Appendix II: Gender Affirming Hormones for Transgender Women in HPTN 091

Introduction

This section is based on several transgender medicine guidelines including the WPATH Standards of Care for the Health of Transgender and Gender Diverse People, Version 8[1], Endocrine Society's Clinical Practice Guideline[2], the UCSF of Excellence for Transgender Health[3] and the Callen-Lorde Community Health Center protocols,[4] which have been adapted for use in a wide variety of settings.

The provision of gender affirming hormone therapy is a cooperative effort between participant and provider. The protocols were developed by compiling the collective knowledge of clinicians, participants, members of the transgender community, and related scientific studies. These guidelines should be seen as a starting point from which the participant and provider can arrive at a care plan appropriate to the participant's needs.

All study visits and procedures should be done per the HPTN 091 Protocol, Appendix Ia and Ic. Sites may contact the CMC for any consultations regarding provision and management of Gender Affirming Hormonal Therapy (GAHT). If any discrepancies between this section and the study protocol are found, the protocol takes precedence. In such cases, please contact Kaila Gomez-Feliciano (kgomez@fhi360.or), Busola

Akingbade (bakingbade@fhi360.org), and Maxine Awekey (mawekey@fhi360.org) immediately.

Visit Frequency for Participants who initiate GAHT on enrollment

Study Visit	GAHT Visit	Labs
Screening	Not applicable	Per protocol
Enrollment	Not applicable	Per protocol + GAHT labs
GAHT Initiation Visit	10 days following the collection of samples for estradiol and total testosterone testing	None
Week 13 (Month 3)	Week 12 +	Per protocol + GAHT labs

Section 1: GAHT Counseling and Education

Although GAHT is first provided during the GAHT initiation visit, it's important to start the discussion at the Enrollment Visit, for participants randomized to the Immediate Arm, or at Week 26 (Month 6), for participants randomized to the Delayed Arm. During the GAHT initiation visit and each quarterly visit, participants will have the opportunity to receive GAHT counseling and support. The following are procedures for the GAHT counseling:

1. Introduce purpose of Hormone Counseling & Education Session

- Counsel about the known risks and benefits of exogenous hormone therapy.
- Assess acute, active mental health complaints that may be adversely affected by GAHT.
- Assess and provide psychosocial supports and referrals as indicated.

2. Assess participant's day-to-day mood/mental health

- Counsel participant on the psychoactive effects of hormones:
- Some mood/mental health problems such as depression and anxiety may be addressed by hormones, some symptoms are not
- Some mood/mental health problems, including depression, anxiety and psychosis, may be exacerbated by hormones.

Gather information about participant's mood/mental health for the purpose of forecasting symptoms that may be intensified by GAHT:

- If participant has untreated, non-acute symptoms, offer and refer participant to supportive mental health services (such as psychotherapy or psychiatry)
- If participant has acute, untreated mood problems, discuss ways GAHT and mood problems can be managed safely. Guide participant to discuss these symptoms with the medical provider who will be prescribing GAHT.

3. **Explore participant's social transition needs such as peer support, psychotherapy, identifying documentation changes, care coordination, and legal advocacy. As indicated, refer participant to internal and external resources.**

   Elicit any additional questions the participant may have about available services, and/or physical or social transition.

4. **Arrange an additional counseling if:**

   Participant is unable to establish informed consent in the first session
   Participant is interested in accessing additional support and/or counseling around GAHT.

5. **Document visit in health record:**

   including overall assessment of participant's ability to provide informed consent and any relative or absolute contraindications elicited during evaluation.

Section 2: GAHT Initiation Visit

Participants may begin co-located GAHT any time after either:
The Enrollment Visit for participants in the Immediate Intervention Arm, OR
The Week 26 (Month 6) visit for participants in the Deferred Intervention Arm.
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. Lab results should be available prior to GAHT dispensation.

Review lab results and discuss implications of abnormal findings.
Determine if contraindications exist to GAHT (if contraindications exist to an agent choose alternative regimen) Appendix A.

Discuss with the participant the preferred route of hormones and prescribe three months of the appropriate regimen:

- The usual regimen is an estrogen + anti-androgen.
- Choose one form of estrogen and androgen blocker. If a woman has undergone gonadectomy (orchiectomy) then only estrogen is needed.
- For women with significant cardiovascular risk factors, smoker or over age 45 transdermal estradiol is preferred.
- If there is a risk for hyperkalemia (e.g., renal disease, on ace inhibitors) then spironolactone should be avoided or used with extreme caution.
- If there is a history of meningioma, liver disease, sickle cell disease avoid cyproterone.

PROGESTERONE: Progesterone is not recommended as a part of the hormone regimen. It has not been shown to increase breast size and may contribute to adverse outcomes.

