



Brigham and Women's Hospital

Founding Member, Mass General Brigham

Overview of Transgender Care

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Medical school: **Royal College of Surgeons in Ireland**
Internal medicine residency, chief medical residency,
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Current position: Clinician-educator, BWH

- Director of Education, Center for Transgender Health, BWH
- Endocrinology fellowship program director, BWH
- Education editor, NEJM Group

Disclosures

- Consultant: Merck
- None of the medications discussed have been FDA-approved for gender affirmation
- Images: The Gender Spectrum Collection (<https://genderphotos.vice.com>) unless otherwise specified

Learning Objectives

On completion of this activity, learners will be able to:

- ☐ Review terminology used in trans health
- ☐ Describe principles of gender-affirming hormone therapy (GAHT)
- ☐ Describe the impact of GAHT on cardiovascular health
- ☐ Respond to some common contemporary patient requests regarding their GAHT

Using the correct terms helps promote precise communication

- **Gender identity:** A person's inner sense of being a man, woman, something else, or no gender
- **Sex assigned at birth:** The sex recorded at birth, generally based on appearance of external genitalia (**AFAB / AMAB; biological**)
- **Transgender and gender diverse (TGD):** People whose gender identity differs from what is typically associated with their sex designated at birth (**≠cisgender**)
- **Gender incongruence:** ICD-11 (WHO) term (~~transsexualism, gender identity disorder, gender dysphoria~~)
- **Trans woman (≈MtF = ~~Male-to-female~~ ≈ transfeminine):** AMAB whose gender identity is female
- **Trans man (≈FtM = ~~Female-to-male~~ ≈ transmasculine)**
- **Nonbinary:** Gender identity falling outside of traditional binary man/woman

Amber

- 27-year-old patient
- Designated male sex at birth
- Gender identity: Woman (she/her pronouns)
- Past history of HIV infection diagnosed 1 year ago
- Meds: bicitgravir, emtricitabine & tenofovir alafenamide
- HIV viral load undetectable, CD4 745/mm³

Amber

- The patient is requesting to start gender-affirming hormone therapy (GAHT).
- She recently started to take her friend's birth control tablets but is hoping to get medically supervised GAHT
- How do you address her request?

Healthcare for TGD individuals

Peer support groups, voice therapy, prostheses, legal

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graph TD; A[Peer support groups, voice therapy, prostheses, legal] --> B[Confirmation of gender identity and assessment for coexisting mental health conditions]; A --> C[Gender-affirming hormone therapy]; B --> D[Gender-affirming surgeries]; C --> D; D --> E[Primary / specialty care and routine health maintenance];
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Confirmation of
gender identity and
assessment for
coexisting mental
health conditions

Gender-affirming
hormone therapy

Gender-affirming
surgeries

Primary / specialty care and routine health maintenance

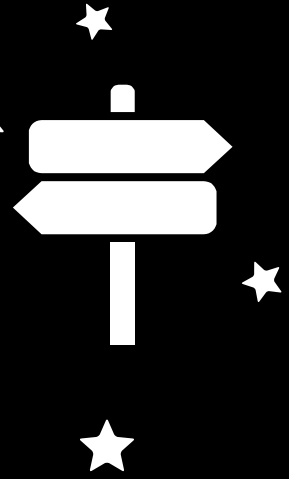
Pre-hormone medical evaluation

- Confirm presence of gender incongruence
- Medical history, $\pm$ labs, for contraindications / risks
- Discuss goals and concerns
- Discuss fertility goals and contraceptive needs
- Obtain informed consent
- Adjustments in current political climate?

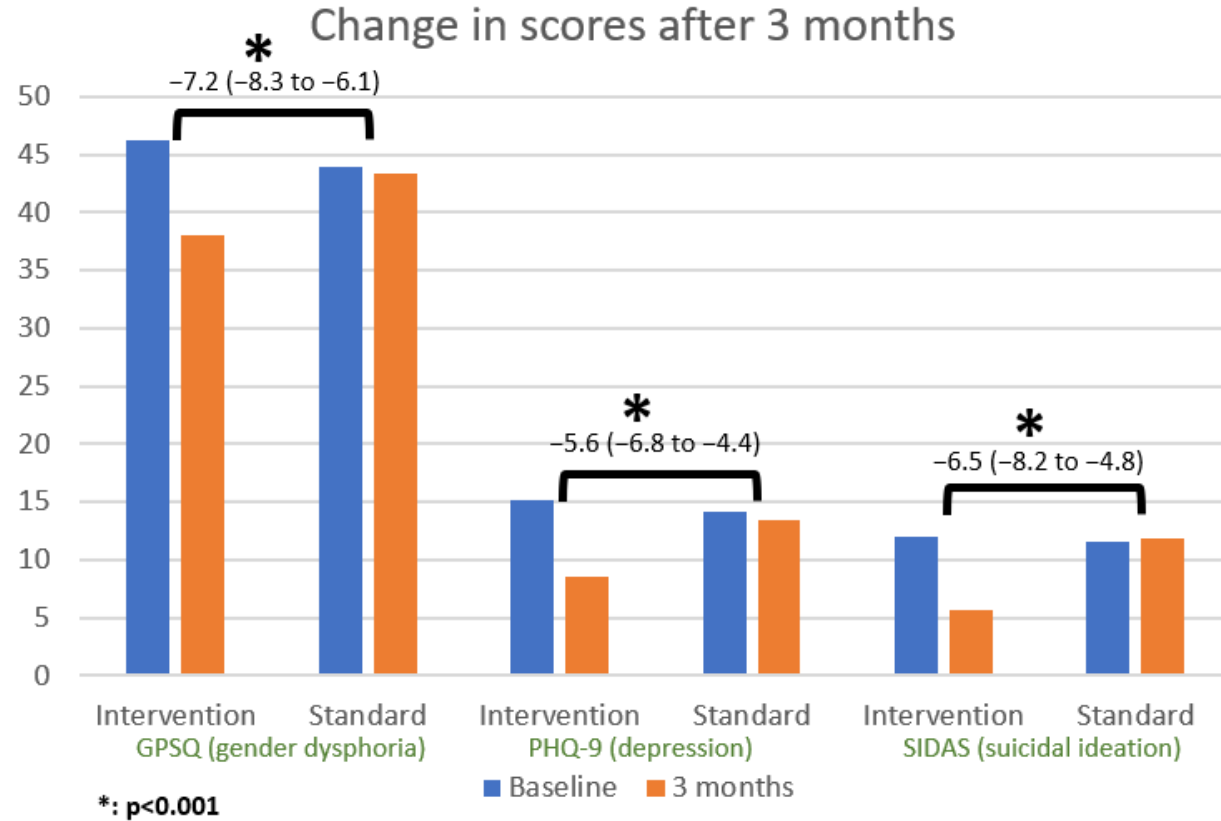
**Mental health
provider input
helps
promote a
successful
gender
affirmation**

