HIV Prevention Trials Network

Letter of Amendment # 3 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: 5 October 2022
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.

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.

HIV Prevention Trials Network

Letter of Amendment # 3 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

Protocol Version 1.0, dated 13 April 2020

Date of Letter of Amendment: 5 October 2022
Final Version

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 accrual period is being extended to ideally four months, but not more than six months, from the 12 months after all sites opened to accrual. Accrual has been difficult for sites due to the impact of the COVID 19 pandemic. The HPTN 091 SMC and the HPTN Leadership reviewed and agreed with the update.

   See revisions 1 and 2

2. The inclusion criterion #3 has been updated to specify the PrEP agents used in the study are oral PrEP. This specification was added to account for injectable cabotegravir (CAB LA) being approved by the US FDA. The HPTN 091 protocol was developed specifically for use with daily oral PrEP, including the study design, eligibility criteria, and visit schedules. The study is assessing the feasibility, acceptability, and impact of a multi-component strategy to improve pre-exposure prophylaxis (PrEP) uptake and adherence that integrates delivery of biomedical HIV prevention co-located with gender-affirming transgender care (hormonal therapy and medical monitoring) and Peer Health Navigation (PHN) using Strengths-Based Case Management (SBCM) professional supervision. If participants, who at the time of enrollment, are using or are interested in using CAB LA, the study would not be able to provide co-located services. This would impact the ability to randomize participants per study protocol, since participants on CAB LA would not receive co-located services. HPTN 091 is a multisite study, and not all sites have access to CAB LA.

   See revision 3

3. The inclusion criterion #6a was revised to provide more flexibility when assessing participants generalized risk for sexually acquiring HIV infection. The main reason for the update is to minimize exclusion of potential participants who provide what they would consider socially-desirable responses related to their sexual behavior. The updated eligibility language allows the inclusion of transgender women (TGW) who had anal or vaginal sex with one or more partners regardless of whether the partner's HIV serostatus is known.

   See revision 3

4. The inclusion criterion #8b has been updated based on updated liver function information. The assessment of bilirubin was included as part of the eligibility assessment as one more step to safeguard participants safety.

   See revision 3

5. The exclusion criterion #4 has been updated based on new evidence from observational studies that estradiol does not cause significant changes in liver function. The exclusion criteria were overly broad and excluded candidates with liver disease that was not significant and who had normal liver function. The revised criteria appropriately identify participants who have significant hepatic dysfunction who should not be included in this study.

   The use of moderately-high levels of cyproterone acetate has been associated with liver abnormalities with numerous cases of hepatotoxicity reported. Since the hepatotoxicity is

well described, although rare, it is not advisable to use in someone with underlying liver disease. However, use of lower doses is not contraindicated. Therefore, liver abnormalities should be evaluated for each potential participant using or wanting to use cyproterone acetate prior to enrollment.

See revision 4

6. The screening to enrollment window was extended from 30 days to 40 days. This extension allows more time for potential participants to complete the enrollment process and does not have an impact on study participation or study conduct.

   See revision 6

7. The timeframe when the Gender Affirming Hormonal Therapy (GAHT) initiation visit is conducted was updated to allow flexibility on when the visit is conducted. The ideal is to initiate GAHT as close as possible to the collection of samples for estradiol and total testosterone; however, delays in the timeframe of receiving the test results may result in unnecessary retesting and additional study visits. The updated language indicates what would be the ideal timeframe for initiation of GAHT following estradiol and total testosterone testing and what is the maximum amount of time before retesting is required.

   See revisions 2, 5, 7, 8, 10-12

8. Section 6.4.1: Follow Up Procedures for Participants Who Discontinue Study Products was updated to include information on how to manage participants who switch to CAB LA after they are enrolled in the study. If an enrolled participant changes their PrEP choices, they will continue to be followed per protocol, with the exceptions outlined in Section 6.4.1 of the protocol. These participants will be counseled about the protocol specifications; however, it is ultimately the participant's choice which PrEP product is best for them. Participant's PrEP choice will be captured in the study database.

   See revision 9

9. Section 8.4: Accrual and Retention is being updated to expand competitive enrollment to all five study sites. Expanding competitive enrollment to the Rio de Janeiro, Brazil site could ensure the study meets its accrual target within the specified timeframe.

