Metabolic Issues in Transgender Women Living With HIV

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Disclosures

-No relevant financial disclosures

Learning Objectives

- Understand metabolic issues relevant to trans women on feminizing hormonal therapies (FHT).
- Understand potential intersections between metabolic disease, FHT and HIV/ ART.
- Be introduced to other health “highlights” for trans women on FHT and living with HIV.

Terminology Refresher

- “Trans” is short for transgender in lay language
- Transgender is correctly used as an adjective
- Transgender Man: A person who was assigned female sex at birth but identifies and lives as a male.
- Transgender Woman: A person who was assigned male sex at birth but identifies and lives as a woman.

Q: What Do We Know About The US Transgender Population?

A: Very little!

- Traditional estimate: ≈0.6%[1,2] US population, but very little history of systematically trying to capture this info
- 15,000 active duty military, 135K veterans
- Transgender women (TW) in US are 34x more likely to contract HIV[3], prevalence 22% in 2013 vs 0.5% in general adult population[4]
- Transgender persons have highest rates of new HIV infections in US[4]
- 50% of transgender persons living with HIV (PLWH) are in the US South[4] (most are TW)

[1]The Williams Institute, 2016. [2]Am J Public Health 2017;107:216. [3]Lancet Infect Dis 2013;13:214–222. [4]CDC

Providing Care in a Relatively Data Free Zone

HIV

Trans health care

HIV + Trans health care

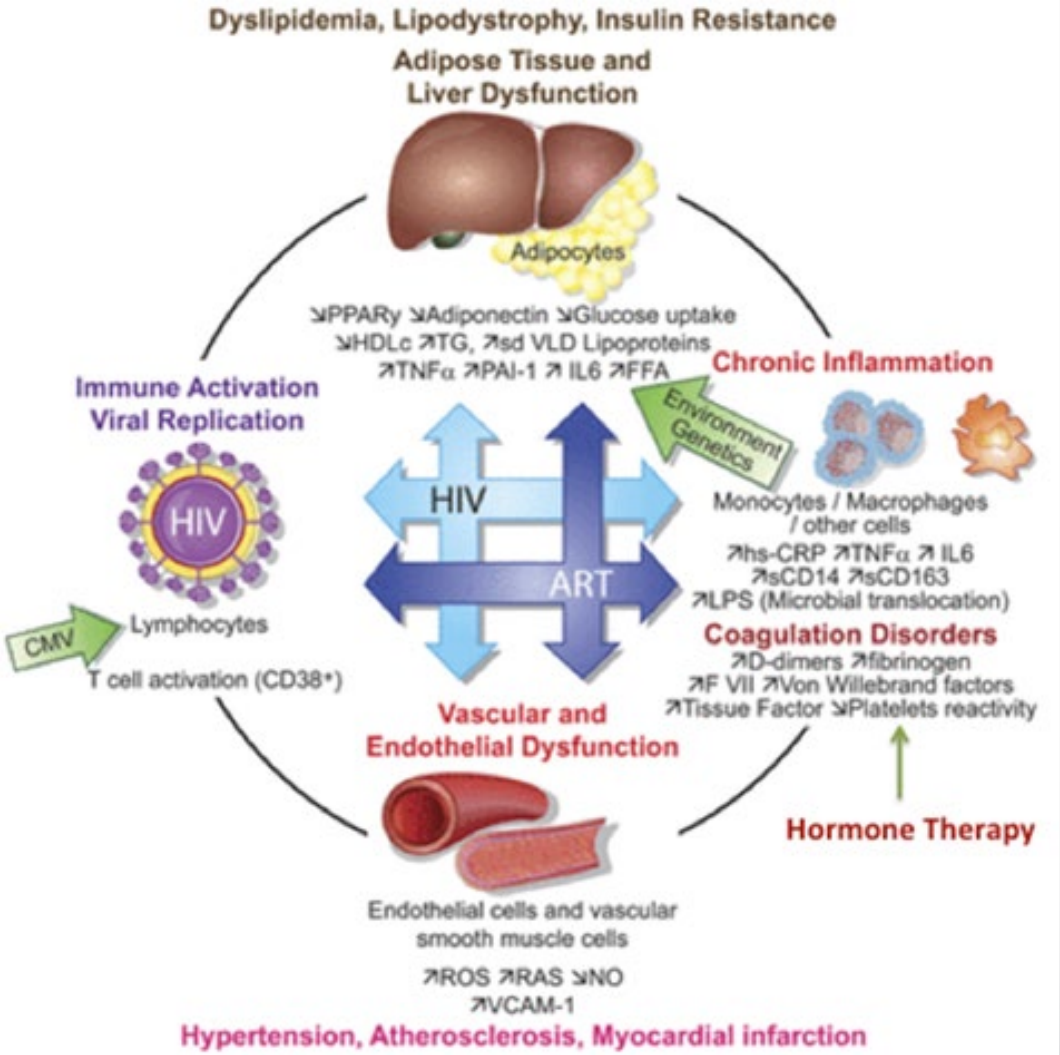
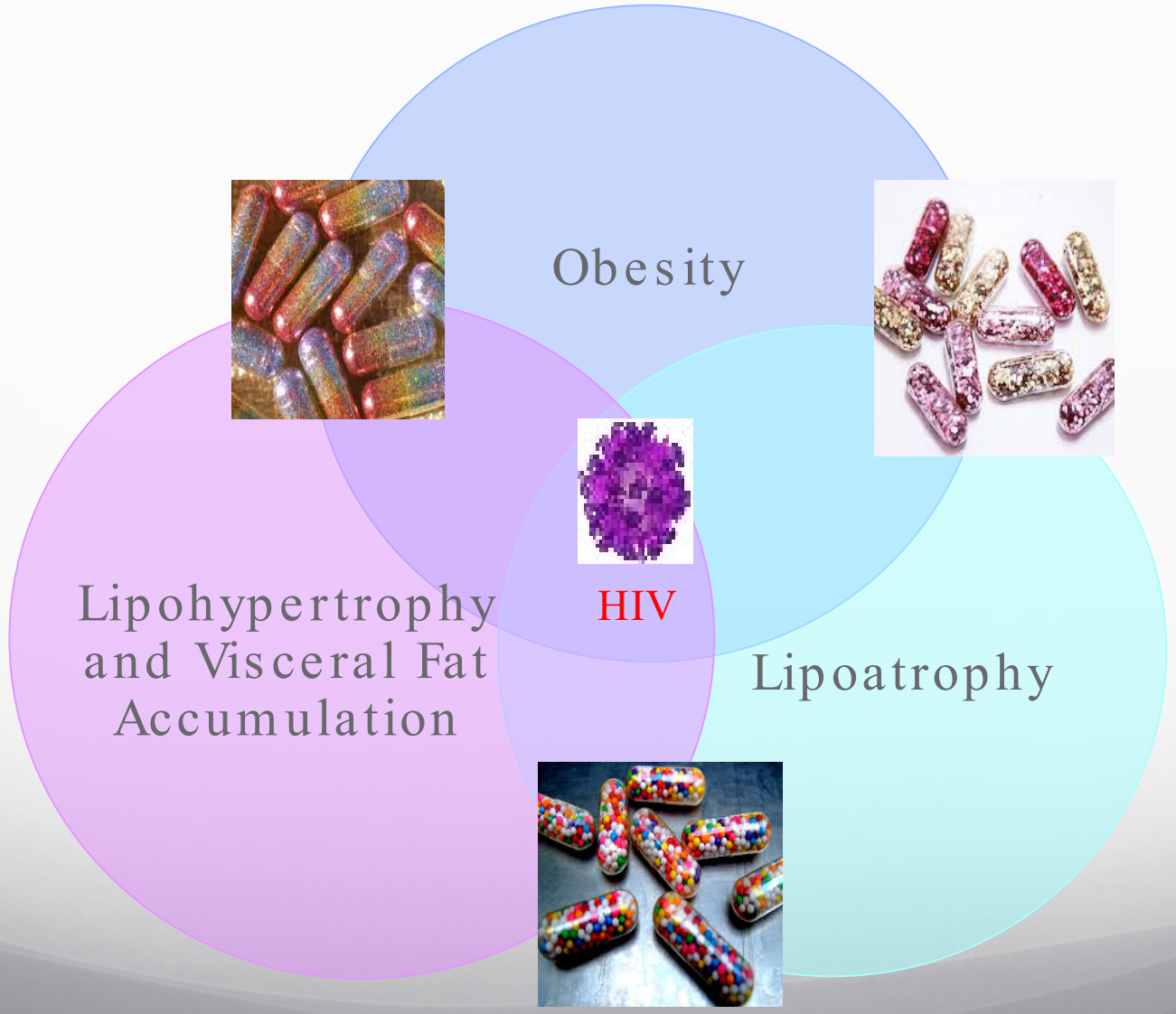


