HPTN 113

Duo: A Phase IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men

DAIDS Document ID: 39073

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)

Pharmaceutical Support Provided by:

Gilead Sciences
ViiV Healthcare

Non-IND Study

Protocol Chair:
Susan Buchbinder, MD

Protocol Co-Chairs:
Jorge Gallardo-Cartagena, MD, MPH
Thiago S. Torres, PhD

Final Version 2.0
30 May 2025

HPTN 113
Duo: A Phase IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men

TABLE OF CONTENTS

PROTOCOL SIGNATURE PAGE 6
LIST OF ABBREVIATIONS AND ACRONYMS 7
PROTOCOL TEAM ROSTER 10
SCHEMA 13
OVERVIEW OF STUDY DESIGN 18
1.0 INTRODUCTION 19
1.1 Background and Rationale 19
1.2 Rationale for Study Design 22
1.2.1 Hypothesis 23
2.0 STUDY OBJECTIVES 23
2.1 Primary Objective(s) 23
2.2 Secondary Objectives 24
2.3 Exploratory Objectives 24
3.0 STUDY DESIGN 24
3.1 Participating Sites 25
3.2 Study Duration 25
4.0 STUDY POPULATION 25
4.1 Inclusion Criteria 26
4.2 Exclusion Criteria 26
4.3 Recruitment Process 27
4.4 Co-Enrollment Guidelines 27
4.5 Participant Retention 27
4.6 Participant Withdrawal 28
5.0 3P MHEALTH PACKAGE 28
5.1 MyPrEP Mhealth Tool 28
5.2 PrEPmate Mhealth Tool 29
5.3 PrEPsmart Mhealth Tool 29
6.0 CONTROL GROUP 29
7.0 STUDY PRODUCT CONSIDERATIONS 30
7.1 Study Product Administration 31
7.2 Study Product Formulation/Content/Preparation/Storage 31
7.2.1 Oral PrEP 31
7.2.2 CAB-LA 31
7.2.3 Doxy-PEP 34

7.3 Study Product Supply 34
7.4 Study Product Accountability 35
7.5 Toxicity Management 35
7.6 Concomitant Medications and Drug Interactions 36
8.0 STUDY PROCEDURES 36
8.1 Screening Visit 37
8.2 Enrollment Visit 38
8.3 Standing Follow-Up Visits 39
8.3.1 Week 4 40
8.3.2 Weeks 20 and 36 40
8.3.3 Week 52/Exit 40
8.4 CAB-LA Injection Visits 41
8.5 PrEP Regimen Switching 42
8.6 Post-Study Drug Access Following Study Exit 42
8.7 Adherence Assessment 43
8.8 Questionnaires Data Collection 44
8.9 Interim Contacts and Visits 45
8.10 Procedures for Participants Who Permanently Discontinue Study Product Early 45
8.11 HIV Testing 45
8.12 Procedures for Participants with Suspected or Confirmed HIV Infection 46
8.13 STIs 47
8.14 Hepatitis B 47
8.15 Qualitative Data Collection 47
8.15.1 In-depth Interviews 47
8.16 Study Visit Windows 48
9.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING 50
9.1 Adverse Event Definition and Reporting 50
9.2 Suspected, Unexpected Serious Adverse Reaction (SUSAR) Assessment 52
9.3 Safety Monitoring and Clinical Data Review 52
9.4 Expedited Adverse Event (EAE) Reporting 53
9.5 Adverse Event Reporting to DAIDS 53
9.6 Reporting Requirements for this Study 53
9.7 Expedited AE Reporting Period 54
9.8 Social Impact Reporting 54
10.0 STATISTICAL CONSIDERATIONS 55
10.1 Objectives and Endpoints 55
10.1.1 Primary Objective(s) and Endpoints 55
10.1.2 Secondary Objective(s) and Endpoints 56

10.1.3 Exploratory Objectives and Endpoints 57
10.2 Sample Size 58
10.3 Accrual and Retention 62
10.4 Random Assignment/Study Arm Assignment 62
10.5 Blinding 62
10.6 Statistical Analysis 62
10.6.1 Primary Analyses 63
10.6.2 Secondary Analyses 64
10.6.1 Missing Data 65
10.6.2 Interim Stopping Plan 65
10.7 Qualitative Analysis 65
11.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT 66
11.1 Local Laboratory Specimens 66
11.1.1 Specimen Storage at Study Sites 67
11.1.2 Virology 67
11.1.3 Pharmacology 67
11.1.4 Other HPTN LC testing 68
11.2 Quality Control and Quality Assurance Procedures 68
11.3 HIV Diagnostic Testing 69
11.4 HIV RNA Testing 69
11.5 Long-Term Local Specimen Storage and Possible Future Research Testing 69
11.6 Biohazard Containment 69
12.0 HUMAN SUBJECTS CONSIDERATIONS 70
12.1 Ethical Review 70
12.2 Informed Consent 70
12.3 Risks 71
12.3.1 Risks associated with F/TDF 72
12.3.2 Risks associated with F/TAF 72
12.3.3 Risks associated with CAB-LA 72
12.3.4 Risks associated with Doxycycline 73
12.4 Benefits 73
12.5 Incentives 73
12.6 Confidentiality 73
12.6.1 Certificate of Confidentiality 74
12.7 Communicable Disease Reporting Requirements 75
12.8 Study Discontinuation 75
13.0 ADMINISTRATIVE PROCEDURES 75

13.1 Source Documentation and Direct Data Entry 75
13.2 Protocol Registration 75
13.3 Study Activation 76
13.4 Study Coordination 76
13.5 Study Monitoring 77
13.6 Protocol Compliance 77
13.7 Investigator's Records 77
13.8 Results Dissemination 78
13.9 Use of Information and Publications 78
14.0 REFERENCES 79
APPENDIX IA: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR ALL PARTICIPANTS 82
APPENDIX IB: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR PARTICIPANTS ON CAB-LA 84
APPENDIX IC: SCHEDULE FOR HIV CONFIRMATION VISIT 85
APPENDIX II: HIV TESTING ALGORITHMS 86
APPENDIX III: SAMPLE INFORMED CONSENT FORM 88

HPTN 113
Duo: A Phase **IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men**

PROTOCOL SIGNATURE PAGE

DAIDS Document ID # 39073

Final Version 2.0
30 May 2025

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 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)

HPTN 113
Duo**: A** Phase **IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men**

LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
aHR	Adjusted Hazard Ratio
AIDS	Acquired immunodeficiency syndrome
ART	Antiretroviral therapy
CAB-LA	Long-acting injectable formulation of cabotegravir
CASI	Computer-Assisted Self Interview
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments of 1988
CMC	Clinical Management Committee
CoC	Certificate of confidentiality
CRF	Case Report Form
CRM	Clinical Research Manager
CRMS	(DAIDS) Clinical Research Management System
CRPMC	(DAIDS) Clinical Research Products Management Center
CRS	Clinical Research Site
CT	*Chlamydia trachomatis*
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DBS	Dried blood spot
DHHS	US Department of Health and Human Services
Doxy-PEP	Doxycycline for STI post-exposure prophylaxis
DSMB	Data and Safety Monitoring Board
EAE	Expedited Adverse Event
EC	Ethics Committee
EMC	Electronic Medical Record
EQA	External Quality Assurance
EWG	(HPTN) Ethics Working Group
F/TAF	Emtricitabine (FTC) and Tenofovir alafenamide (TAF)
F/TDF	Emtricitabine (FTC) and Tenofovir disoproxil fumarate (TDF)
FDA	(United States) Food and Drug Administration
FGD	Focus group discussion
GC	*Neisseria gonorrhea*
GCLP	Good Clinical Laboratory Practices
GEE	Generalized estimating equations

HBV	Hepatitis B
HIV	Human Immunodeficiency Virus
HPTN	HIV Prevention Trials Network
IAS-USA	International Aids Society USA
ICC	Intra-participant correlation coefficient
ICF	Informed consent form
IDI	In-depth interview
IM	Intramuscular
IoR	Investigator of Record
IRB	Institutional Review Board
ISR	Injection site reaction
LC	(HPTN) Laboratory Center
LDMS	Laboratory Data Management System
LFUP	Loss to follow-up rate
LL	Local laboratory
LOC	(HPTN) Leadership and Operations Center
MDD	Minimum detectable difference
mHealth	Mobile Health Tools
MOP	(HPTN) Manual of Operations
NAAT	Nucleic Acid Amplification Test
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
NIHGPS	NIH Grants Policy Statement
OHRP	Office for Human Research Protections
OSCO	DAIDS Office of Clinical Site Oversight
PCR	Polymerase chain reaction
PEP	Post-exposure prophylaxis
PK	Pharmacokinetic
PPE	Personal protective equipment
PrEP	Pre-exposure prophylaxis
PRO	Protocol Registration Office
QA	Quality Assurance
QC	Quality Control
RE	Regulatory entity
RNA	Ribonucleic acid
RSC	Regulatory Support Center
SAE	Serious Adverse Event
SAP	Statistical analysis plan
SDMC	(HPTN) Statistical and Data Management Center
SMC	Study Monitoring Committee
SMS	Short messaging service

SOE	Schedule of Events
SOP	Standard Operating Procedures
SSP	Study Specific Procedures
STI	Sexually transmitted infection
SUS	System Usability Score
SUSAR	Suspected, Unexpected Serious Adverse Reaction
TFV-DP	Tenofovir diphosphate
US	United States
USP	United States Pharmacopeia
WHO	The World Health Organization
3P	MyPrEP + PrEPmate + PrEPsmart tools

HPTN 113
Duo: A Phase IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men

PROTOCOL TEAM ROSTER

PROTOCOL CHAIR
Susan Buchbinder, MD
San Francisco Department of Public Health
and University of California, San Francisco
Email: susan.buchbinder@sfdph.org

PROTOCOL CO-CHAIRS
Jorge Gallardo-Cartagena, MD, MPH
Centro de Investigaciones Tecnológicas
Biomédicas y Medioambientales (CITBM)
Email: jgallardo@citbm.pe

Thiago S. Torres, PhD
Instituto Nacional de Infectología Evandro
Chagas (INI-Fiocruz)
Email: thiago.torres@ini.fiocruz.br

Members listed in alphabetical order:

Justine Beck, PharmD, BCPS
Pharmacist
Pharmaceutical Affairs Branch, DAIDS
NIAID, NIH
Email: justine.beck@nih.gov

Amanda Brown
Clinical Data Manager III
SCHARP, Fred Hutchinson Cancer Center
206-667-2317
Email: abrown@fredhutch.org

Pedro Cahn, MD, PhD
Fundación Huésped
Email: pedro.cahn@huesped.org.ar

Connie Celum, MD, MPH
Professor
University of Washington
Phone: 206-520-3824
Email: ccelum@uw.edu

Valeria Cantos, MD
Assistant Professor
Emory University
Phone: 404-368-2656
Email: vcantos@emory.edu

Carina Cesar, MD
Fundación Huésped
Email: Carina.cesar@huesped.org.ar

Jesse Clark, MD
UCLA Vine St. Clinic CRS
Email: jlclark@mednet.ucla.edu

Maria del Rosario Leon, BA, MSc
Community Working Group Representative
Barranco/San Miguel CRS, IMPACTA
Phone: 240-669-2867
Email: rleon@impactaperu.org

Molly Dyer, MPH
Community Program Associate
HPTN LOC, FHI 360
Phone: 919-321-3851
Email: mdyer@fhi360.org

Susan Eshleman, MD, PhD
Protocol Virologist
Johns Hopkins University, LC
Phone: 410-614-4734
Email: seshlem@jhmi.edu

Maria Ines Figueroa, MD
Site Investigator
Fundación Huésped
Email: Maria.figueroa@huesped.org.ar

Jessica Fogel, PhD
Protocol Co-Virologist
Johns Hopkins University, LC
Phone: 410-614-4698
Email: jfogel@jhmi.edu

Kailazarid Gomez-Feliciano, MPM
HPTN LOC, FHI 360
Phone: 919-321-3486
Email: kgomez@fhi360.org

Beatriz Grinsztejn, MD, PhD
Instituto de Pesquisa Clinica Evandro Chagas-Fiocruz
Phone: 55-21-2270-7064
Email: gbeatriz@ipec.fiocruz.br

Jayla Harris-Wisecarver, MPH
Clinical Research Manager
HPTN LOC, FHI 360
Email: jharris@fhi360.org

Danielle Heyl
HPTN LC QA QC Coordinator
Johns Hopkins University, LC
Phone: 410-614-6737
Email: Dheyl1@jhmi.edu

Tinia Hill
HPTN LCQA QC Coordinator
Johns Hopkins University, LC
Phone: 410-614-6737
Email: Thill54@jhmi.edu

Brenda Hoagland, MD, PhD
Site Investigator
Instituto de Pesquisa Clinica Evandro Chagas-Fiocruz
Email: brenda.hoagland@ipec.fiocruz.br

Cindy Jacobson, PharmD
Pharmacist
HPTN LOC, FHI 360
Phone: 202-464-3616
Email: cjacobson@fhi360.org

Kelika Konda, PhD
Barranco/San Miguel CRS, IMPACTA
Email: Kelika.konda@upch.pe

Raphael **Landovitz, MD, MSc**
UCLA Center for Clinical AIDS Research and Education
Phone: 310-825-3782
Email: rlandovitz@mednet.ucla.edu

Albert Liu, MD, MPH
San Francisco Department of Public Health and University of California, San Francisco
Phone: 415-437-7408
Email: albert.liu@sfdph.org

Tracy Lyons
Clinical Trials Assistant
Email: tlyons@fhi360.org

John Mac Rae
Site Investigator, IMPACTA
San Miguel CRS
Email: jmacrae@impactaperu.org

Yukari C Manabe, MD
HPTN LC STI Representative
Johns Hopkins University, LC
Phone: 410-955-8571
Email: ymanabe@jhmi.edu

Maricel Manalo
Clinical Safety Associate III
SCHARP, Fred Hutchinson Cancer Center
Email: mmanalo@fredhutch.org

Mark Marzinke, PhD, DABCC
Laboratory Pharmacologist
Johns Hopkins University, LC
Phone: 443-287-7516
Email: Mmarzin1@jhmi.edu

Andrea McMunn, PharmD, BCPPS
Pharmacist
Pharmaceutical Affairs Branch, DAIDS
NIAID, NIH
Email: andrea.mcmunn@nih.gov

Andrea Repetto
Clinical Data Manager II
SCHARP, Fred Hutchinson Cancer Center
Phone: 206-667-4441
Email: arepetto@fredhutch.orgg

Jim Rooney, MD
Gilead Sciences, Inc.
Phone: 650-522-5708
Email: Jim.Rooney@gilead.com

Jorge Sanchez, MD, MPH
Asociacion Civil Impacta Salud y Educacion
Phone: 51-1-242-3072
Email: jsanchez@citbm.pe

Hyman Scott, MD, MPH
Bridge HIV/ San Francisco Department of Public Health
Phone: 415-437-7483
Email: hyman.scott@sfdph.org

Aaron Siegler, PhD, MHS
Behavioral Scientist
Emory University
Email: asiegle@emory.edu

Deeksha Sharma
Statistical Research Associate II
SCHARP, Fred Hutchinson Cancer Center
Email: dsharma@fredhutch.org

Lydia Soto-Torres, MD, MPH
Medical Officer
Prevention Sciences Program, DAIDS, NIAID, NIH
Email: lsoto-torres@niaid.nih.gov

Jean de Dieu Tapsoba, PhD
Protocol Statistician
HPTN SDMC, Fred Hutchinson Cancer Center
Phone: 206-667-4119
Email: jtapsoba@fredhutch.org

Javier Valencia, MD
Site Investigator
Barranco/San Miguel CRS, IMPACTA
Email: jvalencia@impactaperu.org

Valdilea Veloso, MD, PhD
Oswaldo Cruz Foundation - Fiocruz
Email: valdilea.veloso@ipec.fiocruz.br

David Zelaya, PhD
Assistant Professor
Brown University School of Public Health
Phone: 401-863-2709
Email: david_zelaya@brown.edu

HPTN 113

Duo: A Phase IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men

SCHEMA

Purpose:	Test a suite of mHealth tools to increase HIV pre-exposure prophylaxis (PrEP) uptake and adherence among young men in communities most affected by the HIV epidemic and evaluate the uptake, adherence, and acceptability of doxycycline for sexually transmitted infection (STI) post-exposure prophylaxis (doxy-PEP).
Justification:	There is a high need for HIV prevention among young men, though uptake of PrEP in this population has been low. This study will assess whether the mHealth intervention increases PrEP uptake and adherence. Furthermore, the study will obtain preliminary efficacy data to inform future research with further geographic or individual representation. It may also serve to influence government recommendations on PrEP rollout and doxy-PEP implementation.
Design:	Phase IIIb, multi-site, individual-level randomized controlled trial
Population:	Young men from communities most impacted by the HIV epidemic, aged 18-29 years
Study Size:	400 young men in the United States
Study Duration:	Approximately 3 years for accrual and follow-up, with each participant being followed for 12 months.
Study Location:	United States (Additional sites may be added pending funding)
Study Regimen:	All participants will be offered HIV PrEP and doxy-PEP. Participants will be randomized 1:1 to receive either the 3P mHealth package (3P: MyPrEP + PrEPmate + PrEPsmart tools) or standard-of-care services arm. Participants will be followed for 52 weeks after enrollment.
Hypothesis:	The 3P mHealth Package will support informed choice and PrEP adherence, leading participants to have improved PrEP uptake and adherence compared with a control group, in an individual-level randomized controlled trial. We also hypothesize that a substantial proportion of participants will take doxy-PEP, and that it will be highly acceptable.
Study Objectives and Endpoints	

Primary Objectives	**Primary Endpoints**
• Determine the efficacy of the 3P mHealth package on PrEP uptake among participants	• PrEP initiation with a documentation of oral PrEP dispensation by the study site at any time during the 52 weeks of study follow-up period.

	• PrEP initiation with documentation of a CAB-LA injection by the study site at any time during follow-up, up to 48 weeks.
• Determine the efficacy of the 3P mHealth package on PrEP adherence among participants	• Protective intraerythrocytic Tenofovir diphosphate (TFV-DP) concentrations for participants choosing to use a TFV-based daily oral PrEP regimen. • Documented CAB-LA injections every 8 weeks, ± 2 weeks (14 days) of the expected dosing, during the preceding period among participants choosing CAB-LA. • Documentation of elected PrEP regimen and timing of PrEP regimen switching at each study visit during the 52 weeks of follow-up. • Self-reported PrEP use and adherence at each study visit. • Self-reported number and timing of anal sex encounters in the past 30 days and TFV-DP concentrations in dried blood spot (DBS) for participants electing to use 2-1-1 oral PrEP.
• Assess doxy-PEP uptake, use, and acceptability, and factors associated with each.	• Doxy-PEP initiation with a documentation of doxycycline dispensation at any time during the 52 weeks of study follow up period. • Self-reported use of doxy-PEP at each follow-up visit during the 52 weeks of study follow-up. • Self-reported number and timing of anal sex encounters in the past 30 days. • Self-reported doxy-PEP acceptability. • Self-reported individual-level sociodemographic, behavioral, and attitudinal characteristics collected at baseline and subsequent study visits during the 52 weeks of study follow-up. • AEs that lead to doxy-PEP hold • Response to qualitative interview questions inquiring about doxy-PEP use for a subset of participants.
• Assess the incidence of HIV infections among participants choosing to use CAB-LA.	• PrEP initiation with documentation of a CAB-LA injection by the study site at any time during follow-up, up to 48 weeks. • Documented on-time CAB-LA injections of the expected dosing, among participants choosing CAB-LA.

	• Documented incident HIV infections among participants choosing to use CAB-LA during the study follow-up period.
Secondary Objective(s)	**Secondary Endpoints**
• Determine the acceptability and use of the 3P mHealth package in the intervention arm	• Self-reported use of the 3P mHealth package among participants randomized to the intervention arm only. • Self-reported acceptability of the 3P mHealth package among participants in the intervention arm only. • Response to qualitative interview questions inquiring acceptability of 3P mHealth package for a subset of participants in the intervention arm only.
• Compare the frequency, directionality, and reasons for PrEP regimen choice, switching, and discontinuation by arm	• Documented PrEP regimen choice during the 52 weeks of study follow-up. • Response to interview questionnaires inquiring reasons for PrEP regimen choice and switching via computer (or tablet)-assisted self-interview (CASI) during the study follow-up period. • Self-reported PrEP use and PrEP discontinuation during the study follow-up period. • Adverse Events (AEs) that lead to PrEP hold or change
• Evaluate demographic, behavioral, and attitudinal factors associated with choice of PrEP regimen	• Documented number of chosen PrEP regimen during the 52 weeks of study follow-up. • Sociodemographic, behavioral, and attitudinal characteristics collected at baseline and subsequent study visits during the 52 weeks of study follow-up.
• Determine the efficacy of the 3P mHealth package on prevention-effective adherence	• Documented incident HIV infection during the 52 weeks of follow-up. • Self-reported HIV risk, including sexual behavior and HIV status of sexual partner. • Protective TFV-DP concentration levels in DBS at weeks 20, 36 and 52 for participants choosing to use oral PrEP. • Documented CAB-LA injections 1 month apart for the first two injections, then every 8 weeks, within the expected dosing window, during the preceding period among participants choosing CAB-LA.

	• Documentation of elected PrEP regimen at each study visit during the 52 weeks of study follow-up. • Self-reported PrEP adherence.
Exploratory Objective(s)	**Exploratory Endpoints**
• Explore the preliminary efficacy of the 3P mHealth package on HIV incidence	• Documented incident HIV infections during the study follow-up period.
• Assess bacterial STI incidence and factors associated with STI incidence among those who do and do not take doxy-PEP.	• Documented incident bacterial STI infections during the follow-up period. • Self-reported use of doxy-PEP at follow-up visits.
• Explore the impact of relative usage of each of the 3P mHealth tools on PrEP uptake and adherence.	• PrEPsmart paradata on app usage frequency and time • PrEPmate paradata on messaging frequency and quantity • MyPrEP paradata on website interaction frequency and time • PrEP uptake as defined above • PrEP adherence as defined above • Documentation of elected PrEP regimen
• Perform exploratory 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; characterization of STIs, and evaluation of virologic, pharmacologic, or STI-based laboratory assays.	• Endpoints will be defined based on which assessments are performed.
• Evaluate the longitudinal use of on-demand and weekly doxycycline with hair doxycycline assessments	• Measures of doxycycline concentration levels in hair at weeks 20, 36, and 52.