   See revision 13

10. The protocol References section was updated to add references related to the liver function eligibility criteria, per revisions 3 and 4.

    See revision 14

11. Section 9 (*Once you enroll in the study, you will have 6 visits over one and a half (1½) years*) of the sample informed consent form (ICF) for sites in the U.S. and the sample ICF for the Brazil site have been updated to reflect the timeframe when the Gender Affirming Hormonal Therapy (GAHT) initiation visit is conducted, as per item # 7 above. The updated language is the same for both ICF templates.

    See revision 15

Revision 1: Schema

Study Duration: For each individual site, the duration of the study is approximately 36-40 months from the time of site activation, depending on accrual timeframe. Accrual will be approximately ~~15~~ **16-18** months following the activation of all study sites individual participants will be followed for 18 months. Once enrolled, each participant will complete eight follow-up visits.

Revision 2: Section 3.4: Study Duration

Once a site is activated, the total study duration is anticipated to be approximately 36-40 months: accrual will be approximately ~~15~~ **16-18** months following the activation of all study sites, with 18 months of follow-up per participant. The total study duration is dependent on the timeframe to complete the run-in phase. Participants will complete 8 study visits: Screening, Enrollment, Week 13 (Month 3), Week 26 (Month 6), Week 39 (Month 9), Week 52 (Month 12), Week 65 (Month 15), Week 78 (Month 18). In addition, an GAHT initiation visit will be scheduled ~~up to~~ **within approximately** 10 days **but no more than 14 days** following the collection of samples for estradiol and total testosterone testing for initiation/re-initiation of GAHT.

Revision 3: 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 **oral** 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~~ ~~s~~exual 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), **and total bilirubin** <2.5 times the upper limit of normal (ULN) **(with the exception of Gilbert's syndrome).**

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 4: 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)~~ **Significant hepatic dysfunction or end-stage liver disease, per the opinion of the site investigator and in consultation with the CMC. For participants using cyproterone acetate, please consult the CMC for any evidence of liver abnormalities.**
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 5: Section 5.2: Study Product Administration

Gender Affirming Hormonal Therapy

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

Participants are not required to accept GAHT to be eligible to participate in the study. All participants can decide to initiate hormonal therapy after enrollment for the Immediate Intervention Arm or at the 6 months visit for the Deferred Intervention Arm, up until, and including, the Week 39 visit. A GAHT initiation visit will be scheduled ~~up to~~ **within approximately** 10 days **but no more than 14 days** following the collection of samples for estradiol and total testosterone testing for initiation/re-initiation of GAHT. If a participant decides to initiate hormonal therapy after Week 39 study visit, hormonal therapy will not be provided through the study and the participant will be linked to gender-affirming services.

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

Revision 6: 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~~ **40** 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~~ **40** days of signing the Screening Informed Consent Form (ICF), all screening procedures must be repeated, starting with the informed consent process. Participants may rescreen once at the discretion of the IoR or their designee, and per guidance found in the SSP Manual. Further rescreening for administrative reasons may be permitted with the approval of the CMC.

Revision 7: Section 6.3: Enrollment Visit

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~~ **within approximately** 10 days **but no more than 14 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 8: Section 6.4: Follow-Up Visits

Follow-up visits will occur on a quarterly basis at Week 13 (Month 3), Week 26 (Month 6), Week 39 (Month 9), Week 52 (Month 12), Week 65 (Month 15), Week 78 (Month 18) after enrollment, as per Appendix Ia. Mental health assessment will be included as part of the medical and physical history assessment. Specific visit windows are outlined in Section 6.5 of the protocol. Per Section 6.3, participants initiating/re-initiating GAHT will need a GAHT initiation visit ~~up to~~ **within approximately** 10 days **but no more than 14 days** after collection of samples for review of baseline endogenous estradiol and testosterone concentrations. See Section 6.4.2 for information on re-initiation procedures.