Figure 1. Contributions of HIV and FHT to metabolic and inflammatory disease. Adapted from Hemkens and Bucher. Eur Heart J. 2014.

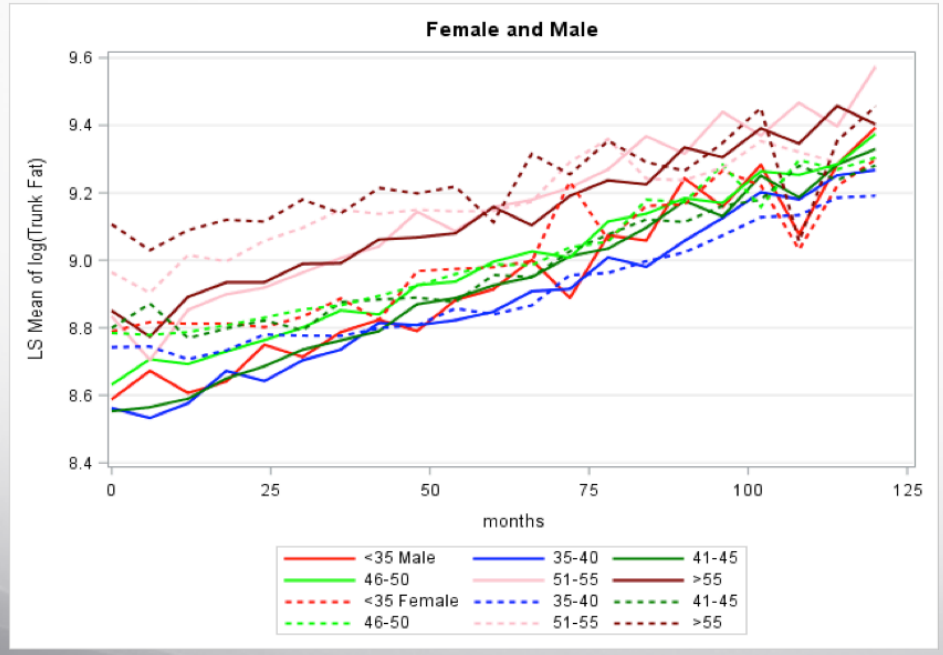
Body Composition: Intersecting Types of AT Dysfunction in HIV



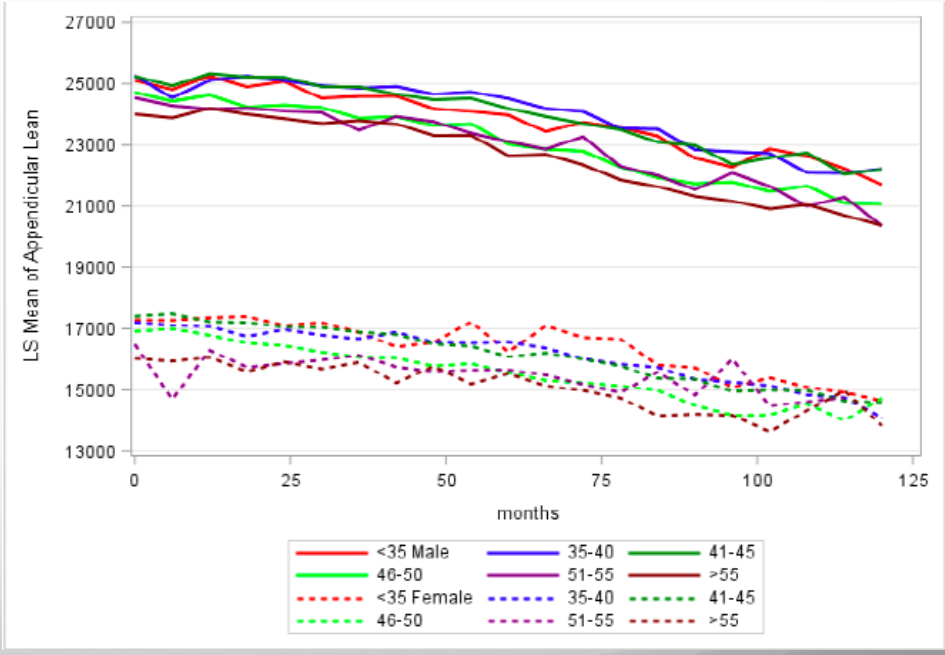
Body Composition in the Modern ART Era

HIV:

