HPTN 091

Integrating HIV Prevention, Gender-Affirmative Medical Care, and Peer Health Navigation for Transgender Women in the Americas: A Vanguard Study

DAIDS Document ID: 38695

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)

Support Provided by:
Gilead Sciences, Inc

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Final Version 1.0
13 April 2020

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

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

_____ _____
Name of Investigator of Record (print name) Date (DD/MONTH/YYYY)

_____
Signature of Investigator of Record

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LIST OF ABBREVIATIONS AND ACRONYMS

AE	Adverse Event
ACASI	Audio Computer-Assisted Self Interview
AIDS	Acquired immunodeficiency syndrome
ALT	Alanine aminotransferase
ART	Antiretroviral therapy
AST	Aspartate transaminase
ARV	Antiretroviral
AUC	Area under curve
BUN	Blood-urea nitrogen
CAB	Community Advisory Board
CBC	Complete blood count
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGM	Cisgender men
CI	Confidence intervals
CLIA	Clinical Laboratory Improvement Act of 1988
Cmax	Maximum plasma concentration that a drug achieves after dosing
CMC	Clinical Management Committee
CPQA	Clinical Pharmacology Quality Assurance
CRM	Clinical Research Manager
CRPMC	(DAIDS) Clinical Research Products Management Center
CRS	Clinical Research Site
CT	*Chlamydia trachomatis*
CTA	Clinical trials agreement
DAERS	DAIDS Adverse Experience Reporting System
DAIDS	Division of AIDS
DBS	Dried blood spot
DHHS	US Department of Health and Human Services
DHI	Drug-Hormone Interaction
DOT	Directly Observed Therapy
EAE	Expedited Adverse Event
EC	Ethics Committee
eCRF	Electronic Case Report Form
EQA	External Quality Assurance
FDA	(United States) Food and Drug Administration
FTC/TAF	Emtricitabine (FTC) and tenofovir alafenamide (TAF); Descovy®
FTC/TDF	Emtricitabine (FTC) and tenofovir disoproxil fumarate (TDF); Truvada®
GAHT	Gender affirming hormonal therapy
GC	*Neisseria gonorrhoeae*
GCLP	Good Clinical Laboratory Practices
GCP	Good Clinical Practices
HIV	Human Immunodeficiency Virus
HIVPC/HIVCC	HIV prevention continuum/HIV care continuum

HPTN	HIV Prevention Trials Network
IATA	International Air Transport Association
ICF	Informed consent form
IDI	In-depth Interview
ICH	International Council on Harmonization
IoR	Investigator of Record
IQA	(DAIDS) Immunology Quality Assurance
IQR	Interquartile range
IRB	Institutional Review Board
LC	(HPTN) Laboratory Center
LDMS	Laboratory Data Management System
LL	Local laboratory
LOC	Leadership and Operations Center
MO	Medical officer
NAAT	Nucleic acid amplification testing
NIAID	(United States) National Institute of Allergy and Infectious Diseases
NIH	(United States) National Institutes of Health
OHRP	Office for Human Research Protections
PHN	Peer Health Navigation
PI	Package Insert
PK	Pharmacokinetic
PRO	Protocol Registration Office
pSMILE	Patient Safety Monitoring and International Laboratory Evaluation
py	Person Year
QA	Quality assurance
QC	Quality control
RE	Regulatory entity
RNA	Ribonucleic acid
ROC	Regulatory Operations Center
RSC	Regulatory Support Center
SBCM	Strengths-based case management
SAE	Serious Adverse Event
SDMC	(HPTN) Statistical and Data Management Center
SMC	Study Monitoring Committee
SOC	Standard of Care
SOE	Schedule of Events
SOP	Standard Operating Procedures
SSP	Study Specific Procedures
STI	Sexually transmitted infection
TGW	Transgender Women
UK NEQAS	United Kingdom National External Quality Assessment Service
US	United States
VQA	(DAIDS) Virology Quality Assurance

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SCHEMA

Purpose: To assess the feasibility, acceptability, and preliminary impact of a multi-component strategy to improve pre-exposure prophylaxis (PrEP) uptake and adherence that integrates delivery of biomedical HIV prevention co-located with gender-affirming transgender care (hormonal therapy and medical monitoring) and Peer Health Navigation (PHN) using Strengths-Based Case Management (SBCM) professional supervision.

Design: Multi-site, open-label study with each participant randomized 1:1 to Immediate Intervention vs. 6-month Deferred Intervention Arms. Both arms will be provided PrEP and sexually transmitted infection (STI) screening and treatment. Participants in the Immediate Intervention Arm will receive co-located gender-affirming medical care and PHN using SBCM starting at the Enrollment Visit. Participants in the Deferred Intervention Arm will receive linkage to external gender-affirming medical care and case management services during the deferred period and will transition to the study intervention six months following the Enrollment Visit.

Population: Transgender Women (TGW), ages 18 or older, HIV-uninfected, at risk of acquiring HIV infection.

Study Size: Approximately 310 HIV-uninfected TGW.

Study Duration: For each individual site, the duration of the study is approximately 36 months from the time of site activation. Accrual will require approximately 15 months (3 months for Implementation testing and 12 months for general study); individual participants will be followed for 18 months. Once enrolled, each participant will complete eight follow-up visits.

Study Sites: Study sites will be listed in the Study Specific Procedures (SSP) Manual and will include four sites in the United States (U.S.) and one site in Brazil.

Study Regimen: The Intervention will include an approved PrEP agent (Descovy® and Truvada® in the U.S., Truvada® in Brazil), STI screening and treatment, co-located gender-affirming medical care, and PHN using SBCM.

Primary Objective(s):

- To assess acceptability and feasibility of delivering integrated HIV prevention services co-located with gender-affirming hormone therapy (GAHT) and PHN using SBCM for TGW.
- To assess PrEP uptake, adherence, and persistence in both the Immediate Intervention Arm and the Deferred Intervention Arm and compare uptake, adherence and persistence of PrEP between the two arms.

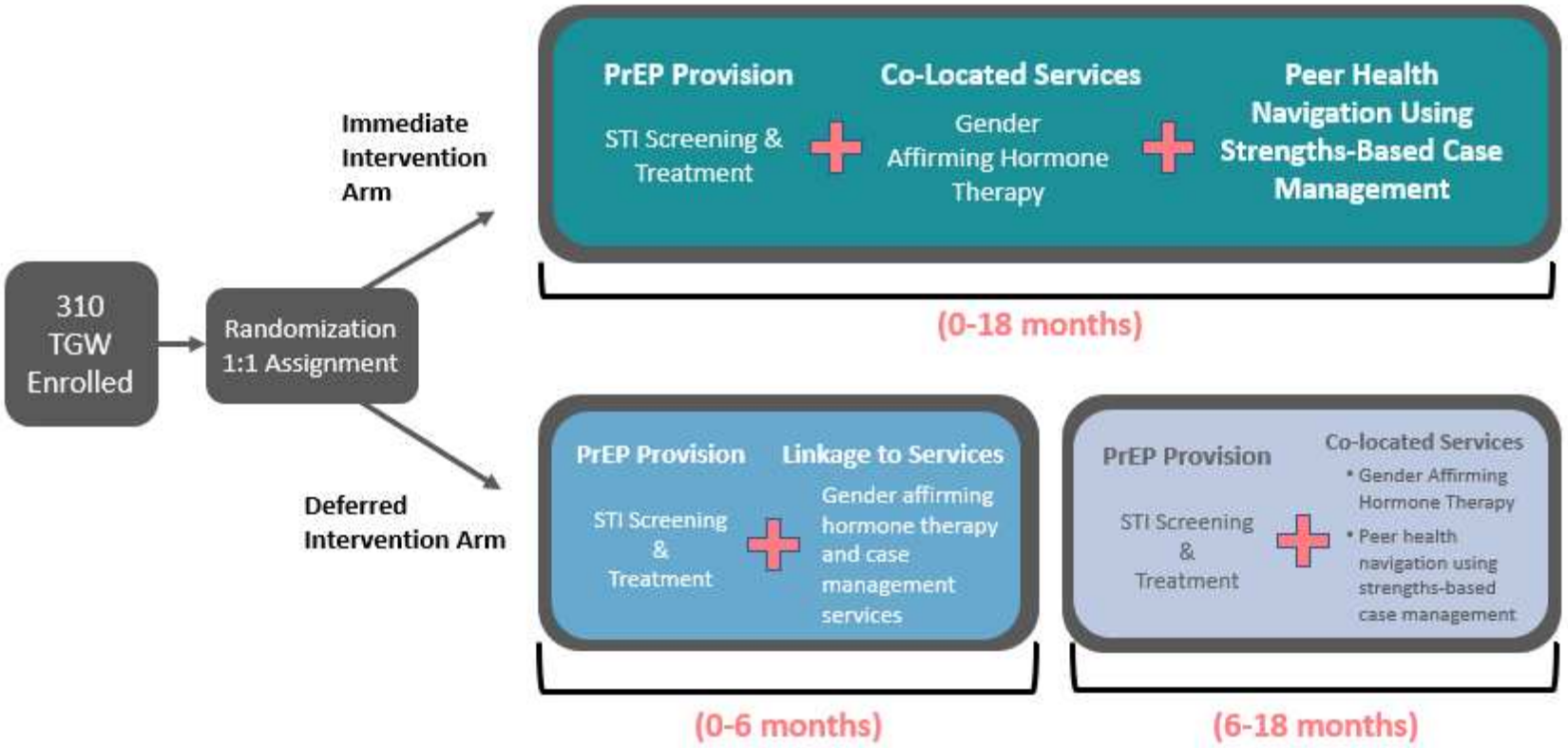
Secondary Objectives:

- To determine annual incidence of HIV infection among study participants.
- To determine baseline prevalence and annual incidence of STIs (*Neisseria gonorrhoeae* [GC], *Chlamydia trachomatis* [CT], and *Treponema pallidum* (syphilis)) and to examine changes in STI incidence over time by study arm.
- To examine changes in sexual risk-taking behavior (e.g., number of serodiscordant or HIV-unknown serostatus sexual partners; number of condomless anal/vaginal sex episodes with these partners).
- To obtain baseline laboratory data to evaluate the cohort's suitability for future PrEP intervention studies (e.g., prevalence of renal insufficiency, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, etc.).
- To identify demographic, behavioral, socioeconomic, and psychosocial factors related to: (1) PrEP uptake and PrEP adherence over time, (2) PrEP persistence, and (3) interest in future HIV research, including research involving injectable and implantable agents for PrEP among HIV-uninfected TGW.
- To assess use of medically-prescribed and non-prescription gender-affirming interventions, including exogenous hormones, soft tissue fillers/silicone, and feminizing surgeries (e.g., breast augmentation, vaginoplasty/labiaplasty, orchiectomy, etc.).

Exploratory Objectives:

- To explore beliefs about drug interactions between gender-affirming hormonal therapy and antiretroviral (ARV) drugs used for PrEP.
- To evaluate TGW experiences of participating in an interventional study that includes biomedical and behavioral assessments, including the social impact of participation.
- To assess the safety of the intervention.
- To use laboratory assessments to characterize incident HIV infections. These assessments may include viral load testing, HIV drug resistance testing, ARV drug testing, phylogenetic analysis, and analysis of the host response to HIV infection.
- To examine the potential impact of hormonal therapy on PrEP concentrations.

FIGURE 1: OVERVIEW OF STUDY DESIGN



1.0 INTRODUCTION

1.1 Background and Rationale

HIV Vulnerability

Transgender women (TGW) have the highest estimated HIV prevalence of any key population and are a priority for HIV prevention and treatment. In all countries where data are available, TGW bear a disproportionate burden of HIV infection, with a global pooled HIV prevalence of 19%.[1] A recent meta-analysis indicates that TGW have a 49-fold increased odds of HIV infection compared to other adults of reproductive age.[1] To date, the vast majority of studies of HIV among TGW have taken place in countries with male-predominant, concentrated epidemics.[2] However, early data from multiple countries in sub-Saharan Africa suggest that TGW have disproportionately high HIV prevalence even within settings of generalized epidemics. Cohort studies demonstrate high HIV incidence rates (ranging from 2–4 cases/100-person year [py]) among TGW[3-5], indicating an urgent need to develop and implement HIV prevention strategies that are both effective and acceptable to improve the health of this key population.[6]

Multiple individual (e.g., socio-demographic, psychological), interpersonal (e.g., violence, gender-power dynamics), and structural (e.g., stigma, discrimination) factors ("situated vulnerabilities"[7]) increase individual risk for HIV acquisition by TGW, and influence outcomes across the HIV prevention continuum (HIVPC)[6,8] (e.g., low rates of PrEP uptake for HIV-uninfected TGW.[9] The risk factors for HIV acquisition/transmission faced by TGW are driven by and associated with structural barriers that limit access to HIV prevention and care, as well as other health services.[6,10,11] Contextualizing HIV prevention services alongside the "situated vulnerabilities" among TGW will help to maximize acceptability and feasibility of HIV care and optimize uptake of HIV prevention services for this key population.[6,10]

Gender Affirming Care

Gender-affirming Hormone Therapy (GAHT) is an unmet need and community priority for TGW across the globe. Hormones have been shown to improve psychological functioning and quality of life for transgender people.[12,13] However, in the majority of geographic settings and contexts, GAHT is not available for TGW via medically-supervised channels.[13] Access to hormones usually occurs outside of the health system via informal, peer networks (e.g., TGW use hormonal contraceptives without appropriate dosing, medical monitoring, or medical follow-up).[14] The development of informal, community-based systems to procure hormonal therapy among TGW is an example of resourcefulness in meeting community needs outside of existing institutional frameworks that marginalize them. However, significant risks are associated with provision of oral or injectable hormonal therapy without regulated hormone formulations, sterile injection equipment, medically supervised dosing and administration, and proper clinical follow-up.

In geographic locations where gender-affirming medical care does exist, TGW face barriers to accessing care, most commonly structural stigma, national identification documents that include sex assigned at birth and legal name are often needed to access healthcare in many countries; these names and gender markers may not match their physical presentation. TGW may also face systems-barriers to care (e.g., lack of trans-competent healthcare providers, limited flexibility in scheduling appointment times). For these and other reasons, many TGW rely on peers for support.[15,16] However, multiple clinical guidelines[17-19] and community health center models[20,21] indicate that clinically-competent gender affirming health care can readily be provided by trained

primary care clinicians[22,23] who may also be best positioned to reach HIV-negative people at risk for HIV acquisition.[24,25]

Pre-Exposure Prophylaxis

Culturally-tailored and holistic HIV prevention interventions are needed that are responsive to the lived experiences and prioritized healthcare needs of TGW communities. Although biomedical interventions, including PrEP, have demonstrated safety and efficacy for prevention of HIV infection among men who have sex with men (MSM) and TGW in clinical trials,[26-28] uptake of PrEP in practice has been limited among TGW (<10% uptake PrEP across TGW sampled).[29,30] Further, re-analysis of TGW taking PrEP in the iPrEx trial found that PrEP adherence was suboptimal (e.g., 18% adherence in TGW).[3] While the iPrEx trial was not designed and powered for analysis of TGW, data from that trial raise questions about reasons for poor adherence, and indicate the need for research to determine methods to improve PrEP delivery and retention among TGW.[3] Further, combination HIV prevention approaches, including promotion of condom use, are more effective than PrEP alone in high-risk populations and are recommended.[10,31-33] While some promising HIV prevention interventions exist, none have been shown to reduce HIV incidence among TGW.[25]

Integrated HIV Prevention and Gender Affirming Services

Cross-sectional data suggest that providing hormonal therapy may facilitate PrEP uptake among TGW.[34-36] These prior studies – mostly cross-sectional, formative, and qualitative – highlight the need for robust interventional research on whether integrated care (e.g., hormonal therapy delivered alongside HIV prevention services) can improve HIV-related outcomes over time, including PrEP uptake and adherence, for TGW communities.[34,37] Integrating hormonal therapy with HIV bio-behavioral prevention interventions and care may improve HIVPC outcomes among TGW. Community concerns about drug-hormone interactions have been identified as barriers to PrEP uptake among TGW.[38,39] Data on drug-hormone interactions are needed to address these barriers and guide appropriate dosing of hormonal therapy for transgender individuals who are also taking PrEP.

A combination intervention that delivers HIV prevention services (e.g., PrEP) with hormonal therapy, supported by PHN using SBCM, represents a potential strategy that could significantly impact the HIV epidemic among TGW. As of December 2018, only four of more than 37 U.S. and international PrEP demonstration projects that include TGW are tailored specifically for transgender people; all others include TGW within a subset of MSM or sex workers, and samples of TGW remain insufficient for inference.[40] Three studies that are transgender-specific are all being conducted in California in the U.S.; one demonstration pilot is being conducted in Lima, Peru (see Table 1).

Hypothesized Mechanisms of Intervention

Hypothesized mechanisms of action are conceptually grounded in gender affirmation and Maslow's hierarchy of needs.[41,42] The hierarchy of needs is shown as a pyramid with the largest, most fundamental level of needs at the bottom (i.e., physiological, safety), and psychological and self-fulfillment needs at the top (i.e., belongingness and love, esteem, self-actualization) (see Figure 2 below). Maslow's theory suggests that at any given time a certain need "dominates" the human organism, and that the most basic needs must be met before the individual will strongly desire (or focus motivation on) the secondary or higher-level needs. Gender affirmation and PHN

using strengths-based case management are hypothesized to meet TGW needs for gender affirmation, thereby facilitating TGW to address other health issues, such as HIV prevention. Thus, gender affirmation is hypothesized to be a pivotal factor in engagement in HIV prevention, including PrEP. Consistent with traditional case management approaches, PHN will help TGW navigate removal of systematic and individual barriers to meet needs and therefore to promote health. In addition, PHN using SBCM will implement an assets-based approach to identify TGW strengths and resiliencies and pragmatically leverage these to promote improved biomedical HIV prevention outcomes.

Table 1. HIV prevention research among transgender persons[40]

Name	Prevention Option	Phase	Sponsors	Countries	Description
Transgender-Focused PrEP Demo Project - Medical Homes Approach	PrEP	Demo Project (PIs: Liu & Wilson)	California HIV/AIDS Research Program (CHRP) of the University of California	U.S.	Patient Centered Medical Home approach to develop and evaluate a comprehensive PrEP education, access, and support package for HIV-uninfected TGW and transmen in the San Francisco Bay Area. The purpose is to determine the acceptability of the tools, PrEP uptake and adherence, most useful support strategies, measure social harms and benefits of PrEP use and potential drug interactions between PrEP and hormone use.
Transgender-Focused PrEP Demo Project - Case Management Approach	PrEP	Demo Project (PI: Morris)	California HIV/AIDS Research Program (CHRP) of the University of California	U.S.	To assess whether a transgender-focused case management approach to contextualize PrEP within the needs of the whole person can improve PrEP linkage and engagement in the transgender population. To examine possible drug interactions between PrEP use and hormonal therapy. To determine whether the drug levels expected to be protective for HIV are achieved by TGW on hormonal therapy, and if taking PrEP is associated with any changes in hormone levels.
Trans Research-Informed Communities United in Mobilization for the Prevention of HIV (TRIUMPH)	PrEP	Demo Project (PI: Sevelius)	The California HIV/AIDS Research Program (CHRP) of the University of California	U.S.	To develop and evaluate a culturally-relevant, community-led PrEP demonstration project, driven by the needs and experiences of TGW of color. To identify the best methods to deliver PrEP safely and effectively to trans communities while achieving the highest levels of adherence possible.

Name	Prevention Option	Phase	Sponsors	Countries	Description
Féminas	PrEP uptake and viral suppression	Single-arm non-randomized (PI: Javier Lama)	amFAR	Lima, Peru	To assess acceptability and feasibility of an intervention that integrates HIV prevention, testing, hormonal treatment, and PHN to improve outcomes across the HIV continuum among TGW (PrEP uptake for HIV-infected TGW; ART and viral suppression for HIV-infected TGW).

An NIH report search (conducted December 30, 2018, using the terms "transgender" and "HIV") identified 122 studies that included transgender individuals, most of the studies were not interventional research (See Table 2).

Figure 2. Maslow's Hierarchy of Human Needs

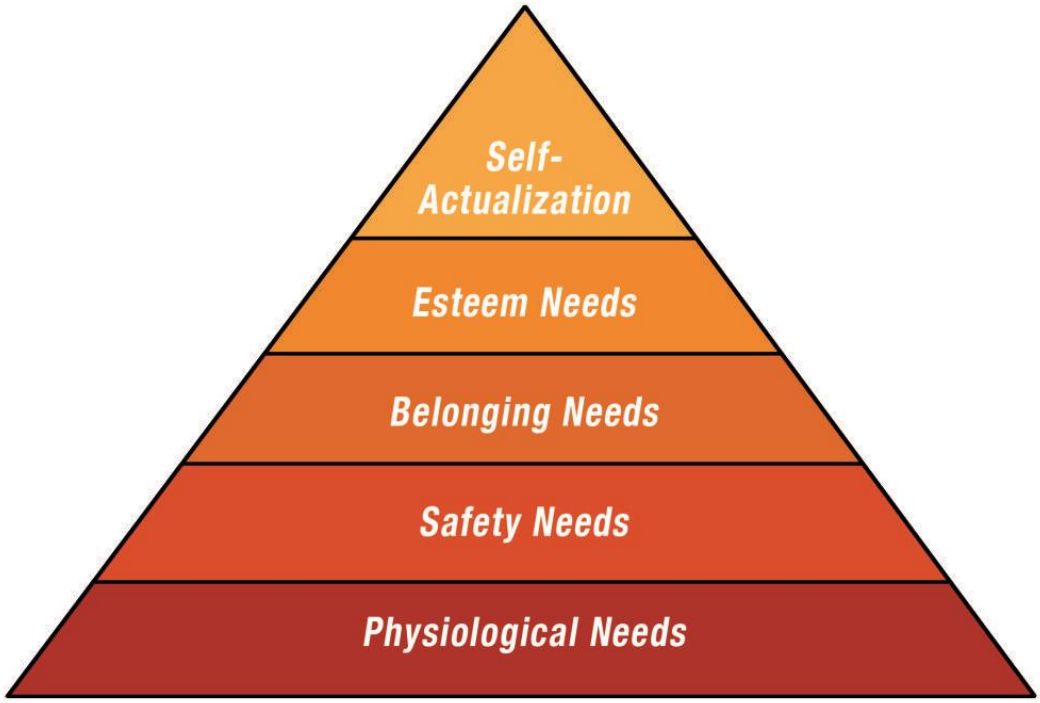


Table 2: Current HIV prevention intervention studies with TGW funded by NIH.

Name	Prevention Option	Design	Sponsors	Countries	Description
TransLife Center (TLC)	Combination HIV Prevention	Single arm trial (PI: Judy Perloff)	NIH (1U01PS005140-01)	U.S.	To evaluate a locally-developed and potentially effective intervention in Chicago, IL which provides combination (e.g., biomedical, behavioral, social/ structural) HIV prevention services to adult TGW at high-risk for HIV infection in a culturally specific and highly accessible environment. This is a single arm trial among 100 HIV-uninfected and sexually-active TGW ages 18+ years. Effectiveness is being evaluated over 12 months (baseline, 6 mo, 12 mo). All participants will receive standard of care (SOC) HIV/STI prevention and testing services, assessment and linkage to PrEP, as indicated.
Chicas Creando Acceso a la Salud (ChiCAS; Girls Creating Access to Health)	Combination HIV Prevention	RCT (PI: Scott Rhodes)	NIH (5U01PS005137-03)	U.S.	To evaluate a locally-developed intervention enrolling 100 Latina TGW who have sex with men randomized to the 4-session small-group combination HIV prevention intervention group or a delayed-intervention comparison group (waitlist) with baseline, 3-month, and 6-month follow-ups. Outcomes include increased self-reported use of condoms, increased HIV testing, increased use of PrEP, increased use of safe transition-related services.

1.2 Rationale for Study Design

The Need for PrEP Intervention Research with Transgender Women

This vanguard study will provide data on the implementation and impact of a multi-component intervention in HIV-uninfected TGW. Implementation across multiple sites, countries, and communities will allow for a broad assessment of barriers and facilitators to an integrated approach in real world settings. Randomization will strengthen the rigor of the data and will provide information needed to determine the appropriate sample size for a full-efficacy trial. Evidence-based PHN using SBCM needs to be adapted for TGW. Several studies of TGW living with HIV have shown that interventions with PHN components improve the HIV care continuum, particularly retention in care, for TGW of color; extending this work to HIV prevention among HIV-negative TGW is a vital next step.[43,44] No interventional studies are currently being fielded that include an integrated interventional model for TGW that contextualizes HIV prevention alongside gender-affirmative care (hormones and other primary care services) and PHN using SBCM. Interventional research is urgently needed to reduce HIV incidence in TGW as part of the shared goal of ending the HIV epidemic.

