HIV Prevention Trials Network

Letter of Amendment # 1 to:

HPTN 091

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

DAIDS Study ID: 38695

Version 1.0, dated 13 April 2020

Date of Letter of Amendment: 26 May 2021
Final Version

The following information impacts the HPTN 091 study and must be forwarded to all responsible Institutional Review Boards/Ethics Committees (IRBs/ECs) as soon as possible for their information and review. This Letter of Amendment (LoA) must be approved by all responsible IRBs/ECs before implementation.

The information contained in this LoA does impact the informed consent forms (ICFs).

Upon receiving final IRB/EC approval for this LoA, sites should implement the LoA immediately. Sites are required to submit an LoA registration packet to the DAIDS Protocol Registration Office (PRO) at the Regulatory Support Center (RSC). As part of the registration package, sites must submit the Letter of Amendment Investigatory Signature Page, signed and dated by the Investigator of Record. Sites will receive a registration notification for the LoA once the DAIDS PRO verifies that all the required LoA registration documents have been received and are complete. A LoA registration notification from the DAIDS PRO is not required prior to implementing the LoA. A copy of the LoA registration notification along with the LoA and any IRB correspondence should be retained in the site's regulatory files.

If the full HPTN 091 protocol is amended in the future, the changes in this LoA will be incorporated into the next version. Text appearing below in highlighted **bold** will be added, and text appearing in highlighted strike-through will be deleted.

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HPTN 091

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LETTER OF AMENDMENT SIGNATURE PAGE

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."

Signature of Investigator of Record

Date

Name of Investigator of Record
(printed)

Summary of Revisions and Rationale

1. The list of abbreviations and acronyms was revised to reflect the revisions made in the protocol.
   See revision 1.
2. The protocol roster was updated to reflect the current protocol team.
   See revision 2.
3. Sections 3.4 was updated and section 6.9.1 was added to provide additional information about interim visits for Peer Health Navigation. These visits are optional to minimize participant burden. We will be capturing the number of PHN sessions completed and number of contacts participants have with PHNs to capture any variability in the intervention.
   See revisions 3, 13.
4. The inclusion and exclusion criteria were updated to clarify the HIV testing requirements at the enrollment visit.
   See revision 4, 5, 9.
5. Section 5.3 was updated to clarify requirements for product storage.
   See revision 6.
6. The timeframe to review implementation testing data was updated to specify that data will be reviewed per site to minimize delays in full protocol enrollment.
   See revision 7.
7. The name of the informed consent was corrected, and text was added to clarify the requirements for collecting medical history and conducting the physical exam required at the Screening Visit.
   See revision 8.
8. Revisions were made to allow for the collection of fasting lipid profile samples at either the Screening or Enrollment Visit.
   See revisions 8, 9.
9. Revisions were made to correct grammatical errors.
   See revisions 10, 15, 27.
10. Revisions were made to clarify that participants enrolled to either study arm are eligible to participate in the Drug-Hormone Interaction Sub-study.
    See revision 11.
11. This section was updated to correct data that will be collected in the study. The deleted items were included erroneously in the protocol.
    See revision 12, 14.
12. Revised to remove GnRH agonists as they will not be available. GnRH agonists are not commonly used and therefore it is unlikely that sites will provide to participants. Additionally, the current national standard for hormonal therapy does not include them because they are not standard of care for GAHT in the U.S.

See revision 16.

13. Sections were updated to better reflect Laboratory Center processes.
    See revisions 17-20.
14. Revisions were made to include DAIDS template language.
    See revisions 21, 22.
15. Section 11.8 was updated to include the Clinicaltrials.gov identifier number.
    See revision 23.
16. The schedule of events outlined in Appendix a-1c were updated to reflect clarifications made in the protocol.
    See revisions 24-26.
17. The informed consent template for sites in Brazil was updated to reflect updates to the protocol, provide clarity, to further explain the study procedures for participants, and to match language in the informed consent template for sites in the United States as appropriate.
    See revision 27.
18. The informed consent template for sites in the United States was updated to reflect updates to the protocol, provide clarity, and to further explain the study procedures for participants.
    See revision 28.

Revision 1: List of Abbreviations and Acronyms

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~~

Revision 2: Protocol Team Roster

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Revision 3: Section 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 **scheduled** 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. **Additional visits may be done between scheduled study visits, please refer to Section 6.9.**

Revision 4: Section 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 **at least one non-reactive test result at** 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.

Revision 5: Section 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 **at least one reactive/positive HIV test result at** 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.

Revision 6: Section 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~~ **Keep container tightly closed** and dispense~~d~~ **only** 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~~**Keep container tightly closed and** dispensed **only** in the original container. Refer to the relevant Package Insert for further information**.**

Revision 7: Section 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~~**navigators** 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**, ideally** over a 3-month period**. At each site, the Implementation Testing period will be completed after the last participant enrolled as part of this group** ~~, 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. **While the Implementation Testing period is happening at the site, no additional participant may be enrolled as part of the full protocol.** ~~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)~~ **study leadership**. 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.

Revision 8: Section 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~~**study** 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.

A thorough medical history and physical exam will be performed at Screening and should include assessment for acute HIV infection and mental health assessment.

~~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.

Revision 9: Section 6.3 Enrollment Visit

HIV test results from Screening **and at least one HIV test result from the Enrollment visit** 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~~**The participant's** medical **and mental** history **should be reviewed and updated as needed,** and ~~should include assessment for acute HIV infection. A~~**a** symptoms-directed physical exam will be done at the Enrollment Visit prior to enrollment**.**

Samples for lipid profile will be taken either at Screening or Enrollment, per clinician's discretion. Participants must have fasted for at least 8 hours, preferably 12 hours, prior to lipid profile sample collection. Sites should verify that a participant has fasted prior to sample collection. If the participant 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.

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.