- Fat and lean mass loss in untreated HIV infection
- Fat gain and lean mass loss in treated HIV infection



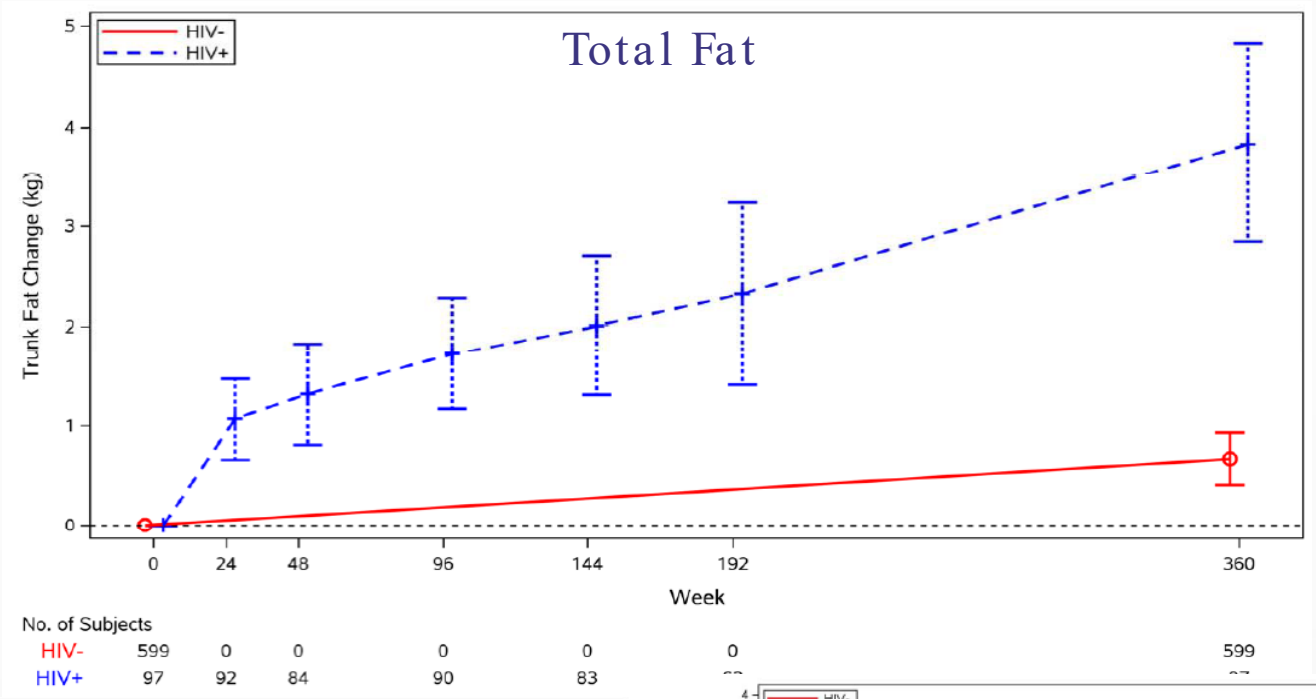
Trunk Fat

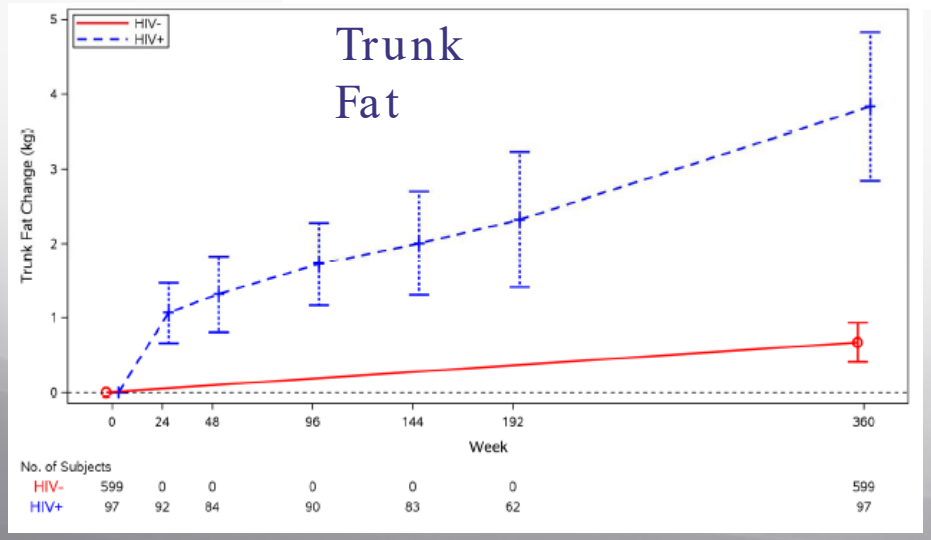


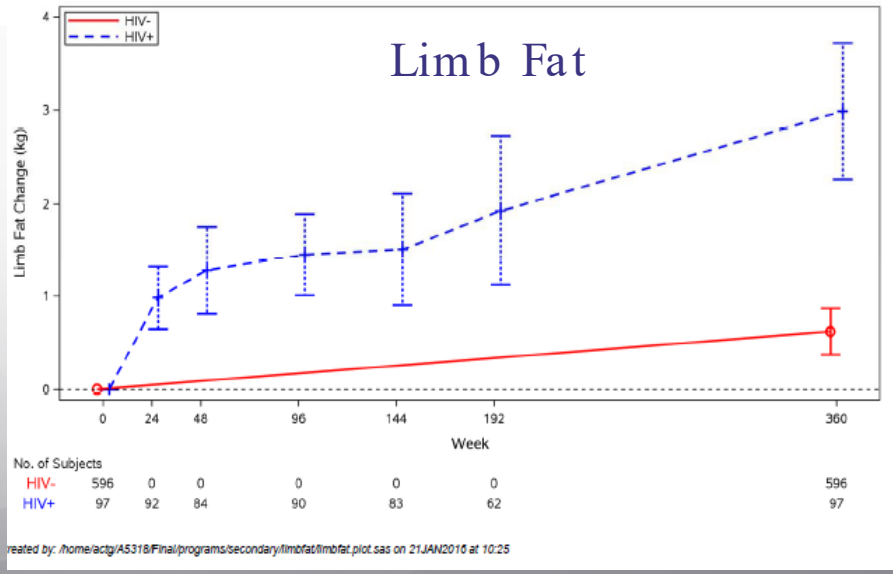
Appendicular Lean Mass

Lake et al. Unpublished data.

Fat Gain PLWH vs HIV- Controls







Grant PM et al. AIDS. 2016 Sep 20.

Body Composition

Trans Women on FHT:

- Visceral (VAT) and subcutaneous (SAT) fat gain and lean mass loss with estrogens and/or testosterone suppression