The Need for Peer Health Navigation Using Strengths-Based Case Management

Transgender peers play a particularly vital role for TGW in fostering trust and engagement with HIV prevention[14,45] activities given the context of social exclusion and extreme marginalization in which the HIV epidemic occurs. The rationale for PHN as an intervention component is that peer-to-peer engagement represents a culturally appropriate and necessary strategy for TGW to engage with and participate in biomedical HIV prevention strategies, including PrEP uptake and adherence.[46]

Peer Health Navigators are individuals who share the same experiences and community membership as participants, and who are trained to provide effective linkages to health and social services in order to mitigate contextual barriers and enhance facilitators to PrEP uptake and adherence. PHN will use SBCM, an evidence-based health promotion model for peer-to-peer engagement.[47,48] Consistent with traditional case management approaches, PHN will help TGW navigate removal of systematic and individual barriers to promote health. In addition, PHN using SBCM will implement an assets-based approach to identify TGW strengths and resiliencies and pragmatically leverage these to promote improved biomedical HIV prevention outcomes.

PHN using SBCM is based on 6 principles: 1) people can learn, grow, and change; 2) need to focus on individual strengths rather than pathology; 3) the community is an oasis of resources; 4) interventions are based on participant self-determination (e.g., the approach invites individuals to identify their internal strengths and abilities, and develop a personal plan to build on these); 5) the peer relationship is primary and essential (e.g., a collaborative effort to work "with" peers to achieve their goals); and 6) active outreach is the preferred mode of intervention (e.g., focused on brainstorming and taking action to identify and discuss ways to overcome personal or system barriers to healthcare, including biomedical HIV prevention engagement.) PHN using SBCM will consist of one-on-one sessions between participants and peers. Sessions will be structured and integrate assessment and planning tools, linkage and navigation to other services (e.g., legal, behavioral, social), provision of information and educational resources, and skills-building activities to empower and affirm participants. Extensive initial and ongoing training will be provided for PHN, adapting existing practice-based curricula.[49] Training will include theory-based behavioral change approaches such as Motivational Interviewing that will help participants to

identify and overcome ambivalence that keeps many people from changing health-seeking behaviors, and the Transtheoretical (Stages of Change) Model which can guide peer assessment of participants' readiness to adopt health-promoting behaviors.[50] PHN will be supervised by a trained case manager and provided with ongoing supportive supervision individually and in a group format. Details of the intervention will be described in the SSP Manual.

The SBCM approach to PHN has been used successfully in prior research including research related to HIV prevention and treatment, research among substance-abusing women in rural settings, and other substance-abusing populations.[51-54]. In a randomized intervention trial for female sex workers in Miami, FL, that compared a strengths-based professional-only case management approach to a strengths-based professional-peer case management approach, both intervention groups displayed significant reductions in HIV risk behaviors and significant increases in use of services at three- and six-months of follow-up.[43,44,54]

While peer navigation has been utilized across many key populations at-risk for HIV infection, a SBCM approach represents an innovation to existing transgender PHN models for biomedical HIV prevention. Rather than a deficits-based approach that foregrounds risk, PHN using SBCM will focus on building strengths and resiliencies for TGW. This is particularly important given TGW are a population burdened by stigma and historically pathologized by medical and research communities alike, which may discourage access to and uptake of HIV prevention services such as PrEP. Further, the stigma-related health and social conditions driving HIV vulnerabilities for TGW necessitate that HIV prevention interventions provide referrals for other concomitant health and social service needs (e.g., mental health treatment, housing services).

The Need to Study a Multi-Component, Integrated Prevention Intervention

Co-location of services includes the provision of both GAHT and PrEP at the same site by the same clinician. A multi-component intervention for TGW that integrates co-location of HIV prevention services and GAHT with PHN using SBCM has not yet been subjected to rigorous scientific methods with study endpoints of acceptability, feasibility, and improved PrEP uptake and adherence for the target population. The proposed study of this multi-component intervention will yield valuable data to guide implementation of biomedical HIV prevention services, especially PrEP, for TGW in the US and globally.

The transgender health literature suggests that integrating HIV prevention services with GAHT may be more acceptable than requiring TGW to obtain these types of care in separate locations (see Section 1.1.). However, these studies have relied on self-reported qualitative data or cross-sectional, often retrospective designs that limit causal inference. It is possible that TGW will prefer to receive HIV prevention and GAHT from separate practices that specialize in PrEP service delivery or in GAHT, respectively rather than via integrated service delivery. It is also possible that co-location of GAHT and PrEP services will not make a difference in TGW's uptake, adherence, and persistence with PrEP. Equipoise remains in the question of the best service delivery models to engage TGW in HIV prevention services. Co-location models represent an uncharted area of prospective, rigorous scientific inquiry with many remaining questions related to both implementation and efficacy. The current study will contribute valuable information to fill this gap in research.

Rigorously assessing the acceptability, feasibility, and preliminary impact on PrEP uptake of a combination approach to HIV prevention for TGW that integrates HIV prevention and GAHT, and that includes peer navigation PHN using SBCM, represents an important next step in interventional research to address the HIV epidemic in TGW.

Selection of Immediate Versus Six-Month Deferred Randomized Trial Design

Randomized clinical trials are considered the most rigorous of study designs. By randomizing participants to immediate versus deferred access to the intervention (i.e., multi-component, co-located services), the trial will be able to compare differences in outcomes between participants who receive the intervention and those who have not yet received the intervention. By allowing access to the intervention after six months, the study responds to consistent input from community consultations with more than 50 TGW at the five study sites that any delay lasting longer than six months would be unacceptable and negatively impact recruitment into the study and retention of participants in the deferred arm.

In addition to the strong community rationale, the current literature on PrEP discontinuation supports the validity of a six-month deferred arm. In a study of 663 MSM and TGW PrEP initiators in Boston, being a TGW was significantly associated with PrEP discontinuation, and the median time to first discontinuation (of seven days or more) was four months.[55] Data from TGW in Brazil found 8% missed the week 4 visit, 8% missed the week 8 visit, and 16% missed the 24-week visit.[56] The proportion missing the week 24 visit was the same at the end of study visit (week 48),[56] suggesting that participants who discontinue PrEP do so by 24 weeks. Among 1086 veterans initiating PrEP via the Veterans Hospital Administration, the median time to PrEP discontinuation (based on 120 day gap in TDF/FTC possession) was 124 days (4 months).[57] In a study among MSM in 3 US cities, PrEP discontinuation was 27% at 3 months and 40% at final 6-month study visit. [58] In short, the literature supports the expectation that we would see a difference between the deferred and intervention arms by six months. Because participants may elect to start PrEP up until week 39 (the last visit before the end of the first year of the study), we will continue to follow participants for another year to assess the impact of the intervention on PrEP persistence.

2.0 STUDY OBJECTIVES

2.1 Primary Objective(s)

The primary objectives of this study are:

- To assess acceptability and feasibility of delivering integrated HIV prevention services co-located with gender-affirming hormone therapy (GAHT) and PHN using SBCM for TGW.
- To assess PrEP uptake, adherence, and persistence in both the Immediate Intervention Arm and the Deferred Intervention Arm and compare uptake, adherence and persistence of PrEP between the two arms.

2.2 Secondary Objectives

The secondary objectives of this study are:

- To determine annual incidence of HIV infection among study participants.
- To determine baseline prevalence and annual incidence of STIs (*Neisseria gonorrhoeae* [GC], *Chlamydia trachomatis* [CT], and *Treponema pallidum (*syphilis)) and to examine changes in STI incidence over time by study arm.

- To examine changes in sexual risk-taking behavior (e.g., number of serodiscordant or HIV-unknown serostatus sexual partners; number of condomless anal/vaginal sex episodes with these partners).
- To obtain baseline laboratory data to evaluate the cohort's suitability for future PrEP intervention studies (e.g., prevalence of renal insufficiency, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, etc.).
- To identify demographic, behavioral, socioeconomic, and psychosocial factors related to: (1) PrEP uptake and PrEP adherence over time, (2) PrEP persistence, and (3) interest in future HIV research, including research involving injectable and implantable agents for PrEP among HIV-uninfected TGW.
- To assess use of medically-prescribed and non-prescription gender-affirming interventions, including exogenous hormones, soft tissue fillers/silicone, and feminizing surgeries (e.g., breast augmentation, vaginoplasty/labiaplasty, orchiectomy, etc.).

2.3 Exploratory Objectives

The exploratory objectives of this study are to:

- To explore beliefs about drug interactions between gender-affirming hormonal therapy and antiretroviral (ARV) drugs used for PrEP.
- To evaluate TGW experiences of participating in an interventional study that includes biomedical and behavioral assessments, including the social impact of participation.
- To assess the safety of the intervention.
- To use laboratory assessments to characterize incident HIV infections. These assessments may include viral load testing, HIV drug resistance testing, ARV drug testing, phylogenetic analysis, and analysis of the host response to HIV infection.
- To examine the potential impact of hormonal therapy on PrEP concentrations.

3.0 STUDY DESIGN

This is a multi-site, open-label, randomized controlled study with participants randomized 1:1 to an Immediate Intervention Arm vs. a Deferred Intervention Arm. The study is designed to evaluate whether a multi-component strategy that integrates biobehavioral HIV prevention services co-located with GAHT and supported by PHN using SBCM demonstrates greater engagement in HIV prevention strategies compared to SOC.

3.1 Study Treatment Conditions

Eligible participants will be enrolled and will be randomized 1:1 to either the Immediate Intervention Arm or Deferred Intervention Arm (See Figure 1). Services for these arms will differ during the first 6 months of study participation.

Immediate Intervention Arm (0-6 months): Participants will be provided PrEP (Truvada® or Descovy®) and STI screening and treatment. The Immediate Intervention Arm will receive co-located services to begin after enrollment that include:

- Provision of GAHT and routine clinical monitoring
- PHN using SBCM

Deferred Intervention Arm (0-6 months): Participants will be provided PrEP (Truvada® or Descovy®) and STI screening and treatment. The Deferred Intervention Arm will receive linkage* to services for the first 6 months.

- Linkage to GAHT and routine clinical monitoring
- Linkage to case management services

* For this study, linkage is defined as the process of ensuring that study participants are connected with a local institution that provides GAHT services including treatment and monitoring. Wherever possible, linkages will be made with sites that can provide GAHT services at no cost to the participant. Each site will establish an agreement with one or more local institutions for this purpose and the agreement must be maintained throughout the study. Sites will develop an SOP describing the process for linkage of participants during the study or as needed once study concludes.

Both Arms (6-18 months): Participants will be provided PrEP (Truvada® or Descovy®) and STI screening and treatment. At the 6 month visit, all participants will be provided co-located care until they have reached 18 months of study participation at which time they will be linked to local services. This will include:

- Provision of GAHT and routine clinical monitoring
- PHN using SBCM

Participants who decline PrEP can remain in follow-up (see Section 6.4.1) and can begin PrEP at any time up to and including their Week 39 visit. Enrolling participants who decline PrEP at baseline allows for an assessment of the impact of the intervention on PrEP uptake over time. If a participant has not been provided PrEP on study by Week 39 and decides to initiate PrEP after the Week 39 study visit, PrEP will not be provided at the study site; rather the participant will be linked to local PrEP services (see Section 5.2 for details). Week 39 is the last visit before the end of the first year of the study which will provide information on PrEP uptake. The second year will provide information on PrEP persistence so PrEP cannot be initiated at the site but as noted, participants can be referred.

The multi-component interventional package including GAHT and PHN using SBCM is outlined in Table 3. During the first six months, the Deferred Intervention Arm includes standard HIV prevention interventions such as risk-reduction counseling (Project RESPECT; Prevention Cohort) and provision of PrEP. Participants in the Deferred Intervention Arm will be linked with institutions that have established a partner agreement with the site. A partner agreement at each site will include at a minimum an agreement to provide care to study participants in a timely manner.

Shown in Table 3 is each intervention component, a brief description, the theoretical foundation, and the staff member(s) responsible for component delivery.

Table 3. Intervention to be Provided: Multi-component HIV Prevention Care Package			
Intervention Component	Description	Theoretical Foundation	Delivered By
Standard of Care for All Participants Throughout the Study			
HIV testing and counseling; STI screening and treatment **Note: TGW screening positive for HBV as part of PrEP provision will be linked to local healthcare services for monitoring and/or treatment.*	Principles from Project RESPECT (review, enhance, situations, plan, examine, challenge, tell)[59] and RESPECT-2,[60,61] evidence-based interventions by the CDC (Centers for Disease Control and Prevention), used in at least one PrEP trial (TFF2)[62]	Motivational interviewing[63] and other theories of behavior change (e.g., information-motivation-behavioral skills; social cognitive theory)[64,65]	Study staff
PrEP education and provision	Education about PrEP and provision of PrEP with behavioral risk assessment[66]	Health behavior change theories[65] and the HIV PrEP continuum[67]	Study staff, including TGW peer navigators
PrEP monitoring and adherence counseling	Principles from Life-steps for PrEP adherence counseling will be provided to participants whose self-reported medication adherence drops below 80%[68,69]	Cognitive-behavioral approach[70]	Study staff
During 6 month Deferral			
Linkage for hormone administration and routine clinical monitoring	The Deferred Intervention Arm will receive linkage to external gender-affirming medical care and case management services during the deferred period.	NA	Partner organization
During Intervention			
Hormone administration and routine clinical monitoring	WPATH international standards and guidelines[13,71,72] as well as best practices from ongoing clinical care[20]	Gender affirmation[41] and hierarchy of needs[42,73]	Study staff
PHN using SBCM	Identifying and leveraging strengths and resiliencies, coordinating care, monitoring kept/missed appointments, troubleshooting barriers to care access (e.g., transportation, stigma), ensuring linkages to follow-up services, making referrals to other gender-affirming social and health services[49]	Minority stress (e.g., stigma in healthcare),[74] complex systems health navigation, theory of strengths[47,75]	TGW peer navigators and study staff

3.2 Sub-Studies

HPTN 091 participants may also be selected to participate in up to two sub-studies or nested cohorts. A qualitative sub-study (n=60) will be embedded to gather in-depth interview data about PrEP experiences, including barriers and facilitators to PrEP uptake and adherence. Another subset of up to 50 participants randomized to the Immediate Intervention Arm who accept hormonal therapy and Descovy® for PrEP at U.S. sites will be enrolled in a Drug-Hormone Interaction (DHI) sub-study. The purpose of the DHI sub-study is to evaluate the relationship between PrEP agents and GAHT. This relationship will be evaluated through the measurement of plasma and peripheral blood mononuclear cell (PBMC) PrEP concentrations prior to and after administration of co-localized GAHT. Hormone concentrations will also be measured at designated time points. See Section 6.6, Section 6.7, and Appendix IC for additional information.

3.3 Participating Sites

Participating sites are listed in the SSP Manual and are located within the U.S. and Brazil.

3.4 Study Duration

Once a site is activated, the total study duration is anticipated to be approximately 36 months: accrual will require approximately 15 months (3 months for Implementation testing, and 12 months for general study), with 18 months of follow-up per participant. The total study duration is dependent on the timeframe to complete the run-in phase. Participants will complete 8 study visits: Screening, Enrollment, Week 13 (Month 3), Week 26 (Month 6), Week 39 (Month 9), Week 52 (Month 12), Week 65 (Month 15), Week 78 (Month 18). In addition, an GAHT initiation visit will be scheduled up to 10 days following the collection of samples for estradiol and total testosterone testing for initiation/re-initiation of GAHT.

4.0 STUDY POPULATION

Approximately 310 HIV-uninfected TGW will be enrolled. Participants will be selected for the study according to the criteria in Section 4.1 and 4.2 and the guidelines in Section 4.3.

Participants will be recruited, screened, and enrolled as described in Section 4.4 and assigned to an intervention group as described in Section 8.5. 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 differential enrollment targets such that overall cross-site enrollment meets overall protocol goals.

4.1 Inclusion Criteria

TGW (assigned male at birth, trans-feminine spectrum – as defined in the SSP Manual – by self-report) who meet all of the following criteria are eligible for inclusion in this study.

1. Eighteen years or older at the time of screening.
2. Willing and able to provide informed consent for the study.
3. Interest in PrEP – as defined in the SSP Manual.

4. Non-reactive HIV test results at Screening and Enrollment.
5. Available to return for all study visits and within site catchment area, as defined per site's Standard Operating Procedures (SOP).
6. At risk for sexually acquiring HIV infection based on self-report of at least one of the following:
    a) Any anal or vaginal sex with one or more serodiscordant or HIV-unknown serostatus sexual partners in the previous 3 months, regardless of condom use.
    b) Anal or vaginal sex in exchange for money, food, shelter, or other goods or favors in the previous 3 months.
    c) History of STI(s) in the past 6 months.
7. Willing to undergo all required study procedures.
8. General good health, as evidenced by the following laboratory values:
    a) Calculated creatinine clearance ≥ 60 mL/minute using the Cockcroft-Gault equation.
    b) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) < 2.5 times the upper limit of normal (ULN.)
    c) HBV surface antigen (HBsAg) negative.

Note: Otherwise eligible participants with laboratory results outside the above-mentioned values, with the exception of those with reactive HIV test, can be re-tested during the screening window. Participants with reactive HIV tests will not be able to rescreen.

Note: Participants who practice receptive vaginal sex cannot be provided Descovy® as it is not approved for this indication.

4.2 Exclusion Criteria

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

1. Any reactive or positive HIV test result at Screening or Enrollment, even if HIV infection is not confirmed.
2. Plans to move away from the site area within the next 18 months.
3. Co-enrollment in any other research study that may interfere with this study (as provided by self-report or other available documentation). Exceptions may be made after consultation with the Clinical Management Committee (CMC).
4. Current or chronic history of liver disease (e.g., non-alcoholic or alcoholic steatohepatitis) or known hepatic or biliary abnormalities (with the exception of Gilbert's syndrome, asymptomatic gallstones, or cholecystectomy).
5. History of deep vein thrombosis, pulmonary embolism, and/or clotting disorder.
6. Active or planned use of medications with significant drug interactions as described in the Package Insert for Truvada® or Descovy®, per clinician's discretion (provided by self-report or obtained from medical history or medical records). See Section 5.8 for a full list of drug interactions.
7. Any other condition, including but not limited to alcohol or substance abuse and uncontrolled medical condition and/or allergies, 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 Co-Enrollment Guidelines

In general, participants in this study should not take part in other concurrent research studies. This is due in part to concerns about participant study burden and safety. The CMC should be consulted for any possible exceptions.

4.4 Recruitment Process

Sites will be responsible for developing appropriate recruitment processes that are geared toward 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 SOP. Strategies may include: consulting and collaborating with local TGW and communities, making use of peer outreach, linking via participant-referrals, engaging in indirect recruitment activities (outreach vs. venues and social media), and obtaining referrals through key community figures or leaders. Recruitment strategies and the yield for each strategy will be meticulously tracked at each site. All advertising materials must undergo approval by each participating site's Institutional Review Board (IRB)/Ethics Committee (EC).

4.5 Participant Retention

Once a participant enrolls in this study, the study site will make every effort to retain them for the entire follow-up period. Optimally, participant retention procedures will be established to minimize missed visits and loss to follow-up. Study site staff are responsible for developing and implementing local SOPs to ensure retention in the study. Components of such procedures may include:

- Thorough explanation of the study visit-schedule and procedural requirements during the informed consent process and re-emphasis at each study visit.
- Thorough explanation of the importance of both study arms to the overall success of the study.
- Collection of detailed locator information at the study Screening Visit, and active review and updating of this information at each subsequent visit, including where the participant lives and other locator venues.
- Use of appropriate and timely visit-reminder mechanisms.
- Immediate and multifaceted follow-up on missed visits.
- Mobilization of trained staff and Peer Navigators 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/AIDS and explain the purpose of HIV prevention research and the importance of completing research study visits.
- Incentives or reimbursements as permitted by local Institutional Review Board/Ethic Committees (IRB/ECs).

4.6 Participant Withdrawal

Participants may voluntarily withdraw from the study for any reason at any time. In general, participants should not be withdrawn from the study, however, the Investigator of Record (IoR) or designee may withdraw participants from the study to protect their safety, after consultation with the CMC.

Participants also may be withdrawn if the study sponsor, government or regulatory authorities (including Office for Human Research Protections [OHRP] and local regulatory authority) or site IRBs terminate the study prior to its planned end date.

Every reasonable effort will be made to complete a final evaluation of participants who terminate from the study prior to the final protocol-dictated study week, and study staff will record the reason(s) for all withdrawals from the study in participants' study records. In such cases, the IoR or designee must contact the CMC for guidance regarding final evaluation procedures.

5.0 STUDY PRODUCT CONSIDERATIONS

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

5.1 Study Product Regimens

Study product is defined as both PrEP and hormonal therapy.

The PrEP agent in this study will either be Descovy® (emtricitabine 200 mg and tenofovir alafenamide 25mg, FTC/TAF) or Truvada® (emtricitabine 200 mg and tenofovir disoproxil fumarate 300 mg, FTC/TDF) as detailed below.

Country	PrEP Agent	Regimen
U.S.	FTC/TAF 200 mg/25 mg (Descovy®) or FTC/TDF 200 mg/300 mg (Truvada®)	Take one tablet orally once daily
Brazil	FTC/TDF 200 mg/300 mg (Truvada®)	Take one tablet orally once daily

Estrogen-based hormonal therapy will be consistent with national/international standards such as the World Professional Association for Transgender Health.

5.2 Study Product Administration

PrEP

FTC/TDF 200mg/300mg (Truvada®) or FTC/TAF 200mg/25mg (Descovy®) will be taken as one tablet orally once daily with or without food during the 18 months of study participation.

Participants do not have to accept PrEP to be eligible to participate in the study. A participant can decide to initiate PrEP administration at any time after enrollment up until, and including, the Week 39 study visit. Once initiated, the study participant may also decide to discontinue taking PrEP at any time during the 18 months of study participation. A participant can reinitiate PrEP after discontinuation up to, and including, Week 65 of study participation. If a participant requests to reinitiate PrEP at site after discontinuation and had originally initiated PrEP use at site by Week 39 of study participation, the participant is eligible to receive PrEP provided by the study at the site. If a participant has not been provided PrEP at the site by Week 39 and decides to

initiate PrEP after the Week 39 study visit, PrEP will not be provided at the study site; rather the participant will be linked to local PrEP services.

For participants in the U.S., a choice of either Descovy® (FTC/TAF) or Truvada® (FTC/TDF) will be offered at the enrollment visit. Participants may choose to switch PrEP study agents during follow-up. Site staff must document in eCRFs which PrEP study product a participant initiates and if study product is switched during follow-up.

For participants enrolled at the site in Brazil, only Truvada® (FTC/TDF) will be offered as PrEP study product as noted in Section 5.1.

Gender Affirming Hormonal Therapy

All participants randomized to the Immediate Intervention Arm, who wish to initiate hormonal therapy, will be dispensed GAHT at the site, provided through the study. Participants randomized to the Deferred Intervention Arm will be linked to offsite hormonal therapy services for 6 months and then will be eligible to receive GAHT at the site, provided through the study. All participants who are provided GAHT through the study will receive doses and be administered therapy through the site consistent with national/international standards such as the World Professional Association for Transgender Health until study termination.

Participants are not required to accept GAHT to be eligible to participate in the study. All participants can decide to initiate hormonal therapy after enrollment for the Immediate Intervention Arm or at the 6 months visit for the Deferred Intervention Arm, up until, and including, the Week 39 visit. A GAHT initiation visit will be scheduled up to 10 days following the collection of samples for estradiol and total testosterone testing for initiation/re-initiation of GAHT. If a participant decides to initiate hormonal therapy after Week 39 study visit, hormonal therapy will not be provided through the study and the participant will be linked to gender-affirming services.

At any time during the study, a participant may decide to discontinue taking hormonal therapy and continue participation in the study (see Section 6.4.1).