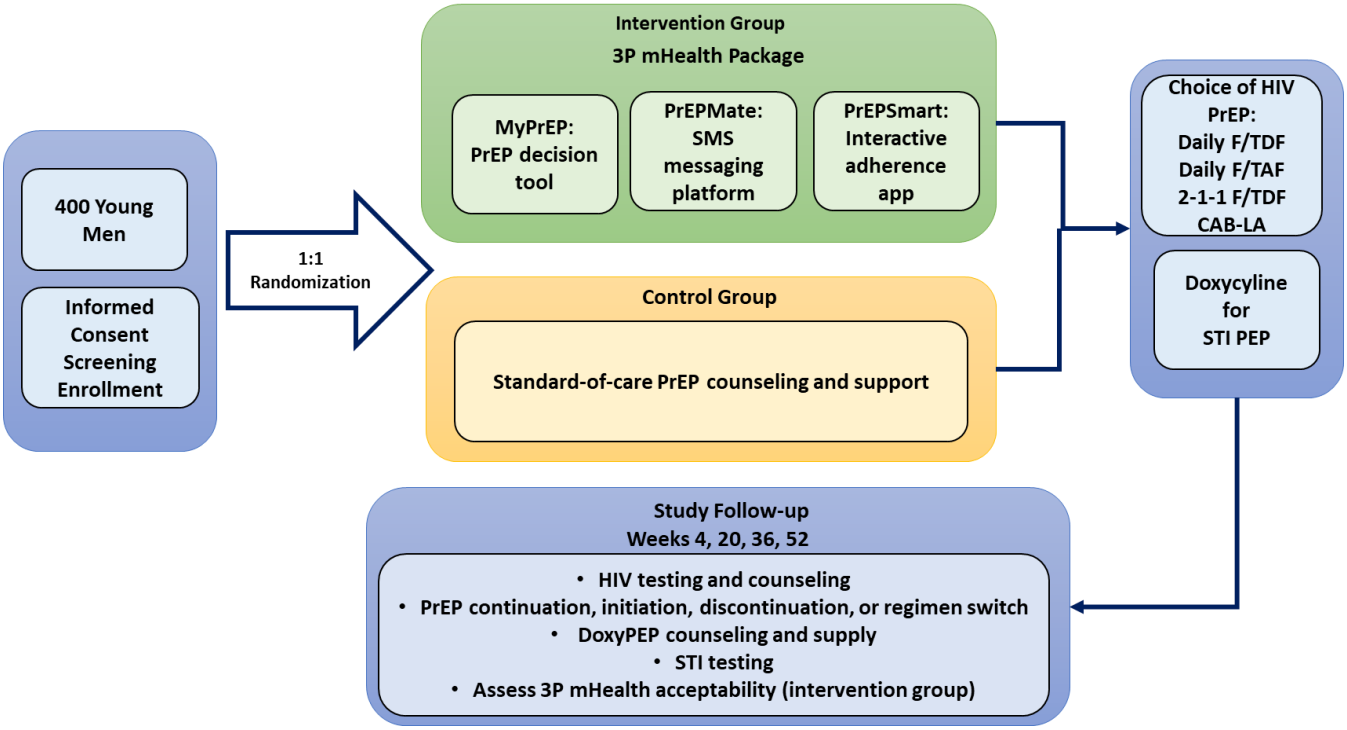
TERMINOLOGY FOR PREP AGENTS

Abbreviation	Compound name	Comments
TDF	Tenofovir disoproxil fumarate	This is the inactive, oral formulation of tenofovir (TFV, trade name: Viread®). The ester form enhances oral absorption and bioavailability. TDF is rapidly metabolized after dosing to the de-esterified pro-drug, which is also inactive.
TFV	Tenofovir	This is the inactive, de-esterified form of TDF. This is the form of the drug that is measured in serum, blood, other body fluids, and non-cellular tissue samples.
TFV-DP	Tenofovir diphosphate	This is the active, phosphorylated form of TFV that is generated in cells. This is the form of the drug that is measured in cells (e.g., peripheral blood mononuclear cells, PBMCs). It is rapidly dephosphorylated to the inactive form outside of cells and has a very short half-life outside of cells in tissue.
FTC	Emtricitabine	FTC is an inactive pro-drug that is activated in cells by phosphorylation. This is the form of the drug that is measured in serum, blood, other body fluids, and non-cellular tissue samples. This is the active form of FTC that is generated in cells. This is the form measured in cells (e.g., PBMCs).
FTC-TP	Emtricitabine triphosphate	This is the active form of FTC that is generated in cells. This is the form measured in cells (e.g., PBMCs).
TAF	Tenofovir alafenamide	This is a newer formulation of tenofovir. TAF is absorbed more quickly than TDF and produces higher levels of TFV-DP in cells. TAF can be given in smaller doses, with drug concentrations in blood and less exposure for the kidneys and other organs.
F/TDF	Emtricitabine/ Tenofovir disoproxil fumarate	This is co-formulated oral product containing FTC (200 mg) and TDF (300 mg). This product may be used daily or off-label as an on-demand, 2-1-1 regimen.
F/TAF	Emtricitabine/ Tenofovir alafenamide	This is a co-formulated oral product containing FTC (200 mg) and TAF (25 mg).
CAB	Cabotegravir	CAB is an integrase strand transfer inhibitor.
CAB-LA	Long-acting cabotegravir	This is a long-acting injectable form of CAB used for HIV treatment and prevention.

HPTN 113

Duo**: A** Phase **IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men**

OVERVIEW OF STUDY DESIGN



1.0 INTRODUCTION

1.1 BACKGROUND AND RATIONALE

Pre-exposure Prophylaxis for HIV prevention

Human immunodeficiency virus (HIV) pre-exposure prophylaxis (PrEP), when taken as a daily pill (F/TDF[1] or F/TAF [2]), a 2-1-1 oral regimen (F/TDF) [3], or a bimonthly injectable (CAB-LA) [4], has been shown to be highly effective in reducing HIV incidence. Daily oral F/TDF and F/TAF are United States (US) Food and Drug Administration (FDA) approved for the prevention of HIV. The 2-1-1 or "on-demand" use of F/TDF for HIV prevention is considered off-label use, though it is recommended by the World Health Organization (WHO) and International AIDS Society USA (IAS-USA) for populations of men with same sex behavior. Men at sexual risk are the key population with the highest rate of HIV infection in the Americas, accounting for 69% of new diagnoses in the US in 2019 [5] (the last year with reliable pre-COVID data), and 44% in Latin America [6].. In Latin America, new HIV diagnoses have increased by 31% among men and boys from 2010-2019 [6]. Young men account for a substantial proportion of new HIV infections throughout the Americas. In the US, men 15-24 years old account for 26% of all new diagnoses[5]. In Latin America, men 15-24 years old account for 11% of all new HIV diagnoses [6]. In the recent ImPrEP PrEP implementation project in Peru, Brazil, and Mexico, HIV incidence among participants poorly adherent to PrEP (with a medication possession ratio of <0.6) was 2.9/100 person-years overall, but 4.59/100 person-years in Peru [7]. HIV incidence was highest in 18-24 year olds (5.18/100 person-years overall). In the ImPrEP seroincidence study, the annualized HIV incidence rate among young participants aged 18-24 years not using PrEP or PEP was 3.48% (95% Confidence Interval [CI]: 2.51-4.45) in Brazil and 9.77% (95% CI: 7.34-12.20) in Peru [8]. PrEP uptake in Latin America remains low compared to the size of the eligible population; as of Q4 2024, there were 216,370 PrEP initiations in Brazil, 4,383 in Peru, and 3,927 in Argentina [9].

People now have a choice of three different biomedical prevention tools (F/TDF, F/TAF, and CAB-LA) in 4 different regimens (daily or 2-1-1 for F/TDF, daily for F/TAF, or bimonthly for CAB-LA). However, PrEP uptake remains inadequate globally [11], persistence is poor (with 37-62% of patients discontinuing oral PrEP by 6 months) [12-15], and both uptake and persistence are lowest in the most vulnerable populations, including men in communities most impacted by the HIV epidemic [16, 17] and youth [18, 19]. More tools are needed to improve uptake and adherence of PrEP, particularly for young men.

Post-exposure prophylaxis for STI prevention

Prevalence of sexually transmitted infections (STIs) is high and rising in populations of young men in high incidence communities. In 2019, STIs reached an all-time high for the

6th consecutive year in the US, with more than 2.5 million cases of gonorrhea, chlamydia, and syphilis reported [20]. Gonorrhea among young men increased 264% from 2010-2019, with more than 20% of men in high incidence communities seen at STI clinics testing positive. Chlamydia rates were also high, and highest among young men <20 years of age, for whom more than 20% tested positive. Overall, 47% of all primary and secondary syphilis cases in the US in 2019 were diagnosed in men in these communities. Data on syphilis, chlamydia, and gonorrhea from the ImPrEP PrEP demonstration project in Peru, Brazil, and Mexico, are shown in Table 1. STI incidence and prevalence was high, particularly among young men 18-24 years of age. In a meta-analysis of global syphilis prevalence among men, the pooled prevalence estimate of syphilis in men in Latin America was the highest among all regions (10.6% (8.5–12.9) [21].

Table 1. STI incidence/prevalence in the ImPrEP Study

Demographic	Syphilis[1]	Chlamydia[2]	Gonorrhea[2]
Peru	9.2	14.6	8.9
Brazil	11.9	10.3	6.5
Mexico	8.1	11.4	13.2
18-24 years	10.6	14.2	12.1
25-30 years	9.6	12.2	9.2
≥ 31years	10.1	9.9	7.4

[1] Incidence per 100 person-years
[2] Baseline proportion testing positive

Doxycycline post-exposure prophylaxis (PEP) may be a useful tool in controlling STIs among young men. Recent data have shown that doxycycline, given after sexual encounters (doxy-PEP), can reduce incident chlamydia, gonorrhea, and syphilis among men by 65% [22]. Doxycycline is FDA approved for a number of indications including treatment of certain STIs. While doxy-PEP is an off-label use of the medication, the US Centers for Disease Control and Prevention (CDC) has endorsed its use to prevent bacterial STIs in men with a history of a bacterial STI. In a study of 319 men without HIV on HIV PrEP, taking 200 mg of doxycycline 24 to 72 hours after sex led to a 66% reduction in bacterial STIs (95% CI 54-76%). Doxycycline could be taken up to every day. The median (interquartile range) number of doses taken was 4 (1-10) doses per month, for a median duration of 270 days. Among men on PrEP, doxy-PEP led to significant reductions in gonorrhea (55%) as well as chlamydia (88%) and syphilis (87%), although the number of incident syphilis cases was low. This study further analyzed a subset of 44 participants and found an increase in doxycycline resistance to gonorrhea compared to baseline (from 27% to 38%), likely due to selection of resistant strains. There was no resistance to doxycycline for either syphilis or chlamydia. Participants in the doxycycline arm had reduced staph aureus carriage in the nose; studies of the microbiome have not been completed [22]. The Ipergay study found a 70% reduction in chlamydia and a 63% reduction in syphilis, but no significant reduction in gonorrhea[23], possibly because of higher background rates of gonorrhea resistance to tetracycline in Europe than in the Americas. A later study in similar populations showed a significant reduction of syphilis and chlamydia (adjusted hazard ratio [aHR]: 0.16; 95% confidence

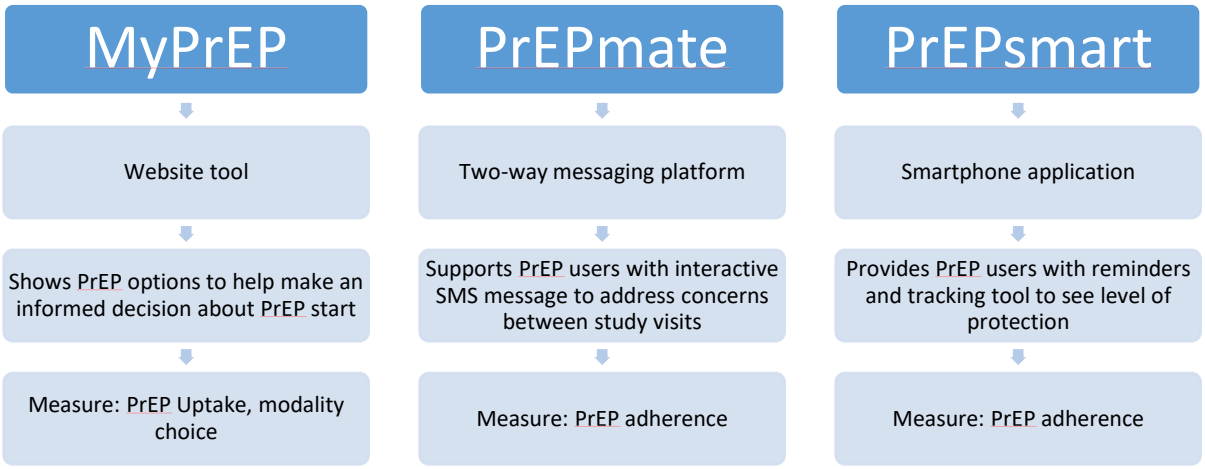
intervals [CI]: 0.08-0.30), as well as a reduction in gonorrhea (aHR: 0.49; 95% CI: 0.27-0.88)[24]. A key issue surrounding the implementation of doxy-PEP for men is the need to gain more data about its use against syphilis, including understanding if doxy-PEP compromises serologic diagnosis syphilis, thus impacting downstream management. Incorporation of doxy-PEP into the proposed study will provide additional data on its uptake and the subsequent number of new syphilis infections. Syphilis has greater morbidity than gonorrhea and chlamydia, and high incidence (10.5 per 100 person years) among participants in ImPrEP[25].

Mobile health tools for HIV and STI prevention

The contraceptive literature suggests that informed decision making about methods improves uptake and adherence to method use [26]. Many of the reasons to decline oral PrEP (e.g., preference to avoid daily pills, side effect profile, infrequent sexual contact, stigma, privacy concerns) may be obviated by choice of PrEP regimen. Bedsider (Bedsider.org) is an online decision support tool for contraceptive choice found to be highly acceptable [27, 28], to significantly increase uptake of a highly effective contraceptive method, and to significantly reduce having a pregnancy scare, an unintended pregnancy, and condomless sex, compared with a control condition [29]. We created a similar decision support tool for oral PrEP for young women in Southern Africa, and demonstrated that it doubled the proportion persisting on PrEP after 1 month [30]: we are adapting this tool for use in young men (**MyPrEP**). Prototypes of MyPrEP were reviewed within the Adolescent Trials Network and in 4 focus groups conducted with young men in the San Francisco Bay Area. Some of the participants were on PrEP; others had not yet started, and all said they would have found the information in MyPrEP helpful at the start of using PrEP. We also developed **PrEPmate**, an interactive, two-way short message system (SMS) platform using personalized communication via weekly check-in messages to support oral PrEP patients between clinic visits. The effectiveness of SMS-based interventions to increase antiretroviral adherence among patients living with HIV has been shown in several studies [31-34], and we have demonstrated that PrEPmate improved daily oral PrEP adherence (80% vs. 57% at 36 weeks, $p<0.01$) in young men in the US [35], leading it to be the first CDC-designated Evidence Based Intervention for PrEP. We have also developed a mobile app to support PrEP adherence for persons using 2-1-1 or daily PrEP **(PrEPsmart)**. This tool allows 2-1-1 oral PrEP users to track both sexual encounters and PrEP pill taking. The app has a timer that reminds participants when it is time to take their next PrEP pill. The app also provides instant feedback on the level of protection afforded by oral PrEP (high, medium, low) depending on their recent oral PrEP-taking habits, a feature widely appreciated by participants. An early version of PrEPsmart was tested in 100 young men in a longitudinal study. The average System Usability Score (SUS) score was 80; participants particularly liked the feature that told them about the level of protection, with 77% ranking it as very helpful and another 13% ranked it as quite helpful. Overall, 94% stated that it helped them in taking PrEP. When asked if they would use the app in the future, 97% responded that they would, and 90% said they would recommend the app to a friend.

We have combined these three tools focused on HIV PrEP support into a package called the 3P mHealth Package (Figure 1). This package of tools is designed to address barriers to PrEP uptake using the MyPrEP tool to help participants make informed decisions about PrEP start. The package will also help address barriers to adherence using the PrEPmate platform and PrEPsmart app.

Figure 1. 3P mHealth tools summary



1.2 Rationale for Study Design

This study will evaluate the effectiveness of the 3P mHealth Package to increase PrEP uptake and adherence among young men, and to measure the uptake, use, and acceptability of doxy-PEP in this population.

If this study demonstrates improved PrEP uptake and adherence, it could lead to a larger trial with further geographic or individual representation. It may also serve to influence government recommendations on PrEP rollout and doxy-PEP implementation.

Individual randomization
Participants will be randomized to one of two arms in a 1:1 ratio which will provide robust data on the impact of the 3P mHealth Package.

Including Multiple PrEP Regimens
PrEP will be provided for participants because this vanguard study is testing an intervention to help with the selection, uptake, and adherence of PrEP use when choices are available. Participants will be able to initiate PrEP and switch regimens at any time during the study. Determining who uses which PrEP approach and whether they persist with PrEP will help jurisdictions, ministries of health, and stakeholders decide which PrEP options to make available, particularly if populations that don't normally initiate or remain on PrEP have higher adherence on a newer regimen.

Study location
This study will have sites in the US (other sites could be added in the future) to address HIV prevention needs among young men where HIV incidence rates remain high. While there is heterogeneity among the study locations and populations, there is value in understanding if the mHealth tools can work across these settings and provide preliminary information about any differences in acceptability or effectiveness in increasing PrEP uptake and adherence.

Fit within the HPTN Specific Aims
This study addresses the HIV Prevention Trials Network (HPTN) Specific Aim 4, to design and conduct integrated biomedical and socio-behavioral strategies for HIV prevention. This study will integrate biomedical interventions to prevent HIV and STIs and mHealth tools that provide uptake and adherence support within a priority population for HIV prevention. If successful, this could provide preliminary data for a larger efficacy trial to test whether the 3P mHealth package can reduce rates of HIV acquisition.

1.2.1 Hypothesis

We hypothesize that the 3P mHealth Package will support informed choice and PrEP adherence, leading participants to have improved PrEP uptake and adherence compared with a control group, in an individual-level randomized controlled trial. We also hypothesize that a substantial proportion of participants will take doxy-PEP, and that it will be highly acceptable.

2.0 STUDY OBJECTIVES

The primary, secondary, and exploratory objectives of the study are listed below. Endpoints related to each objective are described in Section 10.1.

2.1 PRIMARY OBJECTIVE(S)

The primary objectives of this study are to:

1) Determine the efficacy of the 3P mHealth package on PrEP uptake among participants

2) Determine the efficacy of the 3P mHealth package on PrEP adherence among participants

3) Assess doxy-PEP uptake, use, and acceptability, and factors associated with each

4) Assess the incidence of HIV infections among participants choosing to use CAB-LA

2.2 SECONDARY OBJECTIVES

The secondary objectives of this study are to:

1) Determine the acceptability and use of the 3P mHealth package in the intervention arm

2) To compare the frequency, directionality, and reasons for PrEP regimen choice, switching, and discontinuation by arm

3) Evaluate demographic, behavioral, and attitudinal factors associated with choice of PrEP regimen

4) Determine the efficacy of the 3P mHealth package on prevention-effective adherence

2.3 EXPLORATORY OBJECTIVES*

The exploratory objectives of this study are to:

1) Explore the preliminary efficacy of the PrEP support package on HIV incidence

2) Assess bacterial STI incidence and factors associated with STI incidence among those who do and do not take doxy-PEP.

3) To explore the impact of relative usage of each of the 3P mHealth tools on PrEP uptake and adherence.

4) Perform exploratory 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; characterization of STIs, and evaluation of virologic, pharmacologic, or STI-based laboratory assays.

5) To evaluate the longitudinal use of on-demand and weekly doxycycline with hair doxycycline assessments.

*These objectives may be modified based on funding and other considerations.

3.0 STUDY DESIGN

This is a Phase IIIb, multi-site, individual-level randomized, open-label trial with participants assigned 1:1 to receive the 3P mHealth package (intervention) or a PrEP handout (control). All participants will be provided their choice of HIV PrEP agents/regimens (daily oral F/TDF, daily oral F/TAF, 2-1-1 PrEP with F/TDF, or CAB-LA) and doxy-PEP for bacterial STI prevention. The 3P intervention consists of a suite of three mobile health tools to assist with informed choice: an online decision support tool

(MyPrEP), an SMS texting platform for ongoing adherence engagement and support (PrEPMate), and an app that allows oral dose tracking with corresponding levels of protection (PrEPsmart). The applications have been used in other populations and will be tailored for use among young men and tested in focus group discussions (FGD) in a separate study, prior to study start. This study is designed to determine whether the 3P mHealth package supports PrEP uptake and adherence and to measure the uptake, use, and acceptability of doxy-PEP among young men in the Americas.

Approximately 400 young men who meet eligibility criteria will be enrolled in the study. All participants will have study visits at Weeks 4, 20, 36, and 52 following enrollment. Participants choosing to use CAB-LA will have up to seven additional visits for CAB injections in accordance with injection schedules (see Appendix IB). At study visits, all participants will receive HIV counseling and testing, STI testing, PrEP and doxy-PEP provision, and socio-behavioral questionnaires. Participants will be able to switch or stop PrEP regimens at any time. Participants in the intervention group will be counseled on each of the mHealth tools and provided instructions on how they can be accessed and utilized to support informed decision making and adherence to PrEP.

A subset of participants will be invited for qualitative interviews to explore acceptability of the 3P mHealth package and decision-making around PrEP and doxy-PEP use.

3.1 PARTICIPATING SITES

Participating sites are listed in the Study Management Overview Study Specific Procedures (SSP) Manual – Section 1, and are located in the US. Additional sites may be added in the future, pending funding.

3.2 STUDY DURATION

Study duration is approximately three years for accrual and follow-up, and individual participants will be followed on-study for approximately 12 months.

4.0 STUDY POPULATION

Approximately 400 young men from communities most affected by the HIV epidemic 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 guidelines in Section 4.4. Participants will be recruited, screened, and enrolled as described in Section 4.3 and assigned to a study intervention group as described in Section 10.4. Requirements related to participant retention and withdrawal from the study are described in Sections 4.5 and 4.6, respectively. Individual sites will be given enrollment targets such that overall cross-site enrollment meets overall protocol goals.

4.1 INCLUSION CRITERIA

Men who meet all of the following criteria are eligible for inclusion in this study:

1) Men ages 18 – 29 years
2) Men who are in communities most affected by the HIV epidemic.
3) Willing and able to provide informed consent
4) Reports having anal sex with men in the last 6 months.
5) Have certain risk factors for HIV acquisition, defined as any of the following in the past 6 months:
    a. Any condomless anal sex with a man; not including within a monogamous relationship with an HIV-negative partner or an HIV-positive partner who is virally suppressed
    b. Reporting 2 or more male partners, regardless of condom use
    c. Reporting gonorrhea, chlamydia, or syphilis diagnosis
    d. Any stimulant use (e.g., cocaine, amphetamines)
6) Not on PrEP within the past 3 months due to participant choice
7) Interested in learning more about PrEP or starting PrEP
8) No evidence of HIV infection at Screening and Enrollment, based on the HIV testing algorithm
9) Owns an iOS or Android mobile phone and able to successfully download mobile apps and send and receive text messages.
10) Must not share the mobile phone used for their participation in the study.
11) Able to read and write.

4.2 EXCLUSION CRITERIA

Young men who meet any of the following criteria will be excluded from this study:

1) Participated in HPTN 113-01
2) Currently participating in another interventional trial of PrEP agents, or prior enrollment in studies of long-acting PrEP, including HPTN 083
3) Plans to move away from the study area within the next year
4) Currently on doxycycline for STI PEP
5) Has ever used CAB-LA or other long-acting PrEP agent
6) Tetracycline allergy
7) Prior diagnosis of HIV infection
8) Reactive HIV rapid test at Screening or reactive HIV Ag/Ab rapid test at Enrollment, regardless of subsequent HIV test results.
9) Any other condition that, in the opinion of the Investigator of Record (IoR)/designee, would preclude informed consent, make study participation unsafe, complicate interpretation of study outcome data, or otherwise interfere with achieving the study objectives would make the patient unsuitable for the study or unable/unwilling to comply with the study requirements.

