Transgender Health

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San Francisco Department of Public Health
Kalen

- 20 year old “female” patient of yours for the past 2 years comes in asking to begin testosterone.
Alex

- 24 year old patient, new to you and just beginning graduate school, with a male birth assigned sex, comes to see you to discuss estrogen therapy
Izzy

• 17 year old freshman with a genderqueer/non-binary identity comes to see you in late August seeking to begin low dose testosterone
Emily

- 22 year old transgender woman on hormones for 3 years, who is a transfer student and is new to the university, comes to see you to discuss breast augmentation surgery
Identity & Orientation

• Gender Identity
  – How one self-identifies in the way they live and move through the world
  – Mind
  – Female? Male? Something else?

• Gender Expression
  – How one “does” gender
  – Feminine? Masculine? Androgynous?

• Sexual Orientation
Trans* Terminology

• Trans Man / Trans-masculine
  – Female-to-Male/FTM
  – “Female Assigned at Birth (FAAB)”
• MTF / Trans Woman / Trans-feminine
  – “Male-to-Female/MTF”
  – Male Assigned at Birth (MAAB)
• Genderqueer/non-binary/non-conforming
  – Range of identities which lie outside binary M/F
Trans* Terminology

• Lesbian transgender woman
  – Female identity, attracted to women

• Gay transgender man
  – Male identity attracted to men

• Cisgender = non-transgender
During the spring and summer of 2008 the Transgender Law Center (TLC) conducted a study of the economic health of the transgender community in California. We gathered 646 responses from transgender adults living in the state, and found alarmingly high rates of discrimination in employment, housing and healthcare.

**Health Care Access**
Transgender Californians report alarmingly high rates of denial of basic health care services.

- 33% were denied surgery
- 27% were denied hormones
- 21% were denied counseling and mental health services
- 15% were denied gender-specific care (such as pap smears for transmen and prostate exams for transwomen)
- 10% were denied primary health care

Some 30% of the community reports that they postponed care for illness or preventive care due to disrespect or discrimination from doctors or other health care providers. Forty-two percent of respondents delayed seeking care because they could not afford it. Twenty-six percent report health conditions that have worsened because they postponed care.
INJUSTICE AT EVERY TURN: A REPORT OF THE NATIONAL TRANSGENDER DISCRIMINATION SURVEY, EXECUTIVE SUMMARY

Grant, Jaime M., Lisa A. Mottet, Justin Tanis, Jack Harrison, Jody L. Herman, and Mara Keisling.

• Health outcomes for all categories of respondents show the appalling effects of social and economic marginalization, including much higher rates of HIV infection, smoking, drug and alcohol use and suicide attempts than the general population.

• Refusal of care: **19% of our sample reported being refused medical care** due to their transgender or gender non-conforming status, with even higher numbers among people of color in the survey.

• Uninformed doctors: **50% of the sample reported having to teach their medical providers** about transgender care.

• High HIV rates: Respondents reported **over four times the national average of HIV infection**, with rates higher among transgender people of color.\(^{viii}\)

• Postponed care: Survey participants reported that when they were sick or injured, **many postponed medical care due to discrimination (28%)** or inability to afford it (48%).
HIV - Epidemiology

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>HIV prevalence in transgender women (95% CI)</th>
<th>Odds ratio (95% CI)</th>
<th>HIV prevalence in reproductive-age adults</th>
<th>HIV prevalence in reproductive-age males</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spain</td>
<td>150</td>
<td>10.4% (3.2-33.0)</td>
<td>40.9 (20.5-03.1)</td>
<td>0.55%</td>
<td>0.01%</td>
</tr>
<tr>
<td>USA</td>
<td>2705</td>
<td>21.7% (18.4-25.1)</td>
<td>34.2 (31.2-37.5)</td>
<td>0.81%</td>
<td>1.18%</td>
</tr>
<tr>
<td>Pooled estimate*</td>
<td>11066</td>
<td>19.1% (17.4-20.7)</td>
<td>48.8 (31.2-76.3)</td>
<td>0.44%</td>
<td>0.58%</td>
</tr>
</tbody>
</table>

*Degrees of freedom: 14, heterogeneity χ² 214.7, p < 0.05. Test of odds ratio 1-x 16.21, p < 0.001. Income level: L, middle income; M, high income.

Worldwide burden of HIV in transgender women: a systematic review and meta-analysis

Stefan D Baral, Tonia Poteat, Susanne Strømdahl, Andrea L Wirtz, Thomas E Guadamuz, Chris Beyrer

www.thelancet.com/infection  Published online December 21, 2012
How Many Transgender People Are There?

