Table 1: Masculinizing Hormonal Therapy: Testosterone

Gender related effects (anticipated onset/max effect):

- Improved mood, poss 2/2 decreased gender dysphoria - reversible (variable)
- Cessation of menses - reversible (~2-6mo/n/a)
- ↑muscular mass & strength - partly reversible (~6-12mo/2-5yrs)
- Redistribution of body fat - partly reversible (~3-6mo/2-5yrs)
- Voice change to a male range - irreversible (~3-12mo/1-2yrs)
- ↑hair growth of face, chest, extremities - irreversible (~3-6mo/3-5yrs)
- Clitoral enlargement - irreversible (~3-6mo/1-2yr)

Route	Dose	Adverse Effects	Contraindications	Interactions
IM or Sub-Q*		Common: ↑weight, oily skin, acne, vaginal atrophy, male pattern baldness, sweating, snoring, insomnia, emotional changes, ↓ HDL cholesterol level, skin irritation with patch Less Common: peripheral edema, ↑blood pressure, erythrocytosis (polycythemia), transiently abnormal hepatic transaminases, dyslipidemia, obstructive sleep apnea, increased aggressiveness, skin irritation with gels, skin ulceration with patch Rare or plausible but have not been observed: HTN, liver dysfunction, ↑risk of CVD, ↑risk of breast cancer, ↑risk of endometrial hyperplasia, ↑risk of ovarian cancer Unknown: long term affect on fertility—counsel that possible to cause infertility/ options for cryobanking [*T Undeconoate: rare pulmonary microembolism & anaphylaxis; requires injection admin in health care setting by trained professional w/ 30min monitoring afterwards]	Absolute: Pregnancy h/o testosterone-responsive cancers Precautions: Erythrocytosis cardiac, hepatic, renal, or vascular disease with edema or risk of edema, Sleep apnea or high risk of sleep apnea due to obesity or chronic lung disease, dyslipidemia	Warfarin Cyclosporine Insulin
- Testosterone cypionate (cottonseed oil) - Testosterone enanthate (sesame oil) (Typical concentration: 200mg/ml)	Starting: 50-100mg Q2wk or 25-50mg Q1wk Typical: 200mg Q2wk or 100mg Q1wk Max: if >200mg Q2wks needed adjust based on T levels *Sub-Q typically administered weekly (less volume)			
Topical				
Testosterone transdermal patch (Androderm)	Low dose: 2mg daily Starting: 4mg daily Max: 8mg daily Dispensed as: 2mg/day & 4mg/day patches			
Testosterone gel (Testim or Androgel 1%)	Starting: 25mg every morning Typical: 50mg every morning Max: 100mg every morning Dispensed as: - 25mg/5g packets & 50mg/5g packets - Metered dose pump, 12.5mg per pump actuation			
Testosterone gel (Androgel 1.62%)	Starting: 40.5mg daily Typical: 40.5mg daily Usual dosage range: 20.25 mg to 81mg daily Max: if >81mg needed adjust based on T levels Dispensed as: - 20.25mg packets & 40.5mg packets - Metered dose pump, 20.25mg/1.25g per pump actuation			
Testosterone solution (Axiron axillary solution)	Usual: 60mg 1x daily, apply to axilla at same time QAM Range: 30-120mg daily (No published or anecdotal experience w/ this preparation)			
Testosterone Undeconoate (Long acting, ~Q10wk IM)	Newly available in U.S., only via AVEED Risk Eval & Mitigation Strategy (REMS) [see*]; long hx use outside U.S.			

Lab Monitoring for Patients Starting/On Testosterone*

Testosterone	CBC (Hbg/Hct)*	Fasting glucose	Fasting lipids	LFT's	Urine HCG
Monitor Total Testosterone & apply physiologic male range *DPH lab: 241-827* - No baseline - 3mo after starting or dose change - PRN for clinical concern - Testosterone monitoring can be complex. If total testosterone level does not correlate with clinical picture, consider ordering SHBG and calculating bio-available testosterone.	- Baseline - 3mo after starting or dose increase - Annually thereafter * anticipate Hgb/Hct to ^male range	- Baseline if PCOS is suspected	- Per guidelines for males [age appropriate]	- Baseline if PCOS is suspected - Optional 1yr after starting if pt has risks for liver disease (e.g. excessive wt gain, risk behaviors for acquiring viral hepatitis, heavy alcohol use)	- If pregnancy is a possibility: baseline & PRN

*in addition to labs appropriate for patients' age & medical conditions

Notes on testosterone therapy:

Choosing a formulation:

- Choice of testosterone is individualized based on patient needs, availability, co-morbid conditions, and adverse effect profile:
  Injectable
  - Testosterone enanthate and cypionate can be administered IM every 2 weeks for convenience, however some patients experience adverse mood effects due to fluctuations in blood testosterone levels with Q2week injections.
  - May be administered weekly IM or subQ for more stable blood testosterone levels.
  - Testosterone propionate is impractical d/t frequent injection but is an option for those who cannot tolerate other forms.