Revision 9: Section 6.4.1: Follow Up Procedures for Participants Who Discontinue Study Products

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

NOTE: Injectable cabotegravir (CAB LA) will not be provided in this study. Participants that express a desire to switch from oral PrEP to injectable PrEP will be counseled about the study requirements. However, ultimately is the participant's decision which PrEP agent is best for them. Participants who report switching to injectable cabotegravir (CAB LA) will continue to be followed as outlined in this section. CAB LA use will be documented on the Pre-exposure Prophylaxis Log eCRF.

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

Revision 10: Section 6.5: Study Windows

Table 6: Study Visit Windows

Visit	Target Visit Day	Target Visit Window	Allowable Visit Window
Screening			Up to 30 days before enrollment
Enrollment	Day 0		
GAHT Initiation Visit			~~Up to~~ **within approximately** 10 days **but no more than 14 days** post blood collection for estradiol and total testosterone testing
Week 13	Day 91	Day 77 - 105	Day 77 - 153
Week 26	Day 182	Day 168 - 196	Day 154 - 244
Week 39	Day 273	Day 259 - 287	Day 245 - 336
Week 52	Day 365	Day 351 - 379	Day 337 – 427
Week 65	Day 456	Day 442 - 470	Day 428 - 518
Week 78	Day 547	Day 533 - 561	Day 519 – study closure

Revision 11: Appendix Ia: Schedule of Events

	SCR	ENR	GAHT Initiation Visit[4]	Week 13 (Month 3)	Week 26 (Month 6)	Week 39 (Month 9)	Week 52 (Month 12)	Week 65 (Month 15)	Week 78 (Month 18)
Administrative and Behavioral Procedures									
Informed Consent	X	X							
Demographic information	X								
Locator information	X	X	X	X	X	X	X	X	X
Randomization		X							
ACASI[1]		X		X	X	X	X	X	X
HIV prevention counseling (offer condoms/lube)	X	X		X	X	X	X	X	X
Provision of PrEP[2]		X		X	X	X	X	X	
PrEP counseling and support[2]		X		X	X	X	X	X	X
Provision of GAHT[3]			X	X	X	X	X	X	
GAHT counseling and support[3]			X	X	X	X	X	X	X
Peer Health Navigation using Strengths-Based Case Management[5]		X		X	X	X	X	X	X
Clinical Procedures									
Complete medical history, physical	X								
Symptom-directed physical exam	X	X		X	X	X	X	X	X
Interim medical history (including STI symptoms)		X		X	X	X	X	X	X
Concomitant medications	X	X		X	X	X	X	X	X
Blood collection	X	X		X	X	X	X	X	X
Urine collection for urinalysis	X								
Urine collection for GC/CT testing		X		X	X	X	X	X	X
Swab (rectal and pharyngeal)		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)
collection for GC/CT testing									
STI treatment, if indicated	X	X		X	X	X	X	X	X
Hepatitis B vaccination or decline of vaccination		X							
Laboratory Procedures									
Dipstick urinalysis (protein and glucose)	X								
GC/CT for NAAT (rectal, urine, pharyngeal)		X		X	X	X	X	X	X
CBC w/differential		X			X		X		X
LFTs (AST, ALT, TBili, alkaline phosphatase)	X			X	X	X	X	X	X
Fasting lipid profile[6]	X				X				X
Chemistry testing (BUN or urea, albumin and potassium)	X			X	X	X	X	X	X
Creatinine clearance	X			X	X	X	X	X	X
Estradiol and total testosterone testing		X		X	X	X	X	X	X
Syphilis testing		X		X	X	X	X	X	X
HIV testing	X	X		X	X	X	X	X	X
HBV testing (HBsAg, HBsAb, HBcAb-Total)	X								X
HCV testing	X								X
Plasma storage	X	X		X	X	X	X	X	X
Serum storage		X	X[3]	X	X	X	X	X	X
DBS storage		X		X	X	X	X	X	X

[1]Mental health assessment will be included as part of the medical and physical history assessment.
[2]If participant accepts PrEP.

[3]For participants randomized to Immediate Intervention Arm who accept GAHT starts at the Enrollment Visit. For participants randomized to the Deferred Intervention Arm who accept GAHT start ~~up to~~ **within approximately** 10 days[4] **but no more than 14 days** 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~~ **within approximately** 10 days **but no more than 14 days** after collection of samples for estradiol and total testosterone samples for provision of GAHT as described in the protocol.