• 0.5% of Massachusetts respondents to a landline survey were trans identified
  – Am J Pub Health Jan 2012 Conron et al

• Williams Institute (UCLA) estimates 0.3% of adult US population is transgender
  – How many people are lesbian, gay, bisexual, and transgender?; Gates GJ April 2011; Accessed online law.ucla.edu/WilliamsInstitute
Gender Identity and Birth Sex

- Transgender person can be identified by someone whose gender identity ≠ birth sex
  - Research
  - Policy
  - Quality improvement
  - Patient centered
What is your current gender identity? (Check all that apply)
- Male
- Female
- Female-to-male (FTM)/transgender male/trans man
- Male-to-female (MTF)/transgender female/trans woman
- Genderqueer, neither exclusively male nor female
- Additional gender category/(or other), please specify:
  
- Decline to answer

What sex were you assigned at birth on your original birth certificate? (Check one)
- Male
- Female
- Decline to answer
<table>
<thead>
<tr>
<th>Identity</th>
<th>1-Step</th>
<th>2-Step</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Trans</td>
<td>N/A</td>
<td>98.35%</td>
</tr>
<tr>
<td>Trans</td>
<td>0.84%</td>
<td>1.65%</td>
</tr>
</tbody>
</table>

P < 0.00004

First, Do No Harm:
Reducing Disparities for
Lesbian, Gay, Bisexual, Transgender, Queer and Questioning
Populations in California

The California LGBTQ
Reducing Mental Health Disparities Population Report

Prepared for the:
Office of Health Equity
California Department of Public Health
Under California Department of Public Health contract #09-79055-000,
through funds made possible by the Mental Health Services Act

Through a collaborative arrangement between:
Mental Health America of Northern California & Equality California Institute
December 2012
## Sexual orientation among trans respondents

<table>
<thead>
<tr>
<th>Sexual Orientation</th>
<th>Approximate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesbian</td>
<td>25%</td>
</tr>
<tr>
<td>Gay</td>
<td>9%</td>
</tr>
<tr>
<td>Bisexual/Pansexual</td>
<td>22%</td>
</tr>
<tr>
<td>Queer</td>
<td>32%</td>
</tr>
<tr>
<td>Questioning their sexual orientation</td>
<td>1%</td>
</tr>
<tr>
<td>Heterosexual/Straight</td>
<td>10%</td>
</tr>
</tbody>
</table>
Gender ID of trans respondents (15% of overall)

<table>
<thead>
<tr>
<th>Gender Identity</th>
<th>Approximate %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Man/boy</td>
<td>9%</td>
</tr>
<tr>
<td>Woman/girl</td>
<td>7%</td>
</tr>
<tr>
<td>Androgynous</td>
<td>24%</td>
</tr>
<tr>
<td>Genderqueer</td>
<td>32%</td>
</tr>
<tr>
<td>Transgender</td>
<td>11%</td>
</tr>
<tr>
<td>Transman</td>
<td>11%</td>
</tr>
<tr>
<td>Transwoman</td>
<td>6%</td>
</tr>
</tbody>
</table>
What is A Respectful and Culturally Appropriate Care Setting?

• Bathrooms – what bathrooms are transgender people allowed to use? Are there safety issues (for example, transgender women in the men’s room may be at risk of assault)

• Waiting room materials and atmosphere – are there any pamphlets, posters etc... which make transgender people feel comfortable?

• Medical Records, including Electronic Medical Records – is there a way to note patient’s chosen name and pronoun, if they differ from that on legal documents?

BMC Pediatr. 2015; 15: 187. Improving transgender health by building safe clinical environments that promote existing resilience: Results from a qualitative analysis of providers

What is A Respectful and Culturally Appropriate Care Setting?

• Front desk, nurse and provider staff –
  – are clinic staff trained in basic transgender cultural competency?
  – Do they understand the importance of using the chosen name and pronoun, even if they differ from that which is on legal ID?
  – Do they understand how to record and access this information in the medical record?

• Engage the community both in the development of clinical services oriented towards transgender people, as well as for dissemination of awareness about the services.
Evidence for providing a respectful and appropriate transgender care setting

- Improved patient satisfaction
- Improved patient retention
- Patient safety
- Improved care
  - Patients may be more comfortable with sensitive exams when they feel their identity is being respected
  - Patients may be more likely to come in for other needed preventive and primary care, if they feel the clinic offers an accepting and gender affirming environment

Gender Affirming Treatments and Procedures

• Hormone therapy
• Surgery
• Other procedures
  – Hair removal
    • Transgender women -> facial and/or body hair removal
    • Transgender men -> Hair removal at graft site for phalloplasty
  – Speech therapy for voice feminization or masculinization
    • Role of voice surgery is evolving
Gender Affirming Interventions – Non Medical

• Chest binding - > use of a tight bra or elastic bandage to flatten breasts and give a male chest contour

• Packing -> Use of an external penile prosthesis to give a male genital contour

• Tucking -> Displacement of the testicles into the inguinal canal, movement of the penis posteriorly into the perineum, and use of a tight undergarment to give a female genital contour

• Scalp hair replacement procedures – hairpiece, wig, hair transplants
Common Surgeries

- Hysterectomy / oopherectomy
- Vaginoplasty
- Phalloplasty
- Metaoidioplasty
- Breast augmentation
- Mastectomy
- Orchiectomy
- Facial feminization
- Tracheal shaving
- Other “cosmetic” procedures
  - Cosmetic in quotes, since many of these procedures are not at all cosmetic, but instead therapeutic in transgender people
Why offer gender affirming care?