  Topical
  - Topically applied testosterone is absorbed systemically & should be included in total patient dose; decreased dosing of other testosterone is recommended when adding topical to avoid adverse effects.
  - Topical testosterones achieve more physiological daily levels but some patients do not have adequate masculinization.
  - May be used for slower transitions or to maintain masculinization after achieving desired effects w/ other formulations.
  - Risk of skin irritation and exposure of others to testosterone. Educate patients on the risks to children & women of contact with topical testosterone or to unclothed/unwashed skin that topical testosterone products have been applied to.
  - Testosterone ointment, cream, or gels have been used topically, applied directly to facial and body areas and clitoris to promote hair growth and clitoral growth, however all information about effectiveness is anecdotal. Testosterone is rapidly absorbed and available systemically when applied in this way and should be accounted for in planning appropriate dosing.

Dose adjustment:

- Adjust dosing based on patient reported changes and satisfaction in meeting their masculinization goals, and with lab monitoring of testosterone, to ensure not in excess of male physiologic range.

Preventive care r/t testosterone therapy:

- Continue testosterone even after maximum masculinization to prevent osteoporosis for those s/p oophorectomy.
- May use finesteride in usual dosing for prevention of male pattern baldness, particularly for those w/ strong family history.
- Strongly encourage and assist patients with smoking cessation to decrease cardiovascular risk.
- Evaluate for endometrial hyperplasia/uterine cancer for FTM with a uterus if they have bleeding after long period of amenorrhea and they have not had a change to their testosterone dose.
- No evidence that screening with ultrasound will decrease mortality or morbidity of endometrial cancer.

Sexual health r/t testosterone therapy:

- Assess for safer sex practices and hypersexual behavior after beginning testosterone.
- Testosterone is not a contraceptive; educate patient to use contraception if vaginal receptive intercourse with biological men.

Medication interactions:

- Changes in anticoagulant activity may be seen in pts on warfarin, more frequent INR monitoring may be needed.

- Changes in insulin sensitivity or glycemic control may occur in diabetics; testosterone may lower glucose and therefore lower insulin requirement.

Table 2: Feminizing Hormonal Therapy, Part 1: Anti-androgens, Progesterone

Anti-androgen therapy, gender-related effects:

- ↓facial and body hair growth
- ↓progression of male pattern baldness
- ↓libido
- ↓erections
- ↓BPH
- Mild breast growth (irreversible)

Progesterone, gender-related effects:

- anecdotal reports of enhanced breast contour and nipple development (evidence to support additional feminization is weak)

	Dose	Adverse Effects	Contraindications	Interactions	Notes
Spironolactone	Starting: 25-50mg BID Typical: 50mg BID Max: 100mg BID	Mild diuretic Hyperkalemia Excretion of Na, Ca, Cl Impotence	Renal insuff K > 5.5	Digoxin ACEi ARB K-sparing diuretics	Avoid after orchiectomy (but patients with continued beard growth may benefit)
Finasteride	Low: 1mg daily High: 5mg daily				Prescribe if pt unable to take spironolactone Can use in combo w/ spironolactone for rare patients not achieving gender-related effects or to slow male pattern baldness
Dutasteride	Typical: 0.5mg				
Progesterone	Micronized progesterone (natural): 100-200mg QHS Medroxy-progesterone (synthetic): 5-10mg PO daily Depo-provera: 150mg IM Q3mo	Weight gain, depression/mood changes May also have androgenizing affects including hair growth, acne Beyond one year, may increase risk breast CA, CVD			Consider limited use 6-12mo for desired changes—anticipate maximum permanent changes within a year

Table 3: Feminizing Hormonal Therapy, Part 2: Estrogen

Gender-related effects (anticipated onset/max effect):

- Improved mood, poss 2/2 decreased gender dysphoria - reversible (variable)
- Softening of skin, reversible (~3-6mo/unkn)
- ↓libido, reversible (~1-3mo/1-2yrs
- Suppression of testosterone, reversible (~1-3mo)
- Redistribution of body fat, partly reversible (~3-6mo/2-5yrs)
- Shrinkage of testes, partly reversible (~3-6mo/2-3yrs)
- Breast development, irreversible (~3-6mo/2-3yrs)