- Obesity rates increase with FHT
- Progesterone associated with:

  -fat gain

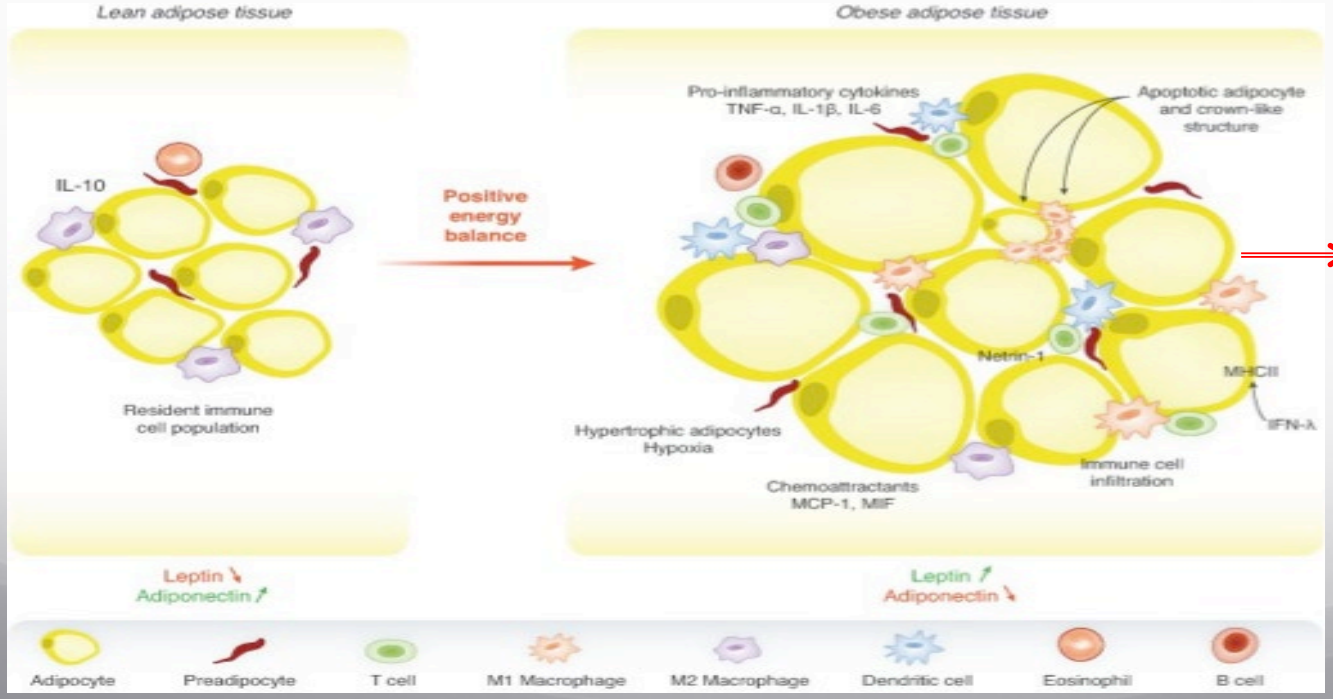
  -increased appetite

  -amplified by estrogen

Body Composition

FHT increases adipocyte size[1]:

- Suggests adipocytes hypertrophy with FHT
- Hypertrophy associated with insulin resistance, diabetes and dysfunctional fat



-Tissue hypoxia
-Adipocyte necrosis
-Metabolic dysfunction
  -IR
  -reduced glucose uptake
  -lipolyisis
  -ffa release