Revision 10: Section 6.4 Follow-Up Visits

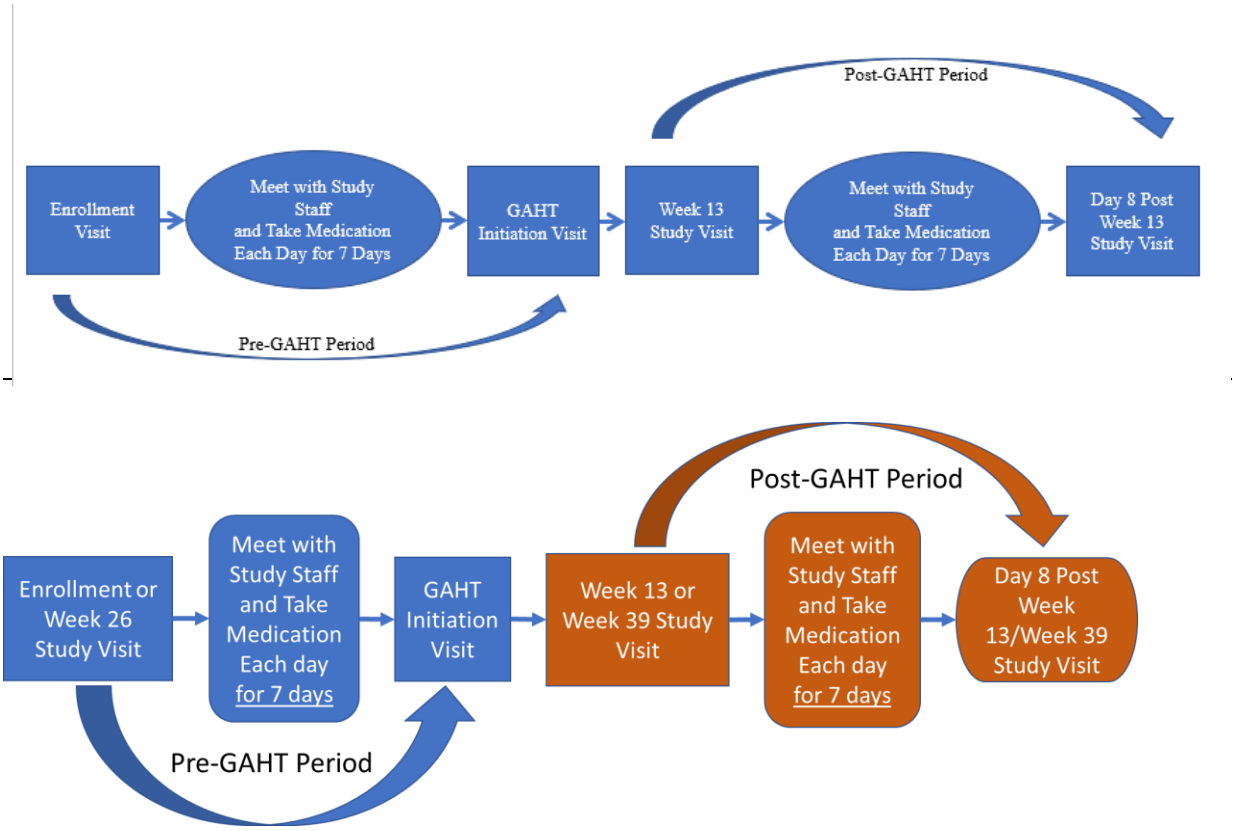
Fast~~ed~~**ing** sample~~s~~**d** for lipid profile testing will be collected at Week 26 (Month 6) and Week 78 (Month 18). Prior to sample collection, sites must confirm with participants that they have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If a participant has 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.

Revision 11: Section 6.7 Drug-Hormone Interaction Sub-study

Consequently, the DHI substudy will include a one-week DOT **pre-GAHT** dosing phase to occur immediately after enrollment ~~(Period 1), and a~~**for participants enrolled to the Immediate Arm or after Week 26 (Month 6) for participants enrolled to the Deferred Arm. The post-GAHT** dosing phase~~, which~~ will occur directly following the participant's first quarterly visit (week 13) **for participants enrolled to the Immediate Arm or after the Week 39 (Month 9) for participants enrolled to the Deferred arm,** 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 **manual**.

Post-GAHT PK assessment initiates at ~~w~~**W**eek13 (month 3**) or Week 39 (Month 9**) in order to streamline the total number of visits required by the study participant. All participants will have a study visit at ~~w~~**W**eek 13~~,~~ **or Week 39 (Month 9),** 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.



Revision 12: Section 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
- **PrEP use**
- 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 **future use 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.

Revision 13: Section 6.9.1 Peer Health Navigation Interim Contacts

During the first six months of the intervention – starting at the Enrollment Visit for participants randomized to the Immediate Intervention and at Week 26 (Month 6) Visit for participants randomized to the Delayed Intervention– participants could receive additional PHN support. As part of the study intervention, study participants will have PHN sessions as described in Appendix Ia: Schedule of Events. In between protocol-required study visits, participants are offered the opportunity to meet with the PHN two additional times, in between regularly scheduled study visits. These additional contacts could be done by phone,

videoconferencing, or in-person at the study site, based on participant's preference and availability. Although these additional contacts are not required, they are highly encouraged to ensure participants have a clear understanding of the study intervention and receive the necessary support. These additional visits/contacts are optional because these will be done at participant's discretion and based on their needs. The number and nature of the contacts will be tracked by peer health navigators at the site. Detailed information about the PHN content and implementation is found on the HPTN 091 SSP Manual.