• Hormone therapy reduces anxiety, depression and improves social functioning & QOL

• Surgery improves global functioning, sexual functioning, family and interpersonal relationships, body image, and quality of life
  - Eur Psychiatry 2002; 17: 353-62
Why offer gender affirming care?

- Regret relating to surgery is very rare (1% or less), and generally relates to surgical complications.

- Note that studies have been conducted in a variety of country/language settings.

- Bundling of hormones and other gender affirming procedures may improve participation in other important health care, such as HIV care or smoking cessation.

- Gender affirming procedures, including hormone therapy, genital, chest, and facial surgery, voice procedures, and hair removal are defined as medically necessary by WPATH SOCv7.
Feminizing Hormones - Goals

- Development of feminine secondary sex characteristics
- Suppression/minimization of masculine secondary sex characteristics
Feminizing hormones – physical effects

- Breast development
- Feminine redistribution of subcutaneous face/body fat.
- Reduced muscle mass
- Reduced body and (to a lesser extent) facial hair
- Changes in perspiration and odors
- Arrest (and possible reversal) of scalp hair loss
Feminizing hormones – other effects

• Reduced libido and erectile function

• Reduced size of testes, reduced or absent ejaculatory fluid and sperm count

• Changes in emotional and social functioning
  – Effects vary from person to person
  – Avoid projecting stereotypes
Feminizing hormones –
general approach

• Estrogen plus:

• Androgen blocker plus:

• (Sometimes) progestagen
Estrogens: 17-beta estradiol

• “Bio-identical” = identical to the estrogen secreted from a human ovary

• Patch, tablet, injected (valerate or cypionate ester) forms most commonly used in transgender care

• Gels, creams, sprays exist for menopausal use, but tend to not deliver high enough dose for feminization
Spironolactone

• Potassium sparing diuretic with properties that block both testosterone synthesis and receptor activity. (9)
  – May cause orthostasis or polyuria
  – Monitor renal function and potassium
  – Use caution with ACE-inhibitors or angiotensin 2 receptor blockers
Progestagens

• Medroxyprogesterone, cyproterone, micronized progesterone are all potential agents

• No data to guide use or role of progestagens in feminizing hormone therapy

• Anecdotal improvement in (7,8):
  – Breast/areaolar development
  – Mood and libido
### Hormone dosing table

<table>
<thead>
<tr>
<th>Estrogen</th>
<th>Initial – low #</th>
<th>Initial</th>
<th>Maximum *</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estradiol oral/sublingual</td>
<td>1mg</td>
<td>2-4mg/day</td>
<td>8mg/day</td>
<td>if &gt; 2mg recommend divided bid dosing</td>
</tr>
<tr>
<td>Estradiol transdermal</td>
<td>50mcg</td>
<td>100mcg</td>
<td>100-400 mcg</td>
<td>Max single patch dose available is 100mcg. Frequency of change is brand/product dependent. More than 2 patches at a time may be cumbersome for patients</td>
</tr>
<tr>
<td>Estradiol valerate IM</td>
<td>&lt;20mg</td>
<td>20mg IM q 2 wk</td>
<td>40mg IM q 2wk</td>
<td>May divide dose into weekly injections for cyclical symptoms</td>
</tr>
<tr>
<td>Estradiol cypionate IM</td>
<td>&lt;2mg</td>
<td>2mg IM q 2 wk</td>
<td>5mg IM q 2 wk</td>
<td>May divide dose into weekly injections for cyclical symptoms</td>
</tr>
</tbody>
</table>

### Progestagen

<table>
<thead>
<tr>
<th>Progestagen</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Medroxyprogesterone acetate (Provera)</td>
<td>2.5mg</td>
</tr>
<tr>
<td>Micronized progesterone</td>
<td>100-200 mg qhs</td>
</tr>
</tbody>
</table>

### Androgen blocker

<table>
<thead>
<tr>
<th>Androgen blocker</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Spironolactone</td>
<td>25mg qd</td>
</tr>
<tr>
<td>Finasteride</td>
<td>1mg qd</td>
</tr>
<tr>
<td>Dutasteride</td>
<td></td>
</tr>
<tr>
<td>Cyproterone</td>
<td></td>
</tr>
</tbody>
</table>

* Maximum dosing does not mean maximal effect, and do not necessarily represent a target or ideal dose. Dose increases should be based on patient response and (if done) monitored hormone levels.