[1]Elbers et al. Metabolism. 1999;48(11):1371-7

Body Composition

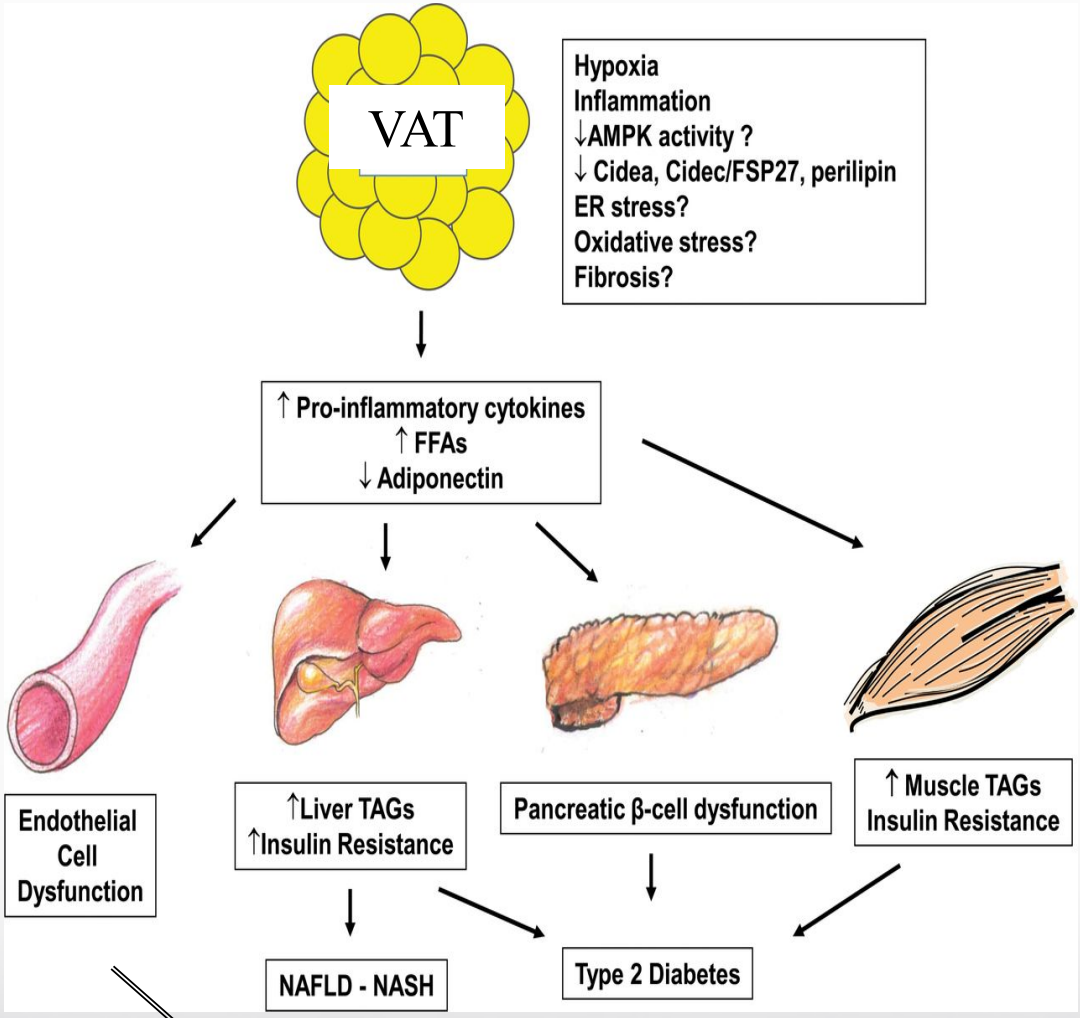
Spironolactone:

- main effect is to block aldosterone action at nephron mineralocorticoid receptor
- secondary effect is increased glucocorticoid activity
- anti-androgen effects through peripheral testosterone to estrogen conversion (breast growth and suppressed libido, erectile function and hair growth)

-Could spironolactone add to estrogen-induced body comp changes?

-Increased glucocorticoid activity could be associated with increased visceral fat, increasing metabolic syndrome risk.

VAT Expansion Associated With Multiple Comorbid Diseases



Adapted from Gauthier MS, Ruderman NB. Biochemical Journal. 1 Sept 2010; 430(2):e1-e4.

What About Sarcopenic Obesity?

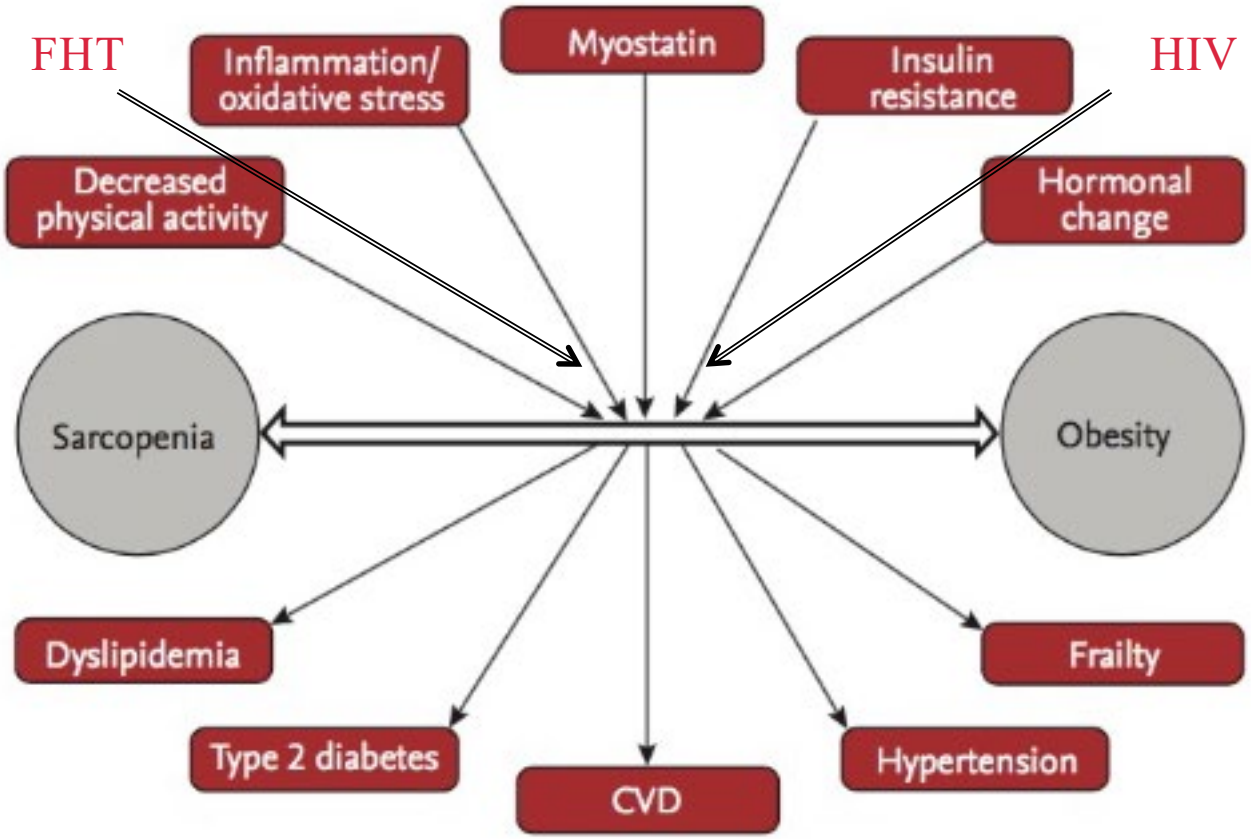


Figure 1. Mechanisms and consequences of sarcopenia and obesity. CVD, cardiovascular disease.