4.3 RECRUITMENT PROCESS

Sites will be responsible for developing appropriate recruitment processes that are geared towards their respective local communities. It is likely that different recruitment methods will be needed for different sites and geographic contexts, therefore recruitment processes and strategies will be defined per site standard operating procedures (SOP). Strategies may include (but are not limited to) consulting and collaborating with local communities, online presence (e.g., advertisements, social media, dating apps), face-to-face recruitment including peer outreach, participant referrals, obtaining referrals through key community figures or leaders, and postering/palm cards at bars, clubs, street fairs, schools, etc. Sites may also choose to recruit from clinic sites such as STI and sexual health clinics. Site-specific advertising materials must undergo approval by the site's responsible Institutional Review Board (IRB)/Ethics Committee (EC).

4.4 CO-ENROLLMENT GUIDELINES

In general, participants in this study will not be allowed to take part in other concurrent interventional research studies during their participation in the study. This is due in part to concerns about: 1) participant study burden, 2) American Red Cross-mandated limitations on per-unit-time phlebotomized blood volumes, and 3) to avoid confounding in the interpretation of the study data. The protocol team should be consulted for any possible exceptions, including for observational studies.

4.5 PARTICIPANT RETENTION

Once a participant enrolls in this study, the study site will make every effort to retain them for 52 weeks of follow-up to minimize possible bias associated with loss-to-follow-up. Study site staff are responsible for developing and implementing local SOPs to target this goal. Components of such procedures may include:

- Thorough explanation of the study visits schedule, procedural requirements, and importance of each study group during the informed consent process and re-emphasis at each study visit.
- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit.
- Use of mapping techniques to establish the location of participant residences and other locator venues.
- Use of appropriate and timely visit reminder mechanisms.
- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained outreach workers to complete in-person contact with participants at their homes and/or other community locations.
- Regular communication with the study community at large to increase awareness about HIV and explain the purpose of HIV prevention research and the importance of completing research study visits.

4.6 PARTICIPANT WITHDRAWAL

Regardless of the participant retention methods described in Section 4.5, participants may voluntarily withdraw from the study for any reason at any time. The IoR/designee also may withdraw participants from the study to protect their safety and/or if they are unwilling or unable to comply with required study procedures after consultation with the Protocol Chair, Division of AIDS (DAIDS) Medical Officer, HPTN Statistical and Data Management Center (SDMC) Protocol Statistician, and Leadership and Operations Center (LOC) Clinical Research Manager (CRM). Withdrawn participants will not be replaced.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities, or site Institutional Review Boards/Ethics Committees (IRBs/ECs) terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation (Section 8.3.3) of participants who terminate from the study prior to 52 weeks, and study staff will record the reason(s) for all withdrawals from the study in participants' study records. Withdrawn participants will not be followed after their final evaluation.

5.0 3P MHEALTH PACKAGE

Participants randomized to receive the 3P mHealth package will have access to the suite of mHealth tools to assist with PrEP uptake and adherence decision making. The 3P mHealth package will not contain any information about doxy-PEP.

Following randomization, qualified study staff will counsel participants in the intervention group about PrEP and all three mHealth tools. Participants will be shown how to download the PrEPsmart app while they are at the Enrollment visit to ensure they can use the tools outside of the clinic.

Participants in the intervention group will also be provided with the control handout (see Section 6.0) at the Enrollment visit during the PrEP counseling session and standard-of-care adherence counseling at follow-up study visits.

5.1 MYPREP MHEALTH TOOL

MyPrEP is a web-based decision support tool that provides information about the different regimens of PrEP. This tool will be utilized during the study Enrollment visit during PrEP counseling, to facilitate participants in making an informed choice about initiating PrEP. Each intervention participant will register to use this website using their email. After which, MyPrEP can also be used at or between any visits when a participant decides to start PrEP or switch PrEP regimens. Participants randomized to the intervention group will also be provided with a web-link to access the MyPrEP tool outside of study visits.

Data regarding frequency of visits to the MyPrEP page will be submitted to the SDMC for analysis.

5.2 PrEPmate mHealth Tool

PrEPmate is an interactive, two-way SMS platform or app that uses personalized communication via weekly check-in messages and pill-taking reminders to support PrEP clients between clinic visits. Participants will utilize their own phone to access the platform. Study staff will be responsible for sending and responding to these weekly messages with participants. Staff responses to participant inquiries will be sent within one business day of receiving the message. Participants may be able to choose an altered frequency of communication, if desired. If the participant reports an adverse event or requires medical attention based on the message(s) received, study staff may request the participant come to the study clinic for an evaluation and/or will refer them for care. At the Enrollment visit, study staff will ensure that participants are able to successfully access the tool on their phone. During follow-up visits, study staff will check-in with participants about their use of PrEPmate and if they have encountered any problems or questions about the platform.

Data regarding frequency and number of messages sent/received via PrEPmate will be submitted to the SDMC for analysis.

5.3 PrEPsmart mHealth Tool

PrEPsmart is an interactive app accessed on the participant's phone that provides the user with information about when the next dose of oral PrEP is due (2-1-1 PrEP only). This tool allows users to track both sexual encounters and PrEP pill taking. The app has a timer that reminds participants when it is time to take their next PrEP pill. The app also provides instant feedback on the level of protection afforded by 2-1-1 oral PrEP (high, medium, low) depending on their recent oral PrEP-taking habits. At the Enrollment visit, study staff will ensure that participants are able to successfully access the app on their phone. During follow-up visits, study staff will check-in with participants about their use of PrEPsmart and if they have encountered any problems or questions about the app.

Data regarding usage of the PrEPsmart application, including frequency and usage time, will be submitted to the SDMC for analysis.

6.0 CONTROL GROUP

Participants randomized to the control group will not receive the 3P mHealth package and will instead receive standard-of-care PrEP counseling from qualified study staff and a handout about the different PrEP options available at the site. The handout will be provided to the participant at Enrollment during the PrEP counseling session and again at any follow-up visit if the participant is interested in starting or switching PrEP methods. The participant may also choose to take the handout home.

Participants in the control group will receive standard-of-care adherence counseling at the study visits.

7.0 STUDY PRODUCT CONSIDERATIONS

Site pharmacists should consult the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for standard pharmacy operations.

Study product is defined as both HIV PrEP and doxy-PEP. Refer to the relevant package insert or investigator's brochure for further information about these study products.

Study Product Regimens

All participants will be offered their choice of PrEP for HIV prevention and doxycycline for STI prevention. Participants do not have to accept PrEP or doxy-PEP to be eligible to participate in the study. A participant may decide to initiate PrEP or doxy-PEP at Enrollment or any time after Enrollment. Once initiated, the participant may discontinue or change PrEP agents/regimens as desired, and they may also reinitiate at any time following a discontinuation. All PrEP initiations, changes, and discontinuations will be recorded on study case report forms (CRFs). doxy-PEP may be discontinued and reinitiated at any time, which will also be recorded on study CRFs.

HIV Prevention

Participants will receive their choice of PrEP supplied through the study for up to 52 weeks from enrollment. PrEP options are shown in Table 2. Sites will offer F/TDF. F/TAF and CAB-LA.

Table 2. PrEP agents and regimens

PrEP Agent	***Regimen***
F/TDF 200 mg/300 mg	One tablet taken orally (PO) once daily OR (off-label 2-1-1 regimen) Two tablets taken PO 2-24 hours before sex, followed by one tablet taken PO 24 hours after the first dose, and one tablet taken PO 24 hours after the second dose
F/TAF 200 mg/ 25 mg	One tablet PO once daily
CAB-LA	One 600 mg intramuscular (IM) injection every 4 weeks for 2 doses, then one 600 mg IM injection every 8 weeks

STI Prevention

Doxycycline for STI prevention (doxy-PEP) will be offered at each site, and if accepted, should be taken orally as a single 200 mg dose. Ideally the dose should be taken within

24 hours after condomless sex but up to 72 hours later. No more than 1 dose (200 mg) should be taken in a 24-hour period. Participants can take up to 200 mg per day for 52 weeks.

7.1 STUDY PRODUCT ADMINISTRATION

Emtricitabine 200 mg/Tenofovir disoproxil fumarate 300 mg (F/TDF) is taken orally with or without food and may be given daily or following the 2-1-1 regimen as outlined in Table 2.

Emtricitabine 200 mg /Tenofovir alafenamide 25 mg (F/TAF) is taken orally with or without food one-time daily.

Long-acting cabotegravir (CAB-LA) is administered as one 600 mg (3 mL) IM injection in the gluteal muscle every 4 weeks for 2 doses. After the initial 2 doses are complete, CAB-LA will be continued at 600 mg IM every 8 weeks.

Doxycycline may be available in multiple strengths. When used as doxy-PEP, it will be dosed as described in Section 7.0 to achieve 200 mg per dose (e.g. two 100 mg capsules to deliver 200 mg, etc.) and should be administered in accordance with the manufacturer's instructions.

7.2 STUDY PRODUCT FORMULATION/CONTENT/PREPARATION/STORAGE

7.2.1 Oral PrEP

Emtricitabine/Tenofovir disoproxil fumarate (F/TDF):
F/TDF is a fixed dose combination tablet containing 200 mg of emtricitabine and 300 mg of tenofovir disoproxil fumarate. F/TDF must be stored at 25°C (77°F), with excursions permitted between 15°C-30°C (59°F-86°F) [see United States Pharmacopeia (USP) Controlled Room Temperature]. F/TDF tablets must be stored and dispensed in the original container.

Emtricitabine/Tenofovir alafenamide (F/TAF):
F/TAF is a fixed dose combination tablet containing 200 mg of emtricitabine and 25 mg of tenofovir alafenamide. F/TAF must be stored at 25°C (77°F), with excursions permitted between 15°C-30°C (59°F-86°F) [see USP Controlled Room Temperature]. F/TAF tablets must be stored and dispensed in the original container.

7.2.2 CAB-LA

CAB-LA is a single-dose vial containing 200 mg/mL of cabotegravir extended-release injectable suspension for administration by IM injection. The formulation does not require dilution prior to administration. CAB-LA injectable suspension must be stored at 2°C-25°C (36°F -77°F), with exposure up to 30°C (86°F) permitted. Do NOT freeze.

CAB-LA may be supplied as a kit with ancillary supplies (APRETUDE kit) or as individual vials.

Preparation of injectable CAB-LA (600 mg/3 mL)

Pharmacists must follow appropriate aseptic technique and sterile preparation procedures/guidance as outlined by local, institution, and pharmacy regulatory authority when preparing CAB-LA.

CAB-LA (not from the APRETUDE kit) should be prepared in a sterile environment, utilizing a pharmacy biosafety cabinet/isolator, class II or better.

CAB-LA from the APRETUDE kit, must be prepared using the kit supplied vial adapter and syringe. If an enclosed sterile environment is required for the preparation of sterile injectable products per local requirements or regulations, the site may do so for the preparation of CAB-LA from the APRETUDE kit.

For individual protection measures such as personal protective equipment (PPE), local requirements and regulations are to be followed. PPE may include disposable gloves, gowns, respirator, and safety glasses.

Any empty vials, unused portion of entered vials, expired or unused prepared study product in a syringe will not be used for another participant and should be discarded in a biohazard container and disposed of in accordance with institutional or pharmacy policy.

CAB-LA Preparation Steps (not from APRETUDE kit):

Materials needed to prepare CAB-LA (not from APRETUDE kit) are outlined in the Pharmacy SSP Manual – Section 1.

1. Remove vial of CAB-LA from storage. If the vials are stored refrigerated (2°C to 8°C), wait at least 15 minutes to equilibrate to room temperature prior to preparation.

2. Shake the vial for 10 seconds by using long arm movements.

3. Invert the vial and inspect to ensure uniform suspension. If solid remains undispersed, repeat steps 2-3 until all material is uniformly suspended.

   NOTE: It is normal to see small air bubbles after shaking the vial for re-suspension.

4. Remove the cap from the vial. Wipe the rubber stopper with an alcohol pad and allow to dry.

5. Attach a needle and draw approximately 1 mL of air into an appropriately sized syringe.

6. Inject the air into the vial to de-pressurize it.

7. Invert the vial, then withdraw 3 mL (600 mg) of CAB-LA into the syringe. Before removing the needle from the vial, de-aerate the syringe by tapping a finger against the barrel and moving the plunger upward to expel air bubbles and excess suspension until the correct dose volume (3 mL) remains in the syringe.

8. Remove and discard preparation needle and attach an IM administration needle or syringe cap to the prepared syringe following institutional standard.

9. Label the syringe barrel following the DAIDS Pharmacy guidelines and local regulations for participant specific labels.

   The prepared CAB-LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C (68°F-77°F) from the preparation time (the time CAB-LA is withdrawn into a syringe) to the time it is administered. It is recommended to inject the CAB-LA suspension immediately after preparation. If this is not possible, do NOT exceed 2 hours between preparation time and administration to the study participant.

   NOTE: The participant-specific prepared CAB-LA in a syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.

CAB-LA Preparation Steps (from APRETUDE kit):

Materials needed to prepare CAB-LA are included in the APRETUDE kit.

1. Remove CAB-LA vials from the kit. If the kits are stored refrigerated (2°C to 8°C), wait at least 15 minutes for the vial to equilibrate to room temperature prior to preparation.

2. Shake the vial for 10 seconds by using long arm movements.

3. Invert the vial and inspect to ensure uniform suspension. If solid remains undispersed, repeat steps 2-3 until all material is uniformly suspended.

   NOTE: It is normal to see small air bubbles after shaking the vial for re-suspension.

4. Remove the cap from the vial. Wipe the rubber stopper with an alcohol pad and allow to dry.

5. Peel off the paper backing from the vial adapter packaging.

6. Ensure the vial is upright on a flat surface and press the vial adapter straight down onto the vial. The vial adapter should click securely into place. Lift off the vial adapter packaging.

7. Draw approximately 1 mL of air into an appropriately sized syringe.

8. Screw syringe onto the vial adapter, then inject the air into the vial to de-pressurize it.

9. Invert the vial, then withdraw 3 mL (600 mg) of CAB-LA into the syringe. De-aerate the syringe by tapping a finger against the barrel and moving the plunger upward to expel air bubbles and excess suspension until the correct dose volume (3 mL) remains in the syringe.

10. Unscrew the syringe from the vial adapter and attach an IM administration needle or syringe cap to the prepared syringe following institutional standards.

11. Label the syringe barrel following the DAIDS Pharmacy guidelines and local regulations for participant specific labels.
    The prepared CAB-LA suspension in a syringe must be stored at controlled room temperature between 20°C to 25°C (68°F-77°F) from the preparation time (the time CAB-LA is withdrawn into a syringe) to the time it is administered. It is recommended to inject the CAB-LA suspension immediately after preparation. If this is not possible, do NOT exceed 2 hours between preparation time and administration to the study participant.

    NOTE: The participant-specific prepared CAB-LA in a syringe is to be de-aerated by administrator prior to injection so that the correct volume can be administered.

7.2.3 Doxy-PEP

Doxycycline must be stored according to the manufacturer's requirements indicated in the package insert.

7.3 STUDY PRODUCT SUPPLY

F/TDF will be purchased through the HPTN LOC for the US sites.

F/TAF will be provided by Gilead Sciences.

CAB-LA will be provided by ViiV Healthcare. Note that oral CAB will NOT be provided in this study.

PrEP study products (F/TDF, F/TAF, and CAB-LA) will be available through the National Institute of Allergy and Infectious Diseases (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist should obtain all the PrEP study

products by following the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trial Networks*.

Doxycycline will NOT be provided centrally through the study and must be obtained locally at each site.

Any study product(s) not provided centrally by the study must comply with the NIAID DAIDS policy that outlines the process for authorizing the use of study products that are not marketed in the United States in NIAID (DAIDS) supported and/or sponsored clinical trials. This policy is available on the NIAID (DAIDS) website at https://www.niaid.nih.gov/sites/default/files/NonFDAapprovedProducts.pdf

7.4 STUDY PRODUCT ACCOUNTABILITY

The site pharmacist is required to maintain complete records of all study products received from the NIAID CRPMC or other sources and subsequently dispensed. At US clinical research sites (CRSs), all unused study products must be returned to the NIAID CRPMC (or as otherwise directed by the sponsor) after the study is completed or terminated. The procedures to be followed are provided in the manual *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks.* At non-US CRSs, the site pharmacist must follow the instructions in the *Pharmacy Guidelines and Instructions for DAIDS Clinical Trials Networks* for the destruction of unused study products.

7.5 TOXICITY MANAGEMENT

The site investigator has the discretion to interrupt PrEP or doxy-PEP at any time if they feel that continued medication use would be harmful to the participant or would interfere with treatment deemed clinically necessary according to the judgment of the investigator. In addition, a Clinical Management Committee (CMC) will be established for this study. The CMC will be available for consultation and decision-making regarding the management of toxicities and study product administration, as per the Clinical, Safety, and AE Management SSP Manual – Section 1 guidance. Clinical or laboratory abnormalities that require follow-up will be documented, and the study staff will contact the participant to schedule an interim visit for care and/or repeat laboratory testing. All participants with a reportable Adverse Event (AE) Grade 3 or higher will be followed until the occurrence resolves or stabilizes or until the participant exits the study. Serious Adverse Events (SAEs) reported as related to PrEP or doxy-PEP will result in temporary hold of the relevant drug. PrEP or doxy-PEP may be reinitiated at the discretion of the investigator.

Product-specific management guidance is included below:

F/TDF: If the participant is using F/TDF for PrEP and the creatinine clearance is <60 mL/min, F/TDF should be held, and the test should be repeated, as per Clinical, Safety, and AE Management SSP Manual – Section 1 guidance. If a level of <60 mL/min is confirmed with re-testing, F/TDF should be discontinued. The participant may be

switched to F/TAF or CAB-LA. If re-testing yields a result >60 mL/min, F/TDF may be resumed following local standard clinical practice.

F/TAF: If the participant is using F/TAF for PrEP and the creatinine clearance is <30 mL/min, F/TAF should be held, and the test should be repeated as soon as possible. If a level <30 mL/min is confirmed, F/TAF should be discontinued. The participant may be switched to CAB-LA. If re-testing yields a result >30 mL/min, F/TAF may be resumed following local standard clinical practice.

CAB-LA: Local injection site reactions (ISRs) are the most frequent adverse reactions associated with cabotegravir IM. In case of signs or symptoms of hypersensitivity (e.g. severe rash) or hepatotoxicity, cabotegravir should be discontinued in consultation with CMC and the participant may be switched to F/TDF or F/TAF. Promptly evaluate participants with depressive symptoms to assess whether the symptoms are related to cabotegravir and to determine whether the risks of continued therapy outweigh the benefits.

Doxycycline: Doxycycline is contraindicated in persons who have shown hypersensitivity to any of the tetracyclines.

7.6 CONCOMITANT MEDICATIONS AND DRUG INTERACTIONS

Information regarding drug interactions is found in the investigator's brochure or package insert of each drug. Sites are required to have the most up-to-date version of the investigator's brochure or package insert in their study-specific files, as well as available for clinical reference.

All concomitant medications taken within 30 days of Enrollment, and anytime thereafter during study participation, will be collected in the study participant's chart. Certain medications will be recorded on study CRFs, these include:

- Medications that are used for the treatment of reportable adverse events that occur during study participation
- Antibiotics, other than doxy-PEP, provided by the study clinic, e.g., for treatment of an STI
- Any PrEP, PEP, or antibiotics obtained outside of the study clinic

Alcohol and recreational or street drug use will be recorded in clinical progress notes if needed for interpretation/documentation of observed participant health status but not recorded as concomitant medications.

8.0 STUDY PROCEDURES

An overview of the study visits and procedures is presented in Appendices IA - IC. Presented below is additional information on specific study procedures. Additional

detailed instructions to guide and standardize all study procedures across sites will be provided in the Accrual, Follow-up, and Retention SSP Manual- Sections 1-4. Visit windows are described below and visit coding is described in the Data Management SSP Manual – Section 1.

All participants will follow the visit schedule outlined below in Table 3 and in Appendix IA. Participants who chose to start CAB-LA will have additional visits according to their individual injection schedule. CAB-LA injection visits will follow the schedule presented in Table 4 and in Appendix IB.

All participants will complete the Exit visit at Week 52, regardless of if/when they start CAB-LA.

8.1 SCREENING VISIT

It is the responsibility of the local site to determine the best approach to screening. For each participant, independent written informed consent will be obtained before any study procedures are initiated. Whenever feasible, the Screening and Enrollment visit will occur on the same day. Sites will optimize visit flow and procedures to efficiently screen and enroll participants during the same visit. If a participant is unable to be enrolled on the same day as Screening, they may return to complete Screening and Enrollment on a different day. Screening and Enrollment may occur over one or more visits however, Enrollment must occur within 45 days of Screening. HIV testing must be completed within 7 days before Enrollment, following the testing algorithms in Appendix II.

Sites will follow the HIV testing algorithm for Screening (See Appendix II). If any result or interpretation other than negative or non-reactive is obtained for any HIV test, additional testing to confirm the suspected HIV infection will be performed during Screening in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be linked to appropriate care. Participants with symptoms of acute HIV infection may be screened but Enrollment should be deferred until appropriate testing has ruled out acute HIV infection. Participants who have any reactive or positive HIV rapid test at Screening or Enrollment are not eligible for enrollment or rescreening, even if local testing does not confirm HIV infection. Other potential participants may be rescreened up to three times at the discretion of the IoR or their designee.

The following procedures will be completed at the Screening visit:

- Conduct the informed consent process
- Collect locator and demographic information.
- Assess self-reported eligibility criteria and other socio-behavioral information.

- Participants will be asked to provide blood for HIV testing and plasma storage and will receive HIV risk-reduction counseling and condoms. HIV test results will be reviewed with the participant.

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.

8.2 ENROLLMENT VISIT

The Enrollment visit should be completed on the same day as Screening, whenever feasible. Sites should confirm that a participant is eligible before proceeding with enrollment procedures, even if Screening and Enrollment procedures occur on the same day. Visit procedures should be sequenced such that procedures are not done unnecessarily for participants found to be ineligible and so that study staff can combine Screening and Enrollment procedures/questionnaires where feasible. The Accrual, Follow-up, and Retention SSP Manual – Section 3 will include visit checklist templates so that study sites can order Screening and Enrollment procedures consistent with protocol requirements and adapted to site-specific realities.

The following procedures will be completed at the Enrollment visit:

- Review locator and other information collected at Screening, if needed.
- Complete abbreviated physical exam and medical history, and concomitant medications.
- Participants will be asked to provide blood samples for HIV, syphilis, Hepatitis B (HBV), and creatinine testing, and plasma and DBS for storage. HIV test results will be reviewed with the participant.
- Participants will be asked to provide samples for three-site GC/CT testing: provider-collected pharyngeal swabs, and self-collected rectal swabs and urine. Rectal swabs may be collected by the provider, if preferred by the participant. Urine will also be kept for storage.
- Assess full eligibility criteria, including additional behavioral information.
- Complete randomization.
- Participants randomized to the intervention group will be provided counseling and information about the 3P mHealth tools. Participants in both groups will receive a handout detailing the different PrEP methods offered in the study and a handout about doxy-PEP.
- Participants will be offered their choice of PrEP regimen and doxy-PEP.

If Enrollment is not completed on the same day as the Screening visit, HIV rapid testing must be completed within 7 days before Enrollment, but other test results are not required to proceed with study enrollment. Pending HBV serology and creatinine results are not a reason to delay enrollment or dissuade a participant's choice of PrEP agent/regimen. If HBV or creatinine results indicate a need for further monitoring or change of PrEP agent/regimen, a study clinician will contact the participant for management. If a participant has a confirmed STI following testing, they will be provided with treatment and counseled on continuing use of doxy-PEP for prevention, following completion of treatment.