-
- Help navigate challenges associated with gender incongruence
 - Educate about options for gender-affirming interventions
 - Plan for change in gender expression
 - Assess eligibility for hormone therapy / surgery and refer
 - Facilitate family support
 - Refer for peer support
 - Evaluate for other mental health concerns
 - Psychotherapy if needed (not to change gender identity)

Goal of transgender hormone therapy:



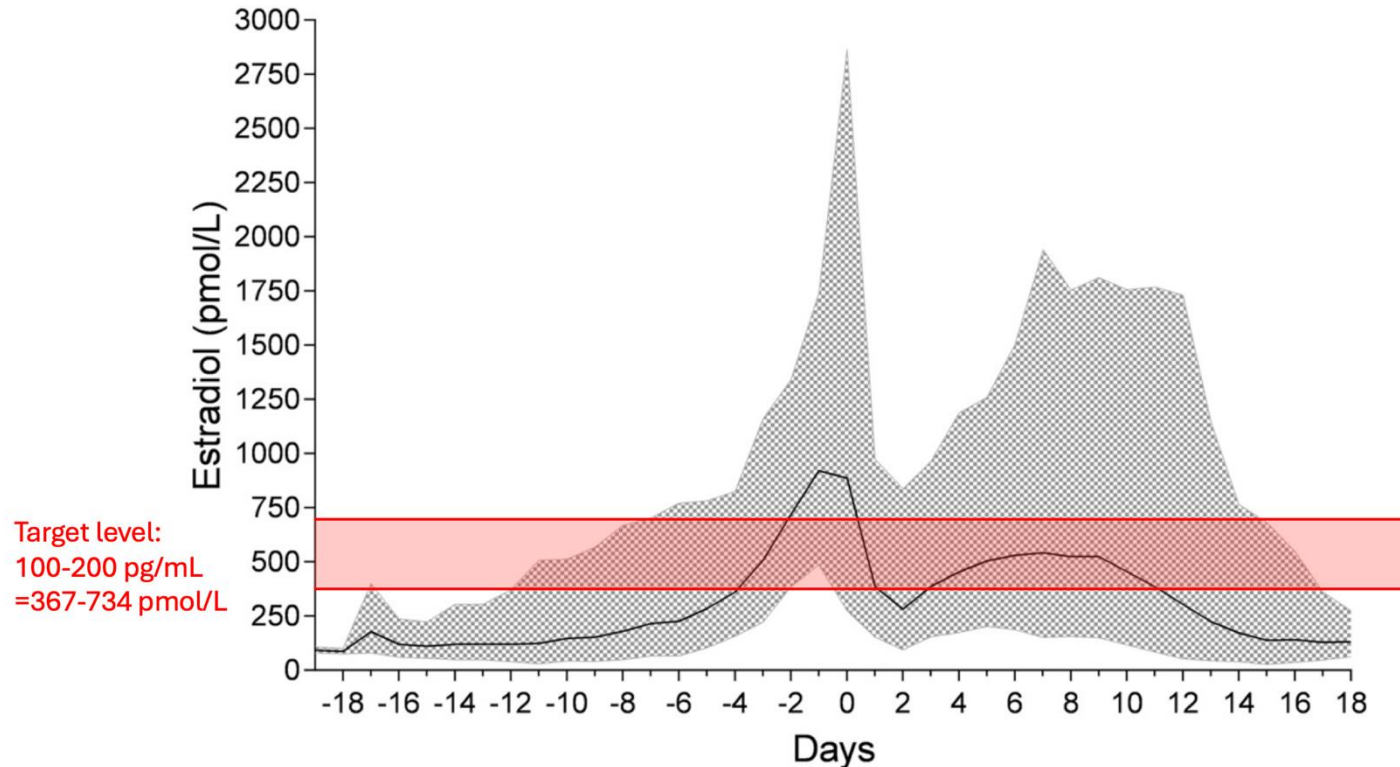
Help the patient affirm their gender identity
by promoting a physical appearance that is
more congruent with gender identity



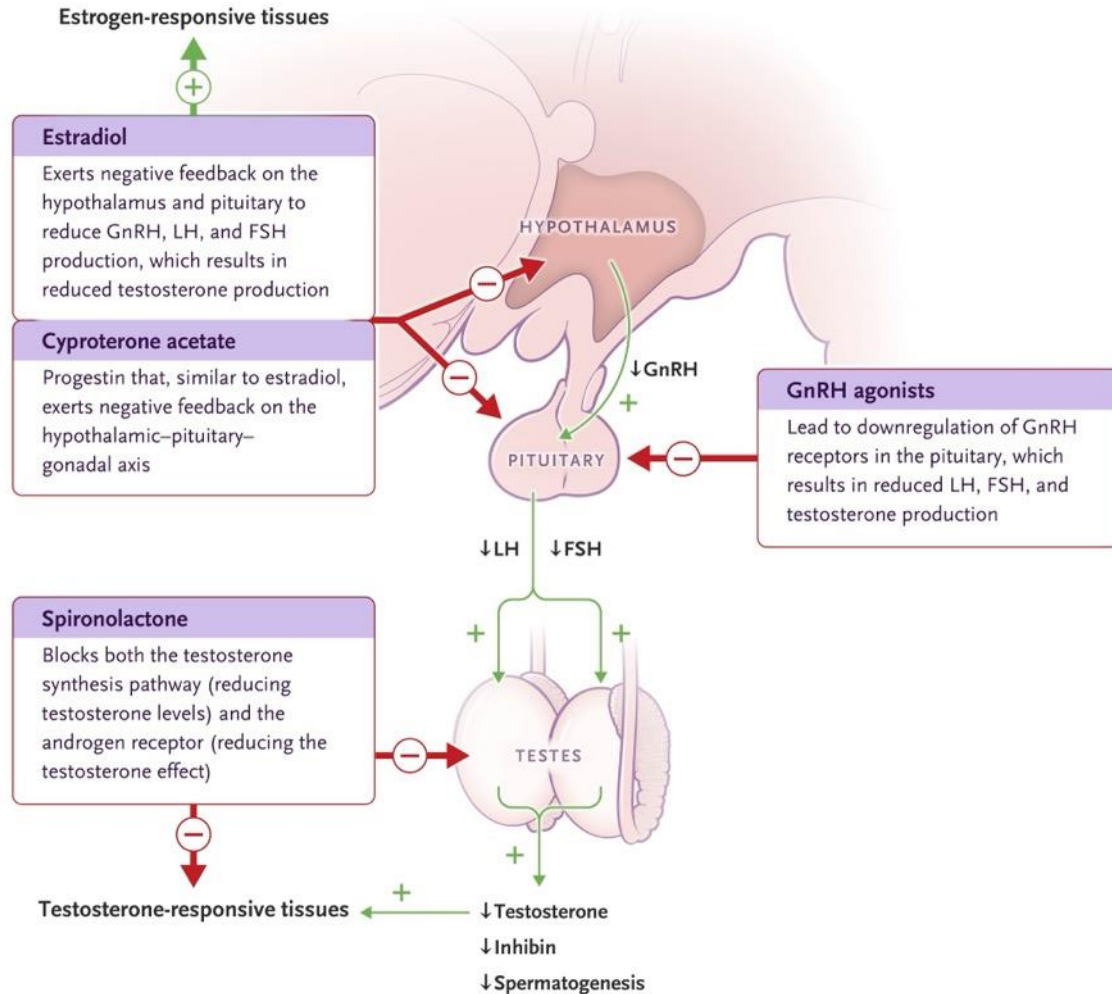
Basics of estrogen-based GAHT (E-GAHT)