Kyung Mook Choi. Korean J Intern Med 2016;31:1054-1060.

Lipids

HIV:

- Lipid disturbances associated with both HIV and ART

FHT:

- 17-α-ethinyl estradiol biggest culprit
- Lower LDL and oxidized LDL[1,2]
- Lower HDL and higher triglycerides[3,4]
- Anti-androgens have similar LDL effects[5]

[1]Gooren et al. Eur J Endocrinol. 2014;170(6):809-19. [2]Topcuoglu et al. J Exp Med. 2005;205(1):79-86. [3]Wilson et al. Maturitas. 2009;62(3):281-6. [4]Elamin et al.. Clin Endocrinol (Oxf). 2010;72(1):1-10. [5]Traish AM. Adv Exp Med Biol. 2017;1043:473-526.

Insulin Sensitivity

HIV:

- Disruptions of hepatic and peripheral insulin sensitivity described in PLWH and with ART

FHT:

- Worsened by estrogens
- Worsened by testosterone deprivation
- Progesterone has weak glucocorticoid agonist properties

Elbers et al. Clin Endocrinol (Oxf). 2003;58(5):562-71.Traish AM. Adv Exp Med Biol. 2017;1043:473-526.

Hepatic Steatosis

HIV:

- Common in PLWH
- D4T is main ART culprit, but weight gain on ART may predispose
- Other HIV-specific factors not well understood
- Worsens dyslipidemia and insulin resistance

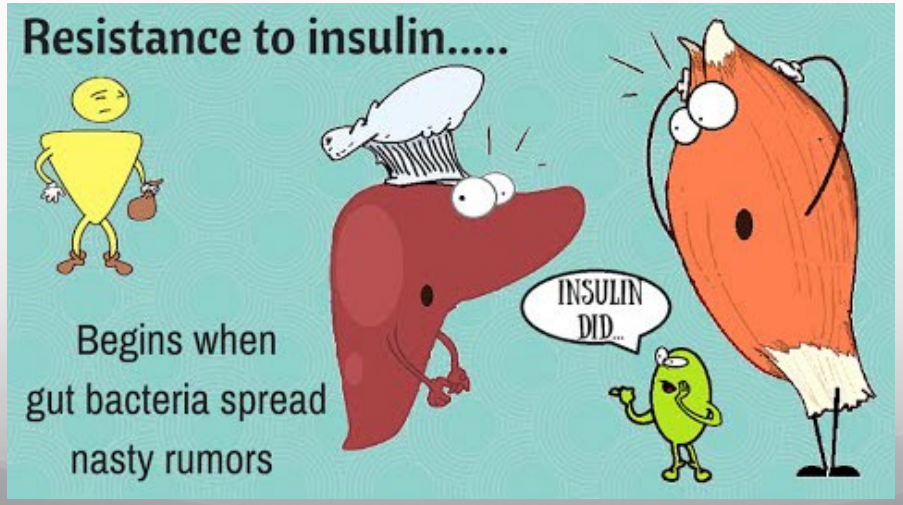
FHT:

- Worsened by testosterone deprivation[1]
- Estrogen deprivation therapy and menopause associated with increased risk

[1]Traish AM. Adv Exp Med Biol. 2017;1043:473-526.

Estrogen, HIV and the Microbiome

- Gut microbiome regulates deconjugation of estrogen to its active forms.
- Disease that lead to decreased gut microbial diversity (HIV!) prevent this, lowering estrogen levels.
- Decreased estrogen levels believed to contribute to development of metabolic disease in post-menopausal women.[1]



[1]Baker et al. Maturitas. 2017 Sep;103:45-53. [2]Chen et al. Trends Endocrinol Metab 2016;27:752-755.

Estrogen, HIV and the Microbiome

- Estrogen therapy can increase microbial diversity[2] and improve gut barrier integrity.[1]
- Estrogen can reduce LPS-induced inflammation.

So could FHT improve HIV-associated microbiome dysfunction and inflammation?

[1]Baker et al. Maturitas. 2017 Sep;103:45-53. [2]Chen et al. Trends Endocrinol Metab 2016;27:752-755.

Cardiovascular Disease

HIV:

- Increased risk with HIV +/- ART effects
- High rates of traditional risk factors in PLWH

FHT:

- Increased risk of thromboembolic disease
- 3-fold increase CVD death rate with current FHT
- Risk highest with combined estrogen/anti-androgen therapy vs estrogen alone
- Risk higher with oral than transdermal estrogens.

Asscheman et al. Eur J Endocrinol. 2011;164(4):635-42. Gooren et al. J Sex Med. 2014;11(8):2012-9. Stegeman et al. BMJ. 2013;347:f5298.

