Longitudinal Changes in Free Testosterone among Older HIV-infected and HIV-uninfected Men

Laurence Slama[1,2], Lisa P. Jacobson[3], Xiuhong Li[3], Frank J. Palella, Jr[2], Joseph B. Margolick[3], Lawrence A. Kingsley[4], Dorothy Wiley[5], Gilles Pialoux[1], Adrian S. Dobs[3], Todd T. Brown[3]

[1]Tenon Hospital, UPMC, Paris, FRANCE, [2]Northwestern University, Feinberg School of Medicine, Chicago, IL, [3]Johns Hopkins University, Baltimore, MD, [4]University of Pittsburgh, Pittsburgh, PA, [5]University of California, Los Angeles, CA,

Introduction

- In the general male population, aging is associated with lower testosterone levels and a reduction in the diurnal variation of testosterone secretion
- The testosterone decline with aging may contribute to age-related comorbidities, including sexual dysfunction, sarcopenia, osteoporosis, glucose abnormalities and cardiovascular disease .
- Cross sectional studies have shown lower than expected testosterone levels among HIV-infected men
- It is unclear whether age-related longitudinal changes in serum testosterone differ by HIV-status
- We undertook a longitudinal nested cohort study with in the Multicenter AIDS Cohort Study (MACS) to determine whether age-related changes in testosterone levels differ among older HIV-infected and HIV-uninfected men.

Methods

Study Design

- The Multicenter AIDS Cohort Study (MACS) is an ongoing multi-center prospective observational study of U.S. men who have sex with men established by NIH in 1984.
- MACS sites include Baltimore, MD/Washington DC, Chicago, IL, Los Angeles, CA, and Pittsburgh PA.
- Participants are seen at semi-annual visits at which an interview, physical examination, and phlebotomy are performed.
- For this nested cohort study, serum samples from HIV-infected men who were ≥ 45 years at initiation of highly active antiretroviral therapy (HAART) were identified.
- To be included, each HIV-infected man was required to have at least one serum sample available prior to HAART-initiation (i.e. baseline visit) and ≥ 2 serum samples in the 10 years following HAART initiation. Visits at which exogenous testosterone use was reported were excluded
- Each eligible HIV-infected man was matched to an HIV-uninfected man by age, race, MACS site and calendar time of pre and post HAART samples

Laboratory Methods

- Testosterone was measured using liquid chromatographic-tandem mass spectrometry. SHBG was measured using radioimmunoassay. Free testosterone (FT) was calculated using the Vermeulen equation
- All assays were performed in the laboratory of Dr Shalender Bhasin (Boston University, Boston).

Methods

Statistical Methods

- Linear mixed effects regression with t-distributed error (with 2 degrees of freedom) was used to determine whether log FT and its rate of change over the study interval differed by HIV-status. A random intercept, assumed to be normally distributed, was included in the mixed model.
- Factors in multivariate models included HIV-status, years after baseline (HAART initiation) , age, race (white(reference), black, and Hispanic), study center, smoking status, history of diabetes mellitus, body mass index, hepatitis C status, and time of blood draw for FT measurements (morning or afternoon). Interaction terms of HIV-status * years-after-baseline and HIV-status * time-of-blood-draw were also included in multivariate models.

Study Subjects

- 306 HIV-infected men met the inclusion criteria for the study.
- Of those, 271 HIV-infected participants were matched with 271 HIV uninfected men.
- 89 HIV-infected and 4 HIV -uninfected men were excluded from our analysis because they had excessively high FT (>150 ng/dL) at >1 visit, suggestive of unreported exogenous testosterone administration.

RESULTS

Baseline Characteristics of HIV-infected and HIV- uninfected participants.

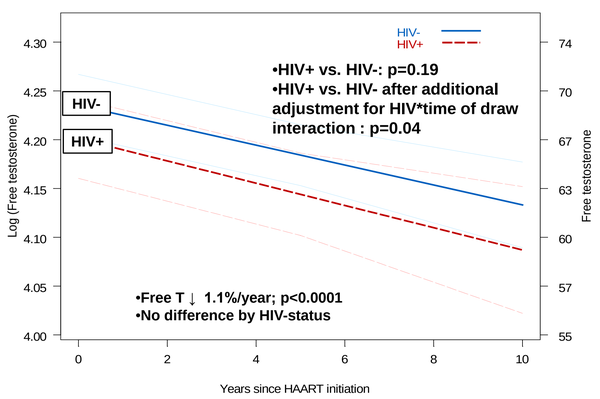
	HIV+ N=182	HIV- N=267	p-value
Race Caucasian	149 (82%)	227 (85%)	0.43
Body Mass Index (kg/m2)	25.1+/6	26.3+/-4	0.002
Diabetes Mellitus	16 (8%)	14 (5%)	0.14
Hepatitis C +	18 (10%)	10 (4%)	0.008
Mean AM FT, ng/dL, 95% CI	67 (65-71)	72 (69-74)	0.037
PM draw	70 (38%)	89 (33%)	0.26

Means +/- SD or percentage; p from t-test or Chi square test

- Median number of FT measurement per participants : 4 (IQR: 3,5)
- Median time of observation: 6 years (IQR: 2.9,9.5)

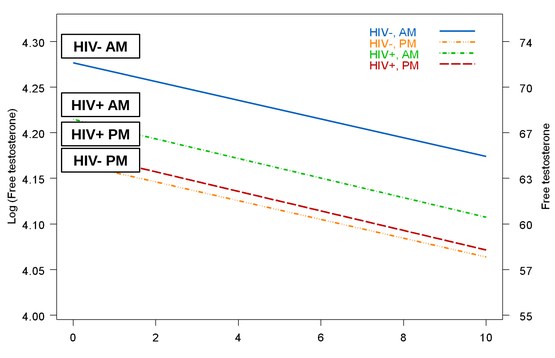
Results

Free testosterone over time by HIV-serostatus*



*additional lines represent 95% confidence intervals

Free testosterone over time stratified by HIV-serostatus and time of draw



- **FT declined significantly in both HIV-infected and HIV-uninfected men, but the annual rate of decline did not differ by HIV**
  - **-1.1% for HIV- infected men (95% CI: -0.4% , -1.8%) v. -1.0% for HIV-uninfected men (95% CI: -0.6%, -1.5%), p = 0.913**
- **When measured in morning samples, FT concentrations were lower among HIV -infected men than HIV-uninfected men**
  - **Baseline mean AM FT: HIV-infected