Formulation	Low dose	Moderate dose	High dose	Very high dose	Comments
Oral estradiol	1-2 mg/d	2-6 mg/d	6-8 mg/d	8-12 mg/d	Can be taken PO or SL BID dosing often recommended
Conjugated equine estrogens	1.25-2.5 mg/d	2.5-5.0 mg/d	5.0-7.5 mg/d	7.5-10 mg/d	Not recommended if estradiol is available (blood levels cannot be monitored)
Estradiol patch	0.1 mg/d	0.1-0.2 mg/d	0.2-0.4 mg/d	0.4-0.6 mg/day	Patch changed once or twice per week Lowest risk of VTE
Estradiol valerate or cypionate (IM or SC)	1-2 mg/wk	2-4 mg/wk	4-6 mg/wk	6-10 mg/wk	Can see fluctuating E2 levels

Estradiol is dosed to achieve levels similar to those in cis women



**Estrogen
alone is
usually not
adequate**



Anti-androgen options

Drug	Initial dose	Typical dose	Comments
Spironolactone	50-100 mg/day	100-300 mg/day	Monitor for hyperkalemia, AKI (rare)
Cyproterone acetate	6.25 mg three times per wk	<12.5 mg/day	Not available in the US. Risk of prolactinoma, meningioma
GnRH agonists	Depending on formulation: 3.75-45 mg, administered IM/SC, frequency ranging from every 1-6 months		Costly

Effect		Onset	Maximum effect
<u>Reversible</u> changes			
Body fat redistribution		3-6 months	2-3 years
Decreased muscle mass / strength		3-6 months	1-2 years
Softening of skin / decreased oiliness		3-6 months	Unknown
Decreased libido		1-3 months	3-6 months
Decreased spontaneous erections		1-3 months	3-6 months
Thinning and slowed growth of body / facial hair		6-12 months	> 3 years
Fully or partially <u>irreversible</u> changes			
Breast growth		3-6 months	2-3 years
Decreased testicular volume		3-6 months	2-3 years
Decreased sperm production		Variable	> 3 years
Minimal / no change			
Androgenic alopecia	Stature/height	Facial bone structure	
Voice	Phallus		

Potential side effects of E-GAHT

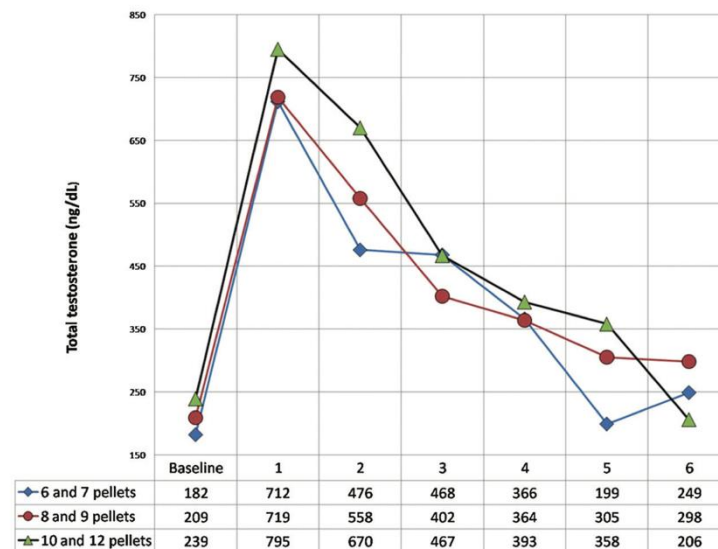
- Venous thromboembolism
- Infertility
- Hyperkalemia (spironolactone)
- Hypertriglyceridemia
- Weight gain

Basics of testosterone-based GAHT (T-GAHT)

Formulation	Low dose	Moderate dose	High dose	Comments
Testosterone gel (transdermal) -1% -1.62%	25-50 mg/d 20.25-40.5 mg/d	50 mg/d 40.5 mg/d	75-100 mg/d 60.75-81 mg/d	Potential for transfer to others
Testosterone cypionate or enanthate (IM or SC)	20-40 mg/wk	50-70 mg/wk	80-100 mg/wk	Titrate dose to achieve levels in male reference range (400-700 ng/dL) – lower if less-than-complete masculinization is desired

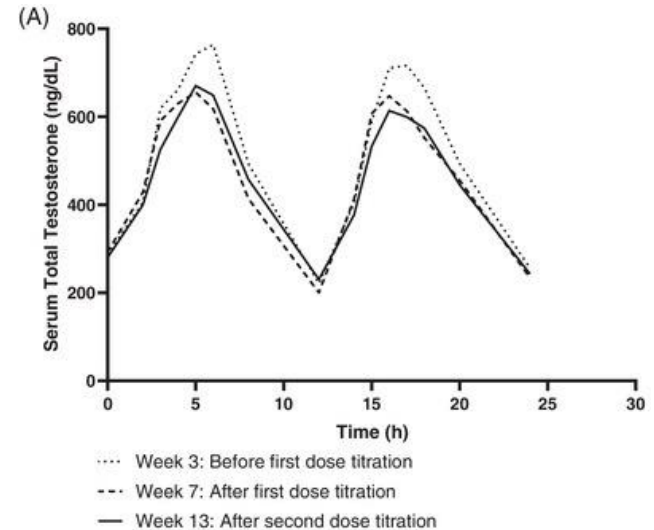
Less commonly used forms of testosterone

- Testosterone pellets
 - Inserted SC via trocar every 12 weeks
 - 75 mg per pellet, typical dose 450-750 mg
 - Adverse effect: Pellet extrusion, infection, bleeding, scarring
 - Cost: ≈\$800 for 450 mg, plus insertion cost