5.3 Study Product Formulation, Content, and Storage

PrEP (Truvada®)

FTC/TDF (Truvada®) is a fixed dose combination tablet containing 200 mg of FTC and 300 mg of TDF. FTC/TDF (Truvada®) 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]. FTC/TDF tablets must be stored and dispensed in the original container. Refer to the relevant Package Insert for further information.

PrEP (Descovy®)

FTC/TAF (Descovy®) is a fixed dose combination tablet containing 200 mg of FTC and 25 mg of TAF. FTC/TAF (Descovy®) 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]. FTC/TAF must be dispensed in the original container. Refer to the relevant Package Insert for further information

Gender Affirming Hormonal Therapy

For participants who are eligible to receive GAHT through the study, the site will need to locally source hormonal therapy for dispensation to the participant. All study drugs obtained locally by the site, for GAHT, will be stored in accordance with the manufacturer's recommendations.

5.4 Study Product Supply

PrEP (Truvada®)

FTC/TDF 200 mg/300 mg (Truvada®) study product tablets are manufactured and provided by Gilead Sciences, Inc. FTC/TDF 200mg/300mg study product will be available through the National Institute of Allergy and Infectious Disease (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain FTC/TDF study product through the CRPMC by following the instructions in the *Pharmacy Guideline and Instructions for DAIDS Clinical Trial Networks* and instructions in the SSP Manual.

PrEP (Descovy®)

FTC/TAF 200 mg /25 mg (Descovy®) study product tablets are manufactured and provided by Gilead Sciences, Inc. FTC/TAF 200mg/25mg study product will be available through the National Institute of Allergy and Infectious Disease (NIAID) Clinical Research Products Management Center (CRPMC). The site pharmacist can obtain FTC/TAF study product through the CRPMC by following the instructions in the *Pharmacy Guideline and Instructions for DAIDS Clinical Trial Networks* and instructions in the SSP Manual.

Gender Affirming Hormonal Therapy

The site will locally procure hormonal therapy for dispensation to participants who wish to initiate therapy and as they become eligible to receive therapy through the site.

NOTE: Any study drug not provided by the study must be a U.S. FDA approved formulation or otherwise comply with the NIAID (DAIDS) policy that outlines the process for authorizing the use of study products not marketed in the U.S. 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

5.5 Study Product Accountability

PrEP (Truvada® or Descovy®)

A written prescription must be provided to the site pharmacist when a participant initiates FTC/TDF or FTC/TAF study product. The prescription should be written to ensure that the participant has enough study product to last through the next study visit. Study product should be dispensed per written prescription and labeled with a participant-specific label that is in accordance with local pharmacy laws and regulations along with the instructions in the *Pharmacy Guideline and Instructions for DAIDS Clinical Trial Networks.*

The site pharmacist must maintain compete records of all study products received from the NIAID CRPMC and subsequently dispensed to study participants. After the study is completed,

terminated, or site is otherwise instructed by the study sponsor, all unused study product must either be returned to the CRPMC (U.S. sites only), or else destroyed (international sites) in accordance with the relevant procedures provided in the manual *Pharmacy Guideline and Instructions for DAIDS Clinical Trial Networks.*

5.6 Adherence Assessments

PrEP and GAHT adherence data will be collected via self-report at each follow-up visit and through laboratory testing.

Self-Report

Participants will be asked self-reported questions about adherence to PrEP and GAHT via an electronic Case Report Forms (eCRF) and/or Audio Computer-Assisted Self Interview (ACASI) within the Follow-up Behavioral Questionnaires. Questions will be worded to reduce stigma associated with lack of adherence.

Biomedical Markers of Adherence

Systemic drug concentrations are reliable and objective markers of adherence. TFV-DP, the intracellular metabolite of TFV, can be measured in red blood cells in dried blood spot (DBS) samples, and provides a longer-term marker of PrEP adherence than measurement of TFV in plasma. As directly observed therapy (DOT) studies have been performed for both FTC/TDF (Truvada®) and FTC/TAF (Descovy®), TFV-DP measurements in red blood cells (collected on DBS) will be used as the primary indicator of PrEP adherence and persistence. These data will be used to understand PrEP adherence in study participants. Data on FTC-TP will also be collected in this study. Plasma will also be collected and may be evaluated to understand short-term PrEP adherence, as plasma provides a more granular and narrower window of PrEP-taking behaviors.

Results from testing to assess biomarkers of PrEP adherence will not be returned to the study site or participants.

In addition to self-report, GAHT use will be evaluated during quarterly visits via the laboratory measurement of total testosterone and estradiol concentrations.

5.7 Toxicity Management

Toxicity management guidelines can be found in Appendix II (Toxicity Management).

5.8 Concomitant and Drug Interactions

Information regarding drug interactions are found in the Package Inserts for Truvada® and Descovy®. Sites need to ensure they have the most up to date version of the Package Inserts in their study-specific files as well as available for clinical reference.

All concomitant medications/preparations (prescription and non-prescription) including alternative/complementary medications/preparations (e.g., herbs, vitamins, etc.) taken within 30 days prior to enrollment and anytime thereafter during study participation will be collected in the study participant's chart and on applicable study eCRFs. Alcohol and recreational or street drug

use reported by a participant during the study will be recorded in the participant's study chart only (and not captured on the Concomitant Medication log for inclusion in the study database).

Additionally, for all participants, sites will document in eCRFs all GAHT and PrEP agents obtained outside the study site on the applicable study eCRFs.

The CMC should be contacted for any questions regarding coadministration of any of the drugs listed below.

Please note that the Package Inserts for Truvada® or Descovy® do not list any prohibited medications. The drug interaction information listed below comes directly from the Package Insert for each product.

Truvada® Drug Interaction:

Drugs Affecting Renal Function

Coadministration of Truvada® with drugs that are eliminated by active tubular secretion may increase concentrations of FTC, tenofovir, and/or the coadministered drug. Some examples include, but are not limited to, acyclovir, adefovir dipivoxil, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs. Drugs that decrease renal function may increase concentrations of FTC and/or tenofovir.

Established and Other Potentially Significant Interactions

Established and Significant[a] Drug Interactions: Alteration in Dose or Regimen May Be Recommended Based on Drug Interaction Trials (Table 7 under section 7.2 of the Truvada® Package Insert)

Concomitant Drug Class: Drug Name	Effect on Concentration	Clinical Comment
NRTI: didanosine[c]	↑ didanosine	Patients receiving TRUVADA and didanosine should be monitored closely for didanosine-associated adverse reactions. Discontinue didanosine in patients who develop didanosine-associated adverse reactions. Higher didanosine concentrations could potentiate didanosine-associated adverse reactions, including pancreatitis, and neuropathy. Suppression of CD4+ cell counts has been observed in patients receiving TDF with didanosine 400 mg daily. In patients weighing greater than 60 kg, reduce the didanosine dose to 250 mg when it is coadministered with TRUVADA. Data are not available to recommend a dose adjustment of didanosine for adult or pediatric patients weighing less than 60 kg. When coadministered, TRUVADA and Videx EC may be taken under fasted conditions or with a light meal (less than 400 kcal, 20% fat).
HIV-1 Protease Inhibitors: atazanavir[c]	↓ atazanavir	When coadministered with TRUVADA, atazanavir 300 mg should be given with ritonavir 100 mg.
lopinavir/ritonavir[c] atazanavir/ritonavir[c] darunavir/ritonavir[c]	↑ tenofovir	Monitor patients receiving TRUVADA concomitantly with lopinavir/ritonavir, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir for TDF-associated adverse reactions. Discontinue TRUVADA in patients who develop TDF-associated adverse reactions.
Hepatitis C Antiviral Agents: sofosbuvir/velpatasvir[c] sofosbuvir/velpatasvir/voxilaprevir[c]	↑ tenofovir	Monitor patients receiving TRUVADA concomitantly with EPCLUSA® (sofosbuvir/velpatasvir) or VOSEVI® (sofosbuvir/velpatasvir/voxilaprevir) for adverse reactions associated with TDF.
ledipasvir/sofosbuvir[c]		Monitor patients receiving TRUVADA concomitantly with HARVONI® (ledipasvir/sofosbuvir) without an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination for adverse reactions associated with TDF. In patients receiving TRUVADA concomitantly with HARVONI and an HIV-1 protease inhibitor/ritonavir or an HIV-1 protease inhibitor/cobicistat combination, consider an alternative HCV or antiretroviral therapy, as the safety of increased tenofovir concentrations in this setting has not been established. If coadministration is necessary, monitor for adverse reactions associated with TDF.

a. This table is not all inclusive.
b. ↑=Increase, ↓=Decrease
c. Indicates that a drug-drug interaction trial was conducted.

Descovy® Drug Interaction:

Drugs Affecting Renal Function

Coadministration of Descovy® with drugs that reduce renal function or compete for active tubular secretion may increase concentrations of FTC, tenofovir, and other renally eliminated drugs and this may increase the risk of adverse reactions. Some examples of drugs that are eliminated by active tubular secretion include, but are not limited to, acyclovir, cidofovir, ganciclovir, valacyclovir, valganciclovir, aminoglycosides (e.g., gentamicin), and high-dose or multiple NSAIDs.

Established and Other Potentially Significant Interactions
Established and Other Potentially Significant[a] Drug Interactions (Table 5 under section 7.3 of the Descovy® Package Insert)

Concomitant Drug Class: Drug Name	Effect on Concentration[b]	Clinical Comment
Antiretroviral Agents: Protease Inhibitors (PI)		
tipranavir/ritonavir	↓ TAF	Coadministration with DESCOVY is not recommended.
Other Agents		
Anticonvulsants: carbamazepine oxcarbazepine phenobarbital phenytoin	↓ TAF	Consider alternative anticonvulsant.
Antimycobacterials: rifabutin rifampin rifapentine	↓ TAF	Coadministration of DESCOVY with rifabutin, rifampin, or rifapentine is not recommended.
Herbal Products: St. John's wort *(Hypericum perforatum)*	↓ TAF	Coadministration of DESCOVY with St. John's wort is not recommended.

a. This table is not all inclusive.
b. ↓=Decrease

6.0 STUDY PROCEDURES

An overview of the study visits and evaluations schedule is provided in Appendix Ia-Ic. Presented in this section is additional information on visit-specific study procedures. Detailed instructions to guide and standardize procedures across sites are provided in the HPTN 091 SSP Manual.

6.1 Implementation Testing

A run-in period will be performed by enrolling a small number of participants at each participating site prior to full study rollout. The purpose is to fully capacitate the peer counselors and the clinicians providing integrated clinical services in the intervention.

The run-in period will follow the same study design (refer to Section 3.0) and schedule of events as the full study (refer to Sections 6.2 – 6.4, 6.6 – 6.8, and Appendix Ia – Ic), with the exception of the Qualitative Data Collection sub-study, but with limited enrollment and follow-up. Accordingly, up to 10% of site's target sample size will enroll over a 3-month period, and each participant in this group will be followed until the last participant enrolled as part of the run-in period at the site completes their 6-month follow-up visit. The number enrolled may vary by site. There will not be a separate consent for participants in the run-in period since all study procedures and relevant consent information will be the same independently if they enroll in the Implementation Testing part of the study or the full study, with the exception of the option to participate in the Qualitative Data Collection sub-study. While the run-in period is ongoing, no additional participants may be enrolled in the protocol.

The run-in period will allow the study sites an opportunity to optimize local study procedures before the full study proceeds. As such, for each study site participating in the run-in period, a study-conduct review will take place after the last participant enrolled has completed their 6-month follow-up visit. This review will be conducted in part by the HPTN Study Management Committee (HPTN SMC). The review will involve an evaluation of key operational components of the study, such as fidelity to intervention and referral procedures, data management procedures, and laboratory procedures, all in accordance with Good Clinical Practice (GCP). The review may also include evaluation of screening, enrollment, and retention data. Follow-up of the participants enrolled in the run-in period will continue uninterrupted during the time the run-in period is being evaluated. This provides for continuity of study operations at the study sites should the full study proceed.

6.2 Screening Visit

It is the responsibility of the local site to determine the best approach to screening. Multiple screening visits may be conducted, if needed, to complete all required procedures. The screening to enrollment window is 30 days, starting on the day the informed consent form is administered. Written informed consent for screening will be obtained before any screening procedures are initiated. Screening procedures will discontinue once ineligibility is determined for participants who do not meet the eligibility criteria. If a participant does not complete all screening procedures within 30 days of signing the Screening Informed Consent Form (ICF), all screening procedures must be repeated, starting with the informed consent process. Participants may rescreen once at the discretion of the IoR or their designee, and per guidance found in the SSP Manual. Further re-screening for administrative reasons may be permitted with the approval of the CMC.

Sites will follow the HIV testing algorithm for Screening included in the SSP Manual. If a reactive/positive result is obtained for any HIV test, the person is not eligible for the study, even if found to be HIV-uninfected upon confirmation. Additional testing to confirm suspected HIV infection during Screening will be performed in accordance with local guidelines. If HIV infection is confirmed, participants will receive counseling and be referred for appropriate care, as necessary.

Participants must have fasted for at least 8 hours, preferably 12 hours, prior to lipid profile sample collection. Sites should verify that a participant is has fasted prior to sample collection. If the patient has not fasted, the specimen should not be collected for lipid profile testing, and the participant should be scheduled to return to the site for sample collection prior to their Enrollment Visit.

Individuals deemed not eligible will be informed that they do not meet the elibility criteria for the study and will be referred for appropriate medical care, if necessary.

6.3 Enrollment Visit

HIV test results from Screening must be available and reviewed prior to enrollment. If a participant has a reactive test at enrollment, HIV infection should be confirmed on a second sample collected on a date different from the Enrollment visit as per the HIV testing algorithm found in the SSP Manual.

The definition of enrollment in this study is the point of randomization. That is, if a site successfully randomizes a participant in the randomization system, that participant is considered enrolled.

A complete medical history and physical exam will be performed at Screening and should include assessment for acute HIV infection. A symptoms-directed physical exam will be done at the Enrollment Visit prior to enrollment.

For participants initiating GAHT, testing for estradiol and total testosterone will need to be performed prior to hormonal therapy initiation. A GAHT initiation visit will be scheduled up to 10 days following the collection of samples for estradiol and total testosterone testing for initiation/re- initiation of GAHT. This timeframe will allow for sufficient time for sites to received laboratory results and for participants taking part in the DHI sub-study to complete the DOT phase.

6.4 Follow-Up Visits

Follow-up visits will occur on a quarterly basis at Week 13 (Month 3), Week 26 (Month 6), Week 39 (Month 9), Week 52 (Month 12), Week 65 (Month 15), Week 78 (Month 18) after enrollment, as per Appendix Ia. Mental health assessment will be included as part of the medical and physical history assessment. Specific visit windows are outlined in Section 6.5 of the protocol. Per Section 6.3, participants initiating/re-initiating GAHT will need a GAHT initiation visit up to 10 days after collection of samples for review of baseline endogenous estradiol and testosterone concentrations. See Section 6.4.2 for information on re-initiation procedures.

Fasted sampled for lipid profile testing will be collected at Week 26 (Month 6) and Week 78 (Month 18). Prior to sample collection, sites must confirm with participants that they have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If a participant has not fasted, the sample should not be collected for lipid testing, and the participant should be scheduled to return for sample collection ideally within 72 hours from the visit.

Participants who voluntarily withdraw from the study or are lost to follow-up will be contacted for an interview to explore reasons for no longer participating. These interviews can be conducted either in person or by phone, based on participant's availability and/or preference.

Week 78 (Month 18) will serve as the Termination Visit. Prior to this visit, participants should be linked to local providers for PrEP, hormonal therapy, and/or STI testing and treatment, as needed, per site SOP.

6.4.1 Follow Up Procedures for Participants Who Discontinue Study Products

A participant may discontinue use of PrEP and/or hormonal therapy and remain on study. Product may be held in response to a clinical event or participant-initiated decision. Discontinuation is defined as not using study product for 30 or more days, independently of the rational for study product discontinuation. If this occurs, study visits continue according to the Schedule of Events (SOE) found in Appendix Ia, with the exceptions noted in Tables 4 and 5.

Table 4: PrEP (held or discontinued)	
Procedure discontinued after product hold	**Notes**
Provision of PrEP	Participant should return remaining PrEP to the site if PrEP is held or discontinued.
PrEP counseling and support	Any participant who wishes to discontinue PrEP should be counseled on the implications of stopping PrEP, be offered additional risk reduction counseling and (if not during a regular visit where it is already provided) HIV testing.
Adherence and acceptability assessments	Adherence and acceptability assessments related to PrEP will be part of the ACASI. These specific questions will be included at the visit in which PrEP is held and discontinued at subsequent visits when product is not being provided (using a skip pattern).

Table 5: GAHT (held or discontinued)	
Procedure discontinued after product hold	**Notes**
Provision of GAHT	Participant should return remaining GAHT to the site if GAHT is held or discontinued.
GAHT counseling and support	Any participant who wishes to discontinue GAHT should be counseled on the clinical implications of stopping GAHT.
Estradiol and total testosterone testing	Hormonal monitoring and testing should be completed at the visit in which GAHT is held and discontinued at subsequent visits when GAHT is not being provided.
Adherence and acceptability assessments	Adherence and acceptability assessments related to GAHT will be part of the ACASI. These specific questions will be included at the visit in which GAHT is held and discontinued at subsequent visits when product is not being provided (using a skip pattern).

6.4.2 Procedures for Participants who Initiate or Re-initiate Study Products

There are some situations when a participant may initiate or re-initiate product use during follow-up. This includes product being held due to a clinical event or because a participant declines either PrEP or GAHT during follow-up. Re-initiation is defined as restarting study product use after 30 or more days off study product.

Participants who decline PrEP can begin (or reinitiate) PrEP at any time up to and including their Week 39 visit unless contraindicated. At the visit when PrEP is to be initiated or reinitiated, the following procedures should be conducted, and **results should be available prior to PrEP dispensation**:

- Creatinine clearance
- HIV testing
- Fasting lipid profile (for participant reinitiating PrEP, lipid profile is not required if done within six months of product re-initiation)

Participants may begin co-located GAHT any time after enrollment (Immediate Intervention Arm) or after the 6-month visit (Deferred Intervention Arm) up to and including the Week 39 visit unless contraindicated. At the visit when co-located GAHT is to be initiated or reinitiated, the following procedures should be conducted, and **results should be available prior to GAHT dispensation**:

- Estradiol and total testosterone testing

If either product was held due to a clinical event, sites need to assess the event and confirm resolution. This may be done by clinical assessment, medical history, and/or laboratory assessment.

The CMC may be consulted for additional guidance prior to initiation/re-initiation of study product(s).

6.4.3 Procedures for Participants with Suspected or Confirmed HIV Infection

HIV testing will be performed at all scheduled study visits (with the exception of the GAHT Initiation Visit). In addition, 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 ribonucleic acid (RNA) test that, is able to detect early HIV infection. If possible, an assay that is U.S. FDA-cleared for early HIV diagnosis such as the Aptima HIV-1 RNA Qualitative Assay should be used.

Regardless of whether HIV RNA testing is used for diagnostic testing, HIV acquisition after study enrollment must be confirmed in all cases using two independent samples collected on different days, as per HIV testing algorithm found in the SSP Manual.

Participants who have any reactive or positive HIV test result during follow-up visits will have further testing to confirm infection, as described in the SSP Manual and Appendix Ib. Samples from participants who are confirmed to be HIV-infected should be sent to a local laboratory for resistance testing to assist with clinical management (results from resistance testing performed in local laboratories should not be reported to the HPTN Statistical Data Management Center [SDMC] or the HPTN Laboratory Center [LC]). The site IoR or designee should consult the HPTN LC if confirmatory testing does not confirm that the participant is HIV-infected.

As outlined in Appendix Ib, participants who are confirmed to be HIV-infected will be linked for local HIV care and will have an additional visit to follow-up on linkage to care three months after the HIV confirmation visit. At this visit, participants will be terminated from the study. Additionally, participants will be offer linkage to GAHT services.

6.5 Visit Windows

For each required study visit, there is an allowable visit window specifying on which study days (post-enrollment) the visit is "allowed" to be completed. The allowable visit windows are

contiguous from visit to visit, and do not overlap. Within each allowable visit window, there is a target visit window and study visits should ideally be conducted within this window. These windows are outlined in Table 6 below. If more than one visit is necessary to complete all visit procedures, these could be completed during multiple days within the allowable visit window.

Table 6: Study Visit Windows

Visit	Target Visit Day	Target Visit Window	Allowable Visit Window
Screening			Up to 30 days before enrollment
Enrollment	Day 0		
GAHT Initiation Visit			Up to 10 days post blood collection for estradiol and total testosterone testing
Week 13	Day 91	Day 77 - 105	Day 77 - 153
Week 26	Day 182	Day 168 - 196	Day 154 - 244
Week 39	Day 273	Day 259 - 287	Day 245 - 336
Week 52	Day 365	Day 351 - 379	Day 337 – 427
Week 65	Day 456	Day 442 - 470	Day 428 - 518
Week 78	Day 547	Day 533 - 561	Day 519 – study closure

6.6 Qualitative Data Collection

In-depth interviews (IDIs) will be conducted with a subset of approximately 60 participants, randomized to either of the study arms, across all five sites or until saturation of information is reached. Additional participants may be enrolled based on characteristics of PrEP use. Individual sites may enroll approximately 12 participants in this sub-study. Approximately half of participants will be of the Immediate Intervention Arm and approximately half will be of the Deferred Intervention Arm. Protocol chairs will work closely with sites to evaluate enrollment targets and overall qualitative goals. The IDIs are designed to better understand decision making around PrEP, experiences with PrEP use, experiences with co-located services, and acceptability of co-located services.

In-depth interviews will be conducted among four groups of participants:

1. TGW who accept/initiate PrEP at enrollment.
2. TGW who decline PrEP at enrollment.
3. TGW who discontinue PrEP at any point after enrollment.
4. TGW who decline PrEP at enrollment and accept PrEP at any point after enrollment.

Approximately 30% of those enrolled in the IDI sub-study at each site should be TGW who decline PrEP at enrollment or discontinue PrEP at any time after enrollment.

Participants who accept/initiate or decline PrEP at enrollment who are selected and consent to participate in the qualitative component at enrollment, will have one interview at baseline (Enrollment), one interview at Week 52 (12 months) and one interview at the end of the study, Week 78 (18 months) for a total of three visits.

To gain a better understanding of participants who discontinue PrEP during the study, some participants at each site will be selected after enrollment to participate in the qualitative component. Participants who are selected and consent to participate in the qualitative component at the point of discontinuation of PrEP during the study will have one interview at the visit they discontinue PrEP and at least one at the end of the study Week 78 (18 months). If time allows an interview should be completed at least 6 months from the initial interview and 6 months from the end of the study.

Among TGW participants who accept/initiate PrEP at enrollment or discontinue PrEP during the study, the qualitative component will explore:

- Decisions and rationale to accept/initiate and/or discontinue PrEP
- Barriers and facilitators to PrEP adherence
- Experiences with co-located services of GAHT and HIV prevention services, including acceptability and PrEP adherence (for those in the Deferred Intervention Arm: Experiences accessing GAHT separately from PrEP services)
- Perception of risk for acquiring HIV

Among TGW participants who decline PrEP at enrollment the qualitative component will explore:

- Decisions and rationale to decline PrEP
- Knowledge and perceptions of PrEP
- Concerns about the use of PrEP
- Perceptions of the benefits of PrEP use
- Acceptability of PrEP use in their community
- Perception of risk for acquiring HIV
- Experience with co-located services of GAHT and HIV prevention services

The semi-structured qualitative interview guide will provide a general structure for the discussion. The interview guide will have a summary section with pre-coded answers and summary fields. The interviewer will document findings during or immediately after the interview to begin processing the information, begin to look for emerging themes, and to recognize when the study is reaching saturation.

All IDIs will be conducted in a private setting within the participants' research site. Interviews will last approximately 60-90 minutes. Interviews will be conducted in a study preferred language, digitally recorded, then transcribed and subsequently translated into English as needed.

Additional information will be included in the SSP.