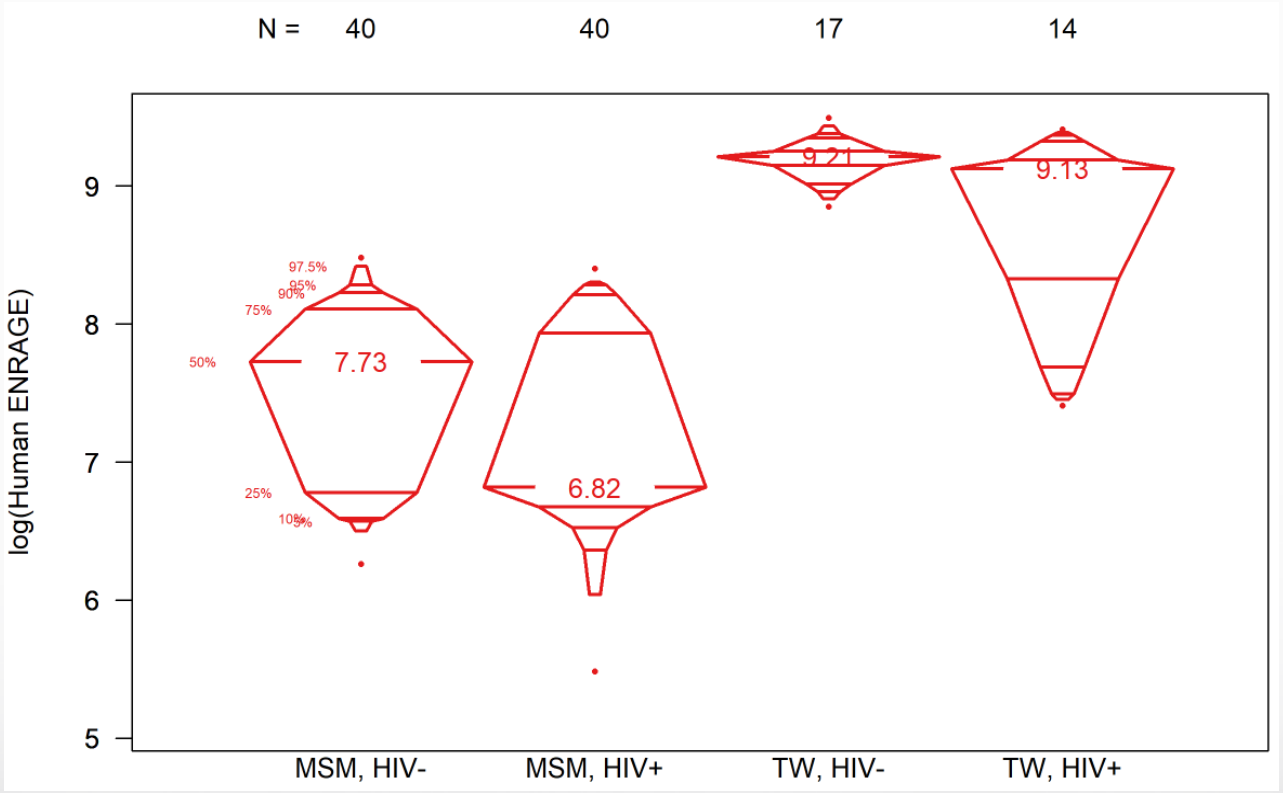
Age-adjusted comorbidity prevalence among TW compared to sex-matched controls

	Trans women before HRT[a]	Trans women	Age-matched control men	Age-matched control women	*P* men	*P* women
VT and/or PE	9.2	60.7	–	–	–	–
Myocardial infarction	4.7	18.7	12.5	0	NS	0.001
TIA/CVD	4.7	23.4	9.4	14.9	0.03	NS
Obesity	56.0	116.8	92.0	107.6	NS	NS
Type 2 diabetes mellitus	37.3	42.0	6.2	14.9	0.04	0.021
Cancer	18.7	28.0	21.9	24.9	NS	NS

- Dramatic risk increase before and after HRT
- Risk greater than controls after FHT

Wierckx et al. Eur J Endocrinol. 2013;169(4):471-8.

CVD Biomarker EN-RAGE* Higher in TW Regardless of HIV Serostatus



*ligand for the receptor for advanced glycation end products

Lake et al. Unpublished data.

Other Effects

HIV and FHT both:

- -increase systemic inflammation
- -alter coagulation pathways
- -cause altered endothelial function

Plus, trans women have high rates of:

- -tobacco use
- -substance use
- -food an housing insecurity

A Note About Finasteride

- Used as an alternative anti-androgen
- May contribute to hepatic steatosis by blocking T conversion to DHT[1]
- Increases:[2,3]

  -glucose, HbA1c, insulin resistance

  -AST/ ALT

  -LDL and total cholesterol

Traish AM. Adv Exp Med Biol. 2017;1043:473-526. [2]Traish et al. Horm Mol Biol Clin Investig. 2017 Jun 21;30(3). [3]Duskova et al. Endocr Regul. 2010 Jan;44(1):3-8.

HIV and FHT: The Perfect Storm?

So Where Do We Intervene?

- Aspirin?
- Metformin?
- Intensive lifestyle?
- All of the above?
- None of the above?

Q: Should we withhold FHT from TW with high metabolic disease/ CVD risk?

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Q: Should we withhold FHT from TW who smoke?

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Q: Should we withhold FHT from TW who smoke?

A: Informed consent is the current standard of care.