# Initial-low dosing for those who desire (or require due to medical history) a low dose or slow upward titration.
Titration of dose

• Slow upward titration of estrogen, and delay or upward titration of spironolactone (if used) may result in subtle enhancement of breast development (7)

• Upward titration of spironolactone can limit orthostatic symptoms, if present

• Goal should be testosterone and estrogen levels in the female physiologic range for your lab (12)

• Clinical endpoints
  – Reduced body hair
  – Reduced erections and ejaculate
  – Breast budding
# Lab monitoring

<table>
<thead>
<tr>
<th>Lab</th>
<th>Comments</th>
<th>Baseline</th>
<th>3 months*</th>
<th>6 months*</th>
<th>12 months*</th>
<th>Yearly</th>
<th>PRN</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN/Cr/K+</td>
<td>Only if spiro used</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Lipids</td>
<td>X if clinically indicated</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>A1c or glucose</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin **</td>
<td></td>
<td></td>
<td>x</td>
<td></td>
<td>x</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>Only if symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>x</td>
</tr>
</tbody>
</table>

* In first year of therapy only
Expected effects and time frames

• Factors which predict both extent of and length of time to achieve feminizing effects:
  – Age at start
  – Genetics
  – Body habitus/shape

• Results are individualized and patients should avoid making comparisons to others

• Maintain reasonable expectations
  – Actual results may not meet desired effects
Monitoring “sex specific” labs

- Hemoglobin/hematocrit (“H&H”)
- Creatinine
- Alkaline phosphatase

- All may vary depending on sex hormone milieu
- Transgender women:
  - May retain elevated muscle mass (Creatinine)
  - May retain higher bone mass (Alkaline phosphatase)
  - Do not menstruate (hemoglobin/hematocrit)
  - Modify reference ranges accordingly (see table) (9)
Sex-specific reference ranges for non-hormone labs

<table>
<thead>
<tr>
<th>Lab measure</th>
<th>Lower Limit of normal</th>
<th>Upper Limit of normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>?</td>
<td>Male value</td>
</tr>
<tr>
<td>H&amp;H</td>
<td>Female value</td>
<td>Male value</td>
</tr>
<tr>
<td>Alk Phos</td>
<td>?</td>
<td>Male value</td>
</tr>
</tbody>
</table>
Tobacco

• Smoking in the setting of any estrogen use is a risk factor for venous thromboembolism (VTE)

• What if unwilling or unable to quit?
  – Harm reduction approach
  – Transdermal estradiol (lower VTE risk)
  – Aspirin 81mg/day
    • Risk/benefit ratio for gastrointestinal hemorrhage is unknown
Pituitary adenoma

• Several cases have been reported in transgender women (19)

• However, Endocrine Society guidelines recommend watchful waiting only in cases of asymptomatic prolactinomas (20)

• Therefore in the absence of visual disturbances, galactorrhea, or headache syndromes, routine monitoring of prolactin not likely of clinical value
Migraines

• Migraines have a clear hormonal component

• Patients with hx of complex/severe migraines should begin at low dose and titrate slowly

• Oral or transdermal routes may be preferred to avoid cyclic levels seen with injected estrogen (24)

• Unclear if the known increased risk of stroke in patients using oral contraceptives with a history of aura applies to transgender patients using 17-beta estradiol
Use of estrogens in the perioperative period

• No clear evidence that transgender women at average risk of VTE should stop estrogen in the perioperative period
  – Lowering dose or changing to transdermal route may be advisable (27)

• Studies of risks of perioperative oral contraceptives (ethinyl estradiol) have mixed results and methodological limitations (28)

• Stopping hormones abruptly in the setting of major surgery and gonadectomy can have negative impact
Venous thromboembolism – data from menopause literature

• Menopausal studies suggest no increased risk when transdermal estradiol used (29)

• Menopausal data on oral 17-beta estradiol is mixed, with risks as high as 2.5-4x increase (10,29)
  – With a background rate of 1:1,000 to 1:10,000 in general population, absolute increase is small (4)
Venous thromboembolism – mediating factors

• Risk may relate to choice of progestagen (10)
  – Norethindrone and other norpregnanes may confer 4x increased risk
  – Medroxyprogesterone may not increase risk

• Risk may be reduced in setting of 17-beta estradiol tablets by using sublingual route

• Equine estrogens may confer increased risk (1,2)
Venous thromboembolism – data in transgender women

• Studies > 10 years old showing 20 to 40 fold increase involved use of up to 200mcg/day of ethinyl estradiol, and did not control for tobacco use (30,31)
  – These studies are not applicable to modern 17-beta estradiol regimens used in an average risk, non-smoking population

• No increased risk has been observed in a large retrospective sample of Dutch transgender women using 17-beta estradiol (5)
Primary and secondary prevention of VTE

• Insufficient evidence to guide the use of estrogen therapy, anticoagulation, or antiplatelet therapy in transgender women with risk factors or personal history of DVT

• Case series of 11 transgender women with activated protein C resistance using transdermal estradiol without anticoagulation or antiplatelet therapy found no VTE after mean 64 months (32)
Primary and secondary prevention of VTE - scenarios

• Role of episodic (i.e. airplane flights) or long term anticoagulation/antiplatelet therapy should be considered in the context of risks of GI or intracranial hemorrhage.