6.7 Drug-Hormone Interaction Sub-study

In the iPrEx trial and the subsequent open-label extension cohort study, 14% of participants who received PrEP self-identified as TGW. While incidence of HIV seroconversion did not differ between cisgender MSM and TGW, TGW exhibited lower PrEP metabolite concentrations.[3] In PrEP clinical trials, while non-adherence is likely the dominant cause of suboptimal drug concentrations, numerous other factors could modify drug concentrations in addition to adherence, including the potential impact of elevated estrogen concentrations on PrEP pharmacology in TGW. Subsequent, smaller studies were conducted to evaluate the potential relationship on estrogen-based GAHT on PrEP pharmacokinetics (PK).[74,76] In the JHU-CFAR TGW study, plasma TFV and FTC trough concentrations (C_{tau}) were 32% (p = 0.01) and 32% (p = 0.04) lower, respectively, in TGW as compared to cisgender men (CGM) after directly observed FTC/TDF dosing to steady-state; median plasma TFV concentrations diverged in CGM vs. TGW approximately 5 hours after-dosing (Figure 3). There was no impact of PrEP on hormone levels. The Thai Red Cross reported that estradiol valerate 2 mg and cyproterone acetate 25 mg reduced TFV concentrations by 18% (C_{tau}), while FTC/TDF did not affect plasma estrogen or testosterone concentrations.[77] AUC changes were of similar magnitude in both studies.

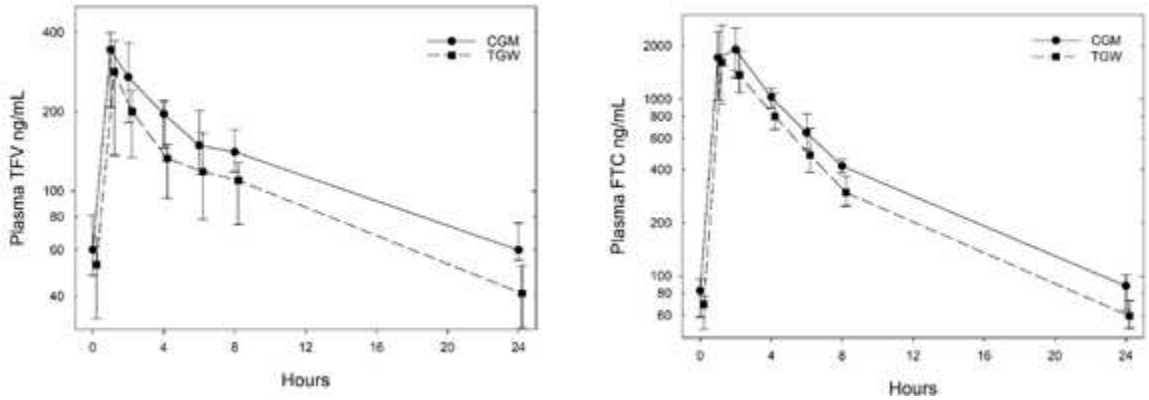


Figure 3. Concentration vs. time plots for plasma tenofovir (TFV, Panel A) and emtricitabine (FTC, Panel B), and peripheral blood mononuclear cell (PBMC) TFV diphosphate (TFV-DP, Panel C) and FTC triphosphate (FTC-TP, Panel D) comparing transgender women (TGW; dashed lines, squares) and CGM (solid lines, circles). Data are medians with error bars indicating lower and upper quartiles. Time values are slightly offset to avoid overlap of data.

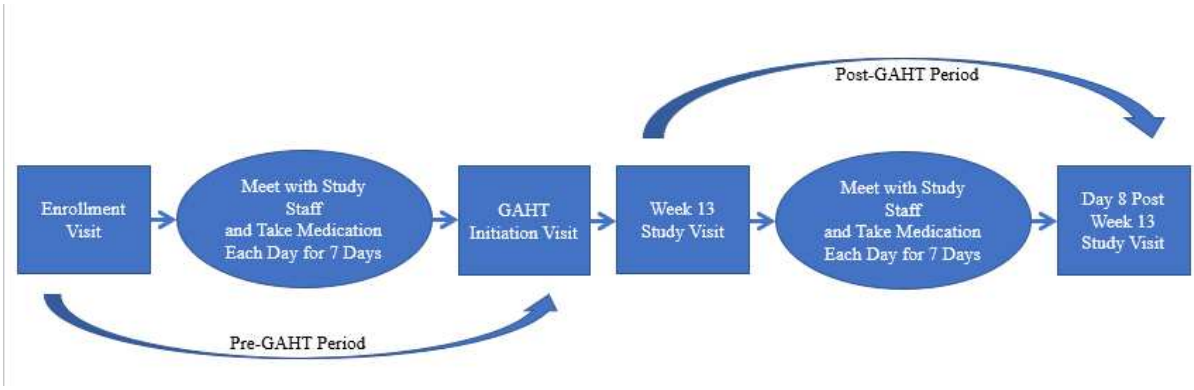
With the recent approval of FTC/TAF (Descovy®) as a prevention option for TGW, the goal of this substudy is to characterize the relationship between GAHT and PrEP concentrations. In order to investigate this relationship, directly observed therapy (DOT) of study product is required to ensure that potential pharmacologic differences are not due to lapses in PrEP adherence. DOT can take place either at the study site or by videoconferencing on a cell phone, computer, or tablet, using a platform like FaceTime, WhatsApp, and Google Duo. These platforms feature end-to-end encryption, meaning that only the communicating users can read the messages. No recordings of session will take place, so no data about the participant will be stored via these apps.

Consequently, the DHI substudy will include a one-week DOT **pre-GAHT** dosing phase to occur immediately after enrollment (Period 1), and a **post-GAHT** dosing phase, which will occur directly following the participant's first quarterly visit (week 13) and will include one-week of DOT of PrEP (Period 2). Refer to Figure 4 for an overview of the visit schedule for the DHI sub-

study. The mechanism used for DOT may be face-to-face or video-based; DOT options will be described in the SSP.

Post-GAHT PK assessment initiates at week 13 (month 3) in order to streamline the total number of visits required by the study participant. All participants will have a study visit at week 13, as described in the main study's schedule of events (Appendix 1a). Therefore, the directly observed therapy (DOT) phase for the post-GAHT PK assessment is coordinated with this visit in order to circumvent the need for an additional participant visit and blood collections, minimizing burden to study participants.

Figure 4. Drug-Hormone Interaction Substudy Visit Schedule



Pharmacologic assessments of TFV, when administered as TDF or TAF, can be conducted in plasma, PBMC, and red blood cells (RBC) collected as DBS. While each offers its advantages, and provides complementary information regarding PrEP usage, because of the DOT-component of the DHI sub-study, analysis will be focused on assessments of TAF and TFV in plasma and TFV-DP (intracellular metabolite of TAF and TDF) in PBMC. Due to the accumulation of TFV-DP in RBC over time, and the significantly longer half-life of TFV-DP in RBC as compared to PBMC and plasma, TFV-DP concentrations from DBS represent *average* concentrations in the months prior to sampling and are therefore relatively resistant to recent changes in adherence. Conversely, plasma PrEP concentrations (and to an extent PBMC PrEP metabolite measurements) are more reflective of recent adherence and are therefore more amenable to evaluate pharmacologic differences following a short period of DOT.

For those participants enrolled in the DHI sub-study, directly following one-week of DOT to ensure PrEP regimen compliance, participants will present for sparse PK sampling. Blood for plasma and PBMC isolation will concurrently occur pre-dose, as well as 1 hour and 4 hours after observed PrEP dosing. Sampling will include plasma isolation for FTC, TAF, and TFV testing, and PBMC isolation for TFV-DP and FTC-TP measurements. This sparse sampling scheme will be used to estimate steady-state pre-dose trough concentration (C_{tau}) for the aforementioned analytes. We will estimate peak (C_{max}), and four-hour area under the concentration time curve (AUC_{0-4}) concentrations for analytes in plasma and PBMC before and after GAHT dosing (Period 1 and Period 2). While the C_{max} and AUC_{0-4} estimates will be crude given, the very sparse sampling, their inclusion will increase the sensitivity of capturing differences in PrEP metabolism caused by the addition of GAHT. In addition, if initial inspection of the data allows and external raw PK data on FTC/TAF dosing are available, a more formal population pharmacokinetic model will be explored to evaluate changes in PK parameters resulting from DHI. Additional serum samples will be collected during the Period 1 (pre-GAHT) and Period 2 (post-GAHT) pre-dose

time points for measurement of endogenous hormones, including estradiol, total and free testosterone, luteinizing hormone, and follicle stimulating hormone. This testing will be conducted retrospectively to provide additional information on the potential influence of GAHT on PrEP (FTC/TAF) pharmacology.

6.8 Behavioral Measures

At enrollment and during follow up visits as noted in Appendix 1a, participants will complete a brief ACASI questionnaire at a private computer terminal located at the study site.

Participants will be queried on the contextual factors and experiences which have shown to have an impact on product use and HIV risk. Items from the following domains will be included in the ACASI interview or eCRF at some or all visits as appropriate:

- Sociodemographic characteristics
    - Gender identity
    - Race/Ethnicity
    - Housing situation
    - Employment status
    - Income, including sex work engagement
- Partnership characteristics and partner's HIV status
- Sexual behaviors
- HIV risk perception
- Barrier and facilitators to PrEP use
- Alcohol and drug use
- Intimate Partner Violence
- Interest in emerging HIV prevention interventions
- Hormonal therapy use and adherence
- Non-prescription hormone and/or soft-tissue filler use including sites of soft-tissue fillers/implants
- Anatomy inventory
- Social, legal and medical gender affirmation
- Access to gender and primary care services
- Beliefs about drug-drug interactions between hormones and PrEP

The acceptability of the intervention and standard of care will also be assessed:

- Co-location of hormonal therapy and PrEP services
- Peer navigation using SBCM
- Referral link to GAHT (as appropriate)

Site Community Advisory Boards (CAB) will assist in developing and piloting this questionnaire.

6.9 Interim Contacts and Visits

Interim contacts and visits may take place between regularly scheduled visits. These contacts/visits may be done at participant request (e.g., to receive further counseling or clarify

any questions) or as deemed necessary by the investigator or designee at any time during the study (e.g., to follow-up on an adverse event). Procedures to be performed during these contacts/visits will be based on the reason for it. All interim contacts and visits will be documented in participants' study records and on eCRFs, if applicable.

7.0 SAFETY MONITORING AND ADVERSE EVENT REPORTING

7.1 Adverse Event Definition and Reporting

An adverse event (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 an investigational product. As such, an AE can be an unfavorable or unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the product.

With appropriate permission of the participant, whenever possible, records from all non-study medical providers related to AEs will be obtained and required data elements will be recorded on study eCRFs. All participants reporting an AE will be followed clinically, until the AE resolves (returns to baseline) or stabilizes.

Study site staff will document in source documents all AEs independently of grading or relationship to study products (e.g. PrEP or hormonal therapy). AEs that will be reported on an eCRF are:

- Grade 3 or higher AEs regardless of relatedness to study products
- Any AE that leads to a study product hold (temporary or permanent) or change in regimen regardless of severity and presumed relationship to study products.
- All Serious Adverse Event (SAE)/ Expedited Adverse Event (EAE)

See Section 7.5 for information on grading of severity of events.

Relatedness is an assessment made by a study clinician of whether or not the event is related to study products. The relationship of all AE to study products (as defined in Section 5.1) will be assessed as specified in Version 2.0, January 2010 of the DAIDS Expedited Adverse Event (EAE) Reporting Manual.

7.2 Expedited Adverse Event (EAE) Reporting

Requirements, definitions, and methods for expedited reporting of adverse events are outlined in Version 2.0 of the DAIDS EAE Manual, 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.

7.3 Reporting to DAIDS

The DAIDS Adverse Event 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.

7.4 Reporting Category for this Study

The Serious Adverse Event (SAE) Reporting Category, as defined in Version 2.0 of the DAIDS EAE manual, will be used for this study (the definition of an SAE is also included in the manual).

These reporting requirements are required for each study participant from enrollment (defined as the act of randomization) until their follow-up in the study ends. After this time, sites must report to DAIDS serious, unexpected, clinical suspected adverse drug reactions, as defined in Version 2.0 of the DAIDS EAE manual, if the study site becomes aware of the event on a passive basis, i.e., from publicly available information.

In addition to submitting EAE information to the DAIDS 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 in accordance with all applicable regulations and local IRB requirements.

7.5 Grading Severity of Events

The Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, Corrected Version 2.1, July 2017, will be used for determining and reporting the severity of adverse events. 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.

7.6 Social Impact Reporting

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 being HIV-infected or at risk or "high risk" for HIV infection). 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 applicable eCRF(s) 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 SSP Manual. While maintaining participant confidentiality, study sites may engage their CAB in exploring the social context surrounding instances of social impacts, to minimize the potential occurrence of such an impact.

8.0 STATISTICAL CONSIDERATIONS

8.1 Review of Study Design

This is a multi-site, open-label study with each participant randomized 1:1 to an Immediate Intervention Arm vs. Deferred Intervention Arm. The study is designed to evaluate whether an intervention that integrates HIV prevention services co-located with GAHT and supported by PHN using SBCM, demonstrates greater engagement in the HIV prevention strategies for HIV-uninfected TGW compared to SOC (i.e., referral for GAHT and case management).

8.2 Endpoints

8.2.1 Primary Endpoints

Consistent with the primary study objective to assess acceptability and feasibility of delivering integrated HIV prevention services co-located with gender-affirming hormone therapy (GAHT) and PHN using SBCM for TGW, the following endpoints will be assessed:

- Number of participants accepting co-located GAHT services at baseline and subsequent quarterly study visits.
- Number of participants who report desire for co-located services at the end of the study.
- Number of participants retained at Weeks 26, 52 and 78 per study arm.
- Number and content (tracking a participant vs. engagement with a participant) of Peer Health Navigator contacts (text message, email, phone, in-person).

Consistent with the primary study objectives to assess PrEP adherence and persistence for HIV-uninfected TGW in the Immediate Intervention Arm vs HIV-uninfected TGW in the Deferred Intervention Arm, the following congruent endpoints will be assessed:

- Time to PrEP initiation as documented in study eCRFs.
- TFV-DP and FTC-TP levels in DBS measured at quarterly follow up visits after PrEP initiation.
- Drug not dispensed among those who initiate PrEP.
- Self-reported adherence to daily PrEP.
- Time to first PrEP discontinuation

8.2.2 Secondary Endpoints

Consistent with the secondary study objectives of determining annual incidence of HIV infection, the following endpoint will be assessed:

- Number of documented incident HIV infections during follow-up.

Consistent with the secondary study objectives of determining baseline prevalence and annual incidence of STIs (gonorrhea [GC], chlamydia [CT], and syphilis) and to examine changes in STI incidence over time by study arm, the following endpoint(s) will be assessed:

- Prevalence of STI infection (GC, CT, syphilis) at baseline.
- Incidence of STI infection (GC, CT, syphilis) during follow-up.

Consistent with the secondary study objective of examining changes in sexual risk-taking behavior (e.g., number of serodiscordant or HIV-unknown serostatus sexual partners; number of condomless anal/vaginal sex episodes with these partners):

- Sexual risk-taking behaviors (e.g., number of serodiscordant or HIV-unknown serostatus sexual partners; number of condomless anal/vaginal sex episodes with these partners) measured by ACASI assessments at enrollment and quarterly through Week 78.

Consistent with the secondary study objective of evaluating the cohort's suitability for future PrEP intervention studies (e.g., prevalence of renal insufficiency, hepatitis B virus (HBV) infection, hepatitis C virus (HCV) infection, etc.), the following endpoint(s) will be assessed:

- Baseline laboratory data on all participants.

Consistent with the secondary study objective to identify demographic, behavioral, socioeconomic, and psychosocial factors related to: (1) PrEP uptake and PrEP adherence over time, (2) PrEP persistence, and (3) interest in future HIV research, including research involving injectable and implantable agents for PrEP among HIV-uninfected TGW:

- Individual-level qualitative interview data on a subset of participants addressing core reasons for initiating, discontinuing and/or refusing PrEP.
- ACASI data addressing core reasons for initiating, discontinuing and/or refusing PrEP.
- Interest in future HIV research, collected at Enrollment and Weeks 26, 52, and 78.
- Additional demographic, behavioral, socioeconomic, and psychosocial characteristics collected at Enrollment and quarterly through Week 78.

Consistent with the secondary study objective to assess use of medically-prescribed and non-prescription gender-affirming interventions, including exogenous hormones, soft tissue fillers/silicone, and feminizing surgeries (e.g., breast augmentation, vaginoplasty/labiaplasty, orchiectomy, etc.), the following endpoint(s) will be assessed:

- ACASI and/or interviewer-administered questionnaires inquiring frequency and type of intervention in the past three months at enrollment and quarterly follow up visits.

8.2.3 Exploratory Endpoints

Consistent with the first three, exploratory objectives described in Section 2.3, the following exploratory endpoints will be assessed.

- Perceived drug-hormone interactions: Questions on beliefs about drug interactions between antiretroviral agents and gender-affirming hormonal therapy collected at enrollment and quarterly follow up visits.
- Experience in intervention trial: Self-reported experiences of participating in an interventional study that includes biomedical and behavioral assessments, including the social impact of participation. Qualitative and quantitative evaluations will be performed at the termination visit.

Consistent with the exploratory study objective to assess safety of the intervention, the following endpoint(s) will be assessed:

- Reasons for discontinuation of any of the study products (GAHT, Truvada®, Descovy®).

- Grade 3 and above adverse events.
- Social harms reported by participants in the intervention arm.
- Additional exploratory endpoints will use laboratory assessments to characterize incident HIV infections. These assessments may include viral load testing, HIV drug resistance testing, ARV drug testing, phylogenetic analysis, and analysis of the host response to HIV infection.

Please refer to Section 8.7.2 for information on the exploratory endpoint related to the potential impact of hormonal therapy on PrEP concentrations.

8.3 Sample Size

There is limited data on PrEP uptake and adherence specific to the TGW population, with the published data being highly variable.[3,56,78-87] Moreover, the TGW population is a hard to reach population requiring multiple sampling and recruitment strategies. Given the unique challenges described above, the sample size is determined on the basis of the statistical power to detect a hypothesized difference in proportions between the Immediate vs Deferred Intervention arms, taking logistical and operational constraints regarding recruitment of HIV-uninfected TGW into consideration.[1]

Figure 5 shows the number of individuals needed per study arm to achieve 90%, 85%, and 80% statistical power to detect a pre-determined difference in proportions $p_1 - p_0$ between the Immediate Intervention Arm vs the Deferred Intervention Arm, under 1:1 randomization, with p_1 and p_0 denoting the proportion of HIV-uninfected TGW satisfying the condition of interest in the Deferred and Immediate Intervention Arms respectively. The horizontal axis depicts a range of plausible values of $p_1 - p_0$.

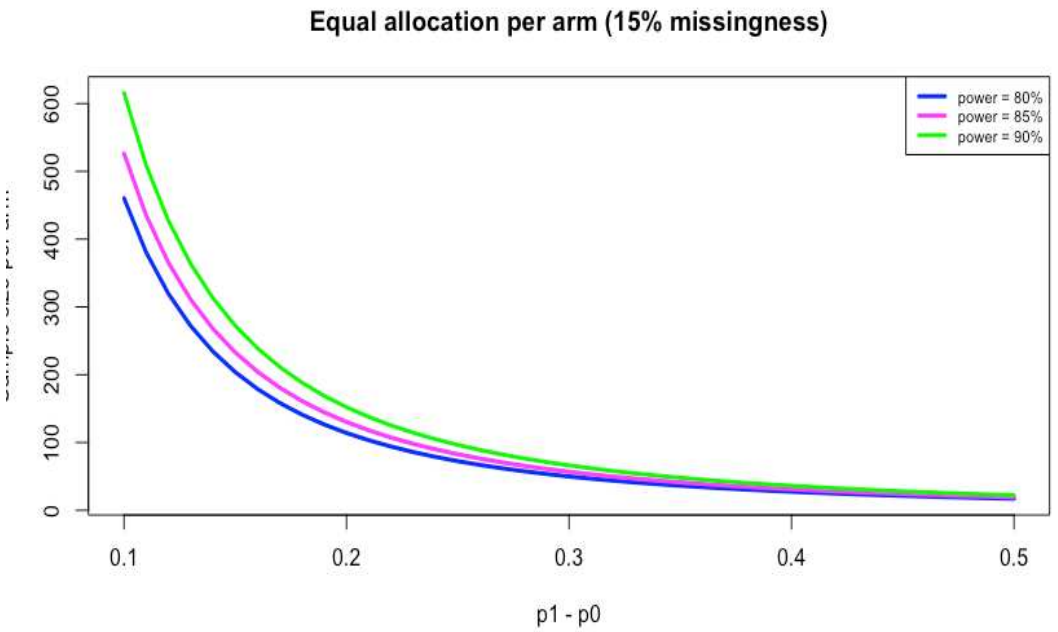


Figure 5. Sample sizes needed to achieve power (80%, 85%, 90%) for a two-sided test in proportions for an individually randomized trial with 1:1 randomization based on different values of hypothesized differences in proportions. For PrEP adherence, the hypothesized value under the alternative is 0.2.

Current research on PrEP uptake is limited, although existing data show low rates of PrEP uptake among TGW.[3,78-80,88,89] Among HIV-uninfected TGW randomized to the Immediate Intervention vs. Deferred Intervention Arms, the study is being powered to detect a 20 percentage-point difference in PrEP adherence and a 25 percentage-point difference in PrEP uptake between the Deferred Intervention Arm and Immediate Intervention Arm at Week 26.[2] We assume that the uptake, adherence and retention rates will be the same for the two PrEP agents (FTC/TAF and FTC/TDF).

We determine the conservative sample sizes needed to detect a difference of $p_1 - p_2$ between proportion of HIV-uninfected TGW adhering to PrEP between the Deferred and Immediate Intervention Arms at week 26, targeting 90% power to detect statistically significant differences at the alpha 0.05-level based on a two-sided test in proportions.[90]A total of 262 HIV-uninfected

TGW will be needed to achieve 90% statistical power for detecting a difference in proportions of 20% adhering to PrEP between the Deferred vs Immediate Intervention Arms. This sample size also satisfies power requirements for PrEP uptake. Assuming an ~85% retention rate throughout the primary 6-month follow-up period, we will target enrolling total of approximately 310 HIV uninfected TGW individuals into study. Projected sample sizes are shown in Table 7. Equal 1:1 randomization is being used.[91,92]

Table 7. Projected Sample Size detecting the assumed differences in proportions at the end of 6-months with 90% power.

	n_1	n_2	n needed	n required (accounting for 15% attrition)	Δ in Proportions (p)	Outcome
PrEP Adherence	131	131	262	310	0.20	Proportion adherent to PrEP at 6 months

^ Initial baseline prevalence estimates derived from studies of TGW women currently in the field.

8.4 Accrual and Retention

Approximately 310 HIV-uninfected TGW will be enrolled and randomized to the Immediate and Deferred Intervention Arms across the five study sites. An average annual retention rate of at least 85 percent will be targeted. Differential enrollment targets will be considered for the sites, with higher enrollment targeted for the Brazil site and competitive enrollment among remaining U.S sites. We estimate 560 TGW will be screened for the study to achieve the enrollment target of approximately 310 TGW (80% of TGW screened).

[a] Considering that the variance, and therefore sample size is largest when p=0.5, we obtain conservative sample sizes by setting H_0: 0.5 –d/2 and H_1: 0.5 + d/2, where d is the hypothesized difference in proportions between intervention and Deferred intervention arms.
[b] Note that since the hypothesized effect size for PrEP adherence is smaller than for PrEP uptake (20% vs 25%), the sample size needed to achieve 90% power based on PrEP adherence will also achieve greater power for PrEP uptake, hence powering the sample size for the prevention cohort study on PrEP adherence.

8.5 Random Assignment/Study Arm Assignment

A stratified/block randomized trial will be used, stratifying differentially by site. Differential number of TGW will be enrolled at each site and randomized 1:1 using a random number generator to each study arm.

8.6 Statistical Analysis

This section briefly describes the final study analyses. Detailed technical specifications of the statistical analyses will be described in a separate Statistical Analysis Plan.

8.6.1 Primary Analyses

Study arms will be compared for baseline characteristics using descriptive statistics.

For each study visit, PrEP uptake will be defined as the proportion of TGW who initiate PrEP at any time up to and including that given visit among all TGW enrolled in the trial. PrEP uptake will be compared between study arms at the end of Week 26 for the primary objective. Confidence limits will be computed using the binomial distribution.