[5] PHN starts at the Enrollment Visit for participants randomized to the Immediate Intervention Arm, and at Week 26 (Month 6) for participants randomized to the Deferred Intervention Arm.

[6] Total cholesterol, HDL, triglycerides, and LDL (either calculated or measured). Participants should have fasted for at least 8 hours, preferably 12 hours, prior to sample collection. If participants are not fasting, do not order the lipid testing and reschedule the participant to return to the same for lipid sample collection: if not collected at the Screening Visit, .sample should be collected prior to the Enrollment Visit; if not collected at Weeks 26 or 78, sample should be collected ideally within 72 hours of the visit.

Revision 12: Appendix Ic: Schedule of Events for Participants in Drug-Hormone Interaction Substudy[1]

Study Procedures	Day 1-7 Before GAHT Initiation Visit	GAHT Initiation Visit[3]	Week 13 Study Visit	Day 1-7 After Week 13	Day 8 <u>After</u> Week 13 (Clinic Visit)
Study Product/Supplies					
DOT	X			X	
In-clinic DOT		X	X		X
Laboratory					
Pre-DOT					
Plasma storage		X			X
Serum storage2		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~~ **approximately within** 10 days **but no more than 14 days** after collection of samples for estradiol and total testosterone samples for provision of GAHT as described in the protocol.

Revision 13: Accrual and Retention

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

Revision 14: References

97 Allen AN, Jiao R, Day P, Pagels P, Gimpel N, SoRelle JA. Dynamic Impact of Hormone Therapy on Laboratory Values in Transgender Patients over Time. J Appl Lab Med. 2021 Jan 12;6(1):27-40. doi: 10.1093/jalm/jfaa192. PMID: 33313748.

98 Bessone F, Lucena MI, Roma MG, Stephens C, Medina-Cáliz I, Frider B, Tsariktsian G, Hernández N, Bruguera M, Gualano G, Fassio E, Montero J, Reggiardo MV, Ferretti S, Colombato L, Tanno F, Ferrer J, Zeno L, Tanno H, Andrade RJ. Cyproterone acetate induces a wide spectrum of acute liver damage including corticosteroid-responsive hepatitis: report of 22 cases. Liver Int. 2016 Feb;36(2):302-10. doi: 10.1111/liv.12899. Epub 2015 Jul 16. PMID: 26104271.

99 Even Zohar N, Sofer Y, Yaish I, Serebro M, Tordjman K, Greenman Y. Low-Dose Cyproterone Acetate Treatment for Transgender Women. J Sex Med. 2021 Jul;18(7):1292-1298. doi: 10.1016/j.jsxm.2021.04.008. Epub 2021 Jun 24. PMID: 34176757.3

100 Hashemi L, Zhang Q, Getahun D, Jasuja GK, McCracken C, Pisegna J, Roblin D, Silverberg MJ, Tangpricha V, Vupputuri S, Goodman M. Longitudinal Changes in Liver Enzyme Levels Among Transgender People Receiving Gender Affirming Hormone Therapy. J Sex Med. 2021 Sep;18(9):1662-1675. doi: 10.1016/j.jsxm.2021.06.011. Epub 2021 Aug 5. PMID: 34366264; PMCID: PMC8444147.

101 Meyer G, Mayer M, Mondorf A, Flügel AK, Herrmann E, Bojunga J. Safety and rapid efficacy of guideline-based gender-affirming hormone therapy: an analysis of 388 individuals diagnosed with gender dysphoria. Eur J Endocrinol. 2020 Feb;182(2):149-156. doi: 10.1530/EJE-19-0463. PMID: 31751300.

Revision 15: Sample Informed Consent Form for Sites in Brazil and Sample Informed Consent for Sites in the U.S.

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 Hormonal Therapy (GAHT), an extra study visit will be scheduled within **approximately** ten (10) days **but no more than fourteen (14) days** after the collection of estradiol and total testosterone testing to pick-up your GAHT. Also, if this is the first time you are using GAHT AND you are taking either spironolactone or cyproterone, you may have an additional study visit approximately one month following GAHT

initiation to check on your health. The study staff will let you know which GAHT you are using, address any questions you may have, and let you know if this visit is necessary.