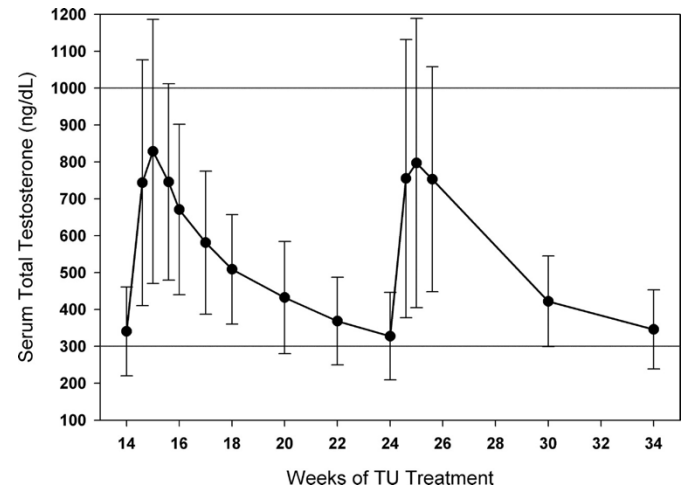
Less commonly used forms of testosterone

- Oral testosterone undecanoate
 - Twice daily capsules
 - Taken with food – absorbed via lymphatic route
 - Different brands and strengths – typical dose 100-400 mg twice daily
 - Limitations: Hypertension, size of capsules, need to take with food
 - Cost: ≈\$200-\$900/month



Less commonly used forms of testosterone

- Injectable testosterone undecanoate
 - Depot injections:
 - 750 mg at t=0, 4 wk, then q10 wk (US)
 - 1000 mg every 10-14 wk (elsewhere)
 - Rare risk of pulmonary oil microembolism – requirement for special certification in US (REMS)
 - Cost: ≈\$1000/dose



Effect	Expected onset	Maximum effect
<u>Reversible</u> changes		
Skin oiliness / acne	1-6 months	1-2 years
Increased muscle mass / strength	6-12 months	2-5 years
Body fat redistribution	1-6 months	2-5 years
Cessation of menses	1-6 months	n/a
Vaginal atrophy	1-6 months	1-2 years
Fully or partially <u>irreversible</u> changes		
Clitoral enlargement	1-6 months	1-2 years
Deepened voice	6-12 months	1-2 years
Facial / body hair growth	6-12 months	4-5 years
Scalp hair loss	6-12 months	Variable
Minimal / no change		
Breast size	Stature / height	

Potential side effects of T-GAHT

- Polycythemia
- Infertility
- Acne
- Androgenic alopecia (“male” pattern hair loss)
- Weight gain
- Hypertension
- Sleep apnea
- Changes to lipid profile (decreased HDL, increased LDL, TG and total cholesterol)

Assessment	Estrogen-based therapy	Testosterone-based therapy
Physical examination	Phenotypic changes, blood pressure, weight	Phenotypic changes, blood pressure, weight
Testosterone	Female range (<50 ng/mL)	Mid-male range (400-700 ng/mL)
Estradiol	Mid-female range (100-200 pg/mL)	Consider – goal is male range (<55 pg/mL)
Side effect monitoring	Electrolytes if on spironolactone Prolactin every 1-2 years	CBC for erythrocytosis

Amber

- Amber has read about long-term risk of heart disease from HIV infection and worries that E-GAHT will increase this even more.
- What is the impact of GAHT on CV risk?

Risk of selected cardiovascular events in transfeminine people

Venous thromboembolism	Ref: Cis men (SIR / OR / HR, 95% CI [adjusted])	Ref: Cis women (SIR / OR / HR, 95% CI [adjusted])
Nota et al, 2019 (SIR)	4.55 (3.59-5.69)	5.52 (4.36-6.90)
Getahun, 2018 (HR)	1.9 (1.4-2.7)	2.0 (1.4-2.8)
van Zijverden, 2025 (SIR)	1.81 (1.33-2.35)	1.74 (1.28-2.26)
Myocardial infarction	Ref: Cis men	Ref: Cis women
Nota et al, 2019 (SIR)	0.79 (0.54-1.11)	2.64 (1.81-3.72)
Getahun, 2018 (HR)	0.9 (0.6-1.5)	1.8 (1.1-2.9)
Alzahrani, 2019 (OR)	1.32 (0.92-1.90)	2.56 (1.78-3.68)
van Zijverden, 2025 (SIR)	0.5 (0.32-0.71)	1.3 (0.84-1.85)
Stroke	Ref: Cis men	Ref: Cis women
Nota et al, 2019 (SIR)	1.80 (1.23-2.56)	2.42 (1.65-3.42)
Getahun, 2018 (HR)	1.2 (0.9-1.7)	1.9 (1.3-2.6)
van Zijverden, 2025 (SIR)	0.94 (0.72-1.19)	1.2 (0.92-1.52)

Risk of selected cardiovascular events in transmasculine people

Venous thromboembolism	Ref: Cis men (SIR / OR / HR, 95% CI [adjusted])	Ref: Cis women (SIR / OR / HR, 95% CI [adjusted])
Nota et al, 2019 (SIR)	0.36 (0.06-1.19)	0.41 (0.07-1.37)
Getahun, 2018 (HR)	1.6 (0.9-2.9)	1.1 (0.6-2.1)
van Zijverden, 2025 (SIR)	1.23 (0.65-1.98)	1.00 (0.53-1.61)
Myocardial infarction	Ref: Cis men	Ref: Cis women
Nota et al, 2019 (SIR)	1.72 (0.70-3.58)	3.69 (1.94-6.42)
Getahun, 2018 (HR)	0.7 (0.3-1.8)	1.3 (0.5-3.9)
Alzahrani, 2019 (OR)	2.53 (1.14-5.63)	4.90 (2.21-10.90)
van Zijverden, 2025 (SIR)	1.51 (0.97-2.15)	4.2 (2.72-6.01)
Stroke	Ref: Cis men	Ref: Cis women
Nota et al, 2019 (SIR)	1.46 (0.59-3.04)	2.42 (1.65-3.42)
Getahun, 2018 (HR)	1.1 (0.6-2.0)	1.3 (0.7-2.5)
van Zijverden, 2025 (SIR)	1.26 (0.83-1.79)	1.55 (1.01-2.20)