Peer Health Navigation Schedule During First Six Months of the Study Intervention

Immediate Intervention Arm PHN Visits	Deferred Intervention Arm PHN Visits
Enrollment	**Week 26 (Month 6)**
GAHT Initiation Visit	**GAHT Initiation Visit**
Optional PHN Contact (To occur between GAHT Initiation and Week 13 (Month 3) study visits)	**Optional PHN Contact (To occur between GAHT Initiation and Week 39 (Month 9) study visits)**
Week 13 (Month 3)	**Week 39 (Month 9)**
Optional PHN Contact (To occur between Week 13 (Month 3) and Week 26 (Month 6) study visits)	**Optional PHN Contact (To occur between Week 39 (Month 9) and Week 52 (Month 12) study visits)**
Week 26 (Month 6)	**Week 52 (Month 12)**

Any other additional PHN interim visits and contacts may be done at participant's request. PHN may also contact participants between required study visits for support and retention purposes.

Revision 14: Section 8.6.1 Primary Analysis

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.

Revision 15: Section 8.7.2 Drug-Hormone Interaction Sub-study

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) **may**~~can~~ be used to evaluate the impacts of hormonal therapy on drug concentrations in this broader population.

Revision 16: Section 9.3.3 Risks Associated with Hormonal Therapy with Estrogen and Anti-androgen

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)~~

Revision 17: Section 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~~ **in accordance with regulatory requirements**. Results will not be returned to the study participants.

Revision 18: Section 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 **an**~~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).

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)~~**an External Quality Assurance (EQA) program and/or a specified sponsor contractor** 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.

Revision 19: Section 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 **an External**~~the DAIDS Immunology~~ Quality Assurance ~~(IQA)~~ program and**/or a specified sponsor contractor 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.~~

Revision 20: Section 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 **an External** ~~the DAIDS Virology~~ Quality Assurance ~~(VQA)~~ program and**/or a specified sponsor contractor and** must demonstrate successful participation in this program. U.S. sites must use CLIA-certified laboratories; ~~participant in the VQA program is recommended~~.

Revision 21: Section 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~~**The DAIDS Site Clinical Operations and Research Essentials (SCORE) Manual**, 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.

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~~**retention**, 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.

Revision 22: Section 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.

Monitoring visits may be conducted on-site or remotely. Remote visits may include remote source document verification using methods specified for this purpose by NIAID. Remote monitoring visits may be performed in place of, or in addition to onsite visits to ensure the safety of study participants and data integrity. The site will make available study documents for site monitors to review utilizing a secure platform that is HIPAA and 21 CFR Part 11 compliant. Selected platforms must be confirmed with the DAIDS Office of Clinical Site Oversight (OCSO) in advance.

Revision 23: Section 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. **The ClinicalTrials.gov Identifier for this study is: NCT04742491.**

Revision 24: 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]~~**ACASI**		X		X	X	X	X	X	X
HIV **testing and** 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	X
Clinical Procedures									
Complete medical ~~history, physical~~**history[1]**	X								
Symptom-directed physical exam[1]	X	X		X	X	X	X	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)
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								
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**[7]	**X**[7]			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)
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
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~~.~~ **and physical exam.**

[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 **site for fasting** ~~same for lipid~~ sample collection**.** ~~: if not collected at the Screening Visit, **the** .sample should be collected prior to the~~**at the** ~~Enrollment Visit; i~~**I**f **fasting sample is** not collected at Weeks 26 or 78, sample should be collected ideally within 72 hours of the visit.

[7] Fasting lipid profile can be collected at either Screening or Enrollment, per clinician's discretion. If the fasting sample is collected at the Screening Visits, it is not required to be collected at the Enrollment Visit. If a fasting sample is not collected either at the Screening or Enrollment Visits, participants should be scheduled to come to the study site for sample collection within 72 hours of the Enrollment visit

Revision 25: 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

*** A separate blood sample (plasma) will be collected for real-time local resistance testing for participants who have confirmed HIV infection**.

****** 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.

Revision 26: Appendix Ic: Schedule of Events for Participants in Drug-Hormone Interaction Sub-study

Study Procedures	Day 1-7 Before GAHT Initiation Visit	GAHT Initiation Visit[3]	Week 13/**Week 39[4]** Study Visit	Day 1-7 After Week 13/**Week 39[4] Study Visit**	Day 8 <u>After</u> Week 13/**Week 39[4] Study Visit** (Clinic Visit)
Study Product/Supplies					
DOT	X			X	
In-clinic DOT[5]		X	X		X
Laboratory					
Pre-DOT					
PBMC storage		**X**			**X**
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.

[4] The DHI substudy will include participants enrolled at US sites participating in the substudy, who accept Descovy as their PrEP agent, and receive GAHT at the site:

- **Immediate Arm: Pre-GAHT dosing phase will start immediately after enrollment and the post-GAHT dosing phase will occur after the Week 13 (Month 3) study visit.**
- **Deferred Arm: Pre-GAHT dosing phase will start immediately after Week 26 (Month 6) and post-GAHT dosing phase will occur after the Week 39 (Month 9) study visit.**

[5] please ensure collection of all pre-DOT samples prior to administration of PrEP

Revision 27: Appendix III: Informed Consent Template for Sites in Brazil

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~~**whether** provid**eing** HIV prevention **services and gender-affirming hormonal therapy for** ~~among~~ transgender women **at the same time and place will help prevent transgender women from getting HIV. It will also study** ~~and assess~~ the safety of ~~this intervention~~**these services together** in the United States and Brazil.
- ~~All participants~~**You** 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~~**You** will be assigned to one of two groups by random chance (an equal chance of being in either arm) **either to the Immediate Intervention or the 6-month Deferred Intervention**. **The Immediate Intervention** ~~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 **6-month Deferred Intervention**~~other~~ group will be linked to services, to help them access services for hormonal therapy ~~until their~~**for the first** 6 month**s of the study** ~~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. **There may be additional contacts or visits in between scheduled visits to provide peer support, to do a health follow-up, or at your request in case you need to see or speak to study staff about the study.**
- 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~~ **becoming infected with** 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.

