Testosterone Replacement Therapy & Monitoring in HIV Infected Men

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Background

- Global testosterone sales have increased 12-fold over the last decade
- US is the 2nd leading consumer worldwide[1].
- Androgen use tripled from 2001-2011 in the US, with 2.9% of men over 40 years of age on testosterone replacement therapy (TRT)[2].
- Establishing biochemical testosterone deficiency is recommended before TRT initiation[3], yet up to 83% of men on TRT lack pre-treatment testosterone measurements[4].

Background 2

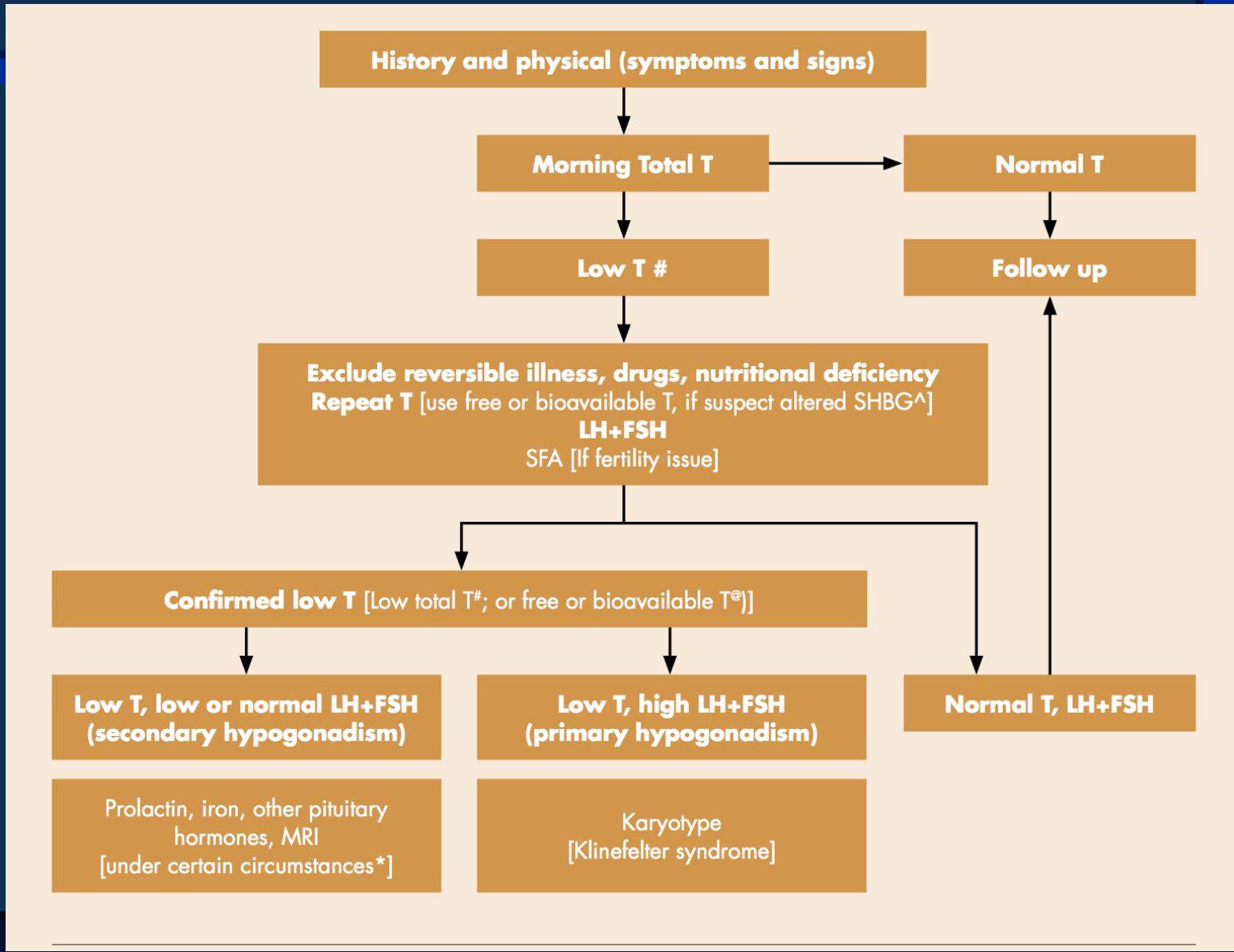
- TRT may increase the risk of cardiovascular events[7, 8], including myocardial infarction[9, 10], stroke[10], thrombosis[11], and death[10].
- HIV is associated with testosterone deficiency[12] in 20-70% of men, despite successful antiretroviral therapy (ART)[3,13]
- HIV associated hypogonadism is expected to increase as this population ages[14]

Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes:

An Endocrine Society Clinical Practice Guideline

Diagnosis in men with signs & symptoms & unequivocally low serum Testosterone level

Diagnostic evaluation of TD



Signs & Symptoms

A. More specific symptoms and signs

- Incomplete or delayed sexual development, eunuchoidism
- Reduced sexual desire (libido) and activity
- Decreased spontaneous erections
- Breast discomfort, gynecomastia
- Loss of body (axillary and pubic) hair, reduced shaving
- Very small (especially <5 ml) or shrinking testes
- Inability to father children, low or zero sperm count
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats

B. Other less specific symptoms and signs

- Decreased energy, motivation, initiative, and self-confidence
- Feeling sad or blue, depressed mood, dysthymia
- Poor concentration and memory
- Sleep disturbance, increased sleepiness
- Mild anemia (normochromic, normocytic, in the female range)
- Reduced muscle bulk and strength
- Increased body fat, body mass index
- Diminished physical or work performance

Confirmation

- Confirm the diagnosis by repeating measurement of morning total testosterone.
- Can add free or bioavailable testosterone in men with low normal levels or where **SHBG abnormality is suspected.**

Conditions associated with decreased SHBG concentrations

- Moderate obesity*
- Nephrotic syndrome*
- Hypothyroidism
- Use of glucocorticoids, progestins, and androgenic steroids*
- Acromegaly
- Diabetes mellitus*

Conditions associated with increased SHBG concentrations

- Aging*
- Hepatic cirrhosis and hepatitis*
- Hyperthyroidism
- Use of anticonvulsants*
- Use of estrogens
- HIV disease

If testosterone deficient…

Primary vs. Secondary

- If deficient check LH and FSH
- If high→ Primary TD
  - Check: Karyotype
- If low to normal → Secondary TD
  - Prolactin, Iron Saturation, pituitary function tests and MRI sella turcica to evaluate for secondary hypogonadism
- Refer to Endocrinology if abnormal otherwise treat

Primary Testicular Failure

- Testicular exam < 6ml
- Karyotype for Klinefelter syndrome
- DXA (BMD)

Do not start in men with…

- Breast or Prostate cancer
- Abnormal rectal exam or PSA
- Hematocrit > 50%
- Severe sleep apnea (untreated)
- Severe LUTS (>19 IPSS)
- Poorly controlled heart failure
- AAs & men with Fam History and PSA >3ng/ml should be referred to urologists first

Treatment

- Aim for mid-normal range 400-700ng/ml
- high & low levels predispose to side effects, residual symptoms, likely PCa and cardiovascular disease
- Need to be monitored (varies by treatment type)
- PSA at baseline and at 3-6 months, then per guidelines

Prostate Cancer

- Can give TRT if clinically localized prostate cancer post prostatectomy with stable PSA for 2 years.

Testosterone replacement therapy among HIV-infected men in the CFAR Network of Integrated Clinical Systems (CNICS). AIDS. Accepted.

CONCISE COMMUNICATION

+ HIV
+ Testosterone
+ Hypogonadism
+ Men's Health
+ Patient Monitoring
+ Testosterone Replacement Therapy (TRT)

Authors declare no conflicts of interest

Objectives

- The objectives of this study were to determine:
  - the rate of testosterone replacement therapy (TRT) initiation
  - TRT predictors
  - patterns of monitoring in HIV-infected men.