At each quarterly visit, the proportion of TGW adherent to PrEP is defined as the proportion of enrolled TGW who have confirmed protective levels of PrEP in their blood at that study visit. PrEP adherence (using either TDF or TAF-based regimens) will be assessed objectively using thresholds established by recently completed DOT studies. TGW who are missing drug level assessments, and who do not have drug dispensed at their most recent visit will be defined as non-adherent at that visit. The proportion of TGW determined to be adherent at Week 26 will be compared between the two study arms for the primary objective. Confidence limits will be computed using the binomial distribution.

PrEP persistence is defined as the average of each participant's mean number of visits adherent to daily PrEP. The mean number of visits adherent to daily PrEP will be (i) zero for TGW who never initiate PrEP during the study and (ii) the proportion of visits where the participant was confirmed to have protective levels of PrEP (using either TDF or TAF-based regimens) in blood according to objective thresholds established by recently completed DOT studies. PrEP persistence will be compared between study arms.

To assess acceptability in future use of the study intervention, the percentage (with 95% CI) of participants who report an interest in future use of co-located GAHT and peer-delivered health navigation model for HIV prevention in the future will be calculated among those enrolled in each study arm.

Descriptive summaries will be used to summarize and assess different aspects of feasibility such as recruitment, retention, and frequency and content of Peer Health Navigator contacts (text message, email, phone, in-person).

The proportion of individuals on each of the two PrEP agents (Truvada® vs Descovy®) will be reported at baseline, 13- and 26-week visits. If a significant imbalance is detected between arms at any of these visits, the primary analysis will be adjusted for PrEP agent using regression and/or causal inference methods. Similar strategies will also be employed if differential missingness is observed in each of the primary endpoints between the two arms.

8.6.2 Secondary Analyses

The data analysis plan is described below for each secondary endpoint defined in Section 8.2.2.

Incident HIV-infections
Descriptive statistics will be obtained for the number of incident HIV infections at each time point by arm. Poisson regression models with person time will be used for estimating HIV incidence by arm.

Sexually transmitted infections (STIs)
Descriptive summaries will be used to present the number of active bacterial STIs and the HBV infections at baseline as compared to selected subsequent visits for each study arm. Logistic regression models will be used to calculate STI prevalence at each time point and Poisson regression models will be used to calculate STI incidence by arm.

Sexual risk-taking behavior
Exploratory statistics will be used to explore and summarize sexual risk-taking behavior collected via ACASI. Summary plots will be produced for longitudinal changes in sexual risk-taking behavior among study participants.

Baseline laboratory data
Descriptive statistics will be obtained to summarize all baseline variables. Logistic regression models will be used for estimating prevalence of baseline conditions.

Reasons HIV-uninfected TGW choose to initiate or refuse PrEP
Descriptive summaries, and exploratory statistics will be used to explore patterns in reasons for refusing PrEP. Reasons for PrEP initiation and/or refusal obtained from qualitative interview data will be listed and compared to quantitative data. Logistic regression will be used for assessing associations between assumed characteristics and PrEP refusal.

Determinants of PrEP uptake, adherence and persistence, and interest in future HIV research
Descriptive summaries, and exploratory statistics will be used to explore patterns in factors affecting interest in PrEP uptake, PrEP adherence, and future HIV research. Regression models will be used to explore associations.

Use of gender-affirming hormone therapy
For each study visit, GAHT uptake will be defined as the proportion of TGW who initiate GAHT at any time up to and including that given visit among all TGW enrolled in the trial. At each quarterly visit, the proportion of TGW adherent to GAHT is defined as the proportion of enrolled TGW at that study visit who self-report taking 80% of prescribed doses of GAHT. GAHT persistence is defined as the average of each participant's mean number of visits adherent to GAHT as prescribed.

8.6.3 Exploratory Analysis

The data analysis plan is described below for each exploratory endpoint defined in Section 8.2.3.

Perceived drug-hormone interactions

Descriptive summaries, and exploratory statistics will be used to summarize data and explore patterns among self-reported perceptions about drug interactions between AUC agents and

gender-affirming hormonal therapy. Longitudinal regression models will be used to assess changes over time.

Experience in intervention trial

Descriptive summaries, and exploratory statistics will be used to summarize data and explore patterns among quantitative data. Qualitative sub-study data analyses will be conducted on an ongoing basis alongside data collection.

Secondary laboratory assessments

Summary plots and descriptive tables of local laboratory values will be generated for baseline values and for values measured during the course of the study by treatment arm and visit. For each local laboratory measure, summary statistics will be presented by treatment arm and timepoint, as well as changes from baseline.

Discontinuation due to adverse events

The number and percentage of participants who discontinue study product administration and who terminate the study early will be tabulated by reason, grade and treatment arm. For any reasonably common AEs (> ~20 events), exploratory analyses will be conducted to assess correlates of the AE, including demographics and duration and patterns of PrEP use, within the limits imposed by the small expected number of events.

8.6.4 Missing Data

Missing outcome data is a threat to the validity of treatment effect estimates in randomized controlled trials. To achieve unbiased statistical estimation and inferences using methods outlined in this protocol, missing data need to be missing completely at random (MCAR). MCAR assumes that missingness does not depend on any observed or unobserved data. When missingness is negligible, statistical methods based on the MCAR assumption can be used with limited impact on the analysis. When the frequency of missing data is more substantial, methods that require the MCAR assumption may give misleading results. In this situation, statistical methods will be performed based on appropriate modeling assumptions and adjusted using weighting methods, or combined with imputation, under the assumption that the data are missing at random (MAR). MAR assumes that the probability of an observation being missing only depends on the observed responses or covariates. Thus, this assumption is less stringent than the MCAR assumption. Weighting adjustments and imputation methods are valid under MAR. We will consider including any of the available baseline predictors of the missing outcomes as covariates in statistical models.[93-96]

8.7 Analysis of Sub-studies

8.7.1 Qualitative Analysis

The qualitative interviews will be audio recorded and transcribed verbatim, then translated into English, if necessary. Transcripts will be uploaded into qualitative data management software for coding and analysis. Data will be coded using a priori topical codes from the interview guides. Codebooks will be modified iteratively based on emergent themes throughout the coding progresses. Any discrepancies between coders will be discussed and resolved by consensus.

Topical codes will then be read across transcripts and grouped by emergent themes within each topic using a content analysis approach.

8.7.2 Drug-Hormone Interaction Sub-study

Driven by logistical and operational constraints, the sub-study will include up to 50 participants in the U.S. randomized to either of the study arms. This participant subset will be sequentially selected from participants who consented to the DHI sub-study and choose Descovy® as the PrEP agent and choose to initiate PrEP and GAHT at the Enrollment Visit. Table 8 shows the resulting statistical power for a range of assumed effect sizes and standard deviations in plasma TFV (when FTC/TDF was the PrEP regimen used).

Table 8. Power to detect differences of 'delta' in TFV concentrations before and after initiating GAHT for different assumed pooled standard deviations, accounting for 15% missingness.

		Pooled Std Deviation				
		40	50	60	70	80
n=50	20	89	72	56	44	36
Delta	30	100	97	89	78	67
	40	100	100	99	95	89
	50	100	100	100	100	98

Descriptive statistics and graphics will be used to summarize the distribution of laboratory assays measured of the sub-sample of TGW participating in the DHI sub-study at each timepoint and over time. Paired comparisons (descriptive and regression based) will be performed to compare changes in these assays pre- and post-initiation of GAHT. Descriptive statistics will be used to explore potential changes in the concentration of PrEP drugs in those receiving GAHT among this subset of TGW. Mathematical models constructed from the data and leveraging data from previous research (e.g., Thai Red Cross and JHU CFAR, DISCOVER) can be used to evaluate the impacts of hormonal therapy on drug concentrations in this broader population.

Endpoint

Consistent with the exploratory objective to examine the pharmacologic relationship between hormonal therapy and PrEP concentrations:

- PrEP drug and metabolite concentrations (plasma: TAF, TFV, FTC; PBMC: TFV-DP, FTC-TP) will be measured.
- Serum estradiol, testosterone (free, total), LH, FSH will be measured.
- Drug and hormone concentrations will be measured prior to and after administration of hormonal therapy.

8.8 Process Evaluation

This study will evaluate the effect of a multi-component intervention on PrEP uptake and adherence. The trial will not be fully powered to investigate which intervention element or component is making the greatest impact on participant outcomes. Process indicators and evaluation measures will be collected (e.g., number, type, and duration of contacts with a PHN) to

learn about the process of intervention implementation and participant engagement with intervention components. Site-level factors will also be evaluated (e.g., availability and ease of transportation to/from sites). Process measures may also enable an in-depth modeling analysis of each element of the intervention to suggest what combination may be making the most impact.

8.9 Data and Safety Monitoring Oversight

Close cooperation between the Protocol Chair, co-Chair, study site Investigator(s), DAIDS Medical Officer (MO), LOC Clinical Research Manager (CRM), SDMC Biostatistician, SDMC staff, HPTN Laboratory Center (LC), and other study team members will be necessary in order to monitor participant safety and to respond to occurrences of toxicity in a timely manner.

The study site investigators are responsible for continuous close monitoring and management of AEs in conjunction with IoRs. 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 and for alerting the CMC if unexpected concerns arise.

A sub-group of the Protocol Team, including the Protocol Chair and co-Chair, DAIDS Medical Officer, site clinicians will serve as members of the CMC. The CMC provides support to site clinicians regarding individual participant clinical management (e.g., questions related to eligibility, toxicity management, clinical holds of study drug, permanent discontinuations, etc.).

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.

Participant safety data is also monitored by the SDMC staff who review incoming safety data for completeness and consistency on an ongoing basis. Events identified as questionable, inconsistent, or unexplained will be queried for verification. AE reports submitted in an expedited manner to the DAIDS Safety Office will be forwarded to the DAIDS Medical Officer for review.

The HPTN Study Monitoring Committee (SMC) will review all safety data. The SDMC will prepare routine study conduct and safety reports for the SMC, which will convene approximately every 6 months or as needed.

The SDMC will prepare routine study conduct and safety reports for the SMC as indicated above. 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.

9.0 HUMAN SUBJECTS CONSIDERATIONS

9.1 Ethical Review

The HPTN Ethics Working Group (EWG) developed the 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 contained in Appendix II and any subsequent modifications — will be reviewed and approved by the HPTN Scientific Review Committee and DAIDS Prevention Science Review Committee with respect to scientific content and compliance with applicable research and human subjects regulations. The protocol, site-specific informed consent form, participant education and recruitment materials, and other requested documents — and any subsequent modifications — also will be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site.

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

9.2 Informed Consent

Written informed consent will be obtained from each study participant. Each study site is responsible for developing study informed consent forms for local use, based on the templates in Appendix II that describes the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. Sites teams should use the appropriate informed consent template based on the approved PrEP agent. 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 informed consent forms. Non-literate participants will be asked to document their informed consent by marking their ICFs (e.g., with an X, thumbprint, or other mark) in the presence of a literate third-party witness. (Further details regarding DAIDS requirements for documenting the informed consent process can be found in the DAIDS Standard Operating Procedure for Source Documentation.)

Each site also will have in place prior to study activation an Informed Consent Process SOP as per the 2017 DAIDS Directives memo:
https://rsc.niaid.nih.gov/sites/default/files/IC_Process_Memo_2017.pdf.

All participants will be offered a copy of their informed consent form.

9.3 Risks

General
It is not expected that this trial will expose human subjects to unreasonable risk.

Phlebotomy may lead to discomfort, feelings of dizziness or faintness, and/or bruising, swelling and/or infection.

Participants may become embarrassed, worried, or anxious when completing their HIV risk assessment and/or receiving HIV counseling. They also may become worried or anxious while

waiting for their HIV test results. Trained counselors will be available to help participants deal with these feelings.

Although study sites will make every effort to protect participant privacy and confidentiality, it is possible that participants' involvement in the study could become known to others, and that social harms may result (i.e., because participants could become known as HIV-infected or at "high risk" for HIV infection). For example, participants may experience stigma and could be treated unfairly or discriminated against, or could have problems being accepted by their families and/or communities.

General Disclaimer

The study products 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.

9.3.1 Risks Associated with FTC/TDF

FTC/TDF may have side effects, some of which are listed below. This list includes the more serious or common side effects with known or possible relationship. Participants taking FTC/TDF will be monitored closely for any side effects and are asked to report all side effects to the study site clinician.

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

- Gastrointestinal intolerance (such as nausea, abdominal pain, diarrhea, or vomiting), most commonly in the first month and typically resolves
- Flatulence (gas), most commonly in the first month and typically resolves
- Headache, dizziness, tiredness, or inability to sleep

Rare, but serious side effects include:

- Rash
- Worsening or new kidney damage
- Bone pain and bone changes such as thinning and softening
- Allergic reaction
- Lactic acidosis (buildup of too much acid in the body). Lactic acidosis can cause shortness of breath, nausea and liver failure.
- Individuals with HBV who suddenly stop taking FTC/TDF may get a “flare” or worsening of hepatitis symptoms.

9.3.2 Risks Associated with FTC/TAF

FTC/TAF may have side effects, some of which are listed below. This list includes the more serious or common side effects with known or possible relationship. Participants taking FTC/TAF will be monitored closely for any side effects and are asked to report all side effects to the study site clinician.

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

Rare, but serious side effects include:

- Worsening or new kidney damage
- Lactic acidosis (buildup of too much acid in the body). Lactic acidosis can cause shortness of breath, nausea and liver failure.

Individuals with HBV who suddenly stop taking FTC/TAF may get a "flare" or worsening of hepatitis symptoms.

9.3.3 Risks Associated with Hormonal Therapy with Estrogen and Anti-androgen

Estrogen therapy
The full medical effects and safety of estrogen therapy are not fully known. Potential adverse effects may include, but are not limited to:

- Increased or decreased cholesterol and/or fats in the blood, which may increase risk for heart attack or stroke
- Increased risk of the following:
  - Deep venous thrombosis, pulmonary embolism
  - Breast tumors/cancer
  - Heart disease, arrhythmias, and stroke;
  - High blood pressure
  - Pituitary tumors
  - anemia
  - Decreased sex drive and sexual functioning
  - Psychiatric symptoms such as depression and suicidal feelings; anxiety; psychosis, and worsening of pre-existing psychiatric illnesses
  - Decreased bone density
  - Genital changes (i.e., smaller testes & penis)
  - Infertility
  - Cholelithiasis

The risks for some of the above adverse events may be increased by pre-existing medical and psychiatric conditions, cigarette smoking, and alcohol use.

Breast growth and infertility may be irreversible and potential outcome increases with length of time on hormones.

Anti-androgen and GnRH agonists

Estrogens are usually given with androgen blockers. Potential adverse effects of androgen blockers may include, but are not limited to:

- Increased levels of potassium in the blood (spironolactone)
- Liver inflammation (flutamide, bicalutamide, cyproterone acetate)
- Decreased bone density (GnRH agonists, e.g., leuprolide, buserelin, histrelin, goserelin)

9.4 Benefits

There may be no direct benefits to participants in this study, however, participants and others may benefit in the future from information learned from this study. Specifically, information learned in this study may lead to the improving HIV prevention services for TGW.

In addition, participants will receive HIV counseling and testing as part of the study screening process as well as evaluations of participant health (creatine clearance, etc.). Participants also will be screened for gonorrhea [GC], chlamydia [CT], and syphilis, and provided treatment if applicable. Participants will be tested for HBV and HCV and referred for vaccination or treatment as applicable.

Participants may benefit from the use of PrEP agents which are known to protect against getting HIV if taken daily as directed. Participants may also benefit from access to GAHT which are established health care for TGW.

9.5 Incentives

Pending IRB/EC approval, participants will be compensated for their time and effort in this study, and/or be reimbursed for travel to study visits and time away from work. Participants may be compensated for their participation in the main study and for each of the sub-studies. Specific information regarding compensation, including what is compensated and the amount will be decided by the site per IRB/EC or local regulatory requirements. Site-specific reimbursement amounts will be specified in the study ICFs and explained to participants.

9.6 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; Gilead Health Sciences; representatives of the HPTN LOC, SDMC, and/or LC; OHRP and other U.S., local and international regulatory entities, and/or site IRBs/ECs.

For sites located in the U.S., the HPTN will obtain a Certificate of Confidentiality from the U.S. Department of Health and Human Services that will be applicable for this study. Sites may register under the Certificate through the HPTN Leadership and Operations Center (LOC) once they have obtained local IRB approvals for the study. This Certificate protects study staff from being compelled to disclose study-related information by any Federal, State or local civil, criminal, administrative, legislative, or other body.

9.7 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.

9.8 Study Discontinuation

The study also may be discontinued at any time by NIAID, the HPTN, Gilead Health Sciences, other government or regulatory authorities (e.g. OHRP), or site IRBs.

Participants may discontinue study participation at any time due to:

- Participant declines further study participation.
- Participant is unable or unwilling to follow all of the study procedures, instructions, or attend to study visits.
- The study is stopped or canceled.
- The study staff feels that staying in the study would be harmful to the participant.

NOTE: Participants who are incarcerated during study follow-up will be temporarily discontinued from study participation while incarcerated. Participants may resume study participation once released.

10.0 LABORATORY SPECIMENS AND BIOHARZARD CONTAINMENT

Laboratory procedures are listed in the SSP Manual and Appendices Ia and Ib.

There are no plans to perform host/human genetic testing in this study.

10.1 Local Laboratory Specimens

As listed in Appendix Ia and Ib, the following types of specimens will be collected for testing at the local laboratory (LL):

- HIV testing (see SSP Manual)
- HBV and HCV testing to include HBsAg, HBsAb, HBcAb-total, HCV antibody tests
- CBC (complete blood count) with differential
- Creatinine for creatinine clearance.
- Chemistry testing (blood-urea nitrogen (BUN) or urea, albumin, and potassium)
- LFTs (AST, ALT, TBili, alkaline phosphatase)
- Fasting lipid profile (total cholesterol, high-density lipoprotein (HDL), triglycerides, low-density lipoprotein (LDL) – calculated or measured; participants should fast for at least 8 hours, preferably 12 hours, prior to sample collection for lipid testing.
- Estradiol and total testosterone
- Syphilis serologic testing
- Dipstick urinalysis (protein and glucose)
- Rectal swabs, pharyngeal swabs, and urine for GC/CT nucleic acid amplification testing (NAAT)

- CD4 cell count (if HIV-infected)
- Real-time resistance testing for clinical management, if indicated and available (if HIV- infected)

Local laboratories will perform Chemistry and Hematology tests as indicated in Appendix I.

If the HIV testing algorithm includes HIV rapid testing, that testing may be performed in the clinic or laboratory.

10.2 Laboratory Center Specimens

The following types of specimens will be collected for testing at the HPTN Laboratory Center (LC)

- Plasma storage
- Serum storage (for the DHI Sub-study)
- DBS storage
- PBMC storage (for the DHI Sub-study)

Each study site will adhere to standards of Good Clinical Laboratory Practice (GCLP) reference, the HPTN Manual of Operations (MOP), the SSP Manual and local SOPs for proper collection, processing, labeling, transport, and storage of specimens to the local laboratory. Specimen collection, testing, and storage at the local laboratory will be documented using the HPTN Laboratory Data Management System (LDMS) as described in the SSP Manual.

All specimens will be shipped in accordance with International Air Transport Association (IATA) specimen shipping regulations. All shipments will be documented using the HPTN LDMS as described in the SSP Manual.

10.2.1 Stored Specimens

Plasma, serum, PBMC, and DBS will be stored at the local site throughout the study. A subset of the stored samples will be shipped to the HPTN LC (located in the U.S.) for Quality Assurance (QA) and other assessments. As indicated below, testing on stored samples will be performed by the HPTN LC or another laboratory designated by the HPTN LC.

10.2.2 Virology

The HPTN LC will perform QA testing, including testing to determine HIV infection status in selected cases. Additional assays may be performed at the HPTN LC or a laboratory designated by the HPTN LC to characterize incident HIV infections. This testing may include: HIV viral load testing, HIV drug resistance testing, ARV drug testing, phylogenetic analysis, and analysis of the host response to HIV infection. Results will not be returned to the sites or study participants, with the exception of HIV testing (if results obtained at the HPTN LC do not agree with site results). Testing may also be performed to analyze HCV infections.

Resistance testing may be performed at the HPTN LC or a laboratory designated by the HPTN LC. This testing may be performed retrospectively 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 in the event of HIV infection, 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.

10.2.3 Pharmacology

Samples for drug concentrations will be collected throughout the study from all participants, although PK testing may be limited to a subset of the samples. Samples will be processed and frozen locally for subsequent shipment to the HPTN LC following procedures outlined in the SSP Manual. Pharmacology testing will be performed at the HPTN LC or at an outside laboratory designated by the HPTN LC. The primary pharmacologic assessments will be performed using assays that have been validated and approved by the Clinical Pharmacology Quality Assurance (CPQA) Committee. Results will not be returned to the study participants.

Stored plasma may also be tested for the presence of other ARV drugs.

10.3 Quality Control and Quality Assurance Procedures

The clinical sites will document that their clinical laboratories are certified under the Clinical Laboratory Improvement Act of 1988 (CLIA-certified) and/or participate in DAIDS sponsored External Quality Assurance (EQA) programs. Laboratories must also follow the DAIDS requirements (link to policy on DAIDS website https://www.niaid.nih.gov/research/daids-clinical-research-laboratory-specimens-management).

LC staff will conduct periodic visits to each site to assess the implementation of on-site laboratory quality control (QC) procedures, including proper maintenance of laboratory testing equipment and use of appropriate reagents. LC staff will follow up directly with site staff to resolve any QC or quality assurance (QA) problems identified through proficiency testing and/or on-site assessments. Throughout the course of the study, the HPTN LC will select a random sample of stored specimens to test for QA purposes. LC staff will follow-up directly with site staff to resolve any QA problems identified through this process.

Local laboratories will perform hematology, chemistry, liver function, lipids, hepatitis, STI, and urinalysis testing as indicated in each relevant SOE. Non-US laboratories performing these tests will be monitored by Patient Safety Monitoring and International Laboratory Evaluation (pSMILE) and must demonstrate successful participation in the relevant EQA programs. U.S. sites should send these tests to CLIA-certified laboratories that participate in EQA programs.

HIV diagnostic tests will be listed on the site Protocol Analyte List (PAL) or a US lab sheet and will be subject to review and acceptance by DAIDS and the HPTN LC.

Throughout the course of the study, the HPTN LC will select a random sample of stored specimens to test for quality assurance (QA) purposes. The total number of specimens undergoing QA testing will represent at least 10 percent of all specimens collected.

The LC will inform site staff of the samples selected for quality assurance testing, and site staff will ship the selected specimens to the LC. The LC will test the specimens for HIV antibody and 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 quality assurance problems identified through this process.

10.4 QC for HIV Diagnostic Testing

Local laboratories will perform testing for HIV diagnosis at Screening, Enrollment, and follow-up visits. Algorithms for HIV diagnostic testing are provided in the SSP Manual.

Throughout the course of the study, the HPTN LC will select a random sample of stored specimens to test for QA purposes. The total number of specimens undergoing QA testing will follow the QA processes as described in the HPTN MOP and at the discretion of the HPTN LC.

The 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 test the specimens for evidence of HIV infection and compare the results of their tests with the results obtained by the local labs. HPTN LC staff will follow-up directly with site staff to resolve any QA problems identified through this process.

10.5 QC for CD4 Cell Count Determination

Local laboratories may also perform CD4 cell count testing. Non-U.S. laboratories performing these tests will be monitored by the DAIDS Immunology Quality Assurance (IQA) program and United Kingdom National External Quality Assessment Service (UNKEQAS) program and must demonstrate successful participation in these programs. U.S. sites must use CLIA-certified laboratories; participation in the IQA program is recommended.

10.6 Quality Assurance for HIV RNA Testing

Local laboratories may also perform HIV RNA/viral load testing as indicated in Appendix Ib or for evaluation of possible acute HIV infection. Non-U.S. sites may use local laboratories for this testing. Non-US laboratories performing these tests will be monitored by the DAIDS Virology Quality Assurance (VQA) program and must demonstrate successful participation in this program. U.S. sites must use CLIA-certified laboratories; participant in the VQA program is recommended.

10.7 Specimen Storage and Possible Future Research Testing

Study sites will store specimens collected in this study at least through the end of the study (which is completion of all study-related testing, including testing at the HPTN LC) and at a minimum one-year post publication of the main paper. In addition, at sites that allow this type of storage, study participants will be asked to provide written informed consent for these samples to be stored after the end of the study for possible future non-protocol listed testing. The specimens of participants who do not consent to long-term storage and additional testing will be destroyed after all of the protocol specified testing (including assessments at the HPTN LC) has been completed.