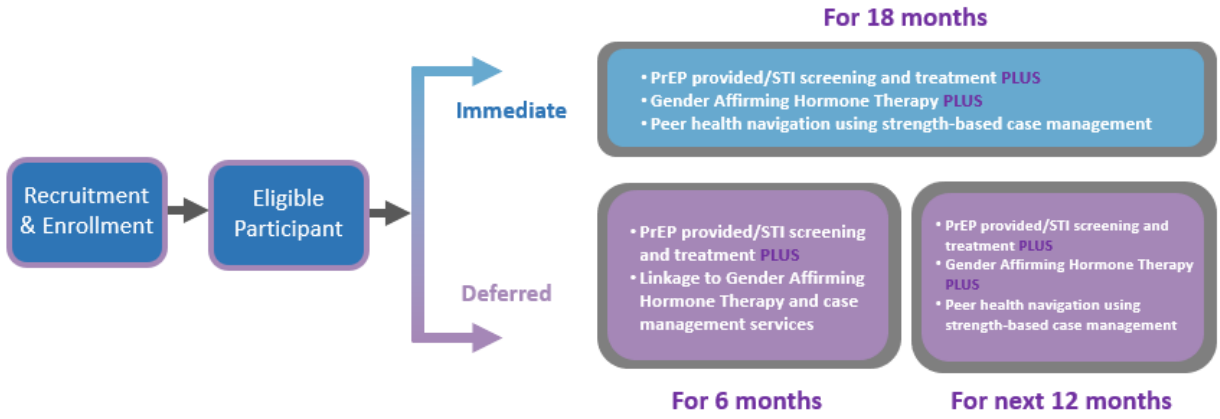
3. Participants will be placed in 1 of 2 groups.

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 **(The Immediate Intervention)** will meet with a provider to start receiving gender-affirming ~~services~~**therapy (GAHT)**~~, including hormonal therapy,~~ at this site right away. This group will also be able to meet with a **Peer Health Navigator**~~peer~~ who can help them access ~~any~~ services they need. **Peer Health Navigators are individuals who share the same experiences and community membership as participants, and who are trained to provide effective information about health and social services.**

The other group **(The 6-month Deferred Intervention)** 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, **give** ~~examine~~ you **a physical exam**, 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~~**kidney and liver issues**.
- Collect urine for: kidney ~~and liver~~ test~~s~~
- Give you a physical exam, that includes obtaining your complete medical **and mental health** 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 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 becoming infected with HIV low.**
- 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~~ **may** 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 **before the blood sample is collected**. If you are not fasting **during the time of the Screening Visit, the blood sample will be collected during**~~, 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.~~

No other samples collected at the time of screening will be kept or used for any other tests other than those listed above.

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~~,~~ **and** STIs **(sexually transmitted infections)**~~, hepatitis B, and hepatitis C.~~
- A blood sample will also be used to test your hormone levels (estradiol and total testosterone). **If the blood sample to test your cholesterol and triglycerides levels was not collected at the Screening visit, we will collect it at this visit. If at this visit we are no able to collect the sample to test your cholesterol and triglycerides, we will ask you to return to the site as soon as possible, ideally within 2 weeks, to collect the sample.**
- Collect urine for: ~~kidney and liver tests~~**STI tests**.
- **Collect rectal and oral swabs to test for STIs**
- **If your blood, urine or rectal swab shows that you have any STIs, we will either treat you or refer you for treatment.**

- 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 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**, and ask questions about your mental health**.
- 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 o~~**O**ffer 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. **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.**

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 unable to come to the clinic for your study visits (for example, if you are hospitalized, in ~~p~~jail, or traveling for an extended amount of time), you may continue in the study once you are able to return to the clinic. Your study duration will not change if you are not able to come to the clinic for an extended amount of time.~~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~~ **kidney function** 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 **your mental health and** any medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood **which will be tested** for: HIV, STIs, **and kidney and liver function. At your final visit (Month 18), we will also test your blood for** hepatitis B, and hepatitis C.
- A blood sample will also be used to test your hormones (estradiol and total testosterone).
- **At the 6 Month and 18 Month study visit, we will also do a blood test to look at the health of your blood. At these visits, we will also 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 before sample collection. Before collecting this sample, we will confirm with you that you are fasting. 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.**
- Collect urine for: kidney and ~~liver~~ **STI** test**ings**~~s~~.
- **Collect rectal and oral swabs to test for STIs.**
- 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 o~~**O**ffer 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~~ **If you are in** ~~to~~ the **6-month** ~~d~~**D**eferred **Intervention** ~~a~~**A**rm**, you** 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~~**you** 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~~ **health navigator** who can help ~~them~~ **you** access any services ~~they~~ **you** need.
  - ~~Participants are~~**You will be** able to start Gender Affirming Hormon**al**~~e~~ Therapy at the site anytime after ~~their~~ **your** 6 month visit and up to Week 39. During this time

~~participants~~ **you** can choose to ~~start and~~ stop Gender Affirming **Hormonal** Therapy at the site.

- ~~For participants randomized to~~**If you are in** the ~~i~~**I**mmediate **Intervention** ~~a~~**A**rm, ~~these~~ **your** visits will include:
  - The opportunity to receive hormone therapy, counseling and support at the site. ~~Participants~~ **You** are able to ~~starts and~~ stop Gender Affirming Hor~~o~~mon**al~~e~~** Therapy at any time.
  - Meet with a ~~trained staff member~~**Peer Health Navigator** who is a peer who can help ~~them~~ **you** access any services they need.

Regardless of the group you are randomized to, participants are not required to take Gender Affirming Hormon**al** ~~e~~ 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**, or to meet with a Peer Health Navigator**. If you choose to start Gender Affirming Hormon**al**~~e~~ Therapy**,** an extra study visit will be scheduled within ten **(10)** 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~~ **Both** 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.