A participant is considered enrolled in the study at the point of randomization.

8.3 STANDING FOLLOW-UP VISITS

All participants will complete follow-up visits at Weeks 4, 20, 36, and 52.

At all standing follow-up visits, the following procedures will be completed:

- Update participant locator information.
- Participants will be provided with their choice of PrEP and/or doxy-PEP. If a participant did not initiate PrEP or doxy-PEP at the Enrollment visit, they may initiate either (or both) at their follow-up visit.
- Socio-behavioral information will be collected; CASI will be used to collect some self-reported measures. **CASI questionnaires could be accessed using a computer or a tablet.** Participants will be asked about any social impacts related to study participation.
- Participants randomized to the intervention group will be provided with information and support for the 3P mHealth tools.
- Participants will be asked to provide blood for HIV testing (following Appendix II) and plasma and DBS for storage and will receive HIV risk-reduction counseling and condoms. HIV test results will be reviewed with the participant when available.
- A symptom-directed physical exam and interim medical history, including AE assessment, will be completed.
- Participants will be asked about concomitant medication use and adherence to oral PrEP and use of/acceptability of doxy-PEP.
- Additional testing, treatment, or clinical care may be provided if clinically indicated. This includes STI testing and/or treatment.

- Participants will be asked if they consent to hair sample collection. If a participant provides consent, a sample of ~4-6 strands of hair will be collected from their scalp at follow-up visits, in order to evaluate doxy-PEP adherence based on drug detection in hair. These samples will be stored and then batch-shipped for testing.

8.3.1 Week 4

All participants will return for a visit one month (4 weeks) after Enrollment to complete study procedures as listed above.

Additionally, at the Week 4 visit, participants randomized to the intervention group will be asked about their satisfaction with the 3P mHealth package.

8.3.2 Weeks 20 and 36

All participants will return for a visit 20 and 36 weeks after Enrollment to complete study procedures as described above.

Additionally, at the Weeks 20 and 36 visits, participants will be asked to provide samples for three site GC/CT testing: provider-collected pharyngeal swab, provider or self-collected rectal swab, and self-collected urine. Blood will also be used for syphilis testing. If the participant has symptoms of an STI, treatment will be provided according to local guidelines.

Lastly, starting at Week 36, study staff will begin assessing the participant's plans for continuation of PrEP at study exit so that plans can be made for accessing oral PrEP or CAB-LA within the community following exit.

8.3.3 Week 52/Exit

The final study visit will occur for all participants at Week 52. If a participant withdraws from the study or is terminated early, study staff should attempt to complete the exit visit procedures.

In addition to all procedures completed at Weeks 20 and 36, at the Week 52/Exit visit, participants will:

- Receive a final supply of oral PrEP and doxy-PEP or a CAB-LA injection from the study clinic, if desired. All efforts will be made to link participants to ongoing HIV and STI prevention resources and clinics for continued access after their study participation ends (see Section 8.6).

- Participants randomized to the intervention group will be asked about their satisfaction with the 3P mHealth package.

- Participants using oral PrEP will have a creatinine test and results will be returned to participants with a referral to clinical care if needed.

- Urine (collected for STI testing) will also be kept for storage.

8.4 CAB-LA INJECTION VISITS

Participants who elect to use CAB-LA for HIV prevention will be required to attend all standing follow-up visits (see Section 8.3) and will have additional visits to maintain the appropriate injection schedule (4 weeks after the initial injection, then every eight weeks), see Section 8.16 and Appendix IB. Participants on oral PrEP or no PrEP have five scheduled study visits, participants who start CAB-LA at Enrollment have eight scheduled study visits, and participants who start CAB-LA after enrollment could have up to 12 scheduled study visits, depending on the CAB-LA start date. Participants may elect to start CAB-LA at Enrollment or at any time following Enrollment. Study staff will make all efforts to align CAB-LA injections with standing visits in order to minimize additional visits only for injections, aiming to have eight visits for all CAB-LA users. Additional information on the timing of CAB injection visits and visit windows are described in Section 8.16 and the Accrual, Follow-up, and Retention SSP Manual – Section 2 and Data Management SSP Manual – Section 1; these SSP Manual sections also provide details on adjustment of visits for CAB-LA injections that occur off-schedule.

If a participant is receiving a CAB-LA injection at a standing follow-up visit, all follow-up visit procedures should be completed as described in Section 8.3. At any visit during which a CAB-LA injection is provided, the following procedures should be completed, if not already done as part of the standing visit:

- Update participant locator information.

- Participants will be asked to provide blood for HIV testing (following Appendix II) and plasma storage and will receive HIV risk-reduction counseling and condoms. HIV test results will be reviewed with the participant when available.

- A symptom-directed physical exam and interim medical history, including AE assessment and concomitant medication use, will be completed.

- Additional testing, treatment, or clinical care may be provided if clinically indicated. This includes STI testing and/or treatment.

Initial Injection

All participants who elect to use CAB-LA will have HIV testing performed, completed within 7 days prior to their first injection. HIV testing requirements are described in

Appendix II. If a participant has a reactive or positive HIV test, the CAB-LA injection will not be administered. The CMC and LC should be consulted if any HIV test from this visit is reactive or positive to determine appropriate follow-up testing and clinical management. Additional testing, treatment, or clinical care will be provided if clinically indicated.

Subsequent Injections

Participants will not be able to initiate CAB-LA after Week 48 of study participation (i.e. the last opportunity to initiate CAB-LA is at Week 48 post-enrollment). This will ensure that all participants have time to receive the initial loading dose and arrange for community follow-up after the end of study participation.

8.5 PrEP Regimen Switching

Participants will be able to switch their PrEP regimen at any time. If a participant would like to change their PrEP regimen from CAB-LA to oral PrEP or oral PrEP to CAB-LA, an HIV ribonucleic acid (RNA) test must be performed – but the results do not need to be available – before they begin the new PrEP regimen (see Appendix II). If the participant is starting oral PrEP, it may be dispensed before the test results are received; however, they should be counseled not to start taking the medication until contacted by study staff to confirm their HIV status. An HIV RNA test is not required to change between daily and 2-1-1 F/TDF or between F/TDF and F/TAF.

8.6 Post-Study Drug Access Following Study Exit

Prior to the final study visit (starting at Week 36), participants will be asked about their preference for continuing PrEP beyond the end of the study. This will allow time to arrange a plan for continued coverage and care at local health clinics. If the participant desires continuation of PrEP, study staff will actively facilitate linkage to care available within the community. Participants who have initiated oral PrEP or CAB-LA between Week 36 and Week 52 will require special care taken to ensure that a plan is in place with adequate time to arrange for follow-up care in the community.

Participants who have received a CAB-LA injection at any point during the study may continue to have detectable CAB levels for more than 12 months post-injection and should be counseled about the possibility of HIV acquisition and resistance during this "tail" phase. For participants who would like to continue CAB-LA, in areas where CAB-LA is available within local health clinics, study staff will assist participants in making an appointment for their next CAB-LA injection. Every effort will be made to ensure that the first CAB-LA injection in the community occurs 8 weeks after the last in-study injection with a visit window of +/- 14 days. If this is not feasible, oral PrEP will be provided to cover the CAB tail until their first community injection. If CAB-LA is not

locally available, participants will be provided with oral PrEP and will be linked to a local clinic that can provide continued oral PrEP.

Participants who wish to continue using doxycycline for STI prevention will be provided with a final 30-day supply at study exit. The study team will help link participants to local providers that can provide doxycycline for STI prevention, if available within the community.

8.7 ADHERENCE ASSESSMENT

This study is assessing the efficacy of standard-of-care adherence counseling with or without the addition of the 3P mHealth package; no additional medication adherence interventions will be implemented. PrEP adherence data will be collected via self-report for oral medications, via documentation of CAB-LA injections, and through biomedical testing for oral PrEP medications. doxy-PEP use data will be collected via self-report and laboratory testing (i.e., plasma and hair).

Self-reported use: Participants will be asked about timing and use of PrEP and doxy-PEP at each follow-up visit via an interviewer-administered CRF and/or CASI. Participants will also be asked about the number and timing of anal/vaginal sex encounters in the past 30 days to assist with understanding adherence for 2-1-1 PrEP and doxy-PEP.

CAB-LA injections: Study staff will record all CAB-LA injections in pharmacy records and study CRFs. Adherence will be defined by administration of CAB-LA within ± 1 week (7 days) of the targeted injection visit for the 2nd injection and within ± 2 weeks (14 days) of targeted injection visits when receiving subsequent injections. This window is most consistent with what will be considered adherent in clinical practice, and with pharmacokinetic data [4].

Biomedical markers of adherence: Adherence to TFV-based oral PrEP regimens will be evaluated through the measurement of intraerythrocytic TFV-diphosphate (TFV-DP) in dried blood spots (DBS) at select study visits; drug concentrations will be utilized in the biomedical assessment of adherence; cutoffs may be specific to F/TDF and F/TAF regimens, as well as participants who use oral TFV-based PrEP in an event-driven manner [35, 36].

Stored plasma may also be used in the assessment of adherence to doxycycline in a subset of participants or visits. Please refer the Pharmacology section of the protocol (Section 11.1.3) for additional details.

Additional considerations for On-Demand (2-1-1) F/TDF PrEP: 2-1-1 F/TDF PrEP adherence will be determined via self-report and intraerythrocytic TFV-DP measurements from DBS. Participants will be asked about their sexual history and PrEP use and timing within the preceding 30 days to understand if sex acts were covered by PrEP use. We will also use biomedical markers of adherence for PrEP. Intraerythrocytic TFV-DP concentrations from DBS will be measured and categorized based on the

number of sex events in the preceding month; each sex event will assume a single 4-dose on-demand drug exposure. For example, for each sex event, if a person is using on-demand F/TDF, we assume that, of 30 possible doses in a month, four were taken (one sex event). We can then estimate on-demand PrEP adherence by taking 4/30th (13.3%) of the adherence cutoff for daily dosing. Importantly, this approach assumes that a participant is at steady state (that a participant has one sex event per month). These categories have been previously described in directly observed dosing studies [36, 37] and defined cutoffs will be included in the Laboratory SSP Manual – Section 1 and/or statistical analysis plan (SAP).

PrEP method switching: Interpretation of adherence will also be influenced by switching of PrEP regimens. We will use the following approaches to help guide our interpretation of oral or injectable PrEP adherence if a participant switches regimens:

- Oral PrEP (daily F/TDF, 2-1-1 F/TDF, daily F/TAF) to CAB-LA: Adherence will be evaluated via intraerythrocytic TFV-DP measurements at study visits prior to the first CAB-LA injection. Adherence after initiation of injections will be evaluated by administration of on-time injections (within ±1 week of targeted injection visit for 2nd injection; within ±2 weeks of targeted injection visit for Q2M injections).

- CAB-LA to oral PrEP: Coverage of CAB-LA adherence will extend from the time of last injection to the targeted next injection + 14 days; this would translate to 10 weeks of adherence coverage for most participants. Intraerythrocytic TFV-DP measurements from DBS would be used after cessation of CAB-LA to evaluate adherence to oral PrEP.

Note: Switches in oral PrEP regimens from F/TDF to F/TAF typically require 5 months of TFV-DP washout before TFV-DP from F/TAF can be attributed solely to F/TAF adherence. Changes in oral PrEP choice will be captured in the study database, and additional adjustments to PrEP adherence categories may be considered.

8.8 QUESTIONNAIRES DATA COLLECTION

Participants will complete questionnaires at study visits according to the schedule in Appendix I. Questionnaires/CRFs will include the following key topics:

- Demographics
- Sexual behavior and other social/health practices associated with HIV acquisition
- Medical history, symptom assessment, and medication use
- PrEP and doxy-PEP use, adherence, and experiences
- Social impacts of study participation
- Acceptability and use of the 3P mHealth tools (intervention group only)

Additional information about the CRFs can be found in the Data Management SSP Manual – Section 1.

8.9 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/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 AEs experienced by study participants, and to evaluate HIV status (e.g., in those with possible acute infection and to determine/confirm HIV status for those on CAB-LA). When interim contacts or visits are completed in response to participant reports of AEs, study staff will assess the reported event clinically, record the event on the CRF, and provide or refer the participant to appropriate medical care.

8.10 PROCEDURES FOR PARTICIPANTS WHO PERMANENTLY DISCONTINUE STUDY PRODUCT EARLY

Participants may choose not to start or to discontinue PrEP or doxy-PEP at any time during the study. In some instances, participants may have PrEP or doxy-PEP withheld by a study clinician for medical reasons.

Participants no longer using PrEP or doxy-PEP will continue with study participation until their final Week 52 visit. Unless medically contraindicated, participants may resume PrEP or doxy-PEP at any time during the study.

8.11 HIV TESTING

The HIV testing algorithms for this study are included in Appendix II. Assays used for this testing must be approved by the HPTN Laboratory Center (LC).

HIV RNA testing will be performed to aid in detection of HIV infection as noted in Appendices IA-C and Appendix II. This includes HIV RNA testing for all participants who are starting PrEP and at HIV confirmation visits. In addition, HIV RNA testing is performed when switching PrEP regimens, and when resuming PrEP (more than 14 days after last oral dose or more than 6 months after the last injection).

Participants will be counseled that if they are using PrEP and an HIV result is returned indicating a reactive or positive result (see Section 8.12). These participants will need to return for further testing and should begin a full antiretroviral treatment (ART) regimen if HIV infection is confirmed.

8.12 PROCEDURES FOR PARTICIPANTS WITH SUSPECTED OR CONFIRMED HIV INFECTION

If a participant has signs or symptoms consistent with acute HIV infection, or expresses a concern about recent HIV acquisition, HIV testing will be performed using a licensed HIV RNA test.

Any participant visit with a reactive or positive HIV test result should be reported to the CMC and include test results from all prior visits. HIV acquisition after study Enrollment must be confirmed at a separate visit using a sample that was collected on a different date than the date where the sample with the reactive/positive test was obtained (see Appendix IC). If the participant has a reactive or positive HIV test at a visit when DBS/plasma storage or STI testing is not required, samples should be collected for STI testing and DBS/plasma storage.

Study product (oral PrEP or CAB-LA) should not be administered in these cases until HIV status is resolved. The study site should contact the CMC for advice on further HIV testing in persons on CAB-LA since it can be difficult to confirm HIV infection, even months after injections are discontinued. If HIV infection is not confirmed on this visit (after CMC review), the study site should follow the recommendations of the CMC for further testing.

At each HIV confirmatory visit, the following procedures should be completed. Note: it is possible for a participant to have more than one confirmatory visit.

- Update participant locator information.
- Complete medical history, including any concomitant medication use.
- Complete physical exam.
- Participants will be asked to provide blood for HIV testing, STI testing, and storage and will receive HIV counseling and condoms.

Any participant confirmed to be living with HIV will be linked to HIV care and treatment at a local clinic. Each study site will have robust procedures to facilitate successful linkage to care.

Participants will be able to stay in the study and continue with their regularly scheduled visits where all study procedures will be completed except those related to HIV PrEP care and HIV testing (i.e., HIV testing, PrEP counseling and provision). Participants living with HIV will be asked about their linkage to care and treatment and may continue doxy-PEP, irrespective of HIV status. Participants who have confirmed HIV infection, should have samples sent to a local laboratory for HIV resistance testing (if available) to assist with clinical management, but these local data are not required to be included in study data.

8.13 STIs

Participants will have STI (GC, CT, and syphilis) testing conducted at Enrollment and Weeks 20, 36, and 52, as outlined in Appendix I. If a participant has signs/symptoms of an STI, they will be provided with syndromic treatment in accordance with local guidelines.

During follow-up, if a participant has STI symptoms, they will have a symptom-directed physical exam and be provided syndromic treatment at the visit in accordance with local guidelines. These participants will also have STI testing as indicated.

Participants will be contacted as soon as possible following a positive STI result and asked to return to the site for treatment (or adjustment of treatment, if required). If the participant is unable to return to the site, they can be referred for treatment, in accordance with local guidelines. Participants will be offered expedited partner therapy or referral letters, in accordance with local guidelines.

8.14 Hepatitis B

Testing for HBV (HbsAg, HbsAb, HbcAb) will be performed at Enrollment. Individuals who have evidence of an HBV infection will be referred to local healthcare services for monitoring and/or treatment of HBV. These individuals will also be counseled that 2-1-1 PrEP should not be utilized and that if they elect daily oral PrEP (F/TDF or F/TAF), there is a potential for a "flare" or worsening of hepatitis symptoms if they discontinue the medication.

Individuals who do not have evidence of a prior HBV infection will be provided with or referred for HBV vaccination in accordance with local guidelines and site operating standards.

8.15 Qualitative Data Collection

8.15.1 In-depth Interviews

In-depth interviews (IDIs) will be conducted with a subset of approximately 12 participants per site (6 in the intervention group and 6 in the control group) at their Week 20 and Week 52/Exit visit (48 total participants). Participants will be purposively selected based on age, behaviors that make a person vulnerable to HIV, PrEP and doxy-PEP use, use of the 3P mHealth tools (intervention group), study group, or any other reason at the discretion of the investigator. Interviews will focus on acceptability of the 3P mHealth package and decision-making about PrEP and doxy-PEP uptake and adherence.

All IDIs will be conducted in a private setting and last approximately 60-90 minutes. A semi-structured qualitative interview guide will provide a general structure for the discussion and consistency across sites. Interviews will be conducted in the participant's

preferred language, digitally recorded, then transcribed and subsequently translated into English as needed. Audio recordings will be kept until primary qualitative analyses are complete or a maximum length of time as required by local regulations.

8.16 STUDY VISIT WINDOWS

There are five required evaluation visits for all participants: Enrollment (Day 0), Week 4, Week 20, Week 36, and Week 52 (Exit). If no PrEP or oral PrEP is chosen as the PrEP regimen, then there are no additional visits (Table 3). If CAB-LA is chosen as the PrEP regimen, then there are additional visits (Table 4) to accommodate the injection schedule of initiation, reload (4 weeks after initiation), and maintenance (every 8 weeks after reload). Visit coding is described in the Data Management SSP Manual – Section 1.

For each study visit, there is an allowable visit window specifying when the visit should be completed. Within each allowable visit window, there is a target visit window when the visit should ideally be completed. If more than one visit is necessary to complete all visit procedures, these can be completed during multiple days within the allowable visit window. Typically, allowable visit windows do not overlap. However, this study is designed to have injection visit windows that overlap with evaluation visit windows, for the CAB-LA PrEP regimen.

For the evaluation visits required for all participants (Enrollment Day 0, Week 4, Week 20, Week 36, and Week 52/Exit), the allowable windows are very wide (7 to 28 days before target to 83 days after target) because the procedures at those visits are not strongly time-sensitive. However, the allowable windows for injections are narrow (+/-3 days for the second injection and +/- 7 days for subsequent injections) to ensure that CAB-LA is given at clinically appropriate intervals. Injection visits are therefore planned to overlap with Week 4, Week 20, Week 36, and Week 52 study visits, inside the allowable visit windows for these visits, to minimize additional visits. While it is preferred that the injection visits coordinate with the Week 4, Week 20, Week 36, and Week 52 study visits, this may not always be possible. Assessing visit on-time status is done with respect to each specific visit window. In an example from Table 4 below, if an injection is given at day 252 (Week 36) but the Week 36 evaluation procedures are not done until 50 days later at day 302, both of these are considered “on time” because they are within their respective visit windows.

Participants can change PrEP regimens at any time. Participants may choose to start CAB-LA at Enrollment or at a different time during follow-up. The total number of CAB-LA injections given will vary depending on when a participant elects to start CAB-LA, although study staff will aim to minimize extra visits solely for CAB-LA injections. If an injection cannot be given on time, and the participant wants to continue with CAB-LA, the site will attempt to get the participant back on the appropriate injection schedule as quickly as possible. The protocol team and CMC will be consulted for any participant who may need an injection outside of the documented injection window. If the protocol team and CMC determine that procedures are allowed outside of the documented injection window, then that will be noted in the database. Additional information about

visit and injection windows for those on CAB-LA is provided in the Data Management SSP Manual – Section 1.

Table 3. Visit Windows for Oral PrEP or no PrEP

Target Visit Day	Study Visit Name	Target Visit Window	Allowable Visit Window	Base Visit Day*	Days from Base Visit Day
0	Enrollment				
28	Week 4 evaluation	-7/+7	-7/+83	0	28
140	Week 20 evaluation	-14/+ 14	-28/+83	0	140
252	Week 36 evaluation	-14/+14	-28/+83	0	252
364	Week 52/Exit	-14/+14	-28/+84	0	364

**The planned target visit day for each evaluation visit and termination visit is based on the date of the Enrollment visit. Regardless of where in the allowable visit window an evaluation visit was completed, the target visit day for the following evaluation visit is based off the planned days from Enrollment, not planned days from the previous visit.*

Table 4. Visit Windows for CAB-LA PrEP

Target Visit Day	Name	Target Visit Window	Allowable Visit Window	Base Visit Day*	Days from Base Visit Day
0	Enrollment + Initial dose				
28	Reload dose	-3/+3	-3/+3	0	28
28	Wk 4 Evaluation	- 7/+7	-7/+83	0	28
84	8 wk dose	-7/+7	-7/+7	28	56
140	8 wk dose	-7/+7	-7/+7	84	56
140	Wk 20 Evaluation	-14/+14	-28/+83	0	140
196	8 wk dose	-7/+7	-7/+7	140	56
252	8 wk dose	-7/+7	-7/+7	196	56
252	Wk 36 evaluation	- 14/+14	-28/+83	0	252
308	8 wk dose	-7/+7	-7/+7	252	56
364	8 wk dose	-7/+7	-7/+7	308	56
364	Wk 52/Exit	- 14/+14	-28/+84	0	364

NOTES:

- *The planned target visit day for injection visits is based on the date of the previous injection visit because the injection visits are based on the injection regimen.*
- *Regardless of when in the allowable visit window an injection visit was completed, the target visit day for the following injection visit is based off the previous injection visit (previous injection), not planned days from Enrollment.*
- *The planned target visit day for evaluation visits and Exit visit is based on Enrollment date.*
- *Regardless of when in the allowable visit window an evaluation visit was completed, the target visit day for the following evaluation visit is based off the planned days from Enrollment, not planned days from the previous visit.*

9.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

9.1 ADVERSE EVENT DEFINITION AND REPORTING

An AE is defined as any untoward medical occurrence in a clinical research participant administered an investigational product and which does not necessarily have a causal relationship with the investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

In this study, the only study drugs provided to participants will be US FDA-approved medications. F/TDF used as 2-1-1 HIV PrEP and doxycycline for STI PEP are off-label use of FDA-approved products.

Study site staff will document all AEs, including grade, relatedness, and seriousness, in source documents. Only the following AEs will be considered reportable and recorded in the study database:

- Any SAE, regardless of relatedness to study products
- Any AE that leads to a study product hold or change in regimen, regardless of relatedness or severity
- Any Suspected, Unexpected Serious Adverse Reaction (SUSAR) as defined in Section 9.6 (expedited reporting to DAIDS)
- Other AEs of special interest as defined in Section 9.6 (expedited reporting to DAIDS)

It will be important that site teams routinely review clinical events that occur among their participants and alert study leadership if any individual incidents or trends raise concern about the conduct of the study at that site or raise the possibility of serious or unanticipated risks to study participants posed by the trial. If such a risk is identified by either site staff or other study team members, it will be reported and responded to as described below in Section 9.4.