Samples from participants who did not successfully enroll in the study may be discarded once sample lists are provided by the HPTN SDMC in consultation with the HPTN LC.

10.8 Biohazard Containment

As the transmission of HIV and other blood-borne pathogens can occur through contact with contaminated needles, blood, and blood products, 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 U.S. CDC. All infectious specimens will be transported in accordance with United States regulations (42 Code of Federal Regulations (CFR) 72) and in accordance with IATA. 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.

11.0 ADMINISTRATIVE PROCEDURES

11.1 Protocol Registration

Initial Registration of the protocol by the DAIDS Protocol Registration Office (PRO) is required prior to implementation of this protocol. As part of this process, each site must have the protocol and protocol ICF(s) approved, as appropriate, by their local 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 informed consent forms (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.

Following Initial Registration, any full protocol amendments require submission of a protocol registration packet to the DAIDS PRO as described above; however, the DAIDS PRO WILL NOT review and approve site-specific ICFs. Upon receiving final IRB/EC and any other applicable RE approval(s) for an amendment, sites should implement the amendment immediately. Sites will receive a 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.

There may be cases where a site submits as their Initial Registration a protocol amendment (Version 2.0 or higher of a protocol); in such cases, the instructions for Initial Registration will be followed.

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://rsc.niaid.nih.gov/clinical-research-sites/daids-protocol-registration-policy-and-procedures-manual.

11.2 Study Activation

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

determined to be necessary for any subsequent amendments, study implementation may not be initiated until a study activation notice is provided to the site by the HPTN LOC.

11.3 Study Coordination

Assignment of all sponsor responsibilities for this study will be specified in a Clinical Trials Agreement (CTA) executed by DAIDS and Gilead Sciences, Inc.

Study implementation will be directed by this protocol as well as the SSP Manual. The SSP Manual, which will include links to the DAIDS SOPs for Source Documentation and Essential Documents, as well as links to the 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.

Electronic study case report forms will be developed by the study team and HPTN SDMC. Study data is entered into the eCRFs and cleaned using the Medidata Rave electronic data management system, compliant with International Council on Harmonization (ICH) Good Clinical Practices (GCP) and CFR guidelines. Queries will be entered and distributed to the study sites for verification and resolution within the Medidata Rave study database.

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 AE incidence will be monitored closely by the team as well as the HPTN SMC. The protocol team's CMC will address issues related to study eligibility and AE management and reporting as needed to assure consistent case management, documentation, and information-sharing across sites.

11.4 Study Monitoring

On-site study monitoring will be performed in accordance with DAIDS policies. Study monitors will visit the site to:

- verify compliance with human subjects and other research regulations and guidelines;
- assess adherence to the study protocol, SSP Manual, and local counseling practices; and
- confirm the quality and accuracy of information collected at the study site and entered into the study database.

Site investigators will allow study monitors to inspect study facilities and documentation (e.g., informed consent forms, clinic and laboratory records, other source documents, case report forms), 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, Gilead Sciences, Inc., site IRBs/ECs, OHRP and other U.S., local and international regulatory entities. A site visit log will be maintained at each study site to document all visits.

11.5 Protocol Compliance

The study will be conducted in full compliance with the protocol. The protocol will not be amended without prior written approval by the Protocol Chair and DAIDS Medical Officer. All

protocol amendments must be submitted to and approved by the relevant IRB(s)/EC(s) and the RSC prior to implementing the amendment.

11.6 Investigator's Records

The Investigator will maintain, and store in a secure manner, complete, accurate, and current study records throughout the study. Under the U.S. 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, eCRFs, notations of all contacts with the participant, and all other source documents.

11.7 Use of Information and Publications

Publication of the results of this study will be governed by HPTN policies. Any presentation, abstract, or manuscript will be submitted by the Investigator to the HPTN Manuscript Review Committee, DAIDS, and Gilead Sciences, Inc., for review prior to submission.

11.8 ClinicalTrials.gov

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

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Appendix Ia: Schedule of Events

	SCR	ENR	GAHT Initiation Visit[4]	Week 13 (Month 3)	Week 26 (Month 6)	Week 39 (Month 9)	Week 52 (Month 12)	Week 65 (Month 15)	Week 78 (Month 18)
Administrative and Behavioral Procedures									
Informed Consent	X	X							
Demographic information	X								
Locator information	X	X	X	X	X	X	X	X	X
Randomization		X							
ACASI[1]		X		X	X	X	X	X	X
HIV prevention counseling (offer condoms/lube)	X	X		X	X	X	X	X	X
Provision of PrEP[2]		X		X	X	X	X	X	
PrEP counseling and support[2]		X		X	X	X	X	X	X
Provision of GAHT[3]			X	X	X	X	X	X	
GAHT counseling and support[3]			X	X	X	X	X	X	X
Peer Health Navigation using Strengths-Based Case Management[5]		X		X	X	X	X	X	X
Clinical Procedures									
Complete medical history, physical	X								
Symptom-directed physical exam	X	X		X	X	X	X	X	X
Interim medical history (including STI symptoms)		X		X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X
Blood collection	X	X		X	X	X	X	X	X
Urine collection for urinalysis	X								

	SCR	ENR	GAHT Initiation Visit[4]	Week 13 (Month 3)	Week 26 (Month 6)	Week 39 (Month 9)	Week 52 (Month 12)	Week 65 (Month 15)	Week 78 (Month 18)
Urine collection for GC/CT testing		X		X	X	X	X	X	X
Swab (rectal and pharyngeal) collection for GC/CT testing		X		X	X	X	X	X	X
STI treatment, if indicated	X	X		X	X	X	X	X	X
Hepatitis B vaccination or decline of vaccination		X							
Laboratory Procedures									
Dipstick urinalysis (protein and glucose)	X								
GC/CT for NAAT (rectal, urine, pharyngeal)		X		X	X	X	X	X	X
CBC w/differential		X			X		X		X
LFTs (AST, ALT, TBili, alkaline phosphatase)	X			X	X	X	X	X	X
Fasting lipid profile[6]	X				X				X
Chemistry testing (BUN or urea, albumin and potassium)	X			X	X	X	X	X	X
Creatinine clearance	X			X	X	X	X	X	X
Estradiol and total testosterone testing		X		X	X	X	X	X	X
Syphilis testing		X		X	X	X	X	X	X
HIV testing	X	X		X	X	X	X	X	X
HBV testing (HBsAg, HBsAb, HBcAb-Total)	X								X

	SCR	ENR	GAHT Initiation Visit[4]	Week 13 (Month 3)	Week 26 (Month 6)	Week 39 (Month 9)	Week 52 (Month 12)	Week 65 (Month 15)	Week 78 (Month 18)
HCV testing	X								X
Plasma storage	X	X		X	X	X	X	X	X
Serum storage		X	X[3]	X	X	X	X	X	X
DBS storage		X		X	X	X	X	X	X

[1]Mental health assessment will be included as part of the medical and physical history assessment.
[2]If participant accepts PrEP.
[3]For participants randomized to Immediate Intervention Arm who accept GAHT starts at the Enrollment Visit. For participants randomized to the Deferred Intervention Arm who accept GAHT start up to 10 days[4] following the Week 26 (Month 6) study visit.
[4]These procedures apply to GAHT Initiation Visit for both study arms. To be scheduled up to 10 days after collection of samples for estradiol and total testosterone samples for provision of GAHT as described in the protocol.
[5] PHN starts at the Enrollment Visit for participants randomized to the Immediate Intervention Arm, and at Week 26 (Month 6) for participants randomized to the Deferred Intervention Arm.
[6] Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing and reschedule the participant to return to the same for lipid sample collection: if not collected at the Screening Visit, .sample should be collected prior to the Enrollment Visit; if not collected at Weeks 26 or 78, sample should be collected ideally within 72 hours of the visit.

Appendix Ib: Schedule of Events for Participants who Have a Reactive or Positive HIV Test Result During Study Follow-up[1]

STUDY PROCEDURES	HIV Confirmation Visit	Termination Visit [2]
Administrative and Regulatory		
Collect/Review Locator information	X	X
Provide reimbursement	*	*
Schedule next study visit/contact	*	*
Provide/Follow-up on Linkage to Care	X	X
Provide linkage for hormonal therapy	*	*
Behavioral/Counseling		
HIV pre-/post-test counseling	X	
Behavioral Questionnaire (ACASI and/or Interviewer-administered forms)		X
Clinical		
Medical history	X	X
Physical exam	X	X
Record/update AEs	*	*
Provide available test results	X	
Concomitant medications	X	X
Treat or refer UTI/RTI/STI	*	
Laboratory		
HIV confirmatory testing	X	
CD4 cell count	X	
HIV viral load	X	
Chemistry testing (BUN or urea, and potassium)	X	
LFT (AST, ALT, total bilirubin, alkaline phosphatase)	X	
Estradiol and total testosterone testing	X	
Plasma storage	X	
Serum storage* (DHI Substudy only)	X	
DBS storage	X	
Study Products/Supplies		
Collect unused study product	X	
Provision of condoms	X	X

* If indicated

[1] Participants who are not confirmed HIV-positive will not be terminated from the study. See SSP Manual for further information.

[2]Termination visit for participants who seroconvert during the study will be scheduled 13 weeks (3 months) after the HIV Confirmation Visit.

Appendix Ic: Schedule of Events for Participants in Drug-Hormone Interaction Substudy[1]

Study Procedures	Day 1-7 Before GAHT Initiation Visit	GAHT Initiation Visit[3]	Week 13 Study Visit	Day 1-7 After Week 13	Day 8 <u>After</u> Week 13 (Clinic Visit)
Study Product/Supplies					
DOT	X			X	
In-clinic DOT		X	X		X
Laboratory					
Pre-DOT					
Plasma storage		X			X
Serum storage[2]		X			X
DBS storage		X	X		X
Post-DOT					
1 hour - Plasma storage for PK		X			X
1 hour - PBMC storage for PK		X			X
4 hours - Plasma storage for PK		X			X
4 hours – PBMC storage for PK		X			X

[1]Only participants enrolled in the U.S. and using Descovy as the PrEP agent qualify for enrollment into the DHI sub- study.
[2]Samples will be tested for estradiol, free and total testosterone, LH, and FSH. Results will not be returned to participants.
[3]To be scheduled up to 10 days after collection of samples for estradiol and total testosterone samples for provision of GAHT as described in the protocol.

APPENDIX II: TOXICITY MANAGEMENT

A. General Guidance:

Guidelines for clinical management and temporary product hold/permanent discontinuation of study product are outlined in this section. In general, the IoR/designee has the discretion to hold study product temporarily at any time if she/he feels that continued product use would be harmful to the participant or interfere with treatment deemed clinically necessary. Unless otherwise specified below, the IoR/designee should immediately consult the CMC for further guidance on resuming study product, continuing the hold temporarily, or progressing to permanent discontinuation of study product. The IoR/designee will document all temporary product holds and permanent discontinuations on applicable eCRFs.

Management of toxicities under Section A apply to all study products – PrEP and GAHT.

Grade 1 or 2

In general, a participant who develops a Grade 1 or 2 AE, regardless of relationship to study product may continue product use. If the IoR opts to temporarily hold study product, the CMC must be notified.

Grade 3

Participants who develop a Grade 3 AE that is judged by the IoR/designee to be unrelated to study product may continue product use but must immediately consult the CMC regarding further management.

For participants who develop a Grade 3 AE that is judged by the IoR/designee to be related to product, study product must be temporarily held until the CMC can be consulted regarding potential resumption or other further management.

If study product is resumed and the same Grade 3 AE recurs at any time during the study, the IoR must consult the CMC for guidance on product use and clinical management. If the Grade 3 AE is deemed related to study product, study product must be temporarily held until the CMC can be consulted regarding permanent discontinuation or other further management.

Grade 4

A participant who develops a Grade 4 AE, regardless of relationship to study product, will have the study product temporarily held. The IoR/designee must consult the CMC and continue the temporary product hold until a recommendation is obtained from the CMC. If, in consultation with the CMC, product use is resumed, and the same AE recurs at Grade 4 level at any time during the study, study product must then be permanently discontinued.

AST and/or ALT Elevations

Careful assessments should be done to rule out alcohol, non-study medication-related drug toxicity, herbal medications/supplements, or viral hepatitis as the cause of elevation in AST and/or ALT of any grade. The IoR/designee must carefully assess the participant for any symptoms or signs of hepatoxicity, including fatigue, malaise, anorexia and nausea, jaundice, acholic stools, right upper quadrant pain or hepatomegaly. If the AST and/or ALT elevation is considered most likely to be due to concomitant illness or medication, standard management, including discontinuation of the likely causative agent (if clinically indicated), should be undertaken.

If symptoms or signs of clinical hepatitis are present, the IoR/designee must temporarily hold study product and test the participant for hepatitis (including HBsAg plus any other testing indicated by the local standard of care). If hepatitis B infection is confirmed, consult the CMC.

Grade 1

Continue product use and repeat ALT and AST testing within two weeks. Consult with the CMC if there are any safety concern.

Grade 2

The IoR/designee must repeat the ALT and AST as soon as possible (at most within 1 week) and then follow the participant weekly until levels are Grade ≤1. The frequency of follow up may be altered at the discretion of the IoR/designee following consultation with the CMC. Study product may continue at the discretion of the IoR/designee, provided the participant is asymptomatic. In the case of symptomatic participants, study product will be held temporarily and management (including resumption of study product) should be arranged in consultation with the CMC.

Grade 3

The IoR/designee must temporarily hold study product and repeat the ALT and AST as soon as possible (at most within 1 week). The participant should then be followed weekly until levels are Grade ≤1, at which point, with concurrence from the CMC, study product may be resumed. If improvement to Grade ≤1 cannot be documented within three weeks, CMC consultation is required.

If following a Grade 3 event(s) the participant is permitted to resume study product, but has one or more events (AST and/or ALT) at a Grade 3 level, the IoR/designee must perform the following:

- Place a temporary hold on study product
- Offer symptomatic treatment (if appropriate)
- Order any clinically relevant laboratory analyses (per judgment of the IoR/designee)
- Consult the CMC for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the study product.

Grade 4

Related to Study Product
Study product should be permanently discontinued for any Grade 4 AE deemed related to study product, in consultation with the CMC. The IoR/designee must follow the participant's ALT and AST at least weekly, or as clinically indicated according to the judgment of the IoR/designee until levels are Grade ≤1.

Not Related to Study Product
The IoR/designee must temporarily hold study product and repeat the ALT and AST as soon as possible (at most within 1 week) and consult the CMC. The participant should then be followed weekly or as clinically indicated until levels are Grade 1, at which point, with concurrence from the CMC, study product may be resumed.

If following a Grade 4 event(s) not related to study product the participant resumes study product, but has one or more events (AST and/or ALT) at a Grade ≥3 level, the IoR/designee must perform the following:

- Place a temporary hold on l study product
- Offer symptomatic treatment (if appropriate)
- Order any clinically relevant laboratory analyses (per judgment of the IoR/designee)
- Consult the CMC for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the study product.

B. Management of Specific PrEP Toxicities

Note – For management of toxicities listed in this section, study product refers only to PrEP.

Nausea, Vomiting, and/or Diarrhea

The IoR/designee may treat a participant with Grade 1 or 2 nausea, vomiting, and/or diarrhea symptomatically (e.g., diet changes, antiemetics, and/or supportive fluids).

For participants with Grade ≥3 or higher nausea and/or vomiting and/or diarrhea, the IoR/designee must:

- Place a temporary hold on study product
- Offer symptomatic treatment
- Order any clinically relevant laboratory analyses (per judgment of IoR/designee)

If the condition(s) improve(s) to Grade ≤2, the participant should resume study product. Note, all symptoms of nausea, vomiting, and/or diarrhea must improve to Grade ≤2 prior to resumption of study product. Should condition(s) not improve to Grade ≤2 within 7 days, the IoR/designee should consult the CMC for guidance.

If following a Grade ≥3 event(s) the participant resume study product, but has recurrence of the same event(s) at a Grade ≥3 level, the IoR/designee must:

- Place a temporary hold on study product
- Offer symptomatic treatment
- Order any clinically relevant laboratory analyses (per judgment of the IoR/designee)
- Consult the CMC for further guidance on continuing the temporary hold or progressing to permanent discontinuation of the study product.

Creatinine Clearance

If the participant is using Truvada®, and the creatinine clearance is <60mL/min, study product should be held, and the test should be repeated as soon as possible (at most within 1 week of the receipt of the results). If a level of <60mL/min is confirmed with retesting, Truvada® study product should be permanently discontinued in consultation with the CMC. If Descovy® is available, the participant should be switched to this medication. If retesting cannot be completed within one week, all attempts should be made by the site to contact the participant for retesting within three additional working days. A participant who fails to undergo confirmatory testing within one week plus three additional working days will require CMC consultation regarding further product management.

If re-testing yields a result ≥60mL/min, the IoR/designee must consult the CMC for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

If the participant is using Descovy®, and the creatinine clearance is <30mL/min, study product should be held, and the test should be repeated as soon as possible (at most within 1 week of the receipt of the results). If a level of <30mL/min is confirmed with retesting, Descovy® should be permanently discontinued in consultation with the CMC. If retesting cannot be completed within one week, all attempts should be made by the site to contact the participant for retesting within three additional working days. A participant who fails to undergo confirmatory testing within one week plus three additional working days will require CMC consultation regarding further product management.

If re-testing yields a result ≥30mL/min, the IoR/designee must consult the CMC for further guidance on resuming product use, continuing the hold temporarily, or progressing to permanent discontinuation.

If clinical suspicion for renal failure exists, local medical resources with clinical expertise in renal failure must be engaged to the extent available.

NOTE: Adverse events related to creatinine clearance should be based on the assessment of BOTH the absolute creatinine clearance AND the change in creatinine clearance from baseline (Screening Visit). When gradable, only the higher grade of these two assessments should be entered on the Adverse Event e-CRF.

C. Management of Specific Hormonal Therapy Toxicities

Note – For management of toxicities listed in this section, study product refers only to hormonal therapy.

Thromboembolism (VTE)

Estrogen therapy should not be administered in patients with significant risk factors for or history of venous thromboembolism. Patients suspected of VTE should have estrogen therapy held while they are referred for evaluation. If a VTE is confirmed, estrogen therapy should be discontinued. If no VTE is found, estrogen therapy may be re-initiated in consultation with the CMC.

Hyperkalemia

Spironolactone potassium-sparing diuretic and mineralocorticoid receptor antagonist that inhibits adrenal aldosterone biosynthesis and can cause elevated serum potassium. For Grade 2 hyperkalemia (5.5 - 6.0 mmol/L), spironolactone should be held and the test repeated within one week of receipt of results. If potassium > 5.5 is confirmed with retesting, spironolactone should be permanently discontinued in consultation with the CMC. If retesting cannot be completed within one week, all attempts should be made by the site to contact the participant for retesting within three additional working days. A participant who fails to undergo repeat potassium testing within one week plus three additional working days will have spironolactone held until results of repeat testing are available.

APPENDIX III: INFORMED CONSENT TEMPLATES

SAMPLE INFORMED CONSENT FORM FOR SITES IN BRAZIL

HPTN 091
Integrating HIV Prevention, Gender-Affirming Medical Care, and Peer Health Navigation for Transgender Women in the Americas: A Vanguard Study

Final Version 1.0
13 April 2020
DAIDS Document ID: 38695

Sponsored by: National Institutes of Health, Division of AIDS, US National Institute of Allergy and Infectious Diseases, US National Institutes of Health. Truvada® is provided by Gilead Sciences, Inc.

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: *[Insert Number]*

INTRODUCTION

You are being asked to take part in a research study. Joining this study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason. This research study is for transgender women who may be at risk for getting Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decided 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 decide to join.

Here is a summary of important information about the study:

- This is a research study.
- Your participation in this study is voluntary.
- This study is being done to learn how to best provide HIV prevention among transgender women and assess the safety of this intervention in the United States and Brazil.
- All participants will be offered medications to prevent HIV, known as Pre-exposure prophylaxis (PrEP). This medication is called Truvada®. When used every day, it most likely will help you to avoid getting HIV.
- All participants will be assigned to one of two groups by random chance (an equal chance of being in either arm). One group will meet with a peer to help them access services and be able to receive hormonal therapy right away at the site. The other group will be linked to services, to help them access services for hormonal therapy until their 6 month visit. At the 6 month visit this group will start to receive hormonal therapy from the site and meet with a peer to help them access services.
- You will come to the site for at least 8 scheduled visits.

- The study will include about 310 participants at five sites. Four of these sites are in the United States and one site is in Brazil.
- Periodic blood and urine test will be taken. Blood samples may cause pain, bruise your arm or make you feel lightheaded.
- There may be some social risks. 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.
- 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.
- We will test you for HIV and other sexually transmitted infections throughout the study.
- The counseling you receive during this study may help you to avoid HIV and other sexually transmitted infections.

More information is given in this form about the study. You should feel that you understand the study before deciding whether you will participate.

ABOUT THE STUDY
The HIV Prevention Trials Network (HPTN) and [insert site name] are doing this study to learn how best to prevent transgender women from acquiring HIV in the United States and Brazil.

About 310 people will participate in this study from the United States and Brazil. Approximately *XX [Site to enter site-specific accrual target*] participants will join the study at [insert site name]. Participants will be in the study for approximately 18 months.

2. The study is testing whether offering gender affirming hormones and HIV prevention services in one location is acceptable, feasible, and improves use of HIV prevention services among transgender women.

This study will enroll people who were assigned male sex at birth and who currently identify as women, transgender women, or along a trans-feminine spectrum, who are age 18 years or older, who are having sex and who are not living with HIV.

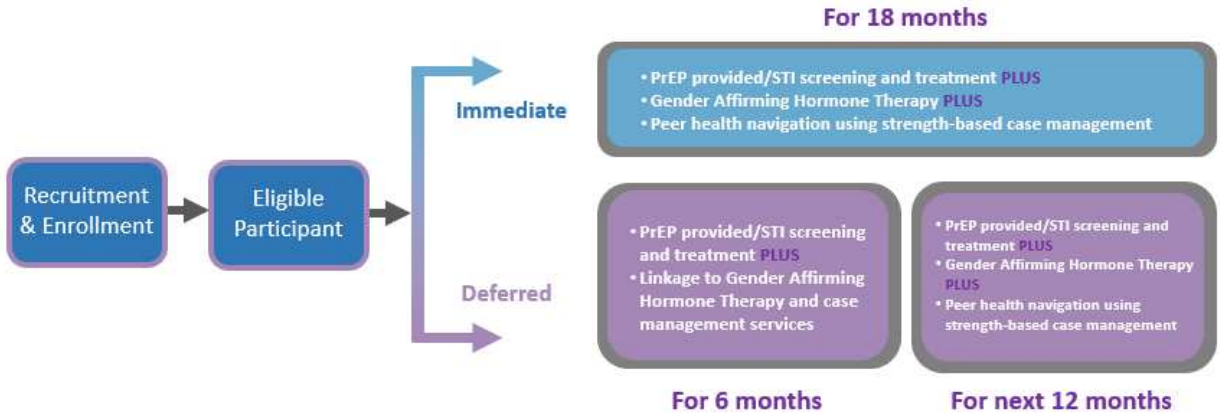
Participants will be offered the opportunity to take medications to prevent HIV. The medication to prevent getting HIV is sometimes called pre-exposure prophylaxis or "PrEP." PrEP is a way to prevent HIV infection for people who do not have HIV (the virus that causes AIDS) by taking a pill every day. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS. The drug being used for PrEP in this study is called Truvada®. Truvada® contains two medicines, tenofovir and emtricitabine. These medicines are also used in combination with other medicines to treat HIV.

The United States Food and Drug Administration (FDA) approved Truvada® for oral PrEP more than 5 years ago, in adult men and women who are at risk of getting HIV. The Brazilian National Health Surveillance Agency (ANVISA) has also approved Truvada® for use as oral PrEP.