Peer Health Navigation Sessions

This study involves peer health navigation. In these sessions, you will meet one-on-one with a peer who will work with you to set goals related to your health, wellbeing, and PrEP use, and help you access any services you may need. The peer health navigation sessions will take place at all scheduled visits. -You may have additional contacts during the first 6 months of the study intervention. If you are randomized to the Immediate Intervention Arm, these additional peer health navigation contacts will occur during the first 6 months of the study. If you are in the Deferred Intervention group, peer health navigation will start at the Month 6 visit, when you start the study intervention.

Peer Health Navigation Schedule During First Six Months of the Study Intervention

Immediate Intervention Arm Peer Health Navigation Visits	**Deferred Intervention Arm Peer Health Navigation Visits**
Enrollment Visit	**Week 26 (Month 6) Visit**
Gender Affirming Hormonal Therapy (GAHT) Initiation Visit	**Gender Affirming Hormonal Therapy (GAHT) Initiation Visit**
Optional Peer Health Navigator Contact (To occur between GAHT Initiation and Week 13 (Month 3) study visits)	**Optional Peer Health Navigator Contact (To occur between GAHT Initiation and Week 39 (Month 9) study visits)**
Week 13 (Month 3) Visit	**Week 39 (Month 9) Visit**
Optional Peer Health Navigator Contact (To occur between Week 13 (Month 3) and Week 26 (Month 6) study visits)	**Optional Peer Health Navigator Contact (To occur between Week 39 (Month 9) and Week 52 (Month 12) study visits)**
Week 26 (Month 6) Visit	**Week 52 (Month 12) Visit**

You may choose to have additional contacts with a Peer Health Navigator between study visits for any support you may need.

These contacts are optional and could be done by phone, videoconferencing, or in person at the study site. You will decide how you want these contacts to take place. Each session with the peer health navigator will be up to 60 minutes, depending on your needs and topic of discussion.

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. **We will tell you if you are selected to participate in the additional interviews.** 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, **and** what parts of the study are helpful or not helpful. **At the end of this form, you will be asked to indicate by providing your initials if you agree to participate in this Sub-study.**

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~~**infections**~~, 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
- ~~, d~~**D**iarrhea
- ~~, v~~**V**omiting
- ~~, g~~**G**as (flatulence~~),)~~
- ~~h~~**H**eadache~~,~~
- **T~~t~~**iredness~~,~~
- ~~f~~**F**eeling faint or weak
- ~~, n~~**N**ot able to sleep~~,~~
- ~~i~~**I**rritated or swollen skin (rash)~~,~~
- ~~b~~**B**one pain~~,~~
- ~~a~~**A**llergic reaction~~,~~
- **L~~l~~**actic acidosis (buildup of too much acid in the body)~~,~~
- ~~s~~**S**tomach (abdominal) pain~~,~~
- **Individuals with hepatitis B virus (HBV) who suddenly stop taking Truvada® may experience "flare" or worsening of hepatitis symptoms.**~~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.
- **Other side effects include: dizziness, depression, abnormal dreams, upper respiratory infections and sinusitis (sinus infection)**

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:

- Increase~~d~~ or decrease~~d~~ of fats in the blood (cholesterol), which may increase risk for heart attack or stroke
- Increased risk of the following:
  - ~~Cause a~~ **B~~b~~**lood clot (Deep venous thrombosis), **and/or blockage of** blood flow ~~is blocked from reaching~~**to** 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 (**associated with drugs like** spironolactone)
- Liver inflammation (**associated with drugs like** flutamide, bicalutamide, cyproterone acetate)
- ~~Decreased bone density~~

Allergic Reaction Risks – As with taking any drug, there is a risk of allergic reaction. If you have a very serious allergic reaction, you may be at risk of death. Some symptoms of allergic reactions are:

- **Rash**
- **Wheezing and difficulty breathing**
- **Dizziness and fainting**
- **Swelling around the mouth, throat or eyes**
- **A fast pulse**
- **Sweating**

Please seek treatment immediately and tell the study doctor and study staff if you have any of these symptoms.

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 **DRUG** 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 **l**~~L~~amivudine (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.

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~~ **be offered** 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.

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 hormon**ale** 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 be reimbursed for your time, effort, and travel to and from the site at each scheduled study visit up to a total of $xx.xx if you complete this study. You will be reimbursed for the visits you complete according to the following schedule [*Sites to modify information about local per local standard]*:

- **$xx.xx for the Screening Visit.**
- **$xx.xx for the Enrollment Visit.**
- **$xx.xx for each Follow-up Visit.**
- **$xx.xx for each Peer Health Navigation session.**

If you do not complete the study, for any reason, you will be reimbursed for each study visit you do complete.

If you have any questions regarding your compensation for participation, please contact the study staff.

[Sites to insert information about local reimbursement for participation in the IDI sub-studies.]

~~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].*~~

Revision 28: Appendix III: Informed Consent Template for Sites in the United States

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 whether ~~to provide~~**providing** HIV prevention services ~~in conjunction with~~**and** gender-affirming hormon**al**~~e~~ therapy for transgender women ~~and assess~~**at the same time and place will help prevent transgender women from getting HIV. It will also study** the safety of ~~this intervention~~**these services together** in the United States and Brazil.
- ~~All participants~~ **You** 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 becoming infected with HIV.
- ~~All participants~~**You** will be assigned to one of two groups by random chance (an equal chance of being in either group) **either** ~~. t~~The Immediate Intervention or the 6-month Deferred Intervention. The Immediate Intervention group will meet with a peer health navigator to help them access services and be offered hormonal therapy right away at the site. The 6-month Deferred Intervention group will be linked to services, that partner with the site to offer gender-affirming hormone therapy for the first ~~six~~ **6** months of the study. 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. **There may be additional contacts or visits in between scheduled visits to provide peer support, to do a health follow-up, or at your request in case you need to see or speak to study staff about the study.**
- ~~**You will have 6 sessions with a peer.**~~
- 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 tests will be taken. Taking the blood samples may cause pain, inflammation of the vein, bruise your arm or make you feel lightheaded. There is also a slight possibility of infection.
- 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 (STIs) throughout the study.
- The counseling you receive during this study may help you to avoid HIV and other **STIs**~~sexually transmitted infections (STIs).~~

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~~ **becoming infected with** 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 **this**~~your~~ site. Participants will be in the study for approximately 18 months.