• Routine VTE prophylaxis with ASA in unselected transgender patients not recommended.

• Routine screening for prothrombotic mutations not recommended in the absence of risk factors (32).

• Estrogen therapy should not be administered in patients with risk factors for or history of VTE who continue to smoke tobacco.
Masculinizing Hormones
Goals of therapy

• Development/emphasis of masculine secondary sex characteristics

• Elimination/minimization of feminine secondary sex characteristics
Masculinizing hormones – physical effects

- Development of facial and body hair
- Redistribution of body fat
- Increased muscle mass
- Deepened/masculine voice
- Increased perspiration, change in urine and body odors
- Frontal and temporal hairline recession, possible male-pattern baldness/crown recession
- Clitoral growth
Masculinizing hormones – other effects

• Increased libido
• Vaginal dryness and atrophy
• Cessation of menses
• Infertility/anovulatory state
• Possible changes in emotional and social functioning
Masculinizing hormones – general approach

- Use of one of several forms of parenteral testosterone

- Other adjuncts may include progestagens, 5-alpha reductase inhibitors or aromatase inhibitors
## Testosterone dosing

<table>
<thead>
<tr>
<th>Androgen</th>
<th>Initial – low dose $^b$</th>
<th>Initial - typical</th>
<th>Maximum - typical</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone Cypionate $^a$</td>
<td>20 mg/week</td>
<td>50mg/week</td>
<td>100mg/week</td>
<td>For q 2 wk dosing, double each dose</td>
</tr>
<tr>
<td>Testosterone Enthanate $^a$</td>
<td>20mg/week</td>
<td>50mg/week</td>
<td>100mg/week</td>
<td>“</td>
</tr>
<tr>
<td>Testosterone topical gel 1%</td>
<td>12.5-25 mg/day</td>
<td>50mg/day</td>
<td>100mg/day</td>
<td>May come in pump or packet form</td>
</tr>
<tr>
<td>Testosterone topical gel 1.62%</td>
<td>20.25</td>
<td>40.5 – 60.75mg/day</td>
<td>103.25mg/day</td>
<td>“</td>
</tr>
<tr>
<td>Testosterone patch</td>
<td>1-2mg</td>
<td>4mg</td>
<td>8mg</td>
<td>Patches come in 2mg and 4mg size. For lower doses, may cut patch</td>
</tr>
<tr>
<td>Testosterone cream</td>
<td>10mg</td>
<td>50mg</td>
<td>100mg</td>
<td></td>
</tr>
<tr>
<td>Testosterone axillary gel 2%</td>
<td>30mg</td>
<td>60mg</td>
<td>90-120mg</td>
<td>Comes in pump only, one pump = 30mg</td>
</tr>
<tr>
<td>Testosterone Undecanoate</td>
<td>N/A</td>
<td>750mg IM, repeat in 4 weeks, then q 10 weeks ongoing</td>
<td>N/A</td>
<td>Requires participation in manufacturer monitored program $^f$</td>
</tr>
</tbody>
</table>

$a$: Available as standard U.S. Pharmacopia (USP) as well as compounded products.  
$b$: Initial – low dose recommended for genderqueer and nonbinary dosing.
Intramuscular vs. subcutaneous routes

• Many providers have administered testosterone using the subcutaneous route with good efficacy and patient satisfaction, and without complications.

• Benefits of subcutaneous administration (3,4) :
  – Smaller and less painful needle,
  – May avoid scarring or fibrosis from long term (possibly > 50 years) intramuscular therapy.
Titration of dosing

• Assess patient goals, tolerance and response
  – Cessation of menses @ 6 mos is a useful clinical endpoint (3)

• Hormone levels can be helpful to guide therapy, especially in cases of side effects or perceived slow progress

• Once testosterone levels in mid-range of male norms (350-1000ng/dl), no likely benefit from increase in dose, unless symptoms of low testosterone (low energy/libido) or continued menses
Testosterone – monitoring hormone levels

• Avoid sub-optimal therapy
  – Clinical endpoints (cessation of menses, voice deepening, growth of facial hair) may under-estimate testosterone levels
  – One study found that 26/31 men achieved cessation of menses after 6 months of testosterone, while only 21/31 achieved male-range testosterone levels (4)

• For injected testosterone, note if peak, trough or mid-cycle level

• Be sure to use male normal range as a reference
Testosterone lab testing

• In most cases monitor only total testosterone

• Bioavailable testosterone:
  – Check if unusual or persistent symptoms or menses
  – Check if unexpected slow progress in the setting of normal total testosterone levels
  – Based on total testosterone, sex-hormone binding globulin, and albumin (5,6)
    • Sex hormone binding globulin is elevated in presence of estrogen and thyroxine, decreased in presence of androgens, prolactin, and high levels of insulin or growth hormone (7)