Effects of estrogen therapy on lipids

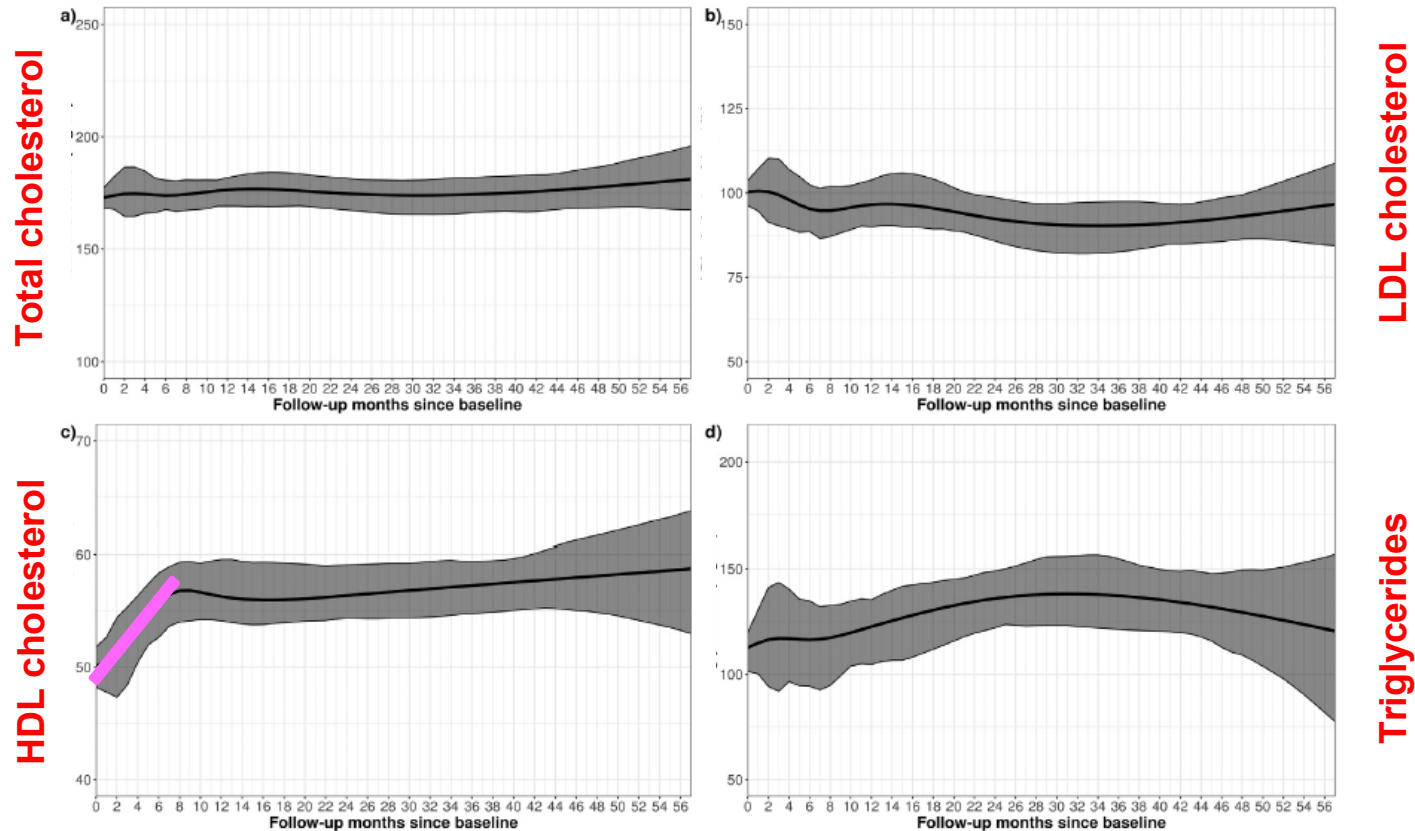


Fig. 1 Lipid parameters across time in trans feminine patients on hormone therapy. Estimated marginal means with bootstrapped 95% confidence intervals in the shaded areas from generalized additive mixed model for lipid parameter across months since baseline.