Seriousness will be defined using Version 2.0, January 2010 of the Manual for Expedited Reporting of Adverse Events to DAIDS, as AEs occurring after exposure to the study drug that:

- Result in death
- Are life-threatening
- Require inpatient hospitalization or prolongation of existing hospitalization
- Result in persistent or significant disability/incapacity
- Are congenital anomalies/birth defects
- Are important medical events that may not result in death, be immediately life-threatening, or require hospitalization but may jeopardize the participant or require intervention to prevent one of the outcomes listed in the definition above.

Relatedness is an assessment made by a study clinician of whether or not the event is related to the study agent. The relationship to the study product will be assessed as specified in Version 2.0, January 2010 of the Manual for Expedited Reporting of Adverse Events to DAIDS.

The Manual for Expedited Reporting of Adverse Events to DAIDS is available on the DAIDS Regulatory Support Center (RSC) website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids

Severity will be assessed using The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017. The DAIDS grading table is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/daids-adverse-event-grading-tables.

9.2 SUSPECTED, UNEXPECTED SERIOUS ADVERSE REACTION (SUSAR) ASSESSMENT

The SUSAR Reporting Category, as defined in Version 2.0 of the DAIDS Expedited Adverse Event (EAE) manual, will be used for this study for expedited reporting to DAIDS. See section 9.6 below for expedited reporting of SUSARs and some other specified adverse events.

The site investigator will assess all SAEs for relatedness and expectedness. A SUSAR is an SAE that is both related and unexpected. The definitions for these terms are specified in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS, which is available on the DAIDS Regulatory Support Center (RSC) website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

9.3 SAFETY MONITORING AND CLINICAL DATA REVIEW

A multi-tiered safety review process will be followed for the duration of this study. The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, and for alerting the CMC if unexpected concerns arise or if they require clinical guidance. Sites are required to have detailed SOPs describing methods for AE reporting and toxicity management to ensure that AEs are reported and managed in accordance with the protocol. Study participants will be provided a 24-hour telephone number and contact information and instructed to contact the study clinician to report any AEs 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.

Close cooperation between the Protocol Chairs, study site Investigator(s), DAIDS Medical Officer, LOC CRM, SDMC Biostatistician, SDMC Clinical Coding and Safety Staff, HPTN LC, and other study team members will be necessary in order to monitor participant safety in a timely manner. The study team will have regularly scheduled conference calls during the period of study implementation, and additional *ad hoc* calls will be convened if required.

The CMC will consist of a sub-group of the protocol team, including physicians from a subset of the sites, the Protocol Chair and Co-Chairs, pharmaceutical sponsor investigators, DAIDS Medical Officer, and DAIDS Protocol Pharmacist. Representatives from the HPTN LOC, HPTN LC, and the HPTN SDMC will be included on communications as observers. The CMC provides support to site clinicians, as needed, regarding individual participant clinical management (e.g., questions related to toxicity management, clinical holds of study drug, permanent discontinuations, CAB-LA injections schedules, etc.).

The SDMC Clinical Safety staff review incoming safety data for completeness and consistency on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification.

The SDMC will prepare routine study conduct and safety reports for the Study Monitoring Committee (SMC), which will meet by conference call approximately every 6 months and will review data aggregated across study arms (e.g., accrual, retention, safety) in an open meeting, and safety and other data by study arm during a closed meeting. More frequent or *ad hoc* reviews of safety reports may be conducted by the SMC as needed. A recommendation to stop the trial may be made by the SMC at any such time that the team agrees an unacceptable type and/or frequency of AEs has been observed. If at any time a decision is made to discontinue the study product in all participants, DAIDS will notify appropriate regulatory agencies, as well as the site IoRs, who will notify the responsible IRBs expeditiously.

A Data and Safety Monitoring Board (DSMB) is not required for this study per HPTN requirements and the NIAID policy on DSMB Operations.

9.4 Expedited Adverse Event (EAE) Reporting

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the Manual for Expedited Reporting of Adverse Events to DAIDS, which is available on the DAIDS Regulatory Support Center (RSC) website at https://rsc.niaid.nih.gov/clinical-research-sites/manual-expedited-reporting-adverse-events-daids.

9.5 Adverse Event Reporting to DAIDS

The DAIDS Adverse Experience Reporting System (DAERS), an internet-based reporting system, must be used for EAE reporting to DAIDS. In the event of system outages or technical difficulties, EAEs may be submitted via the DAIDS EAE form. This form is available on the DAIDS RSC website at https://rsc.niaid.nih.gov/clinical-research-sites/paper-eae-reporting.

For questions about DAERS, please contact NIAID CRMS Support at CRMSSupport@niaid.nih.gov. Please note that site queries may also be sent from within the DAERS application itself.

For questions about expedited reporting, please contact the DAIDS RSC Safety Office at DAIDSRSCSafetyOffice@tech-res.com.

9.6 Reporting Requirements for this Study

The SUSAR Reporting Category, as defined in Version 2.0, January 2010 of the Manual for Expedited Reporting of Adverse Events to DAIDS, will be used for this study. The study agents for which expedited reporting are required are:

- Tenofovir disoproxil fumarate /emtricitabine (F/TDF)
- Tenofovir alafenamide/emtricitabine (F/TAF)
- Cabotegravir – long acting injectable (CAB-LA)
- Doxycycline

In addition to the SUSAR Reporting Category identified above, other AEs that must be reported in an expedited manner are:

- Any SAE that leads to a hold or discontinuation of doxycycline (regardless of whether expected or unexpected)
- Hemolytic anemia
- Intracranial hypertension
- Esophageal ulceration
- *Clostridioides difficile*-associated diarrhea

All EAEs as described above will be followed to clinical resolution or stabilization during the study. In addition to submitting EAE information to the DAIDS RSC Safety Office via DAERS, the site investigator may be required to submit AE and EAE information to local regulatory agencies or other local authorities. Site staff will report information regarding AEs to their IRB, and other local regulatory authorities, in accordance with all applicable regulations and local IRB requirements. Sponsor responsibility for reporting AEs or EAEs to ViiV Healthcare or Gilead Sciences will be specified in a Clinical Trials Agreement between DAIDS and each respective company.

9.7 EXPEDITED AE REPORTING PERIOD

The EAE reporting period for this study begins once a participant is enrolled and continues up through the participant's final study visit. After the protocol-defined AE reporting period, unless otherwise noted, only SUSARs as defined in version 2.0 of the EAE Manual and the other events specified in section 9.6 will be reported to DAIDS if the study staff becomes aware of the events on a passive basis (i.e., from publicly available information).

9.8 SOCIAL IMPACT REPORTING

Social impacts related to study participation will be reported during the study. It is possible that participants' involvement in the study could become known to others, and that a social impact may result (i.e., because participants could be perceived as having HIV/STIs, at an increased likelihood for HIV acquisition). For example, participants could be treated unfairly or could have problems being accepted by their families and/or communities. A social impact that is reported by the participant and judged by the IoR/designee to be serious or unexpected will be reported to the responsible site's IRBs at least annually, or according to their individual requirements.

Social impacts will be collected and reported on CRFs during regular visits. In the event that a participant reports a social impact, 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. Each site will provide such care and counseling in accordance with standardized guidance in the Clinical, Safety, and AE Management SSP Manual – Section 2. While maintaining participant confidentiality, study sites may engage their Community Advisory Board in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

10.0 STATISTICAL CONSIDERATIONS

10.1 OBJECTIVES AND ENDPOINTS

10.1.1 Primary Objective(s) and Endpoints

10.1.1.1 To determine the efficacy of the 3P mHealth package on PrEP uptake among participants

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

- PrEP initiation with a documentation of oral PrEP dispensation by the study site at any time during the 52 weeks of study follow-up period.
- PrEP initiation with documentation of a CAB-LA injection by the study site at any time during follow-up, up to 48 weeks.

10.1.1.2 Determine the efficacy of the 3P mHealth package on PrEP adherence among participants

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

- Protective intraerythrocytic TFV-DP concentrations at Weeks 20, 36 and 52, for participants choosing to use a TFV-based daily oral PrEP regimen.
- Documented CAB-LA injections every 8 weeks, ± 2 weeks (14 days) of the expected dosing, during the preceding period among participants choosing CAB-LA.
- Documentation of elected PrEP regimen and timing of PrEP regimen switching at each study visit during the 52 weeks of follow-up.
- Self-reported PrEP use and adherence at each study visit.
- Self-reported number and timing of anal/vaginal sex encounters in the past 30 days and TFV-DP concentrations in DBS for participants electing to use 2-1-1 oral PrEP.

10.1.1.3 Assess doxy-PEP uptake, use, and acceptability, and factors associated with each

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

- Doxy-PEP initiation with a documentation of doxycycline dispensation at any time during the 52 weeks of study follow-up
- Doxycycline use as measured by plasma and hair samples
- Self-reported use of doxy-PEP at each follow up visit during the 52 weeks of study follow-up.
- Self-reported number and timing of anal/vaginal sex encounters in the past 30 days.
- Self-reported doxy-PEP acceptability.

- Self-reported individual-level sociodemographic, behavioral, and attitudinal characteristics collected at baseline and subsequent study visits during the 52 weeks of follow-up.
- AEs that lead to doxy-PEP hold
- Response to qualitative interview questions inquiring about doxy-PEP use for a subset of participants.

10.1.1.4 Assess the incidence of HIV infections among participants choosing to use CAB-LA

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

- PrEP initiation with documentation of a CAB-LA injection by the study site at any time during follow-up, up to 48 weeks.
- Documented on-time CAB-LA injections of the expected dosing, among participants choosing CAB-LA.
- Documented incident HIV infections among participants choosing to use CAB-LA during the study follow-up period.

10.1.2 Secondary Objective(s) and Endpoints

10.1.2.1 Determine the acceptability and use of the 3P mHealth package in the intervention arm

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

- Self-reported use of the 3P mHealth package among participants randomized to the intervention arm only.
- Self-reported acceptability of the 3P mHealth package among participants in the intervention arm only.
- Response to qualitative interview questions inquiring acceptability of 3P mHealth package for a subset of participants in the intervention arm only.

10.1.2.2 To compare the frequency, directionality, and reasons for PrEP regimen choice, switching, and discontinuation by arm

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

- Documented PrEP regimen choice during the 52 weeks of study follow-up period.
- Response to interview questionnaires inquiring reasons for PrEP regimen choice and switching via self-report/CASI during the study follow-up period.
- Self-reported PrEP use and PrEP discontinuation during the study follow-up period.
- AEs that lead to PrEP hold or change

10.1.2.3 Evaluate demographic, behavioral, and attitudinal factors associated with choice of PrEP regimen

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

- Documented number of chosen PrEP regimens during the 52 weeks of study follow-up.
- Sociodemographic, behavioral, and attitudinal characteristics collected at baseline and subsequent study visits during the 52 weeks of follow-up.

10.1.2.4 Determine the efficacy of the 3P mHealth package on prevention-effective adherence

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

- Documented incident HIV infection during the 52 weeks of follow-up.
- Self-reported HIV risk including sexual behavior and HIV status of sexual partner.
- Protective TFV-DP concentration levels in DBS at weeks 20, 36 and 52 for participants choosing to use oral PrEP.
- Documented CAB-LA injections 1 month apart for the first two injections, then every 8 weeks, within the expected dosing window, during the preceding period among participants choosing CAB-LA.
- Documentation of elected PrEP regimen at each study visit during the 52 weeks of follow-up.
- Self-reported PrEP adherence.

10.1.3 Exploratory Objectives and Endpoints

10.1.3.1 To explore the preliminary efficacy of the 3P mHealth package on HIV incidence

Consistent with the exploratory objectives, the following endpoints will be assessed:

- Documented incident HIV infections during the study follow-up period.

10.1.3.2 To assess bacterial STI incidence and factors associated with STI incidence among those who do and do not take doxy-PEP

Consistent with the exploratory objective, the following endpoints will be assessed:

- Documented incident bacterial STI infection during the study follow-up period.
- Self-reported use of doxy-PEP at follow-up visits.

10.1.3.3 To explore the impact of relative usage of each of the 3P mHealth tools on PrEP uptake and adherence.

Consistent with the exploratory objective, the following endpoints will be assessed:

- PrEPsmart paradata on app usage frequency and time
- PrEPmate paradata on messaging frequency and quantity
- MyPrEP paradata on website interaction frequency and time
- PrEP uptake as defined above
- PrEP adherence as defined above
- Documentation of elected PrEP regimen

10.1.3.4 To perform exploratory 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 host response to antiretroviral drugs; characterization of STIs; and evaluation of virologic, pharmacologic, or STI-based laboratory assays.

Consistent with this objective, endpoints will be defined based on which assessments are performed.

10.1.3.5 To evaluate the longitudinal use of on-demand and weekly doxycycline with hair doxycycline assessments.

Consistent with the exploratory objective, the following endpoints will be assessed:

- Evaluation of doxycycline in hair to assess longitudinal use of on-demand and weekly doxycycline.

10.2 SAMPLE SIZE

The sample size and power calculations were conducted for the primary endpoints, pooling across sites.

PrEP uptake: PrEP uptake will be measured as PrEP dispensation at any time during the follow-up. Participants who do not initiate PrEP before loss-to-follow-up will be classified as non-initiators. Table 5 presents the minimum detectable difference in proportions of PrEP uptake between the 3P versus control arms with 50 participants per arm (per site)and 200 participants per arm (across sites) at 90% power and assuming a two-sided Type-I error of 0.05. The minimum detectable difference (MDD) is given for a range of potential values of PrEP uptake in the control condition. If PrEP uptake is 0.65 in the control condition, the minimum detectable absolute difference in PrEP uptake between the 3P and control arms with 90% power is 14.44% for the assessment across sites. The corresponding minimum detectable absolute difference in PrEP uptake between arm for an assessment by site assuming 50 participants per arm is 26.25%. The MDDs in PrEP uptake are generally smaller than 16.1% for the assessment across sites with the range of the potential values of PrEP uptake in the control condition that have been considered.

Table 5. Minimum detectable difference in proportions of PrEP uptake between 3P and Control arms with 90% power assuming a sample size N=200 per arm (or 50 per arm per site) and assuming a two-sided Type-I error of 0.05.

	Sample size per/arm	
Control arm proportion	**50**	**200**
0.45	31.04%	16.09%
0.5	30.26%	15.92%
0.55	29.21%	15.59%
0.6	27.87%	15.10%
0.65	26.25%	14.44%
0.7	24.31%	13.61%
0.75	22.03%	12.58%

PrEP adherence: PrEP adherence will be assessed at three separate timepoints (Weeks 20, 36 and 52) by TFV-DP concentration levels in DBS for oral PrEP and on-time injection for CAB-LA. Table 6 shows the minimum absolute detectable difference in the average proportions of PrEP adherence over time between the 3P versus control arms with 90% power based on the Donner and Klar's method for power and sample size calculations for clustered binary outcomes [38], assuming a two-sided Type-I error of 0.05, three observations of PrEP adherence per participant, an intra-participant correlation coefficient (ICC) of 0.3 and 0.4, a sample size of N=200 per arm (pooling across sites), 50 per arm (per site) and accounting for a loss-to-follow-up rate of 10% and 15%. The minimum detectable absolute difference is smaller than 15% for the range of the possible values of the PrEP adherence proportion in the control condition for the assessment pooling across sites. For the assessment by site, the minimum detectable difference in the average PrEP adherence between the two arms is generally greater than 20% with the range of possible values of PrEP adherence in the control condition that have been considered.

Table 6. Minimum detectable difference in the average proportions of PrEP adherence over time between 3P and control arms with 90% power assuming a two-sided Type-I error of 0.05, 3 observations of PrEP adherence per participant, an ICC of 0.3 and 0.4, a sample size N=200 per arm (400 participants in total across sites), 50 per arm per site and accounting for a loss to follow-up rate of 10 and 15%.

	LFUP=10%				**LFUP=15%**			
Control arm proportion	**ICC=0.3**		**ICC=0.4**		**ICC=0.3**		**ICC=0.4**	
	Sample size/arm		**Sample size/arm**		**Sample size/arm**		**Sample size/arm**	
	50	**200**	**50**	**200**	**50**	**200**	**50**	**200**
0.45	24.39%	12.44%	25.78%	13.18%	25.06%	12.79%	26.47%	13.56%
0.5	23.93%	12.34%	25.26%	13.07%	24.57%	12.69%	25.92%	13.44%
0.55	23.25%	12.13%	24.50%	12.84%	23.85%	12.47%	25.13%	13.20%
0.6	22.33%	11.79%	23.50%	12.47%	22.89%	12.12%	24.09%	12.82%
0.65	21.18%	11.33%	22.26%	11.97%	21.69%	11.64%	22.79%	12.29%
0.7	19.76%	10.72%	20.74%	11.32%	20.23%	11.01%	21.22%	11.62%

doxy-PEP use: doxy-PEP use will be assessed at three separate timepoints (Weeks 20, 36 and 52) based on self-reports. Table 7 shows the two-sided 95% CIs for the true average proportion of doxy-PEP use over the three timepoints given by a range of possibly observed proportions of doxy-PEP use, assuming a sample size of 400 participants pooling across arms and sites, 3 repeated measures of doxy-PEP use for each participant, an ICC of 0.3 and 0.4, and a loss to follow-up rate of 10% and 15%. For example, if the observed proportion of doxy-PEP use is 0.7, then there is a 95% chance that the true average proportion over the measurement timepoints will be in [0.665, 0.735], assuming a loss to follow-up rate of 10% and an ICC of 0.3.

Table 7. 95% Confidence Intervals for the true average proportion of doxy-PEP use

	LFUP=10%		LFUP=15%	
Observed proportion	**ICC=0.3**	**ICC=0.4**	**ICC=0.3**	**ICC=0.4**
0.45	[0.412,0.488]	[0.410,0.490]	[0.411,0.489]	[0.409,0.491]
0.50	[0.462,0.538]	[0.460,0.540]	[0.461,0.539]	[0.459,0.541]
0.55	[0.512,0.588]	[0.510,0.590]	[0.511,0.589]	[0.509,0.591]
0.60	[0.563,0.637]	[0.561,0.639]	[0.562,0.638]	[0.560,0.640]
0.65	[0.614,0.686]	[0.612,0.688]	[0.613,0.687]	[0.611,0.689]
0.70	[0.665,0.735]	[0.663,0.737]	[0.664,0.736]	[0.662,0.738]
0.75	[0.717,0.783]	[0.715,0.785]	[0.716,0.784]	[0.714,0.786]

doxy-PEP uptake and acceptability: doxy-PEP uptake will be measured as doxy-PEP dispensation by the sites at any time during the follow-up period. doxy-PEP acceptability will be measured at Week 52 by self-report based on a Likert scale. A binary variable for doxy-PEP acceptability can be created by dichotomizing the acceptability score (not acceptable vs. acceptable). Table 8 shows the two-sided 95% CIs for the true proportion of doxy-PEP uptake or doxy-PEP acceptability (based on a dichotomized acceptability variable) for a range of potentially observed proportions of doxy-PEP uptake or acceptability with 400 participants pooling across arms and sites. The calculations for doxy-PEP acceptability accounted for a loss to follow-up rate of 10% and 15% while those for doxy-PEP uptake assumed that participants who did not report doxy-PEP use before loss to follow-up did not use doxy-PEP. For example, there is a 95% chance that the interval [0.655, 0.745] will contain the true proportion of doxy-PEP uptake if the observed proportion is 0.7. Similarly, if the observed proportion of doxy-PEP acceptability is 0.8, there is a 95% chance that the true proportion of doxy-PEP acceptability will lie in [0.759, 0.841], accounting for a loss to follow-up rate of 10% when the assessment if performed by site.

Table 8. 95% Confidence Intervals for the true proportion of doxy-PEP uptake and doxy-PEP acceptability

Observed proportion	LFUP=0	LFUP=10%	LFUP=15%
0.45	[0.401,0.499]	[0.399,0.501]	[0.397,0.503]
0.5	[0.451,0.549]	[0.448,0.552]	[0.447,0.553]
0.55	[0.501,0.599]	[0.499,0.601]	[0.497,0.603]
0.6	[0.552,0.648]	[0.549,0.651]	[0.548,0.652]
0.65	[0.603,0.697]	[0.601,0.699]	[0.599,0.701]
0.7	[0.655,0.745]	[0.653,0.747]	[0.651,0.749]
0.75	[0.708,0.792]	[0.705,0.795]	[0.704,0.796]
0.8	[0.761,0.839]	[0.759,0.841]	[0.757,0.843]
0.85	[0.815,0.885]	[0.813,0.887]	[0.812,0.888]
0.9	[0.871,0.929]	[0.869,0.931]	[0.868,0.932]

10.3 ACCRUAL AND RETENTION

A total of approximately 400 participants will be enrolled and followed for a maximum of 52 weeks. An average annual retention rate of at least 90% will be targeted. Individual sites will be given different enrollment targets with the overall cross-site enrollment meeting the overall protocol goals, but with each site having a target of enrolling a minimum of 60 participants.

10.4 RANDOM ASSIGNMENT/STUDY ARM ASSIGNMENT

Participants will be randomized in a 1:1 ratio to receive the 3P mHealth package or a PrEP handout (control) using randomly-permuted blocks stratified by study site to assure balanced groups within each study site.

10.5 BLINDING

Study participants and study staff will not be blinded to the randomization assignments.

10.6 STATISTICAL ANALYSIS

This section briefly describes the final study analyses. The analysis population for the primary objectives encompasses all participants who were enrolled and randomized to either the 3P or Control arm in the study.
Detailed technical specifications of the statistical analyses will be described in a separate Statistical Analysis Plan.

10.6.1 Primary Analyses

To determine the efficacy of the 3P mHealth package on PrEP uptake among participants

- PrEP uptake is defined as the proportion of enrolled participants who elect to initiate PrEP (with a documented PrEP dispensation by the site) at any time during the 52 weeks of follow-up. Participants who did not initiate PrEP before loss to follow-up will be classified as non-initiators. PrEP uptake will be assessed at Week 52 for each study arm with 95% confidence limits computed using the binomial distribution. A logistic regression model will be used to compare PrEP uptake between the study arms.

To determine the efficacy of the 3P mHealth package on PrEP adherence among participants

- PrEP adherence is assessed at Weeks 20, 36 and 52 through biomedical testing for oral PrEP regimens and documentation of CAB-LA injection for CAB-LA. Adherence measures are described in Section 8.7. Participants on oral PrEP missing an assessment visit and with no PrEP dispensed at their most recent visit will be considered non-adherent. Also, participants who have not yet initiated PrEP at a visit will be considered non-adherent at that visit. The average PrEP adherence at a visit will be computed as the proportion of participants who are determined to be adherent at that visit by study arm. The associated 95% confidence limits will be computed using the binomial distribution. Generalized estimating equations (GEE) with a logit link function will be used to examine differences in adherence proportions between the 3P and Control arms at Weeks 20, 36 and 52, while accounting for potential correlation between PrEP adherence measures over time for each participant. Robust (Sandwich) methods will be used for variance estimation.

To assess doxycycline PEP uptake, use, and acceptability, and factors associated with each.

- doxy-PEP uptake, use and acceptability measures are based on self-reports.

- doxy-PEP uptake is defined as the proportion of participants dispensed doxy-PEP during the 52 weeks of study follow-up period. doxy-PEP uptake will be computed with 95% confidence limits at Week 52. Multivariable logistic regression models will be used to assess association between doxy-PEP uptake and factors including study group, demographic and behavioral characteristics.

- doxy-PEP use will be assessed at Weeks 20, 36 and 52. Doxy-PEP use at an assessment visit will be computed as the proportion of participants reporting use following sex acts, reported at that visit. The corresponding 95% confidence limits will be computed based on the binomial distribution. Multivariable GEE

models will be used to investigate possible associations between doxy-PEP use and factors including study group, demographic and behavioral characteristics.