  – Calculator at http://www.issam.ch/freetesto.htm
Managing injected testosterone

• Use mid-cycle levels for general monitoring
• Use peak and trough in context of
  – Migraines
  – Pelvic cramping
  – Mood swings
  – Low energy

• For patients with wide peak-trough variation and related side effects, consider change to transdermal route, or adjusting dose to allow a shorter dosing interval (8,9)
Individualized approach

• Approach each patient individually, to assess their goals and expectations

• Avoid making guarantees of specific effects and time frames
  – General expect major changes in 1\textsuperscript{st} 1-2 years, but can continue for as many as 5 years (11)

• Age at start, body habitus/shape, and genetics all play a role in extent and rate of changes
Interpreting sex-specific, non-hormone labs

• Due to increased muscle mass, creatinine may be seen elevated into the male normal range.

• Due to erythropoietic effects, Hemoglobin and hematocrit may be seen elevated into the male normal range, especially if amenorrheic.

• Due to increased bone mass, alkaline phosphatase may be seen elevated into the male normal range.
## Interpreting sex-specific, non-hormone labs

<table>
<thead>
<tr>
<th>Lab measure</th>
<th>Lower Limit of normal</th>
<th>Upper Limit of normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>?</td>
<td>Male value</td>
</tr>
<tr>
<td>Hemoglobin/Hematocrit</td>
<td>Male value if amenorrheic*</td>
<td>Male value</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>?</td>
<td>Male value</td>
</tr>
</tbody>
</table>

* If menstruating regularly, consider using female lower limit of normal.
Management after gonadectomy

• Avoid routinely reducing testosterone dose after gonadectomy
  – Testosterone is dosed for complete replacement
  – Unless pt desires lower dose after oopherectomy, maintaining effects will require maintaining physiologic dosing

• For those who desire a lower dose after oopherectomy, titrate dose to maintain LH and FSH at pre-menopausal levels
Erythrocytosis / polycythemia

• May avoid risk by changing to a lower dose/more frequent dosing schedule with lower peak levels, or transdermal routes (8)

• Phlebotomy or donation of blood may be appropriate short term solution

• Pathologic erythrocytosis should be ruled out in all cases
  – Obesity related sleep apnea
  – Tobacco use
  – Neoplasm

• Be sure to use male range values
Coexisting metabolic disorders

- Metabolic syndrome
- Obesity
- Hyperlipidemia
- Impaired glucose tolerance
- Polycystic ovarian syndrome (PCOS)
Coexisting metabolic disorders

• PCOS is not a contraindication to testosterone therapy
  – Do maintain higher index of suspicion for hyperlipidemia and diabetes

• Amenorrhea in the presence of testosterone generally indicates endometrial atrophy (18,19) rather than hyperplasia
Coexisting metabolic disorders

• Psychosocial benefits of testosterone may include positive lifestyle changes which can reduce obesity and glucose and lipid disorders

• These benefits likely outweigh any potential increased metabolic risks
Acne

• Approach is similar to that in non-transgender people

• Acne tends to peak in 1\textsuperscript{st} year of therapy, then declines (20)

• Avoiding supraphysiologic levels, and avoiding excessive peaks associated with prolong (2-4 week) dosing intervals may help minimize acne
Mortality outcomes

• Largest publication to date is Dutch retrospective
  – Compared transgender women and men to natal sex controls
  – Primary outcome: mortality
  – Did not adjust for multiple covariates or use of ethinyl estradiol in the main analysis
  – Findings indicate most increased mortality unrelated to hormone therapy
    • Increase in CV mortality in transgender women should be considered along with benefits of hormone therapy
Table 2  SMR adjusted for age and period of follow-up on hormone treatment by biological sex in 1331 male-to-female and female-to-male transsexual subjects.