Effects of testosterone therapy on lipids

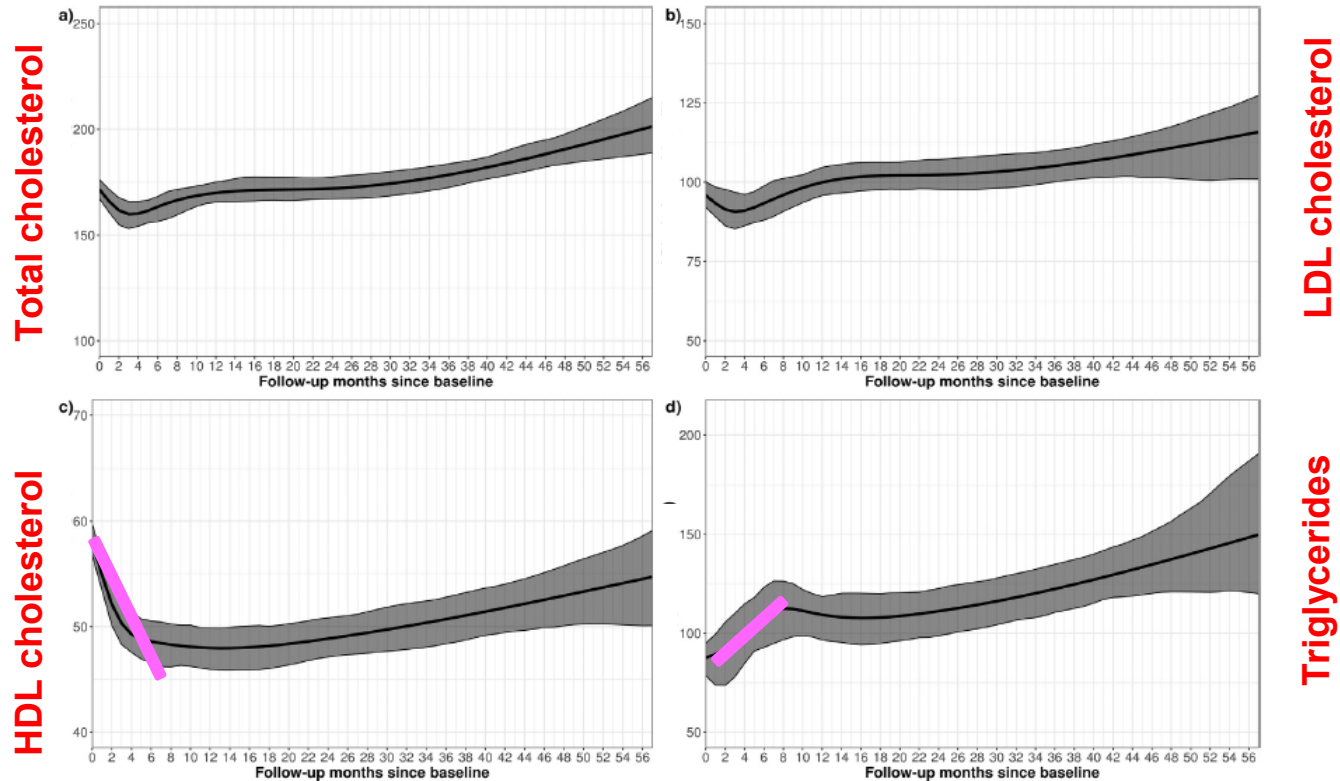
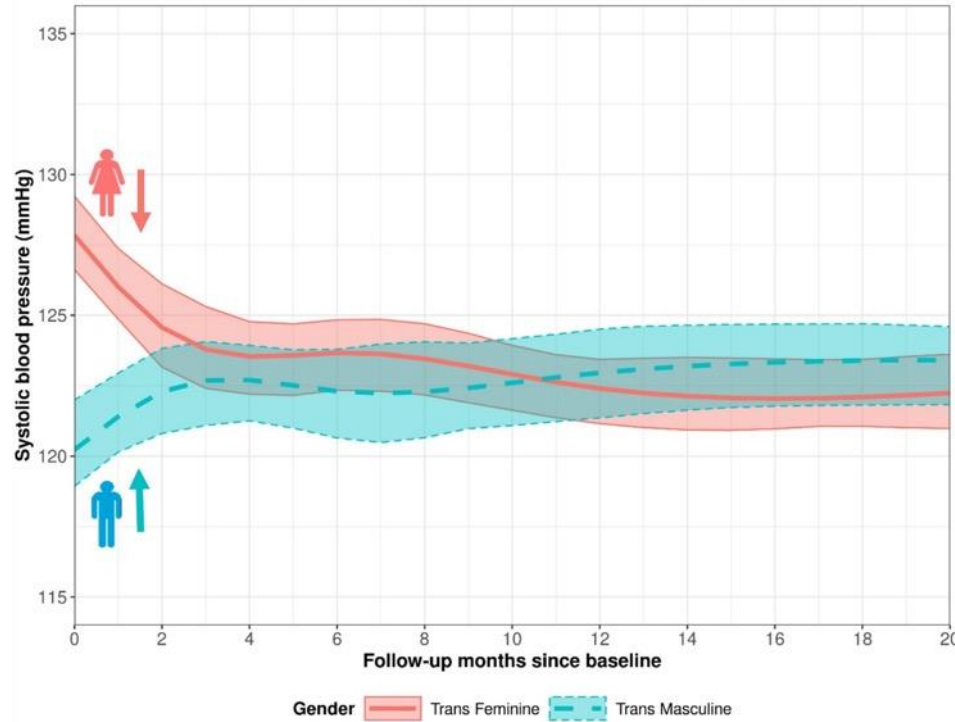
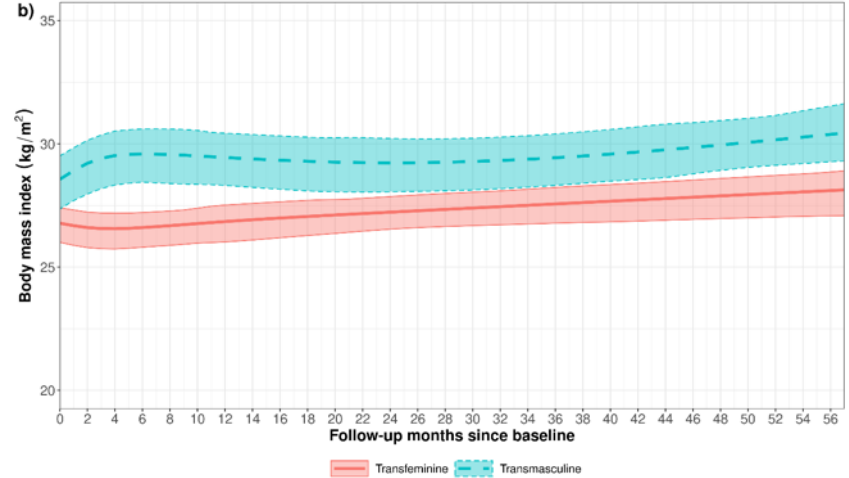
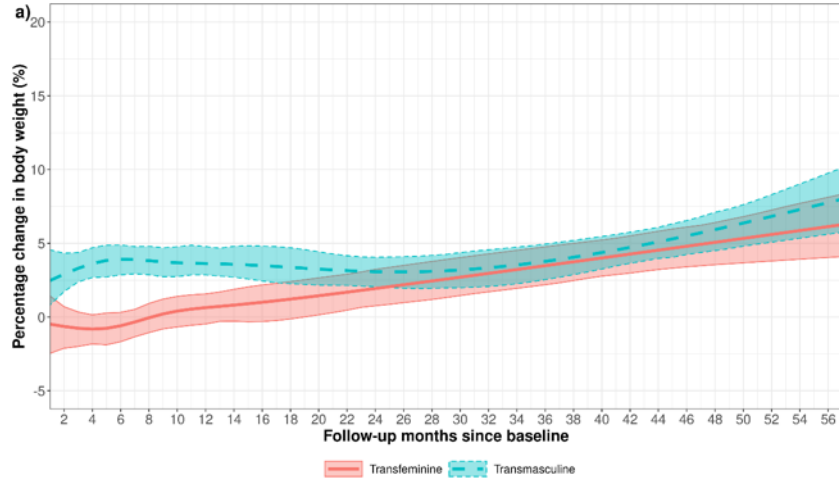


Fig. 2 Lipid parameters across time in trans masculine patients on hormone therapy. Estimated marginal means with bootstrapped 95% confidence intervals in the shaded areas from generalized additive mixed model for lipid parameter across months since baseline.