- Descriptive statistics will be used to summarize doxy-PEP acceptability. Multivariable generalized linear models (with a link function that is appropriate to the scale of the measure for doxy-PEP acceptability) will be used to investigate associations between doxy-PEP acceptability and factors including study group, sociodemographic, and behavioral characteristics.

To assess the incidence of HIV infections among participants choosing to use CAB-LA

- Uptake of CAB-LA is defined as the proportion of participants choosing to initiate CAB-LA with a documented receipt of a CAB-LA injection during the study follow-up period. CAB-LA uptake will be computed with 95% confidence interval.
- Incidence of HIV infection between the date of CAB-LA initiation and the date of switch to oral PrEP (for participants switching from CAB-LA to oral PrEP) or end of follow-up (for participants staying on CAB-LA from initiation through the end of the follow-up period) will be computed with 95% confidence interval among participants choosing to use CAB-LA.

10.6.2 Secondary Analyses

To determine the acceptability and use of the 3P mHealth package in the intervention arm by site.

- Descriptive statistics will be used to summarize the acceptability and use of the 3P mHealth package in the intervention arm by site.

To compare the frequency, directionality, and reasons for PrEP regimen choice and switching, between arms.

- Descriptive statistics will be used to summarize the frequency, directionality, and reasons for PrEP regimen choice and switching by arm. Generalized linear models will be used to assess differences in these descriptive summaries between the study arms. Reasons for PrEP regimen choice and switching obtained from qualitative interview data will be listed by arm.

To evaluate demographic, behavioral, and attitudinal factors associated with choice of PrEP regimen

- Multivariable logistic regression models will be used to separately assess associations between each PrEP regimen choice and demographic, behavioral, and attitudinal factors.

To determine the efficacy of the 3P mHealth package on prevention-effective adherence

- The proportion of enrolled participants with incident STI infection will be computed with 95% confidence limits at Weeks 20, 36 and 52 by study arm.

- The proportion of enrolled participants with incident HIV infection will be computed at Weeks 20, 36 and 52 by study arm.

- The proportion of enrolled participants reporting HIV risk based on self-reported sexual behavior and HIV status of sexual partner will be computed at Weeks 20, 36 and 52 by study arm.

- The proportion of enrolled participants who are determined to be PrEP adherent and potentially at HIV risk (based on incident STI, self-reported sexual behavior and HIV status of partners) will be computed with 95% confidence limits at Weeks 20, 36 and 52 by study arm. GEE models with a logit link function will be used to compare the proportions between the study arms.

10.6.1 Missing Data

All analyses will be performed based on the complete case assuming potential missing data on the outcomes (e.g. TFV-DP concentration levels in DBS, self-reported PrEP/doxy-PEP use, doxy-PEP acceptability) or covariates (e.g. self-reported sociodemographic and behavioral characteristics) are missing completely at random. Weighting and imputation techniques will also be used in sensitivity analyses to adjust for missing observations on the outcomes or covariates under the assumption that the missing data mechanism is missing at random.

10.6.2 Interim Stopping Plan

This study will not have any formal interim reviews of primary or secondary endpoints and therefore there are no set interim stopping plans.

10.7 QUALITATIVE ANALYSIS

The IDIs will be digitally recorded, then transcribed and subsequently translated into English as needed. The study team will review the transcripts for clarity and to identify emergent themes. Transcripts will be uploaded to an appropriate qualitative data analysis software for coding and analysis to further explore participants' acceptability of the 3P mHealth package and decision-making about PrEP and doxy-PEP uptake and use. Codebooks will be developed and modified iteratively based on emergent themes throughout the coding process. Any discrepancies between coders will be discussed and resolved through consensus. Topical codes will then be read across transcripts and grouped by emergent themes within each topic using a content analysis approach. Further

information and details about the qualitative interviews can be found in the Accrual, Follow-up, and Retention SSP Manual – Section 2.

11.0 LABORATORY SPECIMENS AND BIOHAZARD CONTAINMENT

Laboratory procedures are described below, in Appendices IA and IB, and in Section 8.0; additional tests to be performed at a subsequent visit for participants who have a reactive or positive HIV test after Enrollment are described in Appendix IC.

11.1 LOCAL LABORATORY SPECIMENS

As described in Section 8, the following types of specimens will be collected for testing at the local laboratory (LL):

- HIV diagnostic testing (see Appendix II and Laboratory SSP Manual – Section 1)
- HIV RNA PCR
- Chemistry - creatinine
- HBV testing to include: HbsAg, HbsAb, HbcAb
- GC/CT Nucleic Acid Amplification Test (NAAT) for pharyngeal, rectal, urine
- Syphilis serology
- Plasma storage
- DBS storage
- Urine storage
- Hair storage
- Real-time HIV resistance testing for clinical management, if indicated and available (if HIV infected)

Local laboratories (LLs) will perform HIV, HBV, chemistry, and STI testing as indicated in Appendix IA-IC. HIV rapid testing may be performed in the clinic or laboratory.

Each study site must adhere to the HPTN Manual of Operations (MOP), the Laboratory 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. US sites should send these tests to Clinical Laboratory Improvement Amendments (CLIA) compliant laboratories. 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 Laboratory SSP Manual.

11.1.1 Specimen Storage at Study Sites

Plasma, DBS, hair, and urine samples will be stored at the local site/LL throughout the study. A subset of the stored samples will be shipped to the HPTN LC (located in the US) for Quality Assurance (QA) and other assessments. 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 without written approval by the HPTN LC prior to use. Stored samples will be maintained at the site until at least one year after acceptance of the manuscript that describes the primary findings for the study, and after protocol-related testing has been completed. This includes retrospective testing performed at the HPTN LC and laboratories designated by the HPTN LC that is needed to address study objectives. In some cases, the HPTN LC will approve sample destruction before completion of testing for tertiary and exploratory objectives. Study sites may not destroy samples without written permission from the HPTN LC. 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.

11.1.2 Virology

Assays may be performed 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. Results will not be returned to the sites or study participants, with the exception of HIV diagnostic testing (if results obtained at the HPTN LC do not agree with site results).

Resistance testing will be performed at the HPTN LC or a laboratory selected by the HPTN LC. This testing may be performed during the study or at the end of the study. Results of this testing will not be returned to study sites. Because real-time resistance testing may be needed for clinical management, each site will have an SOP as to how they will accomplish real-time local or regional resistance testing to assist with clinical decision making; separate specimens should be collected for that testing.

11.1.3 Pharmacology

Plasma and DBS samples for pharmacology testing will be collected throughout the study from all participants; this testing may be limited to a subset of the samples. Procedures for sample processing and shipping are outlined in the Laboratory SSP Manual – Section 1. Pharmacology testing will be performed at the HPTN LC or at another laboratory selected and approved 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 will be led by the HPTN LC Pharmacology Core, in collaboration with other groups, as needed.

Hair will also be collected and may be used for retrospective assessment of study products or doxycycline. Hair collection may be omitted if the participant declines or has hair that is unsuitable for collection.

In support of this protocol, adherence to TFV-based oral PrEP regimens will be evaluated through the measurement of intraerythrocytic TFV-diphosphate (TFV-DP) in dried blood spots (DBS) at select study visits; drug concentrations will be utilized in the biomedical assessment of adherence; cutoffs may be specific to F/TDF and F/TAF regimens, as well as participants who use oral TFV-based PrEP in an event-driven manner [35, 36]. Stored plasma may also be used in the assessment of adherence to doxycycline in a subset of participants or visits to assess recent doxycycline use (within the last 5-7 days).

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

11.1.4 Other HPTN LC testing

Additional testing may be performed at the HPTN LC or at laboratories designated by the HPTN LC as noted in the Exploratory Objective.

11.2 Quality Control and Quality Assurance Procedures

HPTN LC staff will conduct periodic visits to each 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 quality assurance (QA) problems identified through proficiency testing or on-site visit reviews.

Throughout the course of the study, on a quarterly basis, the SDMC will work with the HPTN LC to select a random sample of stored specimens to test for QA purposes (as described in the MOP), and to assist with and/or to confirm HIV seroconversion events. QA testing may also be performed in some studies for other assessments (e.g., HIV viral load testing). HPTN LC staff will follow-up directly with site staff to resolve any QA problems identified through this process.

The SDMC and/or HPTN LC will inform site staff of the samples selected for QA testing, and site staff will ship the selected specimens to the HPTN LC. The HPTN LC will perform HIV diagnostic testing for QC, endpoint confirmation and end of study confirmation and will work with the SDMC to compare the results of their tests with the results obtained by the local labs. LC staff will follow-up directly with site staff to resolve any QA problems identified through this process.

11.3 HIV DIAGNOSTIC TESTING

The LL will perform testing for HIV diagnosis at Screening and other scheduled visits as described in Appendix IA-C, Appendix II, and the Laboratory SSP Manual – Section 1. HIV infection status will be confirmed at study sites using local HIV testing guidelines and following the advice of the CMC. 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 using a licensed HIV RNA test. Regardless of whether HIV RNA testing is used for diagnostic testing, HIV infection must be confirmed in all cases using two independent samples collected on different days. Algorithms for HIV diagnostic testing are provided in Appendix II and in the Laboratory SSP Manual – Section 1.

11.4 HIV RNA TESTING

Quantitative HIV RNA (viral load) testing will be performed at LLs to assist with HIV diagnosis in participants with possible acute HIV infection and at selected study visits (see above and Appendix II). The type of assay used for RNA testing must be approved by the HPTN LC. Non-US LLs must participate in the DAIDS EQA program, with EQA results that are deemed satisfactory by the HPTN LC. US LLs must use a CLIA-compliant laboratory.

11.5 LONG-TERM LOCAL SPECIMEN STORAGE AND POSSIBLE FUTURE RESEARCH TESTING

Sites are required to store all specimens collected in this study, as described in Section 11.1.1. In some cases, specimens may be stored for longer periods, based upon the capacity of the study site, local regulations, and interests of the study team. In these cases, samples in long-term storage may be available for future research testing by the HPTN LC or other interested investigators, in accordance with HPTN policies for Ancillary Studies. If a site does not have the capacity to accommodate long-term storage (beyond that outlined in Section 11.1.1), the HPTN LC will work with the site to transfer selected samples (identified by the HPTN LC) to the HPTN LC. Study participants will be asked to provide written informed consent for specimens to be stored long-term for possible future testing. Specimens from participants who do not consent to long-term storage and future testing will only be used for testing that is needed to address protocol objectives.

11.6 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.

12.0 HUMAN SUBJECTS CONSIDERATIONS

12.1 ETHICAL REVIEW

The HPTN Ethics Working Group (EWG) 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 form(s) (ICFs) contained in Appendix III will be reviewed and approved by the HPTN Scientific Review Committee and NIAID Prevention Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations.

The protocol, site-specific 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 after 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. Study sites 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.

12.2 INFORMED CONSENT

Written informed consent will be obtained from each study participant. Each study site is responsible for developing study ICF(s) for local use, based on the templates in Appendix III, which describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. If applicable, the study site also is responsible for translating the template form into local languages and verifying the accuracy of the translation by performing an independent back-translation.

Literate participants will document their provision of informed consent by signing their ICF(s). Non-literate participants are not eligible for this study, due to the requirement for

mobile app utilization. Further details regarding DAIDS requirements for documenting the informed consent process are provided in the DAIDS SCORE Manual.

All participants will be offered a copy of their ICFs.

12.3 RISKS

Participants may become embarrassed, worried, or anxious when answering questions about their vulnerability to HIV/STIs or when receiving HIV/STI counseling and testing. Trained study staff will be available to help the participant with these feelings.

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, bruising, and/or swelling. In rare cases, phlebotomy can lead to infection. Participants may experience pain or discomfort in their throat or rectum from the swab collection. In some cases, swab collection may cause bleeding.

Regarding hair sample collection, participants may also have some anxiety or worry about providing a hair sample. The technique is optimized to minimize visible hair removal and has been found to be acceptable in multiple settings, including among adolescents in the US[39]. Participants may decline hair sample collection at any study visit.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that a participant's involvement in the study could become known to others, and that social harms may result (i.e. behaviorally vulnerable to HIV/STIs). For participants in the intervention arm, it is possible that others may see them using the tools, which could lead to social harms. It is also possible that a participant's study product (PrEP and/or doxy-PEP) use may be discovered by family/friends/community members outside of the study clinic and could also lead to social harms. For example, participants could be treated unfairly or discriminated against, experience stigma, or have problems being accepted by their families or communities.

There is a risk of HIV drug resistance if a participant acquires HIV while taking PrEP. The risk associated with completing HIV testing every 4 months among participants who are using oral PrEP, as opposed to the recommended 3-month testing frequency, is not known. There is also a risk that among those using PrEP, HIV testing performance may be altered, delaying detection of HIV infection.

The study products used in this study may have side effects, some of which are listed below. These lists do not include all possible side effects but rather the more serious or common side effects with a known or possible relationship. Participants will be monitored closely for any side effects and will be encouraged to report side effects to the study site clinician.

12.3.1 Risks associated with F/TDF

The following side effects have been commonly associated with the use of F/TDF:

- Gastrointestinal distress (e.g., nausea, abdominal pain, diarrhea, or vomiting). These symptoms are most common the first month of use and typically resolve.
- Headaches, dizziness, tiredness, or inability to sleep.

Rare but serious side effects include:

- Rash
- Worsening or new kidney damage
- Bone pain or bone changes, such as thinning/softening
- Allergic reaction
- Lactic acidosis, which can cause shortness of breath, nausea, and liver failure.
- Individuals with HBV who suddenly stop taking F/TDF may experience a "flare" or worsening of hepatic symptoms.

There may be unknown risks for off-label use of F/TDF as 2-1-1 PrEP.

12.3.2 Risks associated with F/TAF

The most common side effect of F/TAF is nausea.

Rare but serious side effects include:

- Worsening or new kidney damage
- Lactic acidosis, which can cause shortness of breath, nausea, and liver failure.
- Individuals with HBV who suddenly stop taking F/TAF may experience a "flare" or worsening of hepatic symptoms.

12.3.3 Risks associated with CAB-LA

The following side effects have been commonly associated with the use of CAB-LA:

- Injection site pain, swelling, irritation, redness, itching or bruising
- Gastrointestinal distress (e.g. nausea, diarrhea, vomiting, stomach pain)
- Runny nose or sore throat
- Headache
- Fever
- Lack of energy
- Rash or itching
- Depression, including suicidal ideation and suicide attempt
- Increased transaminases

Rare but serious side effects include:

- Allergic reaction
- Stevens-Johnson Syndrome
- Toxic epidermal necrolysis

12.3.4 Risks associated with Doxycycline

The following side effects have been commonly associated with the use of doxycycline:

- Headaches
- Gastrointestinal distress (e.g. nausea, vomiting)
- Skin sensitivity to sunlight

Rare but serious side effects include:

- Allergic reaction
- Intracranial hypertension
- Esophageal ulceration

There may be unknown risks for off-label use of doxycycline for STI PEP, including potential antibiotic resistance.

12.4 BENEFITS

There may be no direct benefit to participants in this study, however, participants and others within their community may benefit in the future from information learned in this study.

Participants will receive HIV counseling and testing and may choose to receive PrEP for HIV prevention, which is known to protect against HIV if taken as directed. Participants will also receive STI testing and treatment and may choose to receive doxy-PEP for STI prevention, which is an investigational use of a marketed drug and has been shown in some studies to reduce the chance of getting GC, CT, and syphilis. Participants will also be tested for HBV and provided or referred for vaccination.

12.5 INCENTIVES

In accordance with IRB/EC approvals, 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).

12.6 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; the manufacturer of the study product; representatives of the HPTN LOC, SDMC, and/or LC other government and regulatory authorities, and/or site IRBs/ECs.

12.6.1 Certificate of Confidentiality

Research participants 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. Participants are told of the use and limits of the CoC in the study ICF. CoCs are automatically deemed to be issued for any NIH-funded research that collects or uses identifiable, sensitive information. However, CoCs may not be effective for data held outside of the US.

In accordance with subsection 301(d) of the Public Health Service Act, the recipient of the CoC shall not:

- Disclose or provide, in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding, the name of such individual or any such information, document, or biospecimen that contains identifiable, sensitive information about the individual and that was created or compiled for purposes of the research, unless such disclosure or use is made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Disclose or provide to any other person not connected with the research the name of such an individual or any information, document, or biospecimen that contains identifiable, sensitive information about such an individual and that was created or compiled for purposes of the research.

Disclosure is permitted only when:

- Required by Federal, State, or local laws (e.g., as required by the Federal Food, Drug, and Cosmetic Act, or state laws requiring the reporting of communicable diseases to State and local health departments), excluding instances of disclosure in any Federal, State, or local civil, criminal, administrative, legislative, or other proceeding;
- Necessary for the medical treatment of the individual to whom the information, document, or biospecimen pertains and made with the consent of such individual;
- Made with the consent of the individual to whom the information, document, or biospecimen pertains; or
- Made for the purposes of other scientific research that is in compliance with applicable Federal regulations governing the protection of human subjects in research.

As set forth in 45 Code of Federal Regulations (CFR) Part 75.303(a) and NIH Grants Policy Statement (NIHGPS) Chapter 8.3, recipients conducting NIH supported research applicable to this Policy are required to establish and maintain effective internal controls

(e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award.

12.7 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.

12.8 STUDY DISCONTINUATION

The study may be discontinued at any time by NIAID, the HPTN, Gilead Sciences, ViiV Healthcare, and/or site IRBs/ECs. Individual participants may discontinue study participation at any time as detailed in Section 4.6.

13.0 ADMINISTRATIVE PROCEDURES

13.1 SOURCE DOCUMENTATION AND DIRECT DATA ENTRY

Direct data entry or direct data capture of study data into the study database is only allowed when capturing information directly from the participant (participant self-report). Sites will document back-up/paper-based procedures, in the event that electronic systems are unavailable for direct data entry of participant data. Other study data will be sourced from electronic or paper source documents prior to being entered into the database. Source documentation tables will be finalized prior to implementation. Additional details about data entry, storage, and quality management will be available in the Data Management SSP Manual – Section 1.

13.2 PROTOCOL REGISTRATION

Initial Registration of the protocol by the DAIDS Protocol Registration Office (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 and sites will receive an Amendment Registration Notification when the DAIDS PRO receives a complete registration packet. A copy of the Amendment Registration Notification should be retained in the site's regulatory files.

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.

13.3 STUDY ACTIVATION

Following successful protocol registration and submission of all required documents, the HPTN LOC staff will "activate" a site. Study implementation may not begin 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 begin until a study activation notice is provided to the site by the HPTN LOC.

13.4 STUDY COORDINATION

Study implementation will be directed by this protocol as well as the HPTN 113 SSP Manual. The DAIDS SCORE Manual, the DAIDS Manual for Expedited Reporting of Adverse Events to DAIDS, and the DAIDS Toxicity Tables, will outline procedures for conducting study visits; data and forms processing; AE assessment, management and reporting; dispensing study products and documenting product accountability; 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. The CMC will help address issues related to individual study eligibility, toxicity management, and AE reporting as needed to assure participant safety, consistent case management, documentation, and information-sharing across sites.

13.5 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, SSP Manuals, 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[40]. 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 local or 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.

13.6 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.

13.7 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 screened and/or enrolled in the study, including ICFs, locator forms, CRFs, and notations of all contacts with the participant; and all other source documents.

13.8 RESULTS DISSEMINATION

All participants will be informed of study results. Local community stakeholders will also be notified of study results, in consultation with the local Community Advisory Boards. Strategies for notifying participants and stakeholders will be defined per site SOPs.

13.9 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, DAIDS, Gilead Sciences and ViiV Healthcare prior to submission.

14.0 REFERENCES

1. S. McCormack *et al.*, *Lancet,* vol. 387, no. 10013, pp. 53-60, Jan 2, 2016, doi: 10.1016/S0140-6736(15)00056-2.
2. K. H. Mayer *et al.*, (in eng), *Lancet,* vol. 396, no. 10246, pp. 239-254, Jul 25, 2020, doi: 10.1016/s0140-6736(20)31065-5.
3. J. M. Molina *et al.*, *The New England journal of medicine,* vol. 373, no. 23, pp. 2237-46, Dec 3, 2015, doi: 10.1056/NEJMoa1506273.
4. R. J. Landovitz *et al.*, (in eng), *The New England journal of medicine,* vol. 385, no. 7, pp. 595-608, Aug 12, 2021, doi: 10.1056/NEJMoa2101016.
5. CDC. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html (accessed April 8, 2022).
6. UNAIDS. https://www.unaids.org/sites/default/files/media_asset/2020_aids-data-book_en.pdf (accessed April 8, 2022).
7. V. G. Veloso *et al.*, (in eng), *Lancet HIV,* vol. 10, no. 2, pp. e84-e96, Feb 2023, doi: 10.1016/s2352-3018(22)00331-9.
8. T. S. Torres *et al.*, presented at the CROI, Seattle, Washington, US, February 19-22, 2023. [Online]. Available: https://www.croiconference.org/abstract/hiv-recent-infection-in-sexual-and-gender-minorities-in-brazil-and-peru-imprep-study/.
9. PrEP Watch. https://www.prepwatch.org/resources/global-prep-tracker/ (accessed 2023).
10. Centers for Disease Control and Prevention. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. (accessed May 2023).
11. AVAC. https://www.prepwatch.org/in-practice/global-prep-tracker/ (accessed April 2, 2021).
12. P. A. Chan *et al.*, *Journal of the International AIDS Society,* vol. 19, no. 1, p. 20903, 2016, doi: 10.7448/IAS.19.1.20903.
13. M. C. Montgomery *et al.*, *PLOS One,* vol. 11, no. 6, p. e0157742, 2016, doi: 10.1371/journal.pone.0157742.
14. L. K. Rusie *et al.*, *Clin Infect Dis,* vol. 67, no. 2, pp. 283-287, Jul 2, 2018, doi: 10.1093/cid/ciy160.
15. I. W. Holloway, E. A. Krueger, I. H. Meyer, M. Lightfoot, D. M. Frost, and P. L. Hammack, (in eng), *PLOS One,* vol. 15, no. 12, p. e0244448, 2020, doi: 10.1371/journal.pone.0244448.
16. H. M. Scott *et al.*, *AIDS,* Aug 20, 2019, doi: 10.1097/QAD.0000000000002347.
17. O. Nieto, R. A. Brooks, A. Landrian, A. Cabral, and A. E. Fehrenbacher, (in eng), *PLOS One,* vol. 15, no. 11, p. e0241340, 2020, doi: 10.1371/journal.pone.0241340.
18. Y. A. Huang, G. Tao, D. K. Smith, and K. W. Hoover, (in eng), *Clin Infect Dis,* vol. 72, no. 3, pp. 379-385, Feb 1, 2021, doi: 10.1093/cid/ciaa037.

19. P. S. Sullivan *et al.*, (in eng), *Annals of epidemiology,* vol. 28, no. 12, pp. 833-840, Dec 2018, doi: 10.1016/j.annepidem.2018.06.009.

20. Centers for Disease Control and Prevention. https://www.cdc.gov/std/statistics/2019/default.htm (accessed May 2023).

21. M. Tsuboi *et al.*, (in eng), *Lancet Glob Health,* vol. 9, no. 8, pp. e1110-e1118, Aug 2021, doi: 10.1016/S2214-109X(21)00221-7.

22. A. F. Luetkemeyer *et al.*, *New England Journal of Medicine,* vol. 388, no. 14, pp. 1296-1306, 2023, doi: 10.1056/NEJMoa2211934.

