the study or study activities. Your child will be identified by a code, and personal information from their records will not be released without their written permission. Any publication of this study will not use your child's name or identify them personally. Your child's personal information may be disclosed if required by law.

Clinic staff will have access to your study records. Your child's records may also be reviewed, under guidelines of the US Federal Privacy Act, by:

The Malawi National Health Science Research Committee (NHSRC)
The University of North Carolina at Chapel Hill (UNC) Institutional Review Board (IRB)
The sponsor of the study (US National Institutes of Health [NIH]), its contractors, and its study monitors
The US Office for Human Research Protections (OHRP)
Other local, US, or international regulatory authorities/entities
The HPTN (HIV Prevention Trials Network) that is conducting this study

The study staff will also use your child's personal information, if needed, to verify that your child is not taking part in any other research studies. This includes other studies conducted by Bwaila STI Clinic and studies conducted by other researchers that study staff know about.

Malawi regulations require study staff to report the names of people who get HIV to the local health authority. Outreach workers from the health authority may then contact your child about informing their partners, since they also should be tested. If your child does not want to inform their partners themselves, the outreach workers will offer to contact them, according to the confidentiality guidelines of the Malawi Ministry of Health.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify your child. At most, the Web site will include a summary of the study results. Your child can search this Web site at any time.

What will happen if your child is injured by this research?

If your child gets sick or injured during the study, contact us immediately.

It is unlikely that your child will be injured as a result of study participation. If your child is injured, the Bwaila STI Clinic will give your child immediate necessary treatment for their injuries. You and your child will not have to pay for this treatment. You and your child will be told where they can get additional treatment for their injuries. There is no program to pay money or give other forms of compensation for such injuries either through this institution or the US NIH. You and your child do not give up any legal rights by signing this consent form.

If your child thinks they have been injured from taking part in this study, call the Principal

Investigator at the phone number provided on this consent form. They will let you and your child know what you should do.

What if you and your child want to stop before your child's part in the study is complete?
You can withdraw your child from this study at any time, without penalty. The investigators also have the right to stop your child's participation at any time. This could be because your child has had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped. If you or your child decide to withdraw, we will ask you to come in for a final visit for collection and storage of blood and urine and STI testing and referral.

Will your child receive anything for being in this study?
Your child will receive the equivalent of approximately 12USD for their time, effort, and travel to and from the clinic at each scheduled study visit.

Will it cost you anything for your child to be in this study?
There will be no cost to you or your child for study related visits, physical examinations, laboratory tests, or other procedures.

Who is sponsoring this study?
This research is funded by Family Health International (FHI 360) through a grant from the US National Institutes of Health (NIH). This means that the research team is being paid by the sponsor for doing the study. The researchers do not, however, have a direct financial interest with the sponsor or in the final results of the study.

What if you or your child have questions about this study?
If you or your child ever have any questions about the study, want to report a social harm, or if your child has a research- related injury, you or your child should contact Dr. Mitch Matoga at +265 999 511 726.

If you or your child have questions about their rights as a research participant, you should contact the Head of Secretariat at the National Health Science Research Committee, Dr Collins Mitambo, at +265 999 397 913.

By mail:
The Head of Secretariat
Malawi National Health Science Research Committee (NHSRC)
Ministry of Health
Phone: +265 726 422
or by email: mohdoccentre@gmail.com

What if you have questions about your child's rights as a research participant?
All research on human volunteers is reviewed by a committee that works to protect your child's rights and welfare. If there are questions or concerns about your child's rights as a research subject, or if you would like to obtain information or offer input, you may contact the Institutional Review Board at 919-966-3113 or by email to IRB_subjects@unc.edu.

SAMPLE ENROLLMENT CONSENT SIGNATURE PAGE

If you have read this consent form, or had it read and explained to you, you understand the information, and you voluntarily agree to join the study, please sign your name or make your mark below.

____ I agree to have my child take part in this study.

____ I do not agree to have my child take part in this study

If selected for an interview:

____ If selected, I agree to allow my child to participate in an interview where they will be asked questions about this research, and the interview will be recorded.

____ If selected, I do not agree to allow my child to participate in an interview where they will be asked questions about this research.

_____	_____
Participant Name (print)	Participant Signature and Date
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date