3. Participants will be placed in 1 of 2 groups.

All participants will be assigned by random chance (an equal chance of being in either arm).) to one of two groups. The difference between the groups is that one group will meet with a provider to start receiving gender-affirming services, including hormonal therapy, at this site right away. This group will also be able to meet with a peer who can help them access any services they need. The other group will be provided with information and assisted in seeking gender affirming services from other providers in their

area who have a partnership with the site, until their 6 month visit. [*Include if your site is unable to refer participants to institutions that can provide GAHT free of cost: If you are randomized to the 6-month Deferred Intervention Arm and choose to seek gender-affirming hormone therapy at a referral site, there may be cost associated with obtaining gender affirming hormonal therapy at that site during the first six months of study participation. Once you transition to the intervention portion of the study, these will be provided to you at the study site at no cost.*] At the 6 month visit, all participants in the study will be able to get gender-affirming services, including hormonal therapy, at the site and meet with a peer. All participants will be in the study for approximately 18 months.



JOINING THE STUDY

4. It is your decision whether 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, you will be asked to sign your name or make your mark 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 a later 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. 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 some questions about yourself, like your age, and your ethnic group.
- Ask where you live and how to contact you.
- Collect ~XX mL (about x teaspoons) of blood which will be tested for: HIV, any of the diseases passed during sex, hepatitis B, hepatitis C and to see if you are healthy.
- Collect urine for: kidney and liver tests
- Give you a physical exam, that includes obtaining your complete medical history, measuring your weight, temperature, blood pressure, looking into your mouth and throat, listening to your heart and lungs, feeling your abdomen (stomach and liver), and ask you about any other medicines you are taking.
- We will offer you condoms and lubricant, and counsel you on how to use them safely.

The results of the HIV test will be available [*site to insert timeframe of testing*]. You will be contacted about the results of your other tests when they are available. A small amount of blood will be stored from this visit. No other samples collected at the time of screening will be kept or used for any other tests other than those listed above.

At this visit, we will collect a blood sample to see your cholesterol and triglycerides levels. Cholesterol and triglycerides are different types of fats that circulate in your blood. High levels of these substances increase your risk for developing heart disease. If the test results show you have high cholesterol and/or triglycerides, the site staff will refer you for medical assessment and treatment. To accurately see your levels of cholesterol and triglycerides, you need to be fasting, meaning you have not eaten, for at least 8 hours, preferable 12 hours. If you are not fasting, we will schedule you to return to the clinic on another day before the Enrollment Visit to collect blood for this test. Remember you need to be fasting before collecting the blood sample.

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, and you will be referred for the appropriate medical care. *(sites to add specifics about this here as necessary)*
- If you have a negative HIV test. We will counsel you on avoiding acquiring HIV and other sexually transmitted infections (STI). We will ask you personal questions about your HIV risk factors such as sexual behavior, alcohol, and drug use.
- If your blood shows that you have any STI, we will either treat you or refer you for treatment.

- If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here for free. We will give you referrals for other health services if you need them. For health problems that are unrelated to the study, we will not pay for care.

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

If you are eligible for this study and decide to take part in the study, you will be asked to return for an "Enrollment Visit." This visit will last about X hours [*sites to fill in the amount of time].*

During the Enrollment Visit, we will:

- Confirm where you live and how to contact you.
- Ask you to answer questions on a computer about your sexual practices, and how you feel about how your life is going.
- Talk with you about HIV and ways to protect yourself from getting it.
- Collect ~XX mL (about x teaspoons) of blood for: HIV, STIs, hepatitis B, and hepatitis C.
- A blood sample will also be used to test your hormone levels (estradiol and total testosterone).
- Collect urine for: kidney and liver tests.
- Give you PrEP pills, and explain how to take them, and any side effects they may cause.
- Give you a physical exam that will include weigh, temperature, blood pressure, any other assessment based on signs and symptoms you may have, and ask about any medicines you are taking.
- Ask you about your medical history.
- If your blood, urine or rectal swab shows that you have any STIs, we will either treat you or refer you for treatment.
- We will offer you condoms and lubricant, and counsel you on how to use them safely.
- Give you the results of tests when they are available.
- The hepatitis B vaccination will be made available for those that have not been previously vaccinated.
- Randomize you (randomly place you) into 1 of the 2 study groups.
    - If you are randomized to the Immediate arm, starting at this visit you will receive peer health navigator support.

BEING IN THE STUDY

9. Once you enroll in the study, you will have 6 visits over one and a half years.

If you decide to join the study, after your Enrollment Visit, you will be asked to come to this site approximately 6 times over the course of one and a half years.

If you are in jail during the study, your study visits will be paused and you may continue in the study once released.

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

After your enrollment visit, the visits will be about 12 weeks apart.

Regardless of the group you are randomized to, during these visits, we will:

- Confirm where you live and how to contact you.

- Ask you to answer questions on a computer about your sexual practices, and how you feel about how your life is going.
- Talk with you about HIV and ways to protect yourself and stay healthy.
- Give you PrEP pills, and explain how to take them, and any side effects they may cause.
    - You are not required to take PrEP. You will be offered PrEP at the site up until Week 39 visit. If interested, PrEP will be provided following creatinine and HIV testing. You may start and stop taking PrEP at anytime.
- Give you a physical exam that will include weigh, temperature, blood pressure, any other assessment based on signs and symptoms you may have, and ask about any medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood for: HIV, STIs, hepatitis B, and hepatitis C.
- A blood sample will also be used to test your hormones (estradiol and total testosterone).
- Collect urine for: kidney and liver tests.
- If your blood, urine or rectal swab shows that you have any STIs, we will either treat you or refer you for treatment.
- We will offer you condoms and lubricant, and counsel you on how to use them safely.

At the 6 Month and 18 Month study visit, we will collect a blood sample to see your cholesterol and triglycerides levels. Cholesterol and triglycerides are different types of fats that circulate in your blood. High levels of these substances increase your risk for developing heart disease. If the test results show you have high cholesterol and/or triglycerides, the site staff will refer you for medical assessment and treatment. To accurately see your levels of cholesterol and triglycerides, you need to be fasting, meaning you have not eaten, for at least 8 hours, preferable 12 hours. If you are not fasting, we will schedule you to return to the clinic on another day, preferable within 72 from the visit, to collect blood for this test. Remember you need to be fasting before collecting the blood sample.

Depending on the group you are randomized to, during these visits:

- Participants randomized to the deferred arm will be provided with information and assisted in seeking gender affirming services from other providers in their area who have a partnership with the site, [XX SITE TO COMPLETE WITH PARTNER ORGANIZATIONS XX], for the first 6 months.
    - At 6 months these participants will have the opportunity to receive hormone therapy, counseling, and support at the site and meet with a trained staff member who is a peer who can help them access any services they need.
    - Participants are able to start Gender Affirming Hormone Therapy at the site anytime after their 6 month visit and up to Week 39. During this time participants can choose to start and stop Gender Affirming Therapy at the site.
- For participants randomized to the immediate arm, these visits will include:
    - The opportunity to receive hormone therapy, counseling and support at the site. Participants are able to start and stop Gender Affirming Horomone Therapy at any time.
    - Meet with a trained staff member who is a peer who can help them access any services they need.

Regardless of the group you are randomized to, participants are not required to take Gender Affirming Hormone Therapy.

You may have more study visits if needed, for example, you may come to the site to get medications, if you are sick, or we need to check on your health. If you choose to start Gender Affirming Hormone

Therapy an extra study visit will be scheduled within ten days after the collection of estradiol and total testosterone testing. If you wish to stop participating in the study early a final visit will be scheduled and a conversion with a member of the site staff.

All study arms are really important for the study. The information from participants in both arms help investigators learn if the intervention actually works.

Before the study ends, we will work with all participants to find supportive services so they can continue receiving hormonal therapy and PrEP if they would like to continue. At your final study visit, we will talk with you about the end of the study, and when the results of the study will be available.

You may stop study participation at any time. If you wish to stop participating in the study early, we will ask you to do a final visit and talk to a member of the site staff either in person or by phone. This visit will be scheduled at your convenience.

10. Interviews with a subgroup [*Not applicable for participants enrolled in the Implementation Testing part of the study*]

Approximately 60 participants across all study sites will be asked to participate in additional interviews. Participants will be chosen from those who: stop taking PrEP during the study, accept, don't accept PrEP at enrollment, or decline PrEP at enrollment and accept PrEP later in the study. These interviews will be no longer than an hour and a half and will happen up to three times during the study. In these interviews a trained interviewer will ask you questions about:

- How you decided to start, not start or stop PrEP
- Things that make it harder or easier to take PrEP
- Experiences in the study
- Knowledge of PrEP
- If you feel you are at risk of becoming HIV positive
- How others you know talk about PrEP use

Taking part in these interviews is voluntary. You do not have to agree to these extra procedures in order to participate in HPTN 091. You can stop the interviews at any time. There is no direct benefit to you for participating in this additional aspect of the study. The interviews will be recorded and transcribed. The information learned from these interviews will help researchers to better understand the experiences of people using PrEP, what parts of the study are helpful or not helpful.

11. 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 should stop taking PrEP right away. You will be asked to come to another visit and then a visit 13 weeks later (about 3 months). We will help you find the care and support you need. One final visit will be scheduled three months later to follow-up on your care.

12. Use of stored blood samples.

Blood samples will be stored at enrollment and at follow-up visits. Some of these samples will be used for quality control testing (to confirm results obtained in site laboratories) and testing for drugs used to prevent HIV infection. If you get HIV infection during the study, some of the stored blood samples will be used to study the HIV virus and your body's response to HIV infection. Some of this work may

involve studying how HIV spreads within the community. 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 and other countries outside of [insert site country]. 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).

We do not plan to do genetic testing or sequencing (for example, the mapping of all of your genes, which is also known as whole genome sequencing) of any kind. Your specimens will never be used for commercial profit.

Some of your blood may be left over at the end of the study [and may/but will not] be used for future research.

Some of the blood collected during this study may be left over after all of the study tests are completed. If you agree, this left-over blood may be stored for future research related to HIV infection, hepatitis infection, and other STIs, 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 for possible future research, you can still be in this study. If you give permission, you will not be asked to give permission again once a researcher requests to use your samples after the study is over. 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.

RISKS OF THE STUDY

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

STUDY PROCEDURES

Getting an HIV test may cause you anxiety. You may become emotionally upset if you find out that you have acquired HIV. The study staff will provide emotional support and work with you to connect with a medical provider for your HIV infection.

Taking blood samples may cause some pain, bruise your arm, swelling, 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 be nervous while you are waiting for your HIV test result. If the tests show that you have HIV, you may worry about your health and future. You will receive counseling before and after the test to help address your concerns. [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 will be tested for gonorrhea, chlamydia and syphilis. [*Note to sites: Insert here any reporting responsibilities for your state or local jurisdictions or reporting of these infections to public health authorities].*

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 high risk for acquiring HIV.

SENSITIVE QUESTIONS

Due to the sensitive nature of some of the questions asked in the computer survey, you may feel uncomfortable answering questions about your sexual practices and possible risk for HIV and other STIs (sexual transmitted infections) and drug and alcohol use. Study staff are trained to give you emotional support if needed. Also, you can choose not to answer questions that make you feel uncomfortable. You are free to discontinue participating in the study at any time without consequences.

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 test positive for HIV during the study, you will be asked to stop taking PrEP. If you continue to take PrEP after acquiring HIV, there is a chance that drug resistance may occur.

Possible side effects in PrEP research studies when using Truvada®:

- Nausea, diarrhea, vomiting, gas (flatulence), headache, tiredness, feeling faint or weak, not able to sleep, irritated or swollen skin (rash), bone pain, allergic reaction, lactic acidosis (buildup of too much acid in the body), stomach (abdominal) pain, and "flare" or worsening of hepatitis due to suddenly stopping the drug. This mainly happened in the first month and went away, and happened in about 10% or one in ten people.
- A small number (1% or one in one hundred people) showed a small decrease in how their kidneys work, this stopped when the people stopped taking the drug.
- Changes in how much calcium and other minerals are in your bone which keeps them strong (bone mineral density) were very rare in people taking the drug who did not have HIV and have always gotten better when the drug was stopped.

Possible side effects in Gender Affirming Hormone Therapy:

Estrogen therapy

The full medical effects and safety of estrogen therapy are not fully known. Potential adverse effects may include, but are not limited to:

- Increased or decreased of fats in the blood (cholesterol), which may increase risk for heart attack or stroke
- Increased risk of the following:
  - Cause a blood clot (Deep venous thrombosis), blood flow is blocked from reaching the lungs (pulmonary embolism)
  - Breast tumors/cancer
  - Heart disease, the heart beats too fast or too slow (arrhythmias), and stroke;
  - High blood pressure

- Abnormal growths on your pituitary gland (pituitary tumors)
- Low levels of iron in the blood (anemia)
- Decreased sex drive and sexual functioning
- Psychiatric symptoms such as depression and suicidal feelings; anxiety; psychosis, and worsening of pre-existing psychiatric illnesses
- Decrease in how much calcium and other minerals are in your bone which keeps them strong (bone mineral density)
- Genital changes (i.e., smaller testes & penis)
- Inability to have children (infertility)
- Create harden deposits of digestive fluid (gallstones) in your gallbladder (Cholelithiasis)

The risks for some of the above adverse events may be increased by pre-existing medical and psychiatric conditions, cigarette smoking, and alcohol use.

Breast growth and inability to have children (infertility) may be irreversible and potential outcome increases with length of time on hormones.

Anti-androgen and GnRH agonists

Estrogens are usually given with androgen blockers. Potential adverse effects of androgen blockers may include, but are not limited to:

- Increased levels of potassium in the blood (spironolactone)
- Liver inflammation (flutamide, bicalutamide, cyproterone acetate)
- Decreased bone density

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. The questions we will ask you about your sexual behavior may make you feel uneasy. 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. You may also experience stigma and may be treated differently as a result of being involved in a study about HIV because people 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 at high risk and treat you unfairly as a result.

RECTAL SWABS

You may experience pain or discomfort in your rectum from the swab. In some cases, you may have some bleeding.

HIV RESISTANCE

If you decide to take PrEP and then become acquire HIV, there is a risk that the HIV you have could be "resistant" to the PrEP agent used in the study, Truvada®. This may then mean that you may not be able to be treated with the PrEP agent nor the drugs which are combined together to make the PrEP agent (Tenofovir and Emtricitabine). Viral drug resistance to these drugs can also cause cross resistance (meaning your virus is also resistant to other drugs as well as the drugs in the PrEP agent) to more commonly used drugs such as Lamivudine (3TC). Your doctor would need to prescribe different drugs that are used to treat HIV infection. These other drugs may have more side effects or may be less easy to

take than a treatment that has the PrEP agent. The PrEP agent alone is never enough for treatment of HIV infection, so additional drugs are always needed for treatment. If you become infected, we will perform a blood test to see if there is any evidence of resistance to the PrEP agent.

OTHER RISKS

We do not know if there are other risks if you use herbal treatments or supplements while you are taking the study medications. Please tell study staff if you are using any herbal treatments or supplements. In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers immediately.

BENEFITS OF THE STUDY

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

We will test you for HIV and other sexually transmitted infections throughout this study. If you take Truvada® every day, it most likely will help you to avoid HIV. The counseling you get during this study may help you to avoid HIV and other sexually transmitted infections. If you have or acquire HIV, this counseling may help you to learn how to better care for yourself and avoid passing HIV to your sexual partners. If you acquire HIV or another STI, we will refer you for care and/or treatment. At the screening visit we will also check if you have hepatitis B or C infection. If needed, we will refer you for hepatitis B vaccination to protect you from getting it in the future. During the study you will have tests to check on the health of your blood, liver, and kidneys. If any health problems are found, you will be referred for care. At every visit you will receive condoms and lubricant free of charge.

Prior to completing this study, the study staff will discuss with you places where you can access HIV prevention services, including regular HIV testing and PrEP provision. The staff will provide you with referral to these services.

Additionally, if needed, the study staff can provide referral to other services such as STI testing and treatment and provision of gender affirming hormonal therapy.

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

15. 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 medication may be causing bad effects, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

16. 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 all of the study procedures or instructions.
- 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 study 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 site one last time to *[modify with early termination procedures:* check your blood, examine you, and ask you questions].

17. 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 eligible for. 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 and testing. We will tell you about those places if you wish.

18. There [sites to choose applicable language: is no/may be] cost to you to be in this study.

Language for sites with the ability of referring participants to institution that can provide GAHT free of cost: There will be no cost to you for study related visits, study products, physical examinations, laboratory tests, or other procedures.

Language for sites unable of referring participants to institution that can provide GAHT free of cost: If you are randomized to the 6-month Deferred Intervention Arm and choose to seek gender-affirming hormone therapy at a referral site, there may be cost associated with obtaining gender affirming hormonal therapy at that site during the first six months of study participation. Once you transition to the intervention portion of the study, these will be provided to you at the study site at no cost.

19. 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 site at each scheduled visit. [*Sites to insert information about local reimbursement for general study participation, and participation in the IDIs sub-study, if applicable].*

20. 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 samples will be labeled with a code that can only be traced back to your study site. Your name, where you live, and other personal information will be protected by the study site. The results of any tests done on these samples will not be included in your health records. You will be identified by a code, and personal information from your records will not be released without your written permission. Any publication of this study will not use your name or identify you personally. Your personal information may be disclosed if required by law.

Study 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]*
- Study staff and monitors
- The sponsor of the study (US National Institutes of Health [NIH]), its contractors, and its study monitors

- The U.S. Office for Human Research Protections (OHRP)
- Other local, US, or international regulatory authorities/entities
- The HPTN that is conducting this study
- Gilead Sciences Inc. the company that makes Truvada®, the drug used in this study
- And (*insert any other applicable local 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 test positive for [*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*]. All study records will be kept for at least three years after the end of the research, or longer if needed to comply with local regulations.

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

21. 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. 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.

22. 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].

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

SIGNATURE PAGE

HPTN 091, Integrating HIV Prevention, Gender-Affirming medical Care, and Peer Health Navigation for Transgender Women in the Americas: A Vanguard Study, Version X.0

SCREENING AND ENROLLMENT CONSENT

(Modify as needed per protocol requirements)
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 or make your mark below. Also, please indicate by providing your initials in the spaces below the additional sample collection, , or long-term storage that you agree to.

_____ I agree to take part in this study.

_____ I agree to have samples of my blood stored and used for future testing after study-related testing has been completed.

_____ I do not agree to have samples of my blood stored and used for future testing after study-related testing has been completed.

_____ I agree to participate in an interview where I will be asked questions about this research, and the interview will be recorded. [*Not applicable for participants enrolled in the Implementation Testing part of the study]*

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

_____	_____
Participant Name (print)	Participant Signature and Date (For non-literate participants, it could be their mark (e.g. X) or thumbprint)
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date

SAMPLE INFORMED CONSENT FORM FOR SITES IN THE UNITED STATES

HPTN 091
Integrating HIV Prevention, Gender-Affirming Medical Care, and Peer Health Navigation for Transgender Women in the Americas: A Vanguard Study

Final Version 1.0
13 April 2020
DAIDS Document ID: 38695

Sponsored by: National Institutes of Health, Division of AIDS, US National Institute of Allergy and Infectious Diseases, US National Institutes of Health. Study. Descovy® and Truvada® are provided by Gilead Sciences, Inc.

PRINCIPAL INVESTIGATOR: *[Insert Name*]

PHONE: *[Insert Number]*

INTRODUCTION

You are being asked to take part in a research study. Joining this study is voluntary. You may refuse to join, or you may withdraw your consent to be in the study, for any reason. This research study is for transgender women who may be at risk for getting Human Immunodeficiency Virus, or HIV. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS.

Before you decided 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 decide to join.

Here is a summary of important information about the study:

- This is a research study.
- Your participation in this study is voluntary.
- This study is being done to learn how to best provide HIV prevention among transgender women and assess the safety of this intervention in the United States and Brazil.
- All participants will be offered medications to prevent HIV, known as Pre-exposure prophylaxis (PrEP). These medications are called Descovy® and Truvada®. When used every day, it most likely will help you to avoid getting HIV.
- All participants will be assigned to one of two groups by random chance (an equal chance of being in either arm).). One group will meet with a peer to help them access services and be able to receive hormonal therapy right away at the site. The other group will be linked to services, to help them access services for hormonal therapy until their 6 month visit. At the 6 month visit this group will start to receive hormonal therapy from the site and meet with a peer to help them access services.
- You will come to the site for at least 8 scheduled visits.

- The study will include about 310 participants at five sites. Four of these sites are in the United States and one site is in Brazil.
- Periodic blood and urine test will be taken. Blood samples may cause pain, bruise your arm or make you feel lightheaded.
- There may be some social risks. 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.
- 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.
- We will test you for HIV and other sexually transmitted infections throughout the study.
- The counseling you receive during this study may help you to avoid HIV and other sexually transmitted infections.

More information is given in this form about the study. You should feel that you understand the study before deciding whether you will participate.

ABOUT THE STUDY

The HIV Prevention Trials Network (HPTN) and *[insert site name]* are doing this study to learn how best to prevent transgender women from acquiring HIV in the United States and Brazil.

About 310 people will participate in this study from the United States and Brazil. Approximately *XX* [*Sites to enter site-specific target*] participants will join the study at [insert site name]. Participants will be in the study for approximately 18 months.

2. The study is testing whether offering gender affirming hormones and HIV prevention services in one location is acceptable, feasible, and improves use of HIV prevention services among transgender women.

This study will enroll people who were assigned male at birth and who currently identify as women, transgender women, or along a trans feminine spectrum, who are age 18 years or older, who are having sex and who are HIV negative.

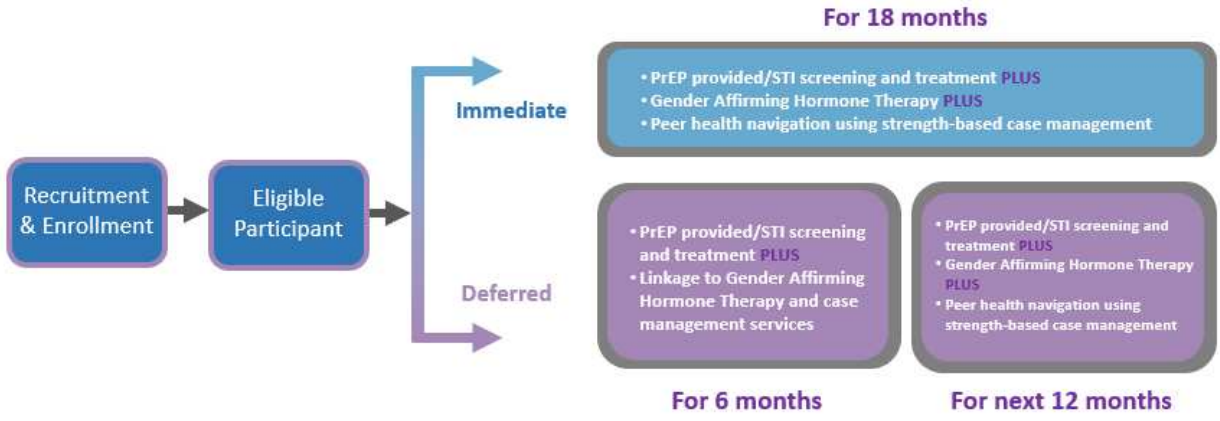
Participants will be offered the opportunity to take medications to prevent HIV. The medication to prevent getting HIV is sometimes called pre-exposure prophylaxis or "PrEP." PrEP is a way to prevent HIV infection for people who do not have HIV (the virus that causes AIDS) by taking a pill every day. HIV is the virus that causes Acquired Immunodeficiency Syndrome, or AIDS. The drugs being used for PrEP in this study are called Descovy® and Truvada®. Descovy® and Truvada® are pills that have two drugs in them called "emtricitabine" and "tenofovir alafenamide". These medicines are also used in combination with other medicines to treat HIV.

The United States Food and Drug Administration (FDA) approved Descovy® as oral PrEP in October 2019. Descovy® is similar to Truvada® which was approved for use as oral PrEP by the FDA more than 5 years ago and is made by the same company. Truvada® contains the drugs emtricitabine (FTC) and tenofovir **disoproxil fumarate** (TDF) and Descovy® contains the drugs emtricitabine (FTC) and tenofovir **alafenamide** (TAF). But because one of the drugs in Descovy® is different ("tenofovir alafenamide"), the risks of kidney and bone problems is less. The Brazilian National Health Surveillance Agency (ANVISA) has also approved Truvada® for use as oral PrEP. Participants that chose to take PrEP will be given a

choice of taking either Descovy® or Truvada®. Participants may start or stop taking PrEP at any time in the study and may switch between Descovy® and Truvada®.
Note: Participants who practice receptive vaginal sex cannot be provided Descovy® as it is not approved for this indication.