ESTROGENS: Prescribe three months of ONE of the following estrogens:

Preferred Regimen

Oral Estrogen	Dose	Route & Frequency§	Amount	Refills
Estradiol tablets	2.0mg	Oral, twice daily	3 months	0
Transdermal Estrogen				
Estradiol transdermal patch	25 -200 mcg/day	Transdermal patch (weekly or biweekly)	3 months	0
Alternate Regimen				
Injectable Estrogen	Dose	Route & Frequency	Amount	Refills
Estradiol Valerate 20mg/ml	20 mg	IM, every 2 weeks		0

ANTI-ANDROGENS: Prescribe three months of ONE of the following anti-androgens.

DHT-BLOCKERS: Some clinicians use dihydrotestosterone blockers as a primary anti-androgen, although they are less effective than either spironolactone or cyproterone. DHT-Blockers may also be added to traditional anti-androgens to minimize androgenic hair loss.

Preferred Regimen

Oral Anti-Androgen	Daily Dose	Route & Frequency	Amount	Refills
Spironolactone	100 – 300 mg	Oral, single or divided doses daily	3 months	0
Cyproterone Acetate	10 mg	Oral, one tablet daily	3 months	0
Alternate				
Oral DHT-Blockers	Dose	Route & Frequency	Amount	Refills
Finasteride	5mg	Oral, once daily	3 months	0

1. Order lab work to be drawn at next medical visit
   - Potassium, if taking spironolactone, 1 week after change of dose, if high risk for renal disease or hyperkalemia.
   - ALT, AST, CBC (if taking cyproterone)

2. Arrange medical follow up for GAHT-Naïve participants
    - Participant should return in 4 weeks
    - If patient is taking injectable hormones, she will need to return in 2 weeks for injection.

Section 3: One Month Ad-hoc Safety Visit

Participants who are initiating GAHT for the first time AND their medications include either spironolactone or cyproterone should have an ad-hoc safety visit approximately one month following GAHT initiation. At this visit, sites should do a
clinical evaluation, including vital signs and review of medical history. In addition, the following safety laboratory samples should be collected:

- ALT, AST, CBC (if taking cyproterone)
- Potassium (if taking spironolactone)

Please note, this safety visit is done only if deemed necessary by IoR or designee

Section 4: Quarterly 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. The following GAHT procedures are to take place during these clinical visits (Note: For participants in the Deferred Arm, these procedures will take place starting on their Week 26 visit).

1. Assess vital signs, including blood pressure.
2. Take history with focus on
    a. Participant's tolerance of hormones and anti-androgens
    b. Any side effects participant may be experiencing
    c. Cessation of erections (for participants who want to retain erectile function)
    d. Mental health
    e. Social support
3. Review lab results and discuss implications of abnormal findings. Titrate the dosage of hormones based on results of laboratory tests (estradiol and testosterone levels).
    a. Serum testosterone levels should be <50 ng/dL†
    b. Serum estradiol levels 100–200 pg/mL are preferred and should not exceed 300 pg/mL

ESTROGENS: Prescribe three months of ONE of the following estrogens:				
Preferred Regimen				
Oral Estrogen	Dose	Route & Frequency§	Amount	Refills
Estradiol tablets	2.0mg	Oral, twice daily	3 months	0
Transdermal Estrogen				
Estradiol transdermal patch	100 -200 mcg/day	Transdermal patch (weekly or biweekly)	3 months	0
Alternate Regimen				
Injectable Estrogen	Dose	Route & Frequency	Amount	Refills
Estradiol Valerate 20mg/ml	20 mg	IM, every 2 weeks		0

ANTI-ANDROGENS: Prescribe three months of ONE of the following anti-androgens.				
Preferred Regimen				
Oral Anti-Androgen	Daily Dose	Route & Frequency	Amount	Refills
Spironolactone	100 – 300 mg	Oral, single or divided doses daily	3 months	0
Cyproterone Acetate	10 mg	Oral, one tablet daily	3 months	0
Alternate				
Oral DHT-Blockers	Dose	Route & Frequency	Amount	Refills
Finasteride	5mg	Oral, once daily	3 months	0

1. If the participant chose injection by herself, prescribe:

Equipment	Amount
3cc syringe	#10
20-22G x 1.5” needles	#10
Alcohol prep pads	#100
needle disposal (sharps) container	#1

Note: *other needle sizes and amounts may be more appropriate for some participants depending on personal preference and whether participants use different needles for drawing the medication and injecting.*

2. Order lab work to be drawn at next medical visit in 12+ weeks:
   a. Measure serum testosterone and estradiol every 12 weeks in the first year, every 24-48 weeks thereafter†

b. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored 1 week after an increase in dose and every 12 weeks in the first year, every 24-48 weeks thereafter.
c. Prolactin level should be checked every year, or if participant develops symptoms consistent with high prolactin level or prolactinoma (e.g., galactorrhea, headache, double vision)
d. Lipid profile every 6-12 months
e. Liver function tests, including ALT, AST, bilirubin, every 6 months if receiving cyproterone