2. The study is experimental as it is testing whether offering gender-affirming hormon**al**~~es~~ therapy (GAHT) 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**~~s~~ at birth and who currently identify themselves as women, transgender women, or along a trans feminine spectrum, who are age 18 years or older, who are sexually active**,** and ~~who are~~ HIV negative.

Participants will be ~~given the opportunity to take~~**offered** medications to prevent HIV. The medication to prevent becoming infected with 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 one of two forms of "tenofovir". These medicines are also used in combination with other medicines to treat HIV.

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 group) to one of two groups (The Immediate Intervention or the 6-month Deferred Intervention**)**.

The difference between the two groups is that one group (The Immediate Intervention**)** will meet with a clinician to start gender-affirming hormonal therapy (GAHT) at this site right away. This group will also be able to meet with a Peer Health Navigator who can help them access ~~any~~ services they need. Peer Health Navigators are individuals who share the same experiences and

community membership as participants, and who are trained to provide effective information about health and social services.

The other group (The 6-month Deferred Intervention) 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 at no cost:* If you are randomized to the 6-month Deferred Intervention group and choose to seek gender-affirming hormone therapy at a referral site, there may be costs associated with obtaining gender-affirming hormonal therapy at the referral 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.

6. We will ask you questions, ~~examine~~ **give** you **a physical exam**, 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 and date 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 **kidney and liver issues**~~to see if you are healthy~~. The study doctor may be required by law to report the result of these tests to the local health authority.
- Collect urine for: kidney ~~and liver~~ tests
- Give you a physical exam, that includes obtaining your complete medical **and mental health** history, measuring your weight, temperature, blood pressure, looking into your mouth and throat, listening to your heart and lungs, **feeling**~~palpating~~ your abdomen (stomach and liver), and ask you about any other medicines you are taking.
- **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 becoming infected with HIV low.**
- 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. 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~~ **may** collect a blood sample to check 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 check your levels of cholesterol and triglycerides, you need to be fasting, meaning you have not eaten, for at least 8 hours, preferably 12 hours **before the blood sample is collected**. If you are not fasting **during the time of the Screening Visit**, ~~we will schedule you to return to the clinic on another day before the~~**the blood sample will be collected during** Enrollment Visit ~~to collect blood~~ for this test. ~~Remember you need to be fasting before collecting the blood sample.~~

No other samples collected at the time of screening will be kept or used for any other tests other than those listed above.

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

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 becoming infected with it.
- Collect ~XX mL (about x teaspoons) of blood for: HIV **and,** ~~,~~ STIs (sexually transmitted diseases)~~, hepatitis B, and hepatitis C~~. ~~**A blood sample will also be used to test your hormone levels (estradiol and total testosterone).**~~ A blood sample will also be used to test your hormones (estradiol and total testosterone). **If the blood sample to test your cholesterol and triglycerides levels was not collected at the Screening visit, we will collect it at this visit. If you are not fasting at the Enrollment visit, we will ask you to return to the site as soon as possible, ideally within 2 weeks, to collect the sample to test your cholesterol and triglycerides.**
- Collect urine for: ~~kidney and liver~~ **STI** tests.
- **Collect rectal and oral swabs to test for STIs.**
- **If your blood, urine or rectal swab shows that you have any STIs, we will either treat you or refer you for treatment.**
- Give you PrEP pills, explain how to take them, and any side effects they may cause. **You are not required to take PrEP. You may start and stop taking PrEP at anytime.**
- Give you a physical exam that will include measuring your weight, temperature, blood pressure, any other assessment based on signs and symptoms you may have, ~~and~~ ask about any medicines you are taking**, and ask questions about your mental health**.
- 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 Intervention group, starting at this visit you will receive peer health navigator support. 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.

BEING IN THE STUDY

9. Once you enroll in the study, you will have 6 visits over one and a half (1½) 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 (1½) years.

~~If you are in jail during the study, your study visits will be paused and you may continue in the study once released.~~ **If you are unable to come to the clinic for your study visits (for example, if you are hospitalized, in jail, or traveling for an extended amount of time), you may continue in the study once you are able to return to the clinic. Your study duration will not change if you are not able to come to the clinic for an extended amount of time.**

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, 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~~ **kidney function** and HIV testing. You may start and stop taking PrEP at anytime.
- Give you a physical exam that will include measuring your weight, temperature, blood pressure, any other assessment based on signs and symptoms you may have, and ask about **your mental health and** any medicines you are taking.
- Collect ~XX mL (about x teaspoons) of blood **which will be tested** for: HIV, STIs, **and kidney and liver function. At your final visit (Month 18), we will also test your blood for** hepatitis B, and hepatitis C.
- A blood sample will also be used to test your hormones (estradiol and total testosterone).
- At the 6-Month and 18-Month study visits, **we will also do a blood test to look at the health of your blood. At these visits,** we will **also** collect a blood sample to check for 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 check your levels of cholesterol and triglycerides, you need to be fasting, meaning you have not eaten, for at least 8 hours, preferable 12 hours **before sample collection**. **Before collecting this sample, we will confirm with you that you are fasting.** If you are not fasting, we will schedule you to return to the clinic on another day, preferably within 72 from the visit, to collect blood for this test. ~~Remember you need to be fasting before collecting the blood sample.~~

- Collect urine for: kidney and **STI testing**~~liver tests~~.
- **Collect rectal and oral swabs to test for STIs.**
- 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 o~~**O**ffer you condoms and lubricant, and counsel you on how to use them safely.