Route	Dose	Adverse Effects	Contraindications	Inter-actions
Oral		Common ↑weight, emotional changes, ↑risk DVT & PE (esp > 40yo, cigarette smokers, highly sedentary, obese & those w/ underlying thrombophyllic disorders & those using oral estrogens esp ethinyl estradiol) adverse changes in lipid levels, ↑insulin resistance, ↑prolactin levels, decrease in sexually stimulated erections, n/v, migraine/headache, melasma (skin darkening), skin irritation w/ patch Less Common ↑risk of CV events in those >50yo w/ other CV risk factors (esp w/ progesterones + estrogens), ↑ triglycerides w/ oral estrogens (↑risk of pancreatitis & CVD), transient liver enzyme abnormalities, ↑risk of gallbladder stones, ↑risk of DM (particularly w/ FH or other risk factors), ↑BP (note spironolactone reduces BP) Rare or plausible but have not been observed liver damage, prolactinoma, ↑ risk of breast cancer (vs men never exposed to estrogen) Unknown Long term affect on fertility—counsel that possible to cause infertility/options for cryobanking	Absolute Estrogen-dependent cancer Precautions h/o Thromboembolism, CAD, HLD, DM, Cigarette smoking Highly sedentary lifestyle, Migraine, Seizure d/o, Retinopathy, CHF, valvular heart dz, Thrombosis risk for any reason, FH estrogen-dependent tumor	CYP 3A4, 1A2 inhibitors/ inducers
Estradiol PO	Starting: 2-3mg daily Typical: 4mg daily Max: 8mg daily (not intended for long term use, consider at high dose for limited time, eg 1-3yrs)			
Estradiol SL (estradiol micronized, Estrace)	Starting: 0.5-1mg Typical: 2mg daily Max: 4mg daily (may use any PO formulation SL to avoid 1st pass)			
IM				
Estradiol valerate (Delestrogen) (typical concentrations: 20mg/ml, 40mg/ml) **interchangeable w/ estradiol*	Starting: 20 IM Q2wk Average: 20-40mg IM Q2wk Doses higher than 40mg (up to 80mg) could be used rarely, case by case, for limited time only			
Estradiol cypionate (Depo-estradiol) (concentration: 5mg/mL) **not interchangeable w/ delestrogen*	Starting: 2.5-5mg IM Q2wk Average: 5mg IM Q2wk Max: rarely up to 10mg IM Q2wk			
Topical				
Estradiol patch (Climara, Menostar—weekly) (Estraderm Alora, Minivelle, Vivelle-Dot—twice weekly)	*1-4 Patches applied at a time, weekly or biweekly according to brand, to achieve appropriate daily dose* Starting: 0.1mg/24hr Average: 0.2mg/24hr Max: 0.4mg/24hr			
Estradiol gel (Divigel, Elestrin, Estrasorb, Estrogel)	Dosing ranges for transwomen have not been established			
For reference only				
Conjugated equine estrogens (Premarin)	Considered less safe/↑CV risks, difficult to monitor & serious ethical concerns (from urine of immobilized catheterized pregnant horses) Starting: 1.25-2.5mg daily; Typical: 5mg; Max: 10mg			
Ethinyl estradiol	Do not Rx d/t significant ↑risk CV events			

Lab Monitoring for Patients Starting/On Feminizing Hormone Therapy*

	Estradiol	Testosterone	Fasting glucose	Fasting lipids	LFT's	Prolactin	BUN / SCr, Electrolytes
On Estrogen	*Apply physiologic female range DPH lab: upper level 433 pg/ml* - No baseline - Optional 3-6mo after starting or dose change** - Most useful when standard doses not resulting in adequate feminization or to reassure pts on any dose	- 3mo after starting - Based on clinical goals thereafter	- According to guidelines for adults	- According to guidelines for adults	- Optional 1yr after starting if pt has risks for liver disease (e.g. excessive wt gain, risk behaviors for acquiring viral hepatitis, heavy alcohol use)	- Baseline for patients w/ prev unmonitored tx, prev ↑prolactin, prior or current exposure to phenothiazines - Consider at 1yr for pts on high dose estrogen or phenothiazine - Consider PRN for pts suspected of taking doses > prescribed	
On Spironolactone		- Optional 6 mo after starting if not showing expected demasculin-ization					- Baseline - 3 mo after starting or ↑dose (sooner for high risk renal dysfxn) - every 12mo on stable dose - consider closer monitoring in elderly, other high risk pts

*in addition to labs appropriate for patients' age & medical conditions

**Correlation of estradiol blood levels to dosing and to patient satisfaction/alleviation of gender dysphoria is an area of emerging research. The utility of monitoring estradiol levels is unclear, however many consider this monitoring to be standard of care.