3. Arrange follow up:

   a. Medical visit every 12 weeks (per protocol)

†DHT-Blockers will not lower total testosterone levels

Section 5: Special Considerations

1. Participants who have undergone gonadectomy (removal of the testes or ovaries)

Transgender women: Anti-androgens (spironolactone) can be stopped, although participants may wish to continue dihydrotestosterone blockers if androgenic hair loss continues. Monitor bone density, especially in participants with risk factors or who have stopped hormone therapy.

2. Participants over 45 years/smokers

Oral estrogens confer an increased risk of thromboembolic disease. Transdermal routes are preferred over oral estrogen.

3. Participants receiving cyproterone acetate (this medication is not available in the USA)

Cyproterone has been associated with adrenal suppression. The dose should be tapered if not stopping due to adverse effects. There is an increased risk of meningioma. Participants should not start or continue this medication if meningioma is diagnosed. There is a risk of severe hepatic toxicity, and this medication should not be used with a history of liver disease.

Appendix A

Table 1. Medical Risks Associated with Gender Affirming Hormone Therapy (Estrogens)[1]

Very high risk of adverse outcomes:
•Thromboembolic disease
Moderate risk of adverse outcomes:
•Macroprolactinoma
•Breast cancer
•Coronary artery disease
•Cerebrovascular disease
•Cholelithiasis
•Hypertriglyceridemia

Table 2. Medical Risks associated with Cyproterone Acetate & Spironolactone

Cyproterone Acetate • Meningioma • Hepatic toxicity • Adrenal suppression Spironolactone • Hyperkalemia • Hypotension and worsening renal function • Electrolyte and metabolic abnormalities

Table 3. Feminizing Effects in Transgender Females1

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo.	2–3 y
Decrease in muscle mass and strength	3–6 mo.	1–2 y
Softening of skin/decreased oiliness	3–6 mo.	Unknown
Decreased sexual desire	1–3 mo.	3–6 mo.
Decreased spontaneous erections	1–3 mo.	3–6 mo.
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo.	2–3 y
Decreased testicular volume	3–6 mo.	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo.	>3 y
Scalp hair	Variable	—
Voice changes	None	—

Contraindications to Gender affirming Hormone Therapy

Cyproterone Acetate
Liver diseases (including Dublin-Johnson syndrome and Rotor syndrome); Malignant tumors (other than prostatic cancer); Wasting diseases (with the exception of inoperable carcinoma of the prostate) (because of transient catabolic action); History of, or existing thrombosis or embolism; Severe diabetes with vascular changes; Sickle-cell anemia; Severe chronic depression

Estradiol
Known or suspected cancer of the breast; Known or suspected estrogen-dependent neoplasia; Active deep vein thrombosis, pulmonary embolism or history of these conditions; Active or recent (e.g., within the past year) arterial thromboembolic disease (e.g., stroke, myocardial infarction)

Spironolactone
Anuria, acute renal insufficiency; Significant impairment of renal excretory function; Hyperkalemia; Addison's disease; and with concomitant use of eplerenone.

Appendix B

Feminizing Regimens

Anti-androgen	**Starting Dose**	**Average Dose**	**Maximum Dose**
Spironolactone*	25mgday	150mg/day	200mg/day
Finasteride*	1mg/day	1-5mg/day	5mg/day
Cyproterone Acetate*	10 mg/day	10 mg/day	10mg/day
Estrogen	**Starting Dose**	**Average Dose**	**Maximum Dose**
Estradiol valerate oral*	2mg/day	4mg/day	6mg/day
Estradiol valerate	10 mg IM q 2 wks.	20 IM q 2 wks.	30 mg IM q 2 wks.
Estradiol patch	25 mcg/day	50 mcg/day	200mcg/day

1. Coleman E, Radix AE, Bouman WP, Brown GR, de Vries ALC, Deutsch MB, et al Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, International Journal of Transgender Health, 23:sup1, S1-S259, DOI: 10.1080/26895269.2022.2100644
2. Hembree W, Cohen-Kettenis PT, Gooren L, et al. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2017;102(11):3869-3903.
3. Center of Excellence for Transgender Health. Primary Care Protocol for Transgender Participant Care. 2011; http://transhealth.ucsf.edu/trans?page=protocol-00-00.
4. Callen-Lorde Community Health Center. Protocols for the Provision of Hormone Therapy. 2014; https://callen-lorde.org/graphics/2018/04/Callen-Lorde-TGNC-Hormone-Therapy-Protocols.pdf.