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

- ~~Participants randomized to~~ **If you are in** the 6-month Deferred Intervention group**, you** 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~~ **you** will have the opportunity to receive hormonal therapy, counseling, and support at the site and meet with a peer health navigator who can help **you**~~them~~ access any services **you**~~they~~ need.
  - **You will be** ~~Participants are~~ able to start Gender-Affirming Hormon**al**~~e~~ Therapy at the site anytime after **your**~~their~~ 6 month visit and up to Week 39. During this time **you**~~participants~~ can choose to start and stop Gender-Affirming Therapy at the site.
- ~~For participants randomized to~~**If you are in** the Immediate Intervention group, **your**~~these~~ visits will include:
  - The opportunity to receive hormonal therapy, counseling and support at the site. **You**~~Participants~~ are able to start and stop Gender-Affirming Hor~~o~~mon**al**~~e~~ Therapy at any time.
  - Meet with a **P**~~p~~eer **H**~~h~~ealth **N**~~n~~avigator who can help **you**~~them~~ access any services ~~they~~**you** need.

Regardless of the group you are randomized to, participants are not required to take Gender-Affirming Hormon**al**~~e~~ 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**, or to meet with a Peer Health Navigator**. If you choose to start Gender-Affirming Hormon**al**~~e~~ Therapy an extra study visit will be scheduled within ten (10) 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 conversation with a member of the site staff.~~

Both study **groups**~~arms~~ are really important for the study. The information from participants in both **groups**~~arms~~ helps investigators or study doctors learn if the intervention actually works.

Before the study ends, we will work with ~~all participants~~**you** to find supportive services so **you**~~they~~ can continue receiving hormonal therapy and PrEP if **you**~~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.

Peer Health Navigation Sessions

Thise study involves peer health navigation. In these sessions, you will meet one-on-one with a peer who will work with you to set goals related to your health, wellbeing, and PrEP use, and help you access any services you may need. The peer health navigation sessions will take place at all scheduled visits. -You may have additional contacts during the first 6 months of the study intervention. If you are randomized to the Immediate Intervention Arm, these additional peer health navigation contacts will occur during the first 6 months of the study. If you are in the Deferred Intervention group, peer health navigation will start at the Month 6 visit, when you start the study intervention.

Peer Health Navigation Schedule During First Six Months of the Study Intervention

Immediate Intervention Arm Peer Health Navigation Visits	**Deferred Intervention Arm Peer Health Navigation Visits**
Enrollment Visit	**Week 26 (Month 6) Visit**
Gender Affirming Hormonal Therapy (GAHT) Initiation Visit	**Gender Affirming Hormonal Therapy (GAHT) Initiation Visit**
Optional Peer Health Navigator Contact (To occur between GAHT Initiation and Week 13 (Month 3) study visits)	**Optional Peer Health Navigator Contact (To occur between GAHT Initiation and Week 39 (Month 9) study visits)**
Week 13 (Month 3) Visit	**Week 39 (Month 9) Visit**
Optional Peer Health Navigator Contact (To occur between Week 13 (Month 3) and Week 26 (Month 6) study visits)	**Optional Peer Health Navigator Contact (To occur between Week 39 (Month 9) and Week 52 (Month 12) study visits)**
Week 26 (Month 6) Visit	**Week 52 (Month 12) Visit**

You may choose to have additional contacts with a Peer Health Navigator between study visits for any support you may need.

These contacts are optional and could be done by phone, videoconferencing, or in person at the study site. You will decide how you want these contacts to take place. Each session with the peer health navigator will be up to 60 minutes, depending on your needs and topic of discussion.

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 (1 ½) and will happen up to three (3) times during the study. **We will tell you if you are selected to participate in the additional interviews.** 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 this HPTN 091 study. 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, **and** what parts of the study are helpful or not helpful. **At the end of this form, you will be asked to indicate by providing your initials if you agree to participate in this Sub-study.**

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

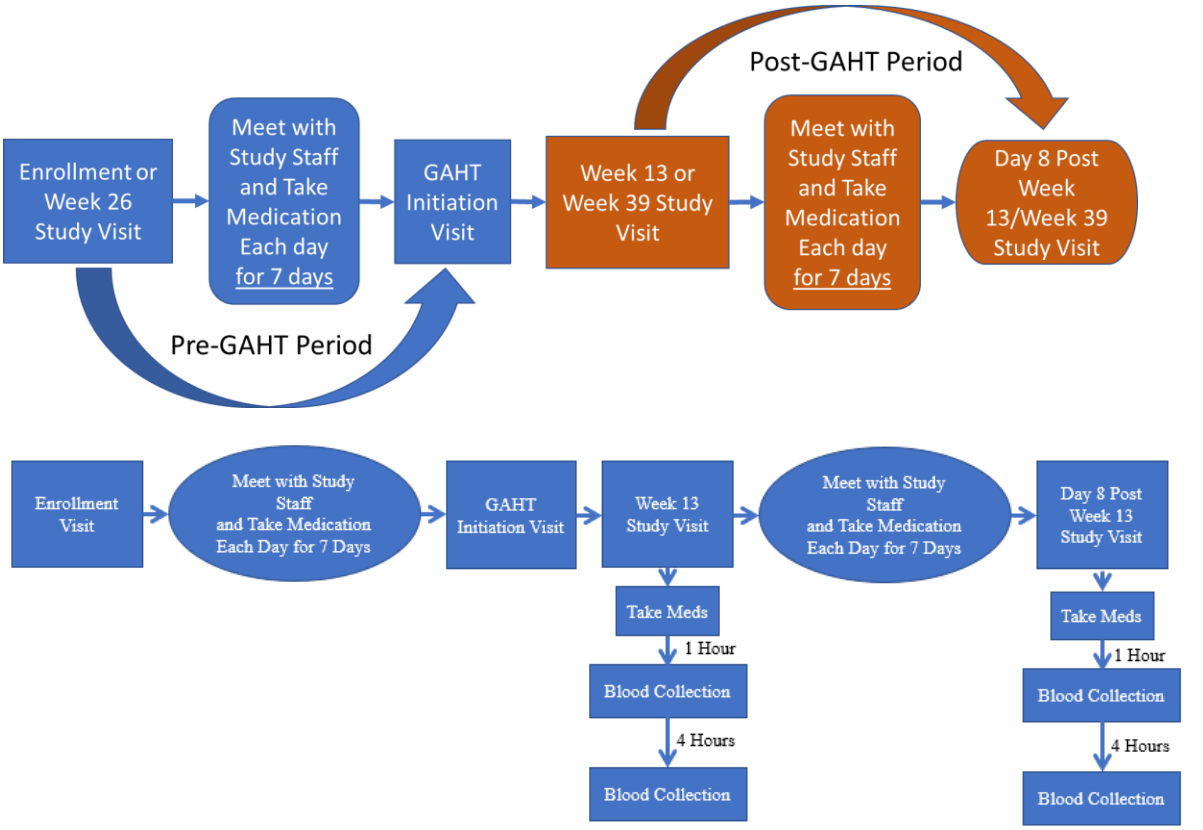
Up to 50 participants across participating sites who ~~are randomized to the Immediate Intervention Arm,~~ agree to use Descovy® as their PrEP agent~~,~~ and participate in the sub-study will provide additional blood that will be used to see if there is interaction between the hormonal therapy and PrEP. 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. -However, there may be a risk of others listening to your conversation. To minimize this risk, we ask that you find a quiet, private space to video conference. You could stop the video conference at any time if you feel someone may be listening to you.