Notes on estrogen therapy:

Choosing a formulation:

- Choice of estrogen is individualized based on patient needs, availability, co-morbid conditions, and adverse effect profile:

Oral

  - Avoid oral estrogen for patients >40yo or CV/thromboembolic risk factors.
  - Estradiol micronized is manufactured to quickly dissolve sublingually but any of the oral estradiol or estradiol valerate preparations can be used sublingually or transbuccaly to decrease possible risk r/t 1st pass effects in the liver and excess thrombotic effects. Sublingual use may result in higher peak levels and lower 24 hr AUC (area under the curve) levels (Price et al., 1997) but clinical significance is unclear.

Topical

  - Skin irritation can be a problem with patches and switching the type of patch may help.
  - Topical estrogen gels are now available and advocated by some providers. (Bushong & Richard A. Martin, n.d.) Experience with these products is anecdotal but benefits should include those of other non-oral forms of dosing.

Injectable

  - Injectable estradiol valerate (delestrogen) may be administered weekly at half the above doses for greater stability of hormone levels if mood swings or other symptoms occur with every other week dosing.
  - Estradiol cypionate (depo-estradiol) has the longest half-life of any of the injectable estrogens and may be appropriate for patients who need less frequent injecting or have trouble with mood fluctuations or other symptoms at the start or end of the injection cycle.

Dose adjustment:

- Prescribe at "starting" dose for patients who have not previously used estrogen, those who want to use "low dose", cigarette smokers and others at high risk of thrombosis, patients with uncontrolled diabetes and/or metabolic syndrome and/or active cardiovascular disease.
- Prescribe higher doses as needed based on clinical goals, response, smoking cessation, stabilization of co-morbid conditions.
- Some medical providers and international guidelines recommend adjusting dosage based on estradiol level using female physiologic normal ranges. (Hembree et.al.)
- Doses should be reduced after maximum feminization (usually after 2-4 years). Some advocate routinely decreasing after 2 years. Reduce after gender affirming surgery (orchiectomy, vaginoplasty, mammoplasty, etc) based on patient goals.

Preventive care r/t estrogen therapy:

- Continue estrogen even after maximum feminization to prevent osteoporosis in those s/p gender affirming surgery.
- Recommended doses for "maintenance" hormone therapy for patients on effective anti-androgen doses or post gender affirming surgery have not been defined but doses recommended for post-menopausal prevention of osteoporosis or the starting doses above have been suggested.
- Stop all estrogens 2-4 weeks prior to any major surgery or other immobilizing event; resume after return to regular activity.
- Daily low dose aspirin is a reasonable intervention for all patients with higher than average risk of thromboembolism.

Table 4: Strategy for managing elevated prolactin

Elevated prolactin levels frequently decrease spontaneously. Therefore:
If prolactin is less than 25, continue to monitor per protocol.
If prolactin is 25-40, ask patient about outside sources of extra estrogen (usually injections) and encourage patient to cease these. Continue to monitor per protocol.
If prolactin is greater than 40, decrease estrogen dose by 1/2 or ask patient to stop estrogens, recheck 6-8 weeks.
If prolactin is greater than 100, stop all estrogens and retest in 6-8 weeks.
If continues high consider MRI of pituitary. If prolactin level is falling, restart estrogen (at lower dose and monitor every 6-8 weeks.
Be aware that common antipsychotics can increase prolactin levels.

Notes on transgender children/adolescents:

- Transgender adolescents under age 18 may be started on the same dosing regimens w/ guardian consent; hormonal interventions in adolescence support alleviation of gender dysphoria by enhancing early development of desired secondary sex characteristics while minimizing the effects of an undesirable natal puberty and thus help to minimize psychosocial distress and associated co-morbidities. SFDPH's Dimensions Clinic for LGBTQ youth is a good resource for consultation or referral.
- Those who are prepubescent or early in adolescence may benefit from GnRH agonists/"puberty blockers" (leuprorelin, nafarelin, goserelin); it is advisable to consult with or refer to an area specialist such as UCSF Child and Adolescent Gender Center. See also Hembree et al., 2009 for dosing.