23. J. M. Molina *et al.*, (in eng), *The Lancet. Infectious diseases,* vol. 18, no. 3, pp. 308-317, Mar 2018, doi: 10.1016/s1473-3099(17)30725-9.

24. Jean-Michel Molina *et al.*, presented at the CROI, Seattle, Washington, US, February 19-22, 2023.

25. M. S. Torres Silva *et al.*, *Lancet HIV,* vol. 11, no. 10, pp. e670-e679, Oct 2024, doi: 10.1016/S2352-3018(24)00211-X.

26. A. L. Gray, J.A. Smit, N. Manzini, and M. Belesinka, "Systematic review of contraceptive medicines; "Does choice make a difference?"," South Africa, 2006.

27. Y. Giho *et al.*, (in eng), *Journal of American college health : J of ACH,* vol. 68, no. 4, pp. 336-340, May-Jun 2020, doi: 10.1080/07448481.2019.1577859.

28. G. M. Gressel *et al.*, (in eng), *Contraception,* vol. 90, no. 6, pp. 588-93, Dec 2014, doi: 10.1016/j.contraception.2014.07.010.

29. K. K. Antonishak J, Swiader L, *Social Marketing Quarterly,* 2015.

30. T. D. Seidman D, Celum C, et al., presented at the HIVR4P, Virtual, 2021.

31. R. T. Lester *et al.*, (in eng), *Lancet,* vol. 376, no. 9755, pp. 1838-45, Nov 27, 2010, doi: 10.1016/S0140-6736(10)61997-6.

32. C. Pop-Eleches *et al.*, *AIDS,* vol. 25, no. 6, pp. 825-34, Mar 27, 2011, doi: 10.1097/QAD.0b013e32834380c1.

33. J. E. Mayer and P. Fontelo, (in eng), *AIDS care,* vol. 29, no. 4, pp. 409-417, Apr 2017, doi: 10.1080/09540121.2016.1214674.

34. D. J. Finitsis, J. A. Pellowski, and B. T. Johnson, (in eng), *PLOS One,* vol. 9, no. 2, p. e88166, 2014, doi: 10.1371/journal.pone.0088166.

35. A. Y. Liu *et al.*, *Clin Infect Dis,* vol. 68, no. 12, pp. 2010-2017, May 30, 2019, doi: 10.1093/cid/ciy810.

36. L. Goldwirt *et al.*, (in eng), *J Antimicrob Chemother,* vol. 76, no. 10, pp. 2675-2680, Sep 15, 2021, doi: 10.1093/jac/dkab253.

37. M. E. Ibrahim *et al.*, (in eng), *AIDS Res Hum Retroviruses,* vol. 37, no. 6, pp. 421-428, Jun 2021, doi: 10.1089/aid.2020.0108.

38. A. Thomson, R. Hayes, and S. Cousens, *Statistics in medicine,* vol. 28, pp. 1739-51, May 30, 2009, doi: 10.1002/sim.3582.

39. C. A. Koss *et al.*, *AIDS Res Hum Retroviruses,* vol. 33, no. 8, pp. 778-783, Aug 2017, doi: 10.1089/aid.2016.0202.

40. Food and Drug Association. https://www.fda.gov/media/136238/download (accessed May 2023).

APPENDIX IA: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR ALL PARTICIPANTS

	Screening	Enrollment	Week 4	Week 20, 36	Week 52/Exit
Administrative and Behavioral Evaluations/Procedures					
Informed Consent	X				
Locator information	X	X[1]	X	X	X
Assess eligibility	X	X[1]			
Demographic information	X				
Social impact assessment			X	X	X
Behavioral assessment (questionnaire or CASI)	X	X	X	X	X
Provide 3P package information[1]		X	X	X	
Satisfaction with 3P assessment (CASI)[2]			X		X
PrEP and doxy-PEP adherence assessment			X	X	X
HIV/STI risk reduction counseling	X	X[1]	X	X	X
Offer condoms and other prevention supplies	X	X[1]	X	X	X
Randomization		X			
Clinical Evaluations/Procedures					
Complete medical history, including medications		X			
Abbreviated physical exam		X			
Interim medical history, including medications			X	X	X
Symptom-directed physical examination			(X)	(X)	(X)
AE assessment			X	X	X
HIV PrEP provision		X	X	X	X
Doxy-PEP provision		X	X	X	X
Blood collection[3]	X	X[1]	X	X	X
Swab collection		X	(X)	X	X
Urine collection		X	(X)	X	X
Hair collection[4]			X	X	X
Hepatitis vaccination or referral		(X)			
STI treatment		(X)	(X)	(X)	(X)
Linkage and navigation to PrEP services				X[5]	X
Laboratory Evaluations/Procedures					
HIV diagnostic testing (see Appendix II)	X	X	X	X	X
HIV RNA PCR testing		X	X[6]	X[6]	X[6]
Creatinine and calculated creatinine clearance		X			X[7]
Hepatitis B serology (HbsAg, HbsAb, HbcAb)		X			
STI testing: GC/CT NAAT (pharyngeal, rectal, urine)		X	(X)	X	X
Syphilis testing		X	(X)	X	X
DBS storage		X	X	X	X

	Screening	Enrollment	Week 4	Week 20, 36	Week 52/Exit
Plasma storage	X	X	X	X	X
Urine storage		X			X
Hair storage[4]					

(If clinically indicated)

[1] Required only if Screening and Enrollment occur on separate visits

[2]Participants assigned to intervention group only

[3] Blood may be collected by fingerstick for HIV rapid testing

[4]If participant consented to hair collection

[5] Planning for linkage and navigation to PrEP services should begin at Week 36

[6] HIV RNA testing should be performed for participants starting PrEP, resuming PrEP, or switching PrEP regimens (see Appendix II). It should also be performed if there is a concern for acute HIV infection.

[7] Participants using oral PrEP only

APPENDIX IB: SCHEDULE OF STUDY VISITS AND PROCEDURES FOR PARTICIPANTS ON CAB-LA

All participants will complete the visits in Appendix IA. Participants who elect to use CAB-LA will also complete procedures in Appendix IB at any visit with a CAB-LA injection. If the injection coincides with a standing visit in Appendix IA, then all procedures for the visit in Appendix IA should be completed in addition to the procedures in Appendix IB; duplicate procedures (e.g., locator information) need not be completed twice.

	First CAB injection	Second CAB injection	Subsequent CAB injections	Final CAB injection
Administrative and Behavioral Evaluations/Procedures				
Locator information	X	X	X	X
HIV/STI risk reduction counseling	X	X	X	X
Offer condoms and other prevention supplies	X	X	X	X
Clinical Evaluations/Procedures				
Interim medical history including medications	X	X	X	X
Symptom-directed physical examination	(X)	(X)	(X)	(X)
AE assessment	X	X	X	X
CAB-LA injection	X	X	X	X
Blood collection[1]	X	X	X	X
Laboratory Evaluations/Procedures				
HIV diagnostic testing (see Appendix II)	X	X	X	X
HIV RNA PCR	X[2]	(X)[2]	(X)[2]	(X)[2]
DBS storage	X	X	X	X
Plasma storage	X	X	X	X

(If clinically indicated)

[1] Blood may be collected by fingerstick for HIV rapid testing

[2] HIV RNA testing should be performed for participants starting PrEP, resuming PrEP, or switching PrEP regimens (see Appendix II). It should also be performed if there is a concern for acute HIV infection.

APPENDIX IC: SCHEDULE FOR HIV CONFIRMATION VISIT

The procedures listed for the HIV confirmation visit apply to participants who have a reactive or positive HIV test at any time during follow-up. This visit must occur on a different date than the date where the sample with the reactive/positive test was obtained.

	HIV Confirmation Visit(s)
Locator information	X
Offer condoms	X
HIV counseling	X
Referral to services for people living with HIV	X
Medical history, including medications	X
Physical exam	X
Blood collection[1]	X
Swab collection	X
STI treatment	(X)
Lab-based HIV Ag/Ab test with reflexive confirmatory testing	X
HIV RNA PCR	X
HIV resistance testing[2]	X
Plasma storage	X
DBS storage	X
STI testing: GC/CT NAAT (pharyngeal, rectal, urine)	X[3]
STI testing: syphilis	X[3]

(If clinically indicated)

[1] Blood collected by fingerstick may be used for HIV rapid testing

[2] Resistance testing should only be performed if HIV infection is confirmed; sites will collect specimens for resistance testing at a local laboratory to assist with clinical management; results from resistance testing performed at local laboratories will not be reported to the SDMC. Stored plasma will not be used for real-time/local resistance testing.

[3] Testing will be done if it has been 4 or more weeks from last STI testing (GC/CT NAAT, syphilis).

APPENDIX II: HIV TESTING ALGORITHMS

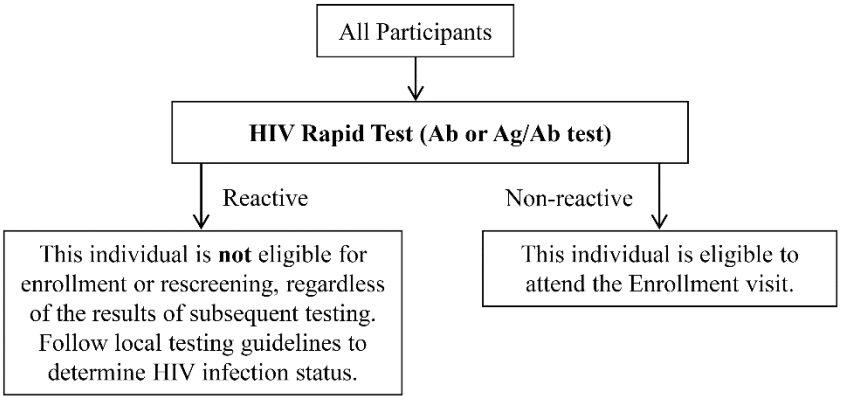
NOTES

Site testing plan: Site-specific HIV testing plans including all test kits used must be approved by the HPTN LC before the study opens.

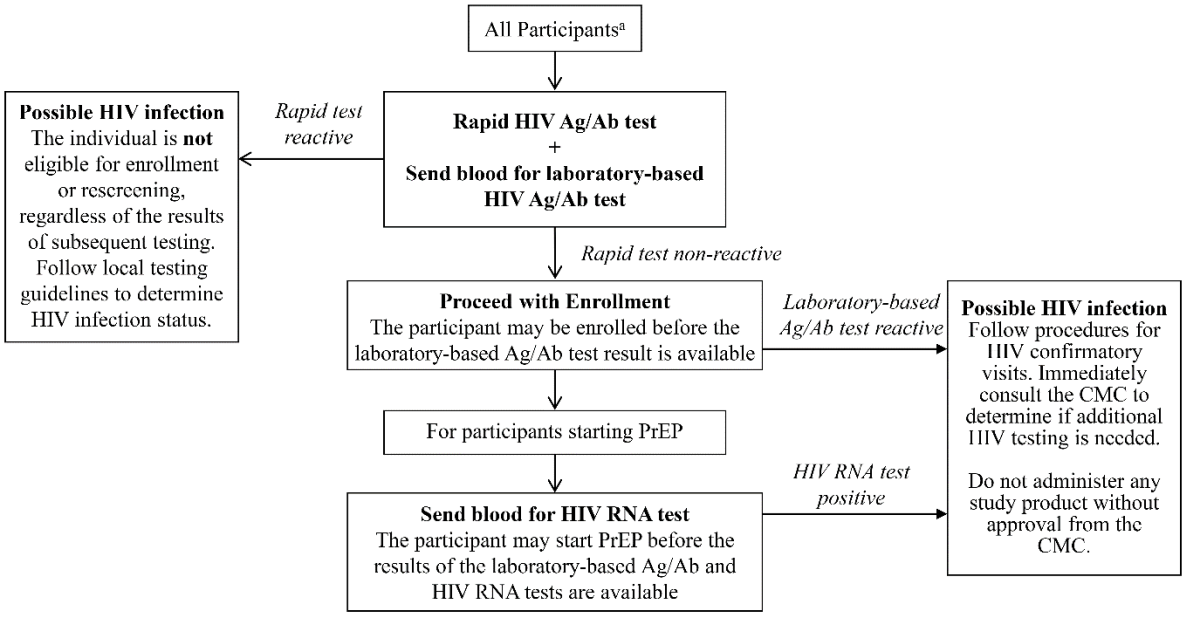
HIV RNA testing: HIV RNA testing must be performed using an assay with a lower limit of quantification of 50 copies/mL or less. If possible, this testing should be performed using a test that is approved by the US FDA for detection of acute HIV infection.

If any HIV test on or after Enrollment is reactive/positive, do not administer oral PrEP or CAB-LA. In those cases, immediately consult the Clinical Management Committee (CMC). Follow local testing guidelines and consult the CMC to determine HIV infection status. Do not administer any further study product without approval from the CMC.

HIV Testing Algorithm at <u>Screening</u> (if Enrollment is performed on a different date)

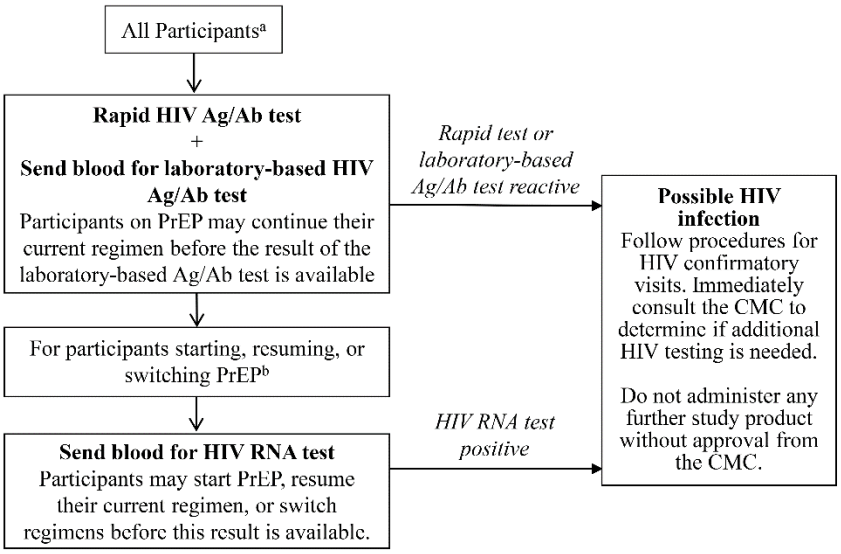


HIV Testing Algorithm at <u>Enrollment</u> (with or without same-day Screening)



[a] If acute HIV infection is suspected, an HIV RNA test should be performed in addition to the testing indicated above. In these cases, enrollment should be deferred until all test results are available for review.

HIV Testing Algorithm at Follow-Up



[a] If acute HIV infection is suspected, an HIV RNA test should be performed in addition to the testing indicated above. In these cases, study product administration should be deferred until all test results from this visit are available for review.
[b] An HIV RNA test is required for: (1) participants starting oral PrEP or CAB-LA, (2) participants resuming oral PrEP after >14 days or resuming CAB-LA after >6 months, and (3) participants switching PrEP from oral PrEP to CAB-LA or from CAB-LA to oral PrEP.

Appendix III: Sample Informed Consent Form

HPTN 113
Duo: A Phase IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men

Final Version 2.0
30 May 2025
DAIDS Document ID: 39073

Sponsored by: Division of AIDS, US National Institute of Allergy and Infectious Diseases, US National Institutes of Health. Study products are provided by Gilead Sciences and ViiV Healthcare.

SITE NAME: [Insert CRS name]

PRINCIPAL INVESTIGATOR: [Insert Name]

PHONE: [Insert Number]

ADDRESS: [insert CRS address]

INTRODUCTION

We are asking you to take part in a research study. Joining this study is voluntary. You may refuse to join, or you may join and change your mind and decide you do not want to be in the study, for any reason, at any time. This research study is for men, 18 – 29 years old, who have anal sex with a man who may be at risk of being exposed to the Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decide whether to join the study, we would like to explain the purpose of the study, the risks and benefits to you, and what is expected of you.

1. You should know key information about this study before you join.

Here is a summary of important information about the study:

- This is a research study.
- Your participation in this study is voluntary. You can decide not to be in this study or change your mind about participating at any time.
- We are trying to learn if mobile apps and tools can help men make choices about HIV prevention methods. We also want to see if these tools help men take HIV pre-exposure prophylaxis (PrEP) as instructed. PrEP is a medicine taken to prevent HIV.

- In this study, all participants will be given a choice of PrEP types – oral pills or an injection (shot/jab). You can choose to use any PrEP option or not use PrEP.
- You will be offered a medication called doxycycline to take after sex. Studies have shown taking this medicine after sex can reduce the risk of getting certain sexually transmitted infections (STIs).
- Participants in the study will be randomly placed into one of two groups. In group A, participants will be provided with 3 mobile health tools and a handout about PrEP. These mobile tools will provide information about the different PrEP options and how to take the medication as directed. In group B, participants will be given standard medical counseling and a handout with information about PrEP.
- This study has 4 standing visits after today. If you are eligible and want to participate, then you will have your first visit now. After today, you will have visits in 4, 20, 36, and 52 weeks. If you decide to take injectable PrEP (injection/shot/jab), you will be asked to come to the clinic more often to get your injections. Injections must be given every 8 weeks after the first two injections are given 4 weeks apart. The study staff will give you more information about the additional visits and when these occur.
- At each study visit, we will ask you questions about your medical history and sexual behaviors. We will ask your permission to collect blood, urine, hair, and swabs for HIV and STI testing. We'll tell you more about these procedures.
- There are some risks to you if you decide to participate in the study. You may be uncomfortable answering questions or having HIV/STI testing. We will do our best to protect your information, but it is possible other people may learn of your participation in the study. All medications given in this study have some side effects. We will tell you about these side effects and what to expect. There might be unknown risks.
- There may be no direct benefit to you if you participate in the study. However, you may benefit from HIV and STI testing, PrEP, and the information you learn about HIV prevention.
- If you decide not to participate in this study, you may receive HIV/STI testing, or HIV prevention services at other places like your local health clinic.

More information is given in this form about the study. You should feel that you understand the study before deciding if you would like to participate.

ABOUT THE STUDY

The HIV Prevention Trials Network (HPTN) and [*insert site name*] are doing this study to see if a set of mobile apps and tools help men make choices about HIV prevention methods. We also want to see if these tools help people keep taking their HIV prevention medication (HIV PrEP). PrEP is medicine that reduces your chance of getting HIV. PrEP works very well when it is taken as prescribed, meaning as it is instructed to be taken by a physician. We also want to learn who would like to take doxycycline (an antibiotic) which helps to prevent bacterial sexually transmitted diseases, and how they take it.

About 400 young men from communities most impacted by the epidemic will participate in this study. Participants will be in the study for up to one year.

2. This study offers HIV PrEP and STI prevention medication to participants. The study is testing a set of mobile health tools to see if it can help people make choices about HIV prevention.

Young men have a higher chance of getting HIV than other people. PrEP is a medicine people can take to help prevent HIV. There are several types of PrEP. There are oral pills taken daily or 'on-demand' taken when you have sex. There are two drug options for the oral pill – Truvada (F/TDF) and Descovy (F/TAF There is also an injectable PrEP (shot/jab) that a clinician gives about 8 weeks apart. The injectable PrEP is called *CAB LA*.

The US Food and Drug Administration (FDA) has approved the oral pills to prevent HIV when taken once every day. The FDA has also approved the injectable PrEP. The FDA is the regulatory group that oversees the approval of all drugs in the US. "On demand" PrEP is a different way to take the oral pills. "On demand" PrEP has worked well to prevent HIV in research studies, but the FDA has not approved taking PrEP pills "on-demand". Taking the pills "on-demand" means you take two pills 2-24 hours before sex, one pill 24 hours after the first pill, and one more pill 24 hours after the second pill (2-1-1 PrEP). Studies showed that taking 'on demand" (2-1-1) PrEP worked just as well to prevent HIV as taking the pill once every day. Many doctors give "on demand" (2-1-1) PrEP to their patients. The FDA has also approved the PrEP injection called CAB. The first two injections must be given 4 weeks apart. After the second injection, the injections are given every 8 weeks. Even with several choices of PrEP, many people do not take PrEP, even if it could help them. In this study, participants will be able to choose what type of PrEP they would like to take. Participants may also choose not to take PrEP, stop at any time during the study, or change to a different type of PrEP.

Sexually transmitted infections (STIs) are increasing worldwide, and especially among young men. Studies have shown that taking the medication doxycycline after sex helps prevent some STIs. Doxycycline is an antibiotic. The STIs it can help prevent are caused by bacteria (like chlamydia, syphilis, and gonorrhea). This way of taking doxycycline to prevent STIs is called "doxy-PEP". Doxy-PEP must be taken as soon as possible, but up to 72 hours after sex. The studies also show that doxycycline taken this way led to few side effects. The FDA has approved doxycycline for other uses but has not approved it for the prevention of STIs. In this study, participants will be offered doxycycline "off-label" for STI prevention (or "doxy-PEP"). "Off-label" means using a medicine for something different from what the FDA originally approved. The "off-label" use of doxy-PEP has been endorsed by the US Centers for Disease Control and Prevention (CDC) to prevent bacterial STIs in young men with a history of bacterial STI. Participants may choose not to take doxycycline or stop at any time during the study.

Even with more options for PrEP, it can be hard to start and stay on PrEP to prevent HIV. We want to know if using a set of mobile health tools could help make choices about starting PrEP. We also want to know if these tools help make it easier to take the PrEP medication as instructed, to prevent HIV.

3. Participants will be placed into one of two groups.

If you decide to be in the study, you will be placed into 1 of 2 study groups. You will be randomly assigned to a group. Random means that you will not choose your group and study staff will not choose your group. It is like flipping a coin or rolling dice. Each group will have approximately 200 participants in it. Here at [*site name*], X [*site to add number of participants expected in each group*] participants will be in each group.

All participants in each group will be offered their choice of HIV PrEP and doxycycline for STI prevention. Participants will also be given handouts about PrEP and doxy-PEP.

If you are assigned to Group A, you will be offered three different mobile tools to use while you are in the study:

- **MyPREP** is a web-based site that provides information about the different HIV PrEP options.
- **PrEPmate** is an SMS platform or app that allows you to have periodic check-ins with study staff to check on your PrEP use. You will be able to ask study staff questions about PrEP between study visits. PrEPmate will also send reminders to take your PrEP medication.
- **PrEPsmart** is a mobile app that allows you to track "on demand" (2-1-1) PrEP use and sex. The app can remind you to take your PrEP. It also shows if you are protected from HIV, depending on when you have taken your PrEP.

If you are assigned to Group B, you will be offered standard of care counseling and the handouts about PrEP and doxyPEP while you are in the study.

All participants will be able to contact study staff if you have questions between visits or decide to begin, change, or stop PrEP use.

JOINING THE STUDY

4. It is your decision if you would like to participate in the study.

This consent form gives information about the study that will be discussed with you. We will help you understand the form and answer your questions before you sign this form. Once you understand the study, and if you agree to take part in it, you will be asked to sign your name on this form. You will be offered a copy of this form to keep.

Before you learn about the study, it is important that you know the following:

- Your participation is voluntary. You do not have to take part in any of the tests or procedures in the study.
- You may decide not to take part in the study, or you may decide to leave the study at any time without losing your regular medical care.
- If you decide not to take part in the study, you can still join another study at another time if there is one available and you qualify.

- You cannot join 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.