Other Medical Care Points

- CVD risk prevention

  -tobacco use

  -ASA

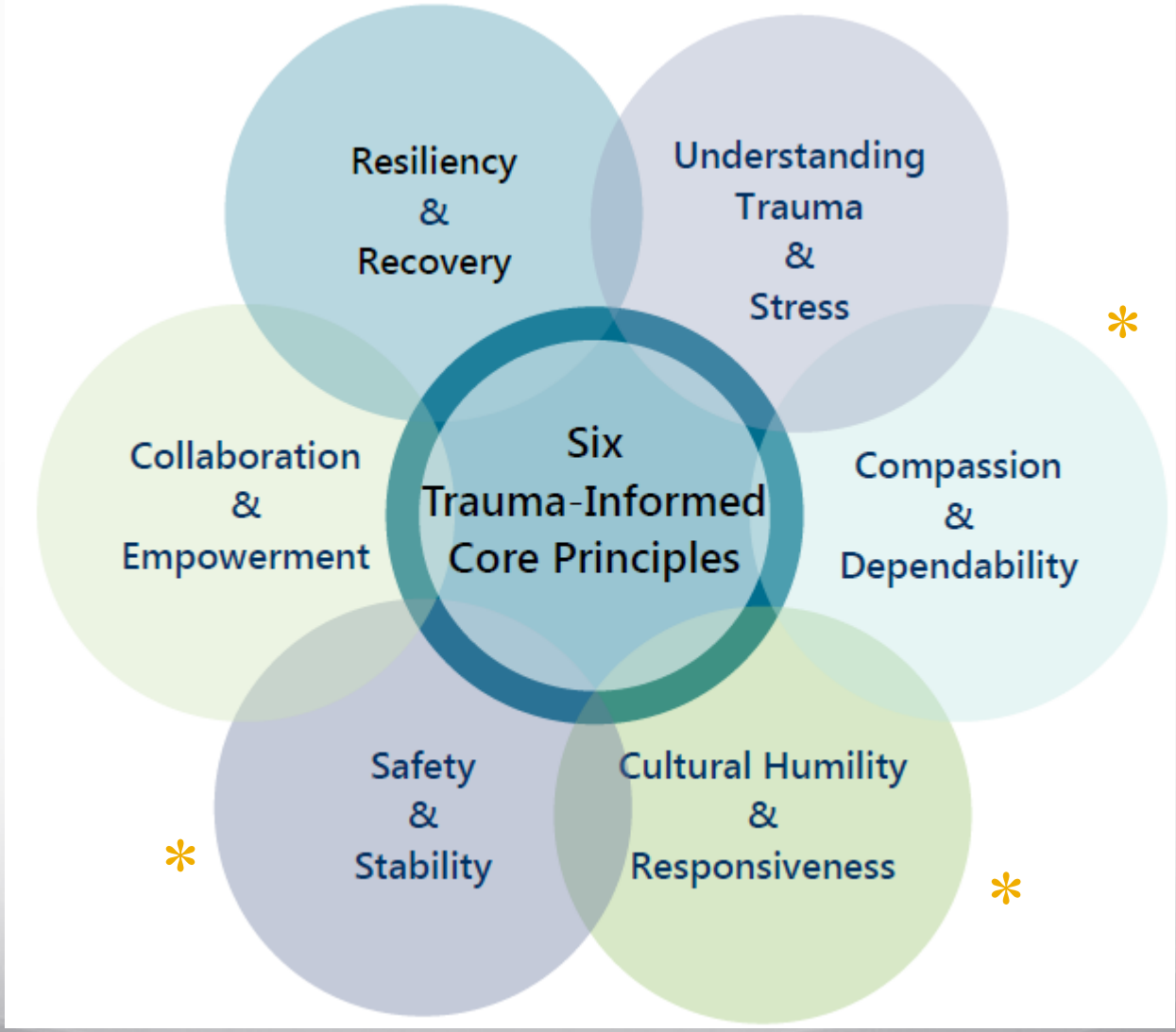
  -lipid-lowering

- Manage HIV transmission risk factors (includes sharing needles for estrogen administration)

- Manage depression/mental illness

- Evidence supports reduced suicide risk and better engagement in HIV care when access to hormones is in place

A Note About Trauma-Informed Care



Other Medical Care Points

- Drug-drug interactions (DDIs) between FHT and ART primarily studied at levels used for birth control and post-menopausal replacement therapy
- No good studies at the FHT doses used by many TW
- Many TW believe there are DDIs. Of 87 TW (54% PLWH)[1]:

  -25% (HIV- 13%, HIV+ 34%) reported unsupervised FHT -
  57% of TW with HIV reported concern for ART-FHT DDIs

  -only 49% had discussed ART-FHT DDI with their provider

  -40% cited this concern as a reason for not taking ART, hormones or both as directed
- Anecdotally, we have heard fear of DDI as a reason to not use PrEP among TW

[1]LGBT Health. 2017 Oct;4(5):371-375.

Provider Resources

1. Me! Jordan.E.Lake@uth.tmc.edu

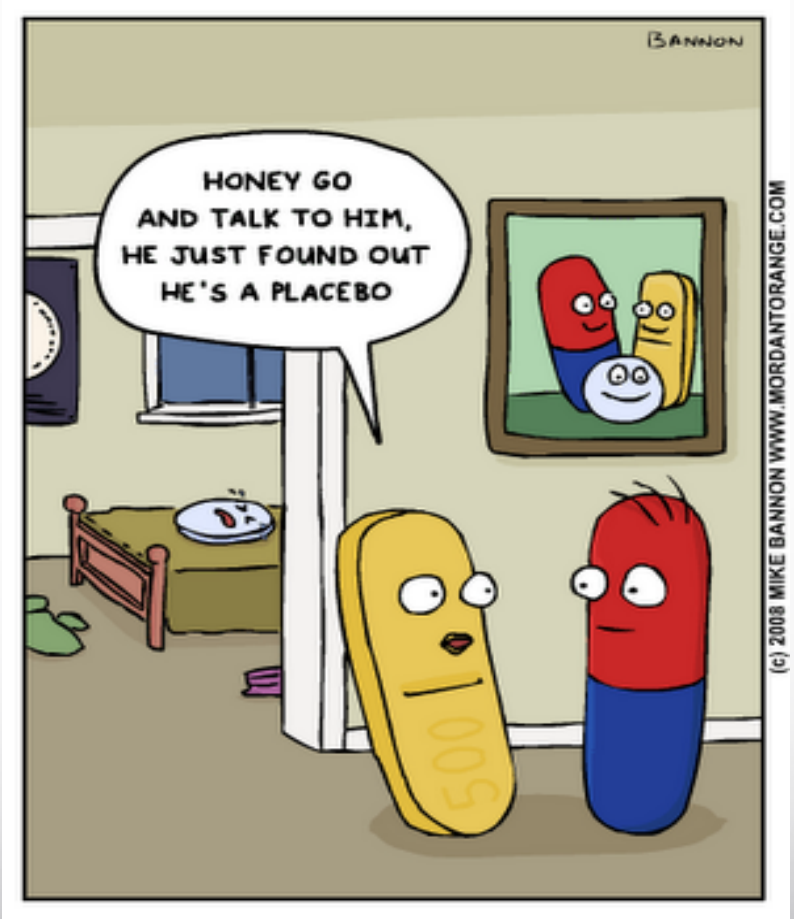
1. Standards of care:

   -World Provider Association for Transgender Health
   http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=3926

   -UCSF Center of Excellence for Transgender Health
   http://transhealth.ucsf.edu/trans?page=home-00-00

2. Fenway LGBT Education Center:
   https://www.lgbthealtheducation.org

Thank you!!


BANNON
HONEY GO AND TALK TO HIM, HE JUST FOUND OUT HE'S A PLACEBO
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