<table>
<thead>
<tr>
<th>Cause of death</th>
<th>Male-to-female transsexuals</th>
<th>Female-to-male transsexuals</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observed cases</td>
<td>SMR (95% CI)</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>28</td>
<td>0.98 (0.88–1.08)</td>
</tr>
<tr>
<td><strong>Lung</strong></td>
<td>13</td>
<td>1.35 (1.14–1.58)</td>
</tr>
<tr>
<td><strong>Digestive tract</strong></td>
<td>3</td>
<td>0.42 (0.28–0.60)</td>
</tr>
<tr>
<td><strong>Hematological</strong></td>
<td>6</td>
<td>2.58 (1.97–3.30)</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td>2</td>
<td>1.59 (0.95–2.46)</td>
</tr>
<tr>
<td><strong>Other: kidney, melanoma, bone, and prostate in MtF. In FTM: leiomyosarcoma</strong></td>
<td>4</td>
<td>0.79 (0.57–1.07)</td>
</tr>
<tr>
<td><strong>Ischemic heart disease</strong></td>
<td>18</td>
<td>1.64 (1.43–1.87)</td>
</tr>
<tr>
<td>Cerebrovascular accidents</td>
<td>5</td>
<td>1.26 (0.93–1.64)</td>
</tr>
<tr>
<td><strong>AIDS</strong></td>
<td>16</td>
<td>30.20 (26.0–34.7)</td>
</tr>
<tr>
<td>Endocrine/diabetes</td>
<td>2</td>
<td>0.85 (0.41–1.32)</td>
</tr>
<tr>
<td>Respiratory system diseases</td>
<td>4</td>
<td>0.85 (0.61–1.14)</td>
</tr>
<tr>
<td>Digestive system diseases</td>
<td>3</td>
<td>1.01 (0.68–1.45)</td>
</tr>
<tr>
<td>Genitourinary system disease (ESRD)</td>
<td>1</td>
<td>1.21 (0.58–2.17)</td>
</tr>
<tr>
<td>Nervous system disease (MS)</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>External causes</td>
<td>24</td>
<td>7.67 (6.84–8.56)</td>
</tr>
<tr>
<td><strong>Illicit drugs use</strong></td>
<td>5</td>
<td>13.20 (9.70–17.6)</td>
</tr>
<tr>
<td>Suicide</td>
<td>17</td>
<td>5.70 (4.93–6.54)</td>
</tr>
<tr>
<td>Unknown/ill-defined symptoms</td>
<td>21</td>
<td>4.00 (3.52–4.51)</td>
</tr>
<tr>
<td>Total</td>
<td>122</td>
<td>1.51 (1.47–1.55)</td>
</tr>
</tbody>
</table>

**CLINICAL STUDY**

**A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones**

Henk Asscheman¹, Erik J Giltay², Jos A J Megens², W (Pim) de Ronde¹, Michael A A van Trotsenburg² and Louis J G Gooren¹
Cancer screening - general approach

- Transgender people may have undergone surgical procedures

- Obtain an organ inventory on each patient to guide cancer screening
  - Rather than relying on “male” and “female” screening guidelines

- Organ based screening should proceed regardless of hormone use

- Lower quality data suggests no overall differences in rates of cancer between transgender people and non-transgender, birth-sex matched controls (1,2)
Breast cancer screening

• What (if any) are the modifications to current breast cancer screening recommendations in non-transgender women

• Ideal screening minimizes mortality and missed diagnoses, while avoiding the false-positive risks of overscreening
Breast cancer in transgender women – available evidence

• Retrospective study of 2,307 Dutch transgender women at single site
  – Incidence estimated at 4.1/100,000 person-years
  – Incidence in general Dutch female population is 155/100,000 person-years

• Retrospective study of 3,566 transgender women in US Veteran’s Affairs health system
  – Standardized Incidence Ratio (SIR) of 0.7 (95% CI 0.03 to 5.57) compared to non-transgender females and SIR of 33.3 (95% CI 21.9 to 45.1) compared to non-transgender men

Recommendations – breast cancer screening for transgender women

• Expert panel (UCSF Center of Excellence for Transgender Health Medical Advisory Board) recommendation to commence screening only in those over age 50 who have had a minimum of 5 years of lifetime estrogen exposure
  – Some providers may choose to discuss the risks and benefits of delayed screening, and wait until a minimum of 10 years of lifetime estrogen exposure
Endometrial Cancer

- Anovulatory state + aromatization of testosterone could result in unopposed estrogen and theoretical risk of hyperplasia or cancer
  - There have been few case reports (3)
- Histologic studies support endometrial atrophy in setting of testosterone administration (4,5)
Endometrial Cancer – Screening?

- Recommendation for endometrial surveillance in amenorrheic transgender men is not evidence based
- Transgender men should be educated to inform their provider of any irregular bleeding, or return of bleeding after amenorrhea on testosterone
Endometrial Cancer – Role of Hysterectomy

• Hysterectomy for primary prevention of endometrial cancer is not recommended

• Hysterectomy may be considered on a case-by-case basis for
  – Management of gender dysphoria
  – Elimination of need for cervical cancer screening in those unwilling to undergo
Ovarian Cancer - Risk

• Currently limited to several case reports (11,12)
• Testosterone does cause histologic changes in the ovary (4,7)
• Transgender men have been found to have increased rates of PCOS (8-10) at baseline
  – However recent data suggests no increased risk of ovarian cancer in non-transgender women (Sept 2014 meta-analysisi see Barry, JA, Hum Repro Update Sep-Oct)
Ovarian Cancer – Screening, Prevention and Evaluation

• There are no current recommendations for routine ovarian cancer screening in non-transgender women of average risk

• Routine oopherectomy with the sole purpose of primary prevention of ovarian cancer is not recommended

• If ovarian imaging is required after vaginectomy, transabdominal or trans-rectal route can be used
PrEP and transgender women – iPrEx subanalysis