5. You must qualify before you can join the study.

If you decide to join this study, we will first do some tests and collect some information from you to find out if you qualify and are able to be a part of the study. These tests and the information collected are described in #6 below. If you qualify, you will be entered into the study. If you do not qualify, you cannot be entered into the study.

6. We will ask you questions, examine you, and test your blood.

To find out if you qualify, we will first conduct a "Screening Visit." Your Screening Visit will happen after you read, discuss, understand, and sign this form. The Screening visit will take about X hours [*sites to fill in the amount of time*].

At the Screening Visit, we will:

- Ask you questions about yourself, like your age and brief medical history
- Ask you to answer questions about your sexual behaviors, history of sexually transmitted infections (STIs), and recent drug use
- Ask about where you live and how to contact you
- Talk with you about HIV and ways to protect yourself from getting it. We will also offer you condoms.
- Collect ~XX [*site to enter site-specific amount*] mL (about 2 teaspoons) of blood for HIV testing

The results of HIV testing will be available [*site to insert timeframe of testing*]. Samples will be collected at the time of Screening for possible future testing.

7. We will confirm if you qualify for the study.

Once all the results of the screening tests are known, the following will happen:

- You will be told your test results and what they mean.
- If you have a positive HIV test you will not be eligible for the study. We will refer you for the medical care you need. *(sites to add specifics about this here as necessary)*
- We will give you referrals for other health services if you need them.

8. If you qualify, you will enter the study.

If you are eligible for this study based on the tests mentioned above and decide to be a part of the study, you will be asked to continue with today's visit for an "Enrollment Visit." If you cannot continue with the visit today, you may come back to the clinic on another day to finish the Enrollment visit. We ask that you come for Enrollment within 45 days. This visit will last about

X hours [*sites to fill in the amount of time*]. If you are not able to complete the Enrollment visit within 45 days from today, and you are still interested in taking part in this study, you can return to the clinic to conduct the screening procedures again.

During the Enrollment Visit, we will:

- Confirm the information you already told us during your eligibility assessment
- Ask you to answer questions on a computer or tablet about your sexual practices
- Talk with you about HIV and ways to protect yourself from getting it. We will offer you condoms.
- Give you a physical exam, to include measuring your height, weight, temperature, blood pressure, and ask you about any other medicines you are taking.
- Collect *[~XX Sites to include site-specific amounts*] mL (about x teaspoons) of blood for HIV, Hepatitis B, and syphilis testing. The HIV test may be done using a fingerstick. We will also use some blood to test how well your kidneys work. This is called creatinine testing. We will also store some blood for study-related testing.
- Collect urine, a swab from your throat, and a swab from your rectum for gonorrhea and chlamydia testing. Study staff will collect the swab from your throat. You can decide if you want to collect the swab from your rectum or if you would like study staff to collect the rectal swab. Some urine will be stored for study-related testing.
- Randomly place you into 1 of the 2 study groups.
- Talk with you about your options for HIV PrEP. If you are in Group A that will use the mobile health tools, we will review the tools together. You will be able to ask questions about the tools and how to use them.
- If you decide to take oral pills for HIV PrEP, we will give you the pills, explain how to take them, and any side effects they may cause.
- If you decide to take injectable CAB for HIV PrEP, we will give you the injection, explain any side effects it may cause, and give you details on when to return for your next injections.
- Talk with you about doxycycline for STI prevention (doxy-PEP). If you choose to use doxycycline, we will give you the pills, explain how to take them, and any side effects they may cause.
- Provide treatment if you have symptoms of an STI
- Give you the results of tests when they are available. [S*ites to add specifics about this here as necessary*] If you test positive for gonorrhea, chlamydia, or syphilis, you will be provided treatment or given a referral. Depending on the results of your hepatitis B test, we will refer you for hepatitis B treatment or vaccination *[site to update if vaccination is available on-site]*.

BEING IN THE STUDY

9. You will have at least 4 visits over one year. You may have more visits if you choose to start CAB injections for HIV PrEP.

If you decide to join the study, after your Enrollment Visit, you will be asked to come to this clinic approximately 4 times over the course of one year. If you choose injectable PrEP, you will have additional visits. The timing of the visits depends on when you have your first injection. The site staff will provide specific information about these visits. It's very important that you receive the injections as instructed by the study staff.

Each visit will last about X hours [*site staff to insert amount of time*].

At all follow-up visits after Enrollment (Week 4, 20, 36, and 52), we will:

- Confirm where you live and how to contact you.
- Ask you questions about yourself, like your use of HIV prevention methods, updates to your medical history, and if you are taking any new medication.
- Ask you to answer questions on a computer about your sexual practices, thoughts about PrEP and about taking doxycycline to prevent sexually transmitted infections.
- Talk with you about HIV and ways to protect yourself from getting it. We will also offer you condoms.
- Ask you about any social impacts you have experienced because you are in the study.
- If you report any medical concerns, we will give you a brief physical exam.
- Collect ~*XX* [*sites to include site-specific amounts*] mL (about *X* teaspoons) of blood for HIV testing. The HIV test may be done using a fingerstick. We will also store some blood for study-related testing.
- Collect ~ 4-6 strands of hair, plucking strands of hair from the back of your head with tweezers, so that we can look at medication in the hair root. The sample will be chosen from a discrete location and be hidden as much as possible. Hair samples will only be collected if you have sufficient hair (1.0cm) for collection.
- Talk with you about HIV PrEP. You may start, stop, or switch PrEP types at these visits. We will ask you how you have taken your PrEP and if you had any side effects.
- If you decide to take oral pills for HIV PrEP, we will give you the pills, explain how to take them, and any side effects they may cause.
- If you decide to take injectable CAB for HIV PrEP, we will give you the injection and explain any side effects it may cause.
- Review the mobile health tools if you are in Group A. At some visits we will ask about your experience using them.
- Talk with you about doxycycline for STI prevention. If you choose to use doxycycline, we will give you the pills, explain how to take them, and any side effects they may cause. We will ask you how you have taken doxycycline for STI prevention.
- Provide treatment if you have symptoms of an STI

At the Weeks 20, 36, and 52 visits, we will also:

- Use some of the blood collected for HIV testing and to test for syphilis.
- Collect urine, a swab from your throat, and a swab from your rectum for gonorrhea and chlamydia testing. Study staff will collect the swab from your throat. You can decide if you want to collect the swab from your rectum or if you would like study staff to collect the rectal swab.

You will be contacted about the results of your other tests when they are available. If you test positive for gonorrhea, chlamydia, or syphilis, you will be provided treatment or given a referral [*sites to add specifics about this here as necessary*].

You may have more visits if you feel sick or we need to check on your health. You may also have more study visits if you feel you need to be seen for HIV or STI symptoms, medication side effects, or refills on your medication.

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. We will also talk with you about a plan to make sure you have a way to continue getting HIV PrEP and doxycycline for STI prevention.

10. If you decide to use CAB for HIV PrEP, you will have extra study visits.

CAB injections must be given on a specific schedule. If you decide to start CAB, you will have one injection followed by a second injection after 4 weeks. After these first two injections, you will have an injection every 8 weeks.

If you start CAB at your Enrollment visit, you will have all of your regular study visits, plus extra visits at weeks 12, 28, and 44. If you decide that you want to start CAB at a different time in the study, the study staff will arrange the extra visits to follow the required injection schedule.

When you come for a CAB injection visit, study staff will:

- Ask you questions about yourself, like your use of HIV prevention methods, updates to your medical history, and if you are taking any new medication.
- Talk with you about HIV and ways to protect yourself from getting it. We will also offer you condoms.
- If you report any medical concerns, we will give you a brief physical exam and complete STI testing if needed.
- Collect ~XX [*sites to enter site-specific amounts*] mL (about x teaspoons) of blood for HIV testing. We will also store some blood for study-related testing.
- Provide treatment if you have symptoms of an STI

11. If you decide to or have to stop taking your HIV PrEP or doxyPEP, we will ask you to stay in the study.

If you permanently stop taking the study drugs 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 complete certain procedures, like answering questions about taking the medication.

In some instances, you may have PrEP or doxy-PEP withheld by a study clinician for medical reasons. We will fully explain to you what will happen if you permanently stop taking your study drugs.

12. 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 the HIV PrEP drugs, and we will help you find the care and support you need. We will test your blood for HIV drug resistance. We will ask you to come back for your regular study visits. We will examine you and ask you about any medications you are taking. We will also update your contact information and provide you with condoms. If you get HIV, you can keep taking doxy-PEP.

13. We may ask you to participate in a long discussion about the study

Some participants will be asked to come for an interview with study staff. We will ask about 48 participants in the study, and [*site to enter # at site*] at this site, to have an interview. At the interview we will ask:

- How you feel about HIV PrEP, doxy-PEP, and other HIV prevention tools
- About your relationships, sexual partners, and sexual behaviors
- If you are in Group A, we will ask you about the mobile health tools and your experience with them.

The interviews require one or two visits (Weeks 20 and 52) and will last around 1 – 1.5 hours. Interviews will be audio-recorded. The audio recordings will be destroyed once primary qualitative analyses are complete [*site to enter if there is a specific requirement for amount of time audio recordings can be kept*].

14. Use of stored specimens.

Samples stored in the study may be used for study-related testing that includes testing related to HIV, STIs, and testing for antiretroviral drugs. If you are living with HIV or get HIV during the study, stored samples may also be used to learn more about HIV viruses, the body's response to HIV, and how HIV is spread in the community. Results from this testing will be used for research only and will not be returned to you or the study sites. Stored specimens (urine, blood) may also be used for future studies related to sexually transmitted infections or doxycycline.

15. Some of your specimens may be left over at the end of the study and may be used for future research. [*site-specific edits may be required*]

Some of your blood and urine may remain in storage after all study-related testing has been completed. If you agree, your stored samples may also be used for future research related to HIV, hepatitis, and other infections passed through sex, and to better understand laboratory tests related to this study.

You will be asked to sign at the end of this consent form to give permission to use your stored samples for future research. Even if you do not give permission to store your blood and urine samples for possible future research, you can still be in this study. If you give permission, you will not be asked to give permission again during the study. However, you may withdraw your consent to use your stored samples for future research at any time. We will then destroy your samples after all of the study-related testing has been completed. If you agree to have your stored samples used for future research, there is no time limit on how long your samples will be stored. The stored samples will be labeled only with your study number and will be tested at special laboratory facilities that may be located in the US. The laboratory doing the testing will not know who you are. Only approved researchers will have access to your samples. Results from this 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. All proposed research studies using your samples will be reviewed by the National Institutes of Health (NIH).

RISKS OF THE STUDY

16. There may be risks to being in this study.

STUDY PROCEDURES

Taking blood samples may cause some pain, bruise your arm, or make you feel lightheaded. In rare cases you may faint. There is also a slight chance of infection when blood is drawn. You may experience pain or discomfort in your throat or rectum when we collect a swab. In some cases, swab collection may cause minor bleeding.

You may be nervous while you are waiting for your HIV or STI test results. If the tests show that you have HIV or an STI, you may worry about your health and future. You will receive counseling before and after the test to help address your concerns. You may feel embarrassed, worried, or anxious when receiving HIV/STI counseling. [*Sites to insert reporting responsibilities in the state the site is located in. Also, include whether if a participant tests positive, the results will become part of public health records, or any other record (medical file, etc.)*]

You may also have some anxiety or worry about providing a hair sample. The study staff will use a method to take hair samples that makes hair removal less noticeable. This method has worked well in other studies. You can say no to having hair samples taken at any time.

DISCLOSURE OF PERSONAL INFORMATION

We will make every effort to protect your confidentiality during the study. However, it is possible that others may learn that you are part of this study and they may think that you are living with HIV or are at increased likelihood of getting HIV. Because of this you could have trouble finding or keeping a job. You could also have problems with your family, friends, and community. We can tell you more about how we will protect your information.

It is also possible that your PrEP and/or doxy-PEP use may be discovered by family/friends/community members outside of the study clinic. If you are in Group A and use the mobile health tools, it is possible other people who have access to your phone may see your information. You can use password protection on your phone to limit access to your phone. The PrEPsmart app will be password-protected to protect your privacy. The PrEPmate SMS messages will not be password protected and will be received directly to your phone. We ask that you do not share your phone with others during your participation in the study to minimize the risk of other people accessing your information. If you use the MyPrEP webpage, it is also possible people who share a computer or internet access may know you looked at the page. If you take a PrEP or doxy-PEP handout with you, other people may see the handout. Because of this, you could be treated unfairly or discriminated against, experience stigma, or have problems being accepted by their families or communities. You should report any concerns about your privacy or safety to the study staff immediately.

SENSITIVE QUESTIONS

The questions we will ask you about your sexual behavior may make you feel uneasy or embarrassed. However, you do not have to answer any question that you do not want to and you can stop answering the questions at any time. Trained study staff will be available to help you with these feelings.

SIDE EFFECTS OF THE STUDY DRUG

The drugs used in this study may have side effects, some of which are listed below. Please note that these lists do not include all the side effects seen with these drugs. These lists include the more serious or common side effects with a known or possible relationship. If you have questions concerning the additional study drug side effects, please ask the medical staff at your site. If you get HIV during the study, you will be asked to stop taking your HIV PrEP. If you continue to take PrEP after you get HIV, there is a chance that drug resistance may occur. Drug resistance means some HIV medications may not work well to treat your HIV.

Truvada (F/TDF):

The following side effects have been commonly associated with the use of F/TDF:

- Gastrointestinal distress (e.g., nausea, abdominal pain, diarrhea, or vomiting). These symptoms are most common the first month of use and typically resolve.

- Headaches, dizziness, tiredness, or inability to sleep.

Rare but serious side effects include:
- Rash
- Worsening or new kidney damage
- Bone pain or bone changes, such as thinning/softening
- Allergic reaction
- Lactic acidosis, which can cause shortness of breath, nausea, and liver failure.
- Individuals with chronic hepatitis B infection who suddenly stop taking F/TDF may experience a "flare" or worsening of hepatic symptoms.

Descovy (F/TAF):

The most common side effect of F/TAF is nausea.

Rare but serious side effects include:
- Worsening or new kidney damage
- Lactic acidosis, which can cause shortness of breath, nausea, and liver failure.
- Individuals with chronic hepatitis B infection who suddenly stop taking F/TAF may experience a "flare" or worsening of hepatic symptoms.

Cabotegravir (CAB):

The following side effects have been commonly associated with the use of CAB-LA:
- Injection site pain, swelling, irritation, redness, itching or bruising
- Gastrointestinal distress (e.g. nausea, diarrhea, vomiting, stomach pain)
- Runny nose or sore throat
- Headache
- Fever
- Lack of energy
- Rash or itching
- Abnormal liver tests
- Depression, including suicidal ideation or suicide attempt

Rare but serious side effects include:
- Allergic reaction
- A serious, painful, and potentially fatal skin reaction (e.g., Stevens-Johnson Syndrome or toxic epidermal necrolysis)

Depression or suicidal behavior while using CAB is more likely to happen if you have a history of depression or other psychiatric illnesses. Please seek immediate medical help if you are having thoughts of harming yourself [*site to enter site-specific contacts or additional details for care as appropriate]*.

Cabotegravir can stay in the body for a long time after the last injection. We do not know exactly how long the drug stays in your body, but it could be up to 12 months or longer. During this time, called the "tail period", the levels are not high enough to protect you from HIV. If you get HIV during this "tail period" you may develop HIV drug resistance. Drug resistance means some HIV medications may not work well to treat your HIV. You should continue to use other effective HIV prevention methods during this "tail period". We will help you learn about your other prevention options (e.g., oral PrEP) during this "tail period".

Doxycycline:

The following side effects have been commonly associated with the use of doxycycline:

- Headaches
- Gastrointestinal distress (e.g. nausea, vomiting)
- Skin sensitivity to sunlight

Rare but serious side effects include:

- Allergic reaction
- Changes in vision or ringing in the ears, also known as intracranial hypertension
- Esophageal ulceration

We do not know if there may be other risks when taking doxycycline for STI prevention. It is possible that using doxycycline for STI prevention may increase the risk that bacteria in your body may become resistant to antibiotics. You should not take more than one dose (200mg) within a 24-hour period.

SOCIAL

There may also be some social risks to participating in this study. You may feel embarrassed or uncomfortable with some of the questions you will be asked, some of the procedures that will be done, or some of the test results that you will receive. You may also experience stigma as a result of being involved in a study about HIV because if people find out you are a part of the study, they may assume that you are living with HIV. Family or friends may worry, get upset or angry, or assume that you are living with HIV or that there is a high likelihood of you getting HIV and treat you unfairly as a result.

HIV DIAGNOSIS

If you decide to take PrEP and then get HIV, there is a risk that the HIV you have could be resistant to some of the medication used to treat HIV. This means that certain HIV medications may not work as well to treat your HIV. The best way to prevent HIV is to take your PrEP exactly as directed.

In this study we will test you for HIV at every study visit. If you are taking oral PrEP, this means you will have HIV testing every 4 months. Usually when someone is taking oral PrEP, it is advised to test for HIV every 3 months. We do not know if testing less often impacts HIV drug resistance in people who get HIV while taking oral PrEP. [*as applicable*, *based* on *site PrEP*

options] If you are using CAB-LA, it can be difficult to detect HIV with the tests usually used in health clinics. For months after you stop using CAB-LA, it still may be difficult to detect HIV. It is important to continue with regular testing and HIV prevention practices to reduce the chances of getting HIV.

OTHER RISKS

We do not know if there are other risks if you participate in this study. You should report any problems to the researchers immediately.

BENEFITS OF THE STUDY

17. There may be no direct benefit to you by participating in the study.

There may be no direct benefit to you from being in the study. However, being in the study may still help you in some ways. We will test you for HIV and other sexually transmitted infections throughout this study. The counseling you get during this study may help you to avoid HIV and other sexually transmitted infections. If you get HIV, this counseling may help you to learn how to better care for yourself and avoid passing HIV to others. If you get HIV, or have another sexually transmitted infection, we will refer you for care and/or treatment. At the Enrollment visit we will also check if you have hepatitis B infection. If needed, we will *[as applicable per site options]* refer you for hepatitis B vaccination or provide it on-site. During the study you will have tests to check on the health of your kidneys. If any health problems are found, you will be referred for care. At every visit you will receive condoms free of charge.

You may choose to receive PrEP for HIV prevention, which is known to protect against HIV if taken as directed. You may also choose to receive doxy-PEP for STI prevention, which is an off-label use of a marketed drug and has been shown in some studies to reduce the chance of getting certain sexually transmitted infections.

You may not receive any other direct benefit from being in this study; however, you or others in your community may benefit from this study later. The information gathered during this study may help to prevent HIV and other infections. This may be beneficial to you and your community.

OTHER INFORMATION ABOUT THE STUDY

18. We will tell you any new information that may affect your decision to be in 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 mobile health tools work very well or do not work very well, 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.

19. You may be withdrawn from the study without your consent.

We may take you out of the study at any time without your consent. This may happen if:

- You are unable or unwilling to follow the study procedures or instructions.
- You could be harmed by continuing to take study medication.
- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to you.
- You are not able to attend clinic visits or complete all of the study procedures.
- Other reasons, as decided by the study staff.
- If we take you out of the study, we may ask you to come back to the clinic one last time to check your blood, examine you, and ask you questions.

20. You have other choices if you choose not to be in this study.

There may be other studies going on here or in the community that you may be able to be a part of. If you wish, we will tell you about other studies that we know about. There also may be other places where you can go for HIV counseling, testing, and to receive PrEP. We will tell you about those places if you wish.

21. There is no cost to you to be in this study.

There will be no cost to you for study related visits, study products, physical examinations, laboratory tests, or other procedures.

22. We will give you [*site to insert amount*] for each study visit.

You will receive [$*xx*] for your time, effort, and travel to and from the clinic at each scheduled visit. [*Sites to insert information about local reimbursement for the study*.]

23. We will do our best to protect your private information.

Every effort will be made to keep your personal information confidential, but we cannot guarantee absolute confidentiality. To keep your information private, your personal information and samples will be labeled with a code number. The coded information can only be traced back to your study clinic. Your name, where you live, and other personal information will be stored separately, and protected by the study clinic. Without personal identifiers, your coded information could be used for future research studies or distributed to another investigator for future studies without obtaining additional informed consent.

The results of any tests done on these samples will not be included in your health records. Personal information from your study records will not be released without your written permission. If you report a serious or unexpected social impact related to the study, we may need to report this to the [IRB] or other regulatory groups as required. 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 [*insert name(s) of site local and/or national Institutional Review Board (IRB) or Ethics Committee*]
- 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)
- The US Food and Drug Administration (FDA)
- Other local, US, or international regulatory authorities/entities
- The HPTN that is conducting this study
- The companies that make the drugs used in this study (Gilead Sciences, Viiv Healthcare)
- And (*insert any other applicable local authorities*]

In addition to the efforts made by the study staff to help keep your personal information confidential, we have obtained a Certificate of Confidentiality from the US Federal Government. This Certificate protects researchers from being forced to tell people who are not connected with this study, such as the court system, about your participation. The Certificate of Confidentiality does not prevent you from releasing information about yourself and your participation in the study. The Certificate cannot be used to resist a demand for information from personnel of the US Government that is used for auditing or evaluation of federally funded projects or for information that must be disclosed in order to meet the requirements of the US FDA. Even with the Certificate of Confidentiality, if the study staff learns of possible child abuse and/or neglect or a risk of harm to you or others, we will tell the proper authorities.

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 [*site name*] and studies conducted by other researchers that study staff know about.

[*Sites to include/amend the following if applicable:] [Local/state/national]* regulations require study staff to report the names of people who get *[HIV and other infections]* passed during sex 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 contact them, according to the confidentiality guidelines of the [*health authority*].

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. 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.

24. If you get sick or injured during the study, contact us immediately.

[*Sites to specify institutional policy:]* It is unlikely that you will be injured as a result of study participation. If you are injured, the [*institution*] will give you immediate necessary treatment for your injuries. You [*will/will not*] have to pay for this treatment. You will be told where you can

get additional treatment for your injuries. [*Must include the following*:] 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.

25. Contact us at any time if you have questions or problems.

If you ever have any questions about the study, or if you have a research-related injury, you should contact [*insert name of the investigator or other study staff] at [insert telephone number and/or physical address*].

If you have questions about your rights as a research participant, you should contact [*insert name or title of person on the IRB or other organization appropriate for the site*] at [*insert physical address and telephone number*].

[*or insert the following information if using Advarra as the sIRB*

By mail:
Study Subject Adviser
Advarra IRB
6100 Merriweather Drive
Suite 600
Columbia, Maryland 21044
or call toll free: 877-992-4724
or by email: adviser@advarra.com

Please reference the following number when contacting the Study Subject Adviser: (insert PRO number).]

If you have questions about who to contact at the research site, you should contact [*insert name of the investigator or community educator or Community Advisory Board member*] at [*insert physical address and telephone number].*

SIGNATURE PAGE

HPTN 113
Duo: A Phase IIIb Individual-Level Randomized Controlled Trial of an Integrated Strategy of HIV PrEP and STI PEP for Young Men

Final Version 2.0
30 May 2025

Informed Consent Form

[*Insert signature blocks as required by the local IRB:]* If you have read this consent form, or had it read and explained to you, and you understand the information, and you voluntarily agree to join the study, please sign your name below. Also, please indicate by providing your initials in the spaces below if you agree to long-term storage of your blood and urine for future research or to participate in an interview.

____ I agree to take part in this study.

____ I agree to have samples of my blood and urine stored and used for future testing related to HIV.

____ I do not agree to have samples of my blood and urine stored and used for future testing related to HIV.

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

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

____ I agree to hair collection.

____ I do not agree to hair collection.

_____	_____
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