Effects of hormone therapy on blood pressure



Effects of hormone therapy on body weight



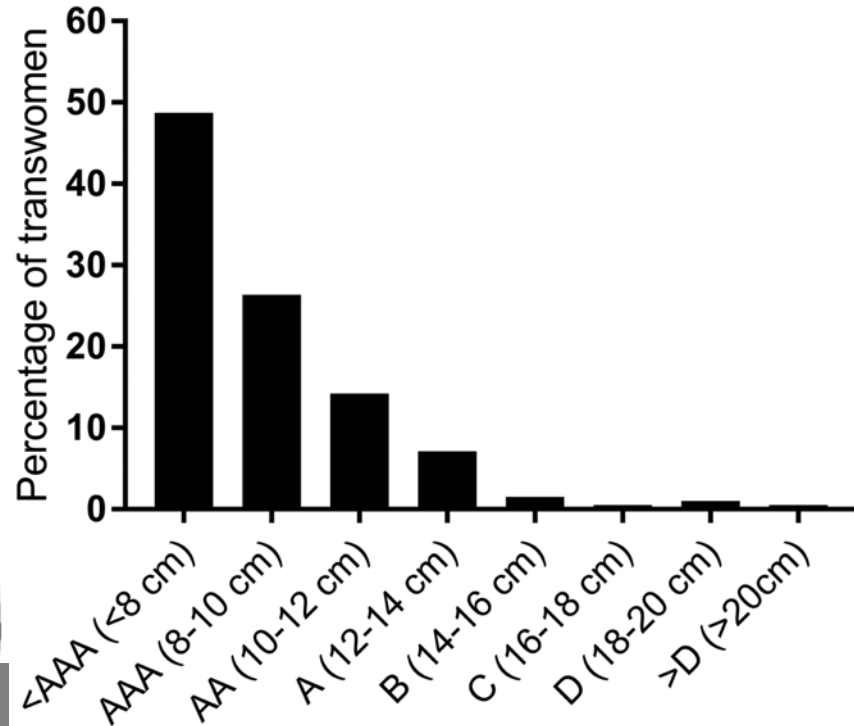
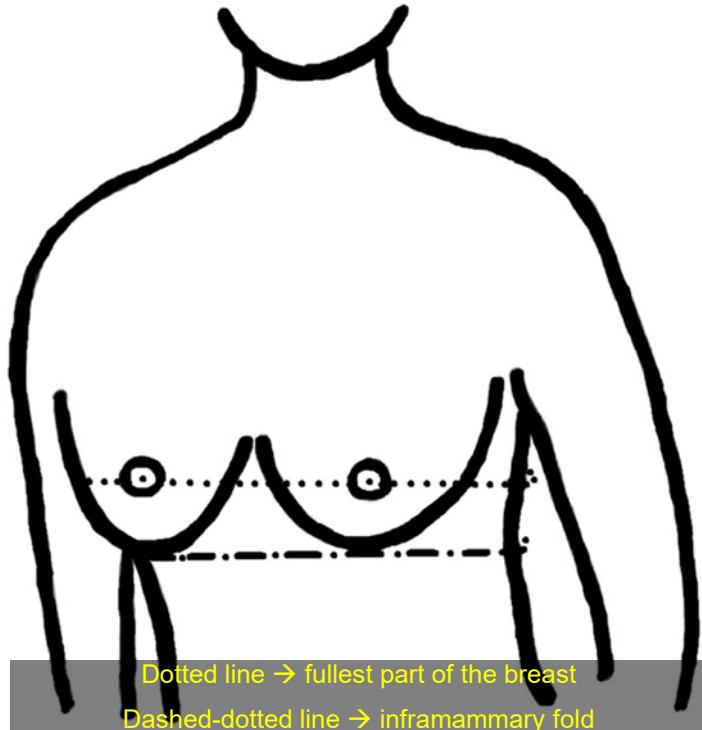
What to do with sex markers in ASCVD risk calculators?

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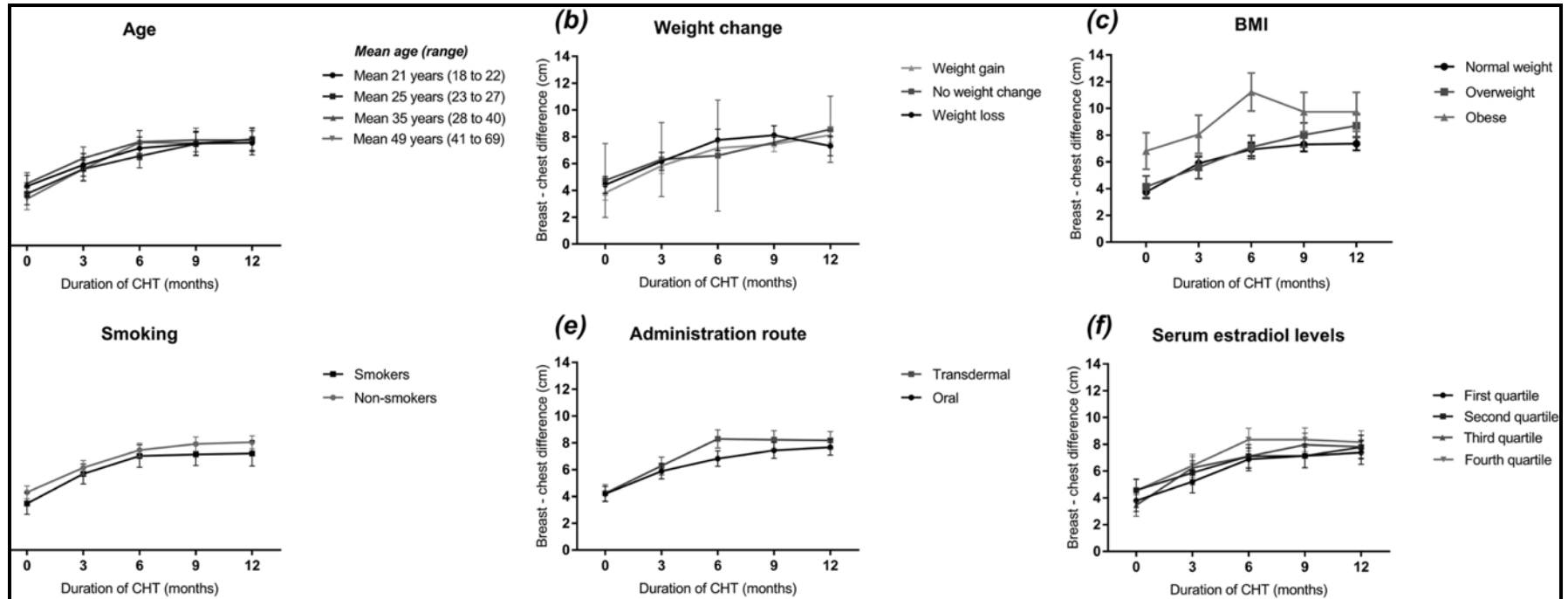
Amber

- Has now been on E-GAHT for 2 years
- Expresses dissatisfaction with breast growth – currently an A cup, no change in past 3-6 months
- Asks about starting progesterone...