Study Design

- Multi-Site Cohort Study
- HIV + Men age > 18 followed in 1 of 7 CNICS sites from 1996-2011.
- Serum testosterone levels, sociodemographic, lab, clinical and medication data, BMI, smoking, alcohol use, and race/ethnicity.
- Excluded men already taking TRT or within 30 days of cohort entry or unknown initiation date
- Medication, chart abstraction, EMRs and pharmacy data for initiation dates.

Study Design 2

- TD = total testosterone < 300ng/dl[3]
  - free testosterone deficiency overlapped total testosterone
- We calculated TRT initiation rate as number of TRT initiation events per person-years (py) of follow-up time from cohort entry to initial TRT date, loss to follow-up, or death.
- TRT initiation predictors with univariable and multivariable Cox regression.

Results: Testosterone Supplementation

- 14,454 men without evidence of TRT prior to CNICS entry with 75,173 py of follow-up time.
- TRT was initiated in 1,482 (10%) men at a median age of 44 (IQR 38-51) years.
- The median time between cohort enrollment and TRT initiation was 868 days (IQR 280-1,907).
- Of the 1584 incident medications, 624 (39%) were intramuscular, 503 (32%) were transdermal, 1 (0.1%) was oral, and 456 (29%) were unspecified.

Results: TRT initiation

- We calculated a TRT initiation rate of 19.7/1,000 py (95% CI 18.7-20.7).
- Higher rates of TRT initiation were associated with:
  - age≥35y, White race, MSM (HIV risk factor), diagnosis of AIDS wasting, protease inhibitor (PI)-based ART, nadir CD4+ T-lymphocyte cell count (CD4)≤200 cells/mm^3, non-smoking, and absence of alcohol abuse.

Multivariate Predictors

- Age < 34 (HR 1.00)
  - Age 35- 50 (HR 1.58, CI 1.37-1.83)
  - Age > 50 (HR 1.82, CI 1.48-2.24)
- White Race (HR 1.72, CI 1.51-1.96)
- AIDS Wasting (HR 2.07, CI 1.64-2.60)
- Nadir CD_4 < 200 cells/mm^3 (HR 1.23, CI 1.02-1.49)
- PI based ART (HR 1.44, CI 1.23-1.68)
- Hep C (HR 1.2, CI 1.04-1.38)
- Not associated: MSM, Hep B, HIV viral load, BMI*, smoking or alcohol use

Assessment of Serum Testosterone

- 992 (67%) of the 1,482 men initiating TRT had pre-TRT serum total testosterone level measured
  - Median pre-treatment level was 358 (IQR 248-499) ng/dl.
  - Pre-TRT testosterone deficiency was found in 360 (24%).
- Serum total Testosterone was measured at least once after TRT initiation in 898 (61%)
  - Median maximum post-TRT level of 569 (IQR 370, 841) ng/dl.
  - Median time to first post-TRT serum total testosterone measurement was 303 (IQR 104, 885) days.
  - The first post-TRT serum total testosterone measurement occurred within six months of TRT initiation in 377 (25%) men.

PSA monitoring

- Over half (55%, 812/1,482) of those initiating TRT were above age 40. In this group, 273 (34%) and 97 (12%) had pre- and six month post-TRT prostate specific antigen (PSA) measurements, respectively.

We did not track

- Hematocrit levels
- Side Effect monitoring
- Erectile Dysfunction
- Bone Mineral Density

Conclusions

- **The rate of testosterone supplementation is higher than reported in the general population**
- **Treatment Is often not accompanied by appropriate laboratory testing**
- **Monitoring & follow up seem poor.**
- **Limitations: under-reporting of testosterone use,**
- **under-reporting of testosterone from outside labs, PSA controversies may effect clinical decisions**

Next Steps

- Explore rates of prostate cancer, advanced prostate cancer and treatment initiation rates for BPH/LUTS after TRT in HIV+ men.
- Explore rates of non-fatal and fatal MI in CNICS cohort

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