~~Participants~~ **If you are** in this sub-study will be asked to

- Agree to take study-provided hormonal therapy and ~~PrEP~~ **Descovy®** as instructed.
- Take **Descovy®** ~~their study drug in~~ **at** the study site or during a video-conference with study staff for seven (7) days in a row. The additional study site visits or video-conferencing will be done for seven (7) days BEFORE the visit where you come to

collect your hormonal therapy. It will also happen for seven (7) 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 with these 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) **for participants enrolled in the Immediate Intervention group or after Week 26 (Month 6) for participants enrolled in the Deferred Intervention group**, your blood will be drawn 3 times: before taking **Descovy®**~~the study drug~~, 1 hour after taking **Descovy®**~~the study drug~~, and 4 hours after taking the **Descovy®**~~study drug~~. **Descovy®** ~~Study product~~ will be taken in front of the study staff. Because of the extra blood draws, this visit will be longer; it will take about [X] hours.
- At the Week 13 visit **for participants in the Immediate Intervention group or Week 39 (Month 9) visit for participants in the Deferred Intervention group**, you will take your study drug at the site in front of the study staff.
- Come for one additional visit 8 days AFTER the Week 13 **for participants in the Immediate Intervention group or Week 39 (Month 9) visit for participants in the Deferred Intervention group,** -visit. This visit will take about [X] hours. At this visit your blood will be drawn 3 times: before taking **Descovy®**~~the study drug~~, 1 hour after taking **Descovy®**~~the study drug~~, and 4 hours after taking **Descovy®**~~the study drug~~. **Descovy®** ~~Study drug~~ 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. At the end of this form, you will be asked to indicate by providing your initials if you agree to participate in th**ise** Sub-study.

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 **PrEP** ~~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 (3) months later to follow-up on your care.

13. Use of stored blood samples.

Some of your blood may be left over at the end of the study and may 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, 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.

SIDE EFFECTS OF THE STUDY DRUGS

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 drug~~**PrEP**. If you continue to take ~~the study drug~~**PrEP** 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
  - 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 liver failure; these are rarely seen
- Individuals with hepatitis B virus (HBV) who suddenly stop taking Descovy® may experience worsening of hepatitis symptoms.
- **Some participants using Descovy® have experience unintentional weight gain and increased cholesterol and triglycerides levels in their blood.**

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
- **Individuals with hepatitis B virus (HBV) who suddenly stop taking Truvada® may experience "flare" or worsening of hepatitis symptoms.**
- ~~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.
- Other side effects include: **d**~~D~~izziness, **d**~~D~~epression, **a**~~A~~bnormal dreams, **u**~~U~~pper respiratory infections and **s**~~S~~inusitis **(sinus infection)**

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 (bad or unwanted) effects may include, but are not limited to:

- Increase~~d~~ or decrease~~d~~ of fats in the blood (cholesterol), which may increase risk for heart attack or stroke
- Increased risk of the following:
  - Blood clots (deep venous thrombosis)~~,~~ **and/or** blo**ckage of blo**od flow ~~is blocked from reaching~~**to** 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 (for example, smaller testes & penis)
- Inability to have children (infertility)
- Creat**ion**e **of** hardened 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 conceive children (infertility) may be irreversible and this 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 (**associated with drugs like** spironolactone)
- Liver inflammation (**associated with drugs like** flutamide, bicalutamide, cyproterone acetate)
- ~~Decreased bone density~~

HIV **DRUG** 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 combination drugs that include Tenofovir and Emtricitabine and are used for treatment of HIV infection. 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 ~~L~~**l**amivudine (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.*

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

We will, however, 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 during the study, 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 **be offered**~~receive~~ condoms and lubricant at no charge.

19. There [*sites to choose applicable language*: is no/may be] cost to you for being 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 drugs, 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 **group**~~Arm~~ and choose to seek gender-affirming hormon**al**~~e~~ 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. Reimbursement for your participation in the study.

You will be reimbursed for your time, effort, and travel to and from the site at each scheduled study visit up to a total of $xx.xx if you complete this study. You will be reimbursed for the visits you complete according to the following schedule ***[Sites to modify information about local per local standard]***:

- $xx.xx for the Screening Visit.
- $xx.xx for the Enrollment Visit.
- $xx.xx for each **F**~~f~~ollow-up **V**~~v~~isit**.**
- **$xx.xx for each Peer Health Navigation session.**