Most trans women have an A cup or smaller after 12 months of E-GAHT

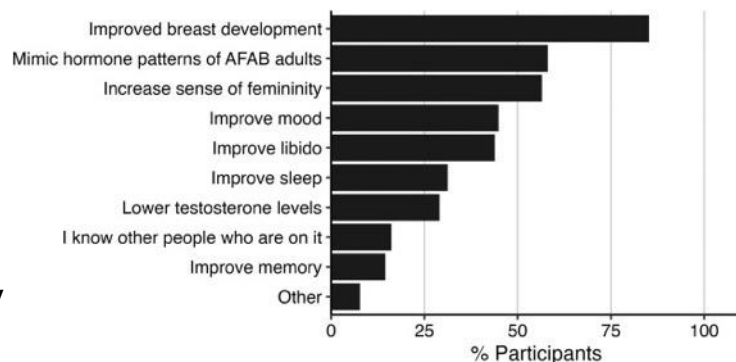


No clinical or laboratory parameters can predict breast development



Potential rationale for progesterone use in E-GAHT

- Role of progesterone in breast / nipple / areola development
- Suppression of testosterone via negative feedback
- Positive effects on sleep and libido / erectile function
- 40-60% of transfeminine patients in the United States have ever taken a progestogen



Current data do not support beneficial effects of progesterone in E-GAHT

- Prior studies with no impact on sleep time, sleep efficiency, borderline significant improvement in sleep latency
- Nolan et al 2022:
 - 42 trans women on E-GAHT randomized to micronized progesterone 100 mg daily for 3 months
 - No significant change in sleep, psychological distress, breast development

Progesterone may have risks

- Cyproterone acetate – meningioma, prolactinoma
 - But not usually used except as an antiandrogen, risks may not translate to other progestogens
- Progestogens in menopausal hormone therapy – breast cancer, cardiovascular disease
 - But primarily based on WHI data with average age 63 years – progestogens routinely prescribed to younger cisgender women in the form of cOCPs
 - WHI used medroxyprogesterone acetate – may have higher cardiometabolic and breast cancer risk than micronized progesterone

Guidelines do not endorse use of progesterone

- “Although there are anecdotal reports of progesterone use for breast development and mood management, there is currently insufficient evidence that potential benefits of progesterone administration outweigh the potential risks.”
- “If, after a discussion of risks and benefits of progesterone treatment, there is a collaborative decision to trial progesterone, the prescriber should see the patient back within a year to review the patient's response to this treatment.”
- A more evidence-based recommendation: Chest feminization surgery

Studies are underway!

Dijkman et al. *BMC Pharmacology and Toxicology* (2023) 24:80
<https://doi.org/10.1186/s40360-023-00724-4>

BMC Pharmacology
and Toxicology

STUDY PROTOCOL

Open Access



Addition of progesterone to feminizing gender-affirming hormone therapy in transgender individuals for breast development: a randomized controlled trial

Benthe A.M. Dijkman^{1,2}, Danithsia Helder^{1,2}, Lidewij S. Boogers^{1,2}, Noor C. Gieles^{1,2}, Jason O. van Heesewijk^{1,2}, Sjoerd te Slaa³, Niels P.T.J. Liberton³, Chantal M. Wiepjes^{1,2}, Christel J.M. de Blok^{1,2}, Martin den Heijer^{1,2} and Koen M.A. Dreijerink^{1,2*}

Recruiting

Progesterone in Gender Affirming Hormone Therapy Study

ClinicalTrials.gov ID **NCT06807580**

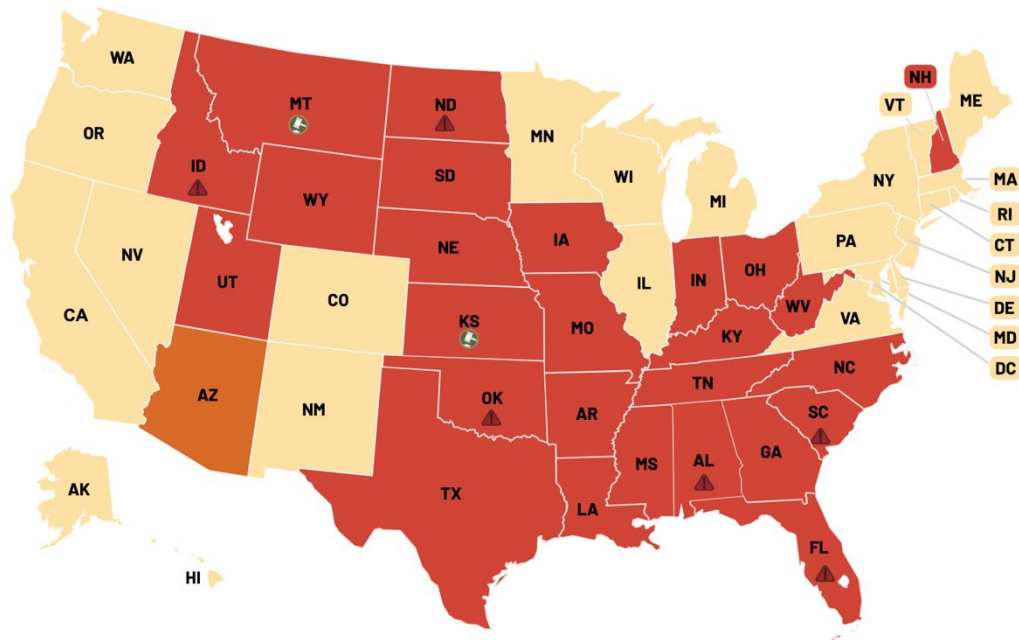
Sponsor Emory University

Information provided by Vin Tangpricha, Emory University (Responsible Party)

Last Update Posted 2025-05-16

Amber

- Amber is started on estradiol and spironolactone pills. A year later, she asks you to help her stockpile medication.
- How do you address her request?



State bans medically necessary medication and surgical care for transgender youth, though ban may not be in effect (see note)
(26 states + 1 territory)

State bans medically necessary surgical care for transgender youth
(1 state)

State does not ban medically necessary care for transgender youth
(23 states + 4 territories + D.C.)

State ban makes it a felony crime to provide certain forms of medically necessary care for transgender youth
(6 states + 1 territory)

Court ruling is currently blocking enforcement of state's healthcare ban
(2 states)

U.S. Territories

American Samoa

Commonwealth of the Northern Mariana Islands

Guam

Puerto Rico

U.S. Virgin Islands



Summary

- Gender-affirming therapy consists of estradiol + antiandrogen, or of testosterone, with dosing adjusted based on levels and clinical effect
- There is not (yet) a formal role for progestogens in feminizing gender-affirming hormone therapy
- Some cardiovascular risk factors worsen with GAHT; while data on CV outcomes are less clear, monitoring and addressing risk factors is recommended
- With changes in federal policy comes requests for stockpiling and other ways of ensuring access – clinicians can keep advocating for their patients

Useful references

- **Hormone treatment:**
Endocrine Treatment of Gender-Dysphoric / Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. Hembree et al, JCEM Nov 2017, 102(11):1-35.
- **HIV drug interaction checker:**
<https://www.hiv-druginteractions.org>
- **Broader overview of transgender care:**
Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, World Professional Association for Transgender Health
- <https://www.tandfonline.com/doi/pdf/10.1080/26895269.2022.2100644>
- **Additional training:**
<https://www.wpath.org/gei>
- **Primary care for transgender individuals:**
UCSF Center of Excellence for Transgender Health (<http://transhealth.ucsf.edu/>)

Thank you!

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