3. Participants will be placed in 1 of 2 groups.

All participants will be assigned by random chance (an equal chance of being in either arm).) to one of two groups. The difference between the groups is that one group will to meet with a clinician to start gender affirming hormonal therapy at this site right away. This group will also be able to meet with a peer who can help them access any services they need. The other group will be provided with information and assisted in seeking gender affirming services from other providers in their area who have a partnership with the site, until their 6 month visit. [*Include if your site is unable to refer participants to institutions that can provide GAHT free of cost:* If you are randomized to the 6-month Deferred Intervention Arm and choose to seek gender-affirming hormone therapy at a referral site, there may be cost associated with obtaining gender affirming hormonal therapy at that site during the first six months of study participation. Once you transition to the intervention portion of the study, these will be provided to you at the study site at no cost.] At the 6 month visit, all participants in the study will be able to get gender-affirming services, including hormonal therapy, at the site and meet with a peer. All participants will be in the study for approximately 18 months.



JOINING THE STUDY

4. It is your decision whether 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, you will be asked to sign your name or make your mark 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 a later 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. 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 some questions about yourself, like your age, and your ethnic group.
- Ask where you live and how to contact you.
- Collect ~XX mL (about x teaspoons) of blood which will be tested for: HIV, any of the diseases passed during sex, hepatitis B, hepatitis C and to see if you are healthy.
- Collect urine for: kidney and liver tests
- Give you a physical exam, that includes obtaining your complete medical history, measuring your weight, temperature, blood pressure, looking into your mouth and throat, listening to your heart and lungs, feeling your abdomen (stomach and liver), and ask you about any other medicines you are taking.
- We will offer you condoms and lubricant, and counsel you on how to use them safely.

The results of the HIV test will be available [*site to insert timeframe of testing*]. You will be contacted about the results of your other tests when they are available. A small amount of blood will be stored from this visit. No other samples collected at the time of screening will be kept or used for any other tests other than those listed above.

At this visit, we will collect a blood sample to see your cholesterol and triglycerides levels. Cholesterol and triglycerides are different types of fats that circulate in your blood. High levels of these substances increase your risk for developing heart disease. If the test results show you have high cholesterol and/or triglycerides, the site staff will refer you for medical assessment and treatment. To accurately see your levels of cholesterol and triglycerides, you need to be fasting, meaning you have not eaten, for at least 8 hours, preferable 12 hours. If you are not fasting, we will schedule you to return to the clinic on another

day before the Enrollment Visit to collect blood for this test. Remember you need to be fasting before collecting the blood sample.

7. We will confirm if you are eligible 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, and you will be referred for the appropriate medical care. *(sites to add specifics about this here as necessary)*
- If you have a negative HIV test We will counsel you on avoiding acquiring HIV. We will ask you personal questions about your HIV risk factors such as sexual behavior, alcohol, and drug use. We will talk with you about ways to keep your risk of getting HIV low.
- If your blood shows that you have any of the diseases passed during sex (sexually transmitted infection or "STI"), we will either treat you or refer you for treatment.
- If we find that you have a health problem during screening or during the study, we will tell you about the care that we can give here for free. We will give you referrals for other health services if you need them. For health problems that are unrelated to the study, we will not pay for care.

8. If you are eligible, you will enter the study.

If you are eligible for this study and decide to take part in the study, you will be asked to return for an "Enrollment Visit." This visit will last about X hours [*sites to fill in the amount of time].*

During the Enrollment Visit, we will:

- Confirm where you live and how to contact you.
- Ask you to answer questions on a computer about your sexual practices, and how you feel about how your life is going.
- Talk with you about HIV and ways to protect yourself from getting it.
- Collect ~XX mL (about x teaspoons) of blood for: HIV, STIs, hepatitis B, and hepatitis C.
- A blood sample will also be used to test your hormones (estradiol and total testosterone).
- Collect urine for: kidney and liver tests.
- Give you PrEP pills, and explain how to take them, and any side effects they may cause.
- Give you a physical exam that will include weigh, temperature, blood pressure, any other assessment based on signs and symptoms you may have, and ask about any medicines you are taking.
- Ask you about your medical history.
- If your blood, urine or rectal swab shows that you have any STIs, we will either treat you or refer you for treatment.
- We will offer you condoms and lubricant, and counsel you on how to use them safely.
- Give you the results of tests when they are available.
- The hepatitis B vaccination will be made available for those that have not been previously vaccinated.
- Randomize you (randomly place you) into 1 of the 2 study groups.
    - If you are randomized to the Inmediate arm, starting at this visit you will receive peer health navigator support.

BEING IN THE STUDY

9. Once you enroll in the study, you will have 6 visits over one and a half years.

If you decide to join the study, after your Enrollment Visit, you will be asked to come to this site approximately 6 times over the course of one and a half years.

If you are in jail during the study, your study visits will be paused and you may continue in the study once released.

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

After your enrollment visit, the visits will be about 12 weeks apart.

Regardless of the group you are randomized to, during these visits, we will:

- Confirm where you live and how to contact you.
- Ask you to answer questions on a computer about your sexual practices, and how you feel about how your life is going.
- Talk with you about HIV and ways to protect yourself and stay healthy.
- Give you PrEP pills, and explain how to take them, and any side effects they may cause.
    - You are not required to take PrEP. You will be offered PrEP at the site up until Week 39 visit. If interested, PrEP will be provided following creatinine and HIV testing. You may start and stop taking PrEP at anytime.
- Give you a physical exam that will include weigh, temperature, blood pressure, any other assessment based on signs and symptoms you may have, and ask about any medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood for: HIV, STIs, hepatitis B, and hepatitis C.
- A blood sample will also be used to test your hormones (estradiol and total testosterone).
- Collect urine for: kidney and liver tests.
- If your blood, urine or rectal swab shows that you have any STIs, we will either treat you or refer you for treatment.
- We will offer you condoms and lubricant, and counsel you on how to use them safely.

At the 6 Month and 18 Month study visit, we will collect a blood sample to see your cholesterol and triglycerides levels. Cholesterol and triglycerides are different types of fats that circulate in your blood. High levels of these substances increase your risk for developing heart disease. If the test results show you have high cholesterol and/or triglycerides, the site staff will refer you for medical assessment and treatment. To accurately see your levels of cholesterol and triglycerides, you need to be fasting, meaning you have not eaten, for at least 8 hours, preferable 12 hours. If you are not fasting, we will schedule you to return to the clinic on another day, preferable within 72 from the visit, to collect blood for this test. Remember you need to be fasting before collecting the blood sample.

Depending on the group you are randomized to, during these visits:

- Participants randomized to the deferred arm will be provided with information and assisted in seeking gender affirming services from other providers in their area who have a partnership with

the site, [XX SITE TO COMPLETE WITH PARTNER ORGANIZATIONS XX], , for the first 6 months.
    - At 6 months these participants will have the opportunity to receive hormonal therapy, counseling, and support at the site and meet with a peer (navigator/counselor) who can help them access any services they need.
    - Participants are able to start Gender Affirming Hormone Therapy at the site anytime after their 6 month visit and up to Week 39. During this time participants can choose to start and stop Gender Affirming Therapy at the site.
- For participants randomized to the immediate arm, these visits will include:
    - The opportunity to receive hormonal therapy, counseling and support at the site. Participants are able to start and stop Gender Affirming Horomone Therapy at any time.
    - Meet with a peer (navigator/counselor) who can help them access any services they need.

Regardless of the group you are randomized to, participants are not required to take Gender Affirming Hormone Therapy.

You may have more study visits if needed, for example, you may come to the site to get medications, if you are sick, or we need to check on your health. If you choose to start Gender Affirming Hormone Therapy an extra study visit will be scheduled within ten days after the collection of estradiol and total testosterone testing. If you wish to stop participating in the study early a final visit will be scheduled and a conversion with a member of the site staff.

All study arms are really important for the study. The information from participants in both arms help investigators learn if the intervention actually works.

Before the study ends, we will work with all participants to find supportive services so they can continue receiving hormonal therapy and PrEP if they would like to continue. At your final study visit, we will talk with you about the end of the study, and when the results of the study will be available.

You may stop study participation at any time. If you wish to stop participating in the study early, we will ask you to do a final visit and talk to a member of the site staff either in person or by phone. This visit will be scheduled at your convenience.

10. Interviews with a subgroup [*Not applicable for participants enrolled in the Implementation Testing part of the study*]

Approximately 60 participants across all study sites will be asked to participate in additional interviews. Participants will be chosen from those who: stop taking PrEP during the study, accept, or don't accept PrEP at enrollment, or decline PrEP at enrollment and accept PrEP later in the study These interviews will be no longer than an hour and a half and will happen up to three times during the study. In these interviews a trained interviewer will ask you questions about:

- How you decided to start, not start or stop PrEP
- Things that make it harder or easier to take PrEP
- Experiences in the study
- Knowledge of PrEP
- If you feel you are at risk of becoming HIV positive
- How others you know talk about PrEP use

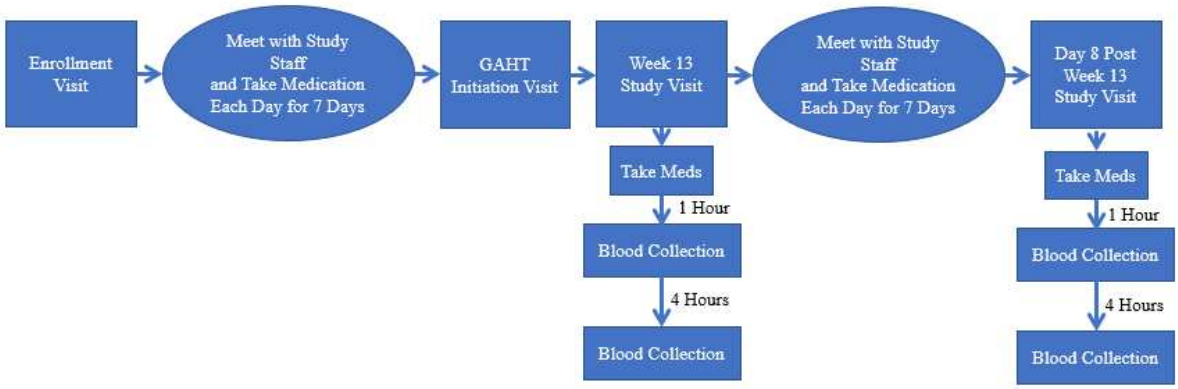
Taking part in these interviews is voluntary. You do not have to agree to these extra procedures in order to participate in HPTN 091. You can stop the interviews at any time. There is no direct benefit to you for participating in this additional aspect of the study. The interviews will be recorded and transcribed. The information learned from these interviews will help researchers to better understand the experiences of people using PrEP, what parts of the study are helpful or not helpful.

11. *[only include at the relevant sites]* Optional Drug-Hormone Interaction sub-study

Up to 50 participants across participating sites who are randomized to the Immediate Intervention Arm, agree to use Descovy® as their PrEP agent, and to participate in the sub-study will provide additional blood that will be used to see if there is interaction between the hormonal therapy and PrEP. To be able to participate in this sub-study you need to be willing to have additional meetings with study staff, this can be in person or by video conferencing. The study staff will discuss with you what option works best. Video conferencing can be done using a cell phone, computer, or tablet, you could use apps like FaceTime, WhatsApp, and Google Duo The video conferencing will not be recorded.

Participants in this sub-study will be asked to:

- Agree to take study-provided hormonal therapy and PrEP as instructed.
- Take their study product in the study site or during a video-conference with study staff for seven days in a row. The additional study site visits or video-conferencing will be done for seven days BEFORE the visit where you come to collect your hormonal therapy. It will also happen for seven days AFTER your Week 13 visit (about 3 months after you join the study). Study staff will provide you with detailed information and guidance about what is expected this additional study site visits or during the video-conference.
- At the visit when you collect your hormonal therapy, which will take place up to 10 days after you enroll (join the study), your blood will be drawn 3 times: before taking the study product, 1 hour after taking the study product, and 4 hours after taking the study product. Study product will be taken in front of study staff. Because of the extra blood draws, this visit will be longer, it would take about [X] hours.
- At the Week 13 visit, you will take your study product at the site in front of the study staff.
- Come for one additional visit 8 days AFTER the Week 13 visit. This visit will take about [X] hours. At this visit your blood will be drawn 3 times: before taking the study product, 1 hour after taking the study product, and 4 hours after taking the study product. Study product will be taken in front of a study staff.



Joining this sub-study is voluntary. You do not have to agree to these extra procedures in order to participate in HPTN 091. There is no direct benefit to you for participating in this sub-study. The information learned from this sub-study will help researchers learn if taking hormonal therapy has an impact on how much PrEP is in your body.

12. If you acquire 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 study drugs. You will be asked to come to another visit and then a visit 13 weeks later (about 3 months). We will help you find the care and support you need. One final visit will be scheduled three months later to follow-up on your care.

13. Use of stored blood samples.

Blood samples will be stored at enrollment and at follow-up visits. Some of these samples will be used for quality control testing (to confirm results obtained in site laboratories) and for testing for drugs used to prevent HIV infection. If you get HIV infection during the study, some of the stored blood samples will be used to study the HIV virus and your body's response to HIV infection. Some of this work may involve studying how HIV spreads within the community. 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 and other countries outside of [insert site country]. 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).

We do not plan to do genetic testing or sequencing (for example, the mapping of all of your genes, which is also known as whole genome sequencing) of any kind. Your specimens will never be used for commercial profit.

Some of your blood may be left over at the end of the study [and may/but will not] be used for future research. (*Sites may require a separate consent form for this)*

Some of the blood collected during this study may be left over after all of the study tests are completed. If you agree, your stored samples may also be used for future research related to HIV infection, hepatitis

infection, and other infections transmitted 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 for possible future research, you can still be in this study. If you give permission, you will not be asked to give permission again once a researcher requests to use your samples after the study is over. 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.

RISKS OF THE STUDY

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

STUDY PROCEDURES

Getting an HIV test may cause you anxiety. You may become emotionally upset if you find out that you have acquired HIV. The study staff will provide emotional support and work with you to connect with a medical provider for living with HIV.

Taking blood samples may cause some pain, bruise your arm, swelling, 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 be nervous while you are waiting for your HIV test result. If the tests show that you have HIV, you may worry about your health and future. You will receive counseling before and after the test to help address your concerns. [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 will be tested for gonorrhea, chlamydia and syphilis. [*Note to sites: Insert here any reporting responsibilities for your state or local jurisdictions or reporting of these infections to public health authorities].*

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 high risk for acquiring HIV.

SENSITIVE QUESTIONS

Due to the sensitive nature of some of the questions asked in the computer survey, you may feel uncomfortable answering questions about your sexual practices and possible risk for HIV and other STIs (sexual transmitted infections) and drug and alcohol use. Study staff are trained to give you emotional support if needed. Also, you can choose not to answer questions that make you feel uncomfortable. You are free to discontinue participating in the study at any time without consequences.

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 test positive for HIV during the study, you will be asked to stop taking your study medication. If you continue to take the study medication after acquiring HIV, there is a chance that drug resistance may occur.

Possible side effects in PrEP research studies when using Descovy®:

- The most common side effects are diarrhea, nausea, headache, tiredness and abdominal pain.
- Worsening or new kidney damage is a rare side effect
- Lactic acidosis (buildup of too much acid in the body) can cause shortness of breath, nausea and live failure, these are rarely seen
- Individuals with HBV who suddenly stop taking Descovy® may experience worsening of hepatitis symptoms.

Possible side effects in PrEP research studies when using Truvada®:

- Nausea, diarrhea, vomiting, gas (flatulence), headache, tiredness, feeling faint or weak, not able to sleep, irritated or swollen skin (rash), bone pain, allergic reaction, lactic acidosis (buildup of too much acid in the body), stomach (abdominal) pain, and "flare" or worsening of hepatitis due to suddenly stopping the drug. This mainly happened in the first month and went away, and happened in about 10% or one in ten people.
- A small number (1% or one in one hundred people) showed a small decrease in how their kidneys work, this stopped when the people stopped taking the drug.
- Changes in how much calcium and other minerals are in your bone which keeps them strong (bone mineral density) were very rare in people taking the drug who did not have HIV and have always gotten better when the drug was stopped.

Possible side effects in Gender Affirming Hormone Therapy:

Estrogen therapy

The full medical effects and safety of estrogen therapy are not fully known. Potential adverse effects may include, but are not limited to:

- Increased or decreased of fats in the blood (cholesterol), which may increase risk for heart attack or stroke
- Increased risk of the following:
  - Cause a blood clot (deep venous thrombosis), blood flow is blocked from reaching the lungs (pulmonary embolism)
  - Breast tumors/cancer
  - Heart disease, the heart beats too fast or too slow (arrhythmias), and stroke;
  - High blood pressure
  - Abnormal growths on your pituitary gland (pituitary tumors)
  - Low levels of iron in the blood (anemia)
  - Decreased sex drive and sexual functioning
  - Psychiatric symptoms such as depression and suicidal feelings; anxiety; psychosis, and worsening of pre-existing psychiatric illnesses
  - Decrease in how much calcium and other minerals are in your bone which keeps them strong (bone mineral density)
  - Genital changes (i.e., smaller testes & penis)
  - Inability to have children (infertility)
  - Create harden deposits of digestive fluid (gallstones) in your gallbladder (cholelithiasis)

The risks for some of the above adverse events may be increased by pre-existing medical and psychiatric conditions, cigarette smoking, and alcohol use.

Breast growth and inability to have children (infertility) may be irreversible and potential outcome increases with length of time on hormones.

Anti-androgen and GnRH agonists

Estrogens are usually given with androgen blockers. Potential adverse effects of androgen blockers may include, but are not limited to:

- Increased levels of potassium in the blood (spironolactone)
- Liver inflammation (flutamide, bicalutamide, cyproterone acetate)
- Decreased bone density

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. The questions we will ask you about your sexual behavior may make you feel uneasy. 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. You may also experience stigma and may be treated differently as a result of being involved in a study about HIV because people 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 at high risk and treat you unfairly as a result.

RECTAL SWABS

You may experience pain or discomfort in your rectum from the swab. In some cases, you may have some bleeding.

HIV RESISTANCE

If you decide to take PrEP and then acquire HIV, there is a risk that the HIV you have could be "resistant" to the PrEP agents in this study, Descovy® or Truvada®. This may then mean that you may not be able to be treated with the PrEP agents nor the drugs which are combined together to make the PrEP agents (Tenofovir and Emtricitabine). Viral drug resistance to these drugs can also cause cross resistance (meaning your virus is also resistant to other drugs as well as the drugs in the PrEP agents) to more commonly used drugs such as Lamivudine (3TC). Your doctor would need to prescribe different drugs which are used to treat HIV infection. These other drugs may have more side effects or may be less easy to take than a treatment that has the PrEP agents. The PrEP agents alone are never enough for treatment of HIV infection, so additional drugs are always needed for treatment. *If you become infected, we will perform a blood test to see if there is any evidence of resistance to the PrEP agents.*

OTHER RISKS

We do not know if there are other risks if you use herbal treatments or supplements while you are using the study medications. Please tell study staff if you are using any herbal treatments or supplements. In addition, there may be uncommon or previously unknown risks that might occur. You should report any problems to the researchers immediately.

BENEFITS OF THE STUDY

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

We will test you for HIV and other sexually transmitted infections throughout this study. If you take Descovy® or Truvada® every day, it most likely will help you to avoid HIV. The counseling you get during this study may help you to avoid HIV and other sexually transmitted infections. If you have or acquire HIV, this counseling may help you to learn how to better care for yourself and avoid passing HIV to your sexual partners. If you acquire HIV, or have another sexually transmitted infection, we will refer you for care and/or treatment. At the screening visit we will also check if you have hepatitis B infection. If needed, we will refer you for hepatitis B vaccination. During the study you will have tests to check on the health of your blood, liver, and kidneys. If any health problems are found, you will be referred for care. At every visit you will receive condoms and lubricant free of charge.

Prior to completing this study, the study staff will discuss with you places where you can access HIV prevention services, including regular HIV testing and PrEP provision. The staff will provide you with referral to these services.

Additionally, if needed, the study staff can provide referral to other services such as STI testing and treatment and provision of gender affirming hormonal therapy.

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

16. 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 medication may be causing bad effects, you will be told about this. You will also be told when the results of the study may be available, and how to learn about them.

17. 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 all of the study procedures or instructions.
- 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 study 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 site one last time to *[modify with early termination procedures:* check your blood, examine you, and ask you questions].

18. 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 eligible for. 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 and testing. We will tell you about those places if you wish.

19. There [*sites to choose applicable language*: is no/may be] cost to you to be in this study.

Language for sites with the ability of referring participants to institution that can provide GAHT free of cost: There will be no cost to you for study related visits, study products, physical examinations, laboratory tests, or other procedures.

Language for sites unable of referring participants to institution that can provide GAHT free of cost: If you are randomized to the 6-month Deferred Intervention Arm and choose to seek gender-affirming hormone therapy at a referral site, there may be cost associated with obtaining gender affirming hormonal therapy at that site during the first six months of study participation. Once you transition to the intervention portion of the study, these will be provided to you at the study site at no cost.

20. 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 site at each scheduled visit. [*Sites to insert information about local reimbursement for the general study, and participation in the IDI and/or the DHI sub-studies.]*

You may be required to provide your social security number to be paid for taking part in this study. Federal tax law requires that you report your research payments when you file your taxes. If your total payments from (Insert facility here) exceed $600 per year, [Insert facility here] will report these payments to the Internal Revenue Service and you will receive a 1099-MISC form from us.

21. 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 samples will be labeled with a code that can only be traced back to your study site. Your name, where you live, and other personal information will be protected by the study site. The results of any tests done on these samples will not be included in your health records. You will be identified by a code, and personal information from your records will not be released without your written permission. Any publication of this study will not use your name or identify you personally. Your personal information may be disclosed if required by law.

Study 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 single Institutional Review Board (IRB)]*
- Study staff and monitors
- The sponsor of the study (US National Institutes of Health [NIH]), its contractors, and its study monitors
- The U.S. Office for Human Research Protections (OHRP)
- Other local, US, or international regulatory authorities/entities

- The HPTN that is conducting this study
- Gilead Sciences Inc. the company that makes Descovy® and Truvada®, the drug used in this study

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 U.S. 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 Certificate of Confidentiality will not be used if disclosure is for other scientific research, as allowed by federal regulations protecting research subjects or for any purpose you have consented to in this informed consent document.

You should understand that a Certificate of Confidentiality does not prevent you from voluntarily releasing information about yourself or your involvement in this research. If an insurer, employer, or other person obtains your written consent to receive research information, then the researchers may not use the Certificate to withhold that information.

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 test positive for [*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*]. All study records will be kept for at least three years after the end of the research, or longer if needed to comply with local regulations.

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

22. 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. 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.

23. 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].

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

SIGNATURE PAGE

HPTN 091, Integrating HIV Prevention, Gender-Affirming medical Care, and Peer Health Navigation for Transgender Women in the Americas: A Vanguard Study, Version X.0

SCREENING AND ENROLLMENT CONSENT

(Modify as needed per protocol requirements)
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 or make your mark below. Also, please indicate by providing your initials in the spaces below the additional sample collection, or long-term storage that you agree to.

_____ I agree to take part in this study.

_____ I agree to have samples of my blood stored and used for future testing after study-related testing has been completed.

_____ I do not agree to have samples of my blood stored and used for future testing after study-related testing has been completed.

_____ I agree to participate in an interview where I will be asked questions about this research, and the interview will be recorded. [*Not applicable for participants enrolled in the Implementation Testing part of the study*]

_____ I do not agree to participate in an interview where I will be asked questions about this research, and the interview will be recorded. [*Not applicable for participants enrolled in the Implementation Testing part of the study]*

_____ I agree to participate in a Drug-Hormone Interaction Sub-study where I will undergo directly observed therapy and have additional blood collections.

_____ I do not agree to participate in a Drug-Hormone Interaction Sub-study where I will undergo directly observed therapy and have additional blood collections.

_____	_____
Participant Name (print)	Participant Signature and Date (For non-literate participants, it could be their mark (e.g. X) or thumbprint)
_____	_____
Study Staff Conducting Consent Discussion (print)	Study Staff Signature and Date
_____	_____
Witness Name (print) (As appropriate)	Witness Signature and Date