• 339 TGW randomized

• TGW compared to MSM
  – Lower education level (p<0.001)
  – More sexual partners (p<0.001)
  – More condomless receptive anal sex (p<0.001)
  – More likely to report STI in last 6 mos (p<0.001)
  – More likely to report transactional sex (P<0.001)
  – More likely to report meth/cocaine (p<0.001)
  – More likely to live alone


HIV pre-exposure prophylaxis in transgender women: a subgroup analysis of the iPrEx trial.
Deutsch MB, Glidden DV, Sevelius J, Keatley J, McMahan V, Guanira J, Kallas EG, Charialertsak S, Grant RM; iPrEx investigators.
iPrEx RCT – results of transgender subanalysis

• Intention to treat
  – 11 seroconversions in the intervention group vs 10 in the placebo group

• As treated
  – None of the TGW who seroconverted had protective drug levels at the time of detection

• Random drug levels
  – Trans or woman ID less likely than MSM to have always detected (P=0.04, OR=0.39, 95% CI 0.16 to 0.96)
iPrEx OLE – Results of transgender subanalysis

- 1603 eligible (192 TGW)
- 1225 participated (151 TGW)
- PrEP uptake comparable to MSM
  - (79% vs 76%, p=0.45)
- TGW less time with protective drug concentrations vs MSM
  (17% vs 35%, P<0.001)
- Among all TGW, trend toward fewer having concentrations indicating > 3 tablets/week vs MSM (OR -0.71, 95% CI 0.49 to 1.03, p=0.07).
iPrEx OLE – Results of transgender subanalysis (continued)

• TGW using hormones less likely to have any (OR 0.32, p=0.002) or protective (OR 0.14, P<0.001) drug levels compared to TGW not using hormones

• TGW using hormones less likely to have any (OR 0.41, p=0.003) or protective (OR 0.10, P<0.001) drug levels compared to MSM

• No difference by use of 17-beta estradiol vs synthetic estrogens (p=0.74)
iPrEx OLE – results of transgender subanalysis (continued)

• 2 TGW seroconversions
  – 1 had DBS below limit of detection
  – 1 had DBS < 2 pills/week
Non-condom Anal Intercourse and Consistency of PrEP Drug Detection

![Graph showing the percent of participants for different categories of sexual orientation and drug usage.](image)
Hormones & ART

• Transgender women may prioritize hormone therapy over other aspects of health and healthcare

• Concerns over interactions with hormones and ART may lead to reduced ART adherence
  – Study of PrEP in transgender women found that hormone therapy was associated with odds ratio of 0.32 (p=0.002) for having drug detected

• Other possible interactions
  – Pill burden?
  – Effects of ART on hormone levels and symptoms?
    • Kearney BP, Mathis A. Pharmacotherapy. 2009 29(8), 924–929

  – Negative effect of hormones on ART is unlikely
No Results

No significant interactions found.

Caution is always advised with multiple medications.
Kalen

- 20 year old “female” patient of yours for the past 2 years comes in asking to begin testosterone.
Alex

- 24 year old patient, new to you and just beginning graduate school, with a male birth assigned sex, comes to see you to discuss estrogen therapy
Izzy

• 17 year old freshman with a genderqueer/non-binary identity comes to see you in late August seeking to begin low dose testosterone
Emily

- 22 year old transgender woman on hormones for 3 years, who is a transfer student and is new to the university, comes to see you to discuss breast augmentation surgery
Transhealth.UCSF.edu

Increasing access to comprehensive, effective, and affirming healthcare services for trans and gender-variant communities

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Learn how we work to improve trans health

Learning Center
Access current guidelines, articles, and online learning

Connect
Find partners, services, and leaders in the field

Calendar
See what's happening in trans health

OUR TOPICS
Routine care
HIV prevention
Cultural competency
Mental health
Policy

WHO WE SERVE
Healthcare providers
Researchers
Community organizers
Transgender persons

Transgender Health Services at UCSF
Primary care services now available at UCSF Mt. Zion with Dr. Maddie Deutsch, an expert in transgender and gender non-conforming primary and hormone care.

Learn more>

EVENTS
2013 United States Conference on AIDS
USCA is the largest AIDS-related gathering in the U.S., bringing together over thousands of workers from all fronts of the HIV/AIDS epidemic, from case managers and physicians, to public health workers and advocates, people living with HIV/AIDS (PLWHAs) and policymakers, to build national support networks, exchange the latest information and learn cutting-edge tools to address the challenges of HIV/AIDS.

OUR PROGRAMS

catch
Sherpas
Primary Care Protocols Project
TRANSITIONS
The UCSF Transgender Care Navigation Program is a collaboration between The Center of Excellence for Transgender Health and the National Center of Excellence in Women's Health. Both Centers work together with partner providers and clinics to assist transgender, gender nonconforming, and nonbinary people seeking general healthcare or gender affirming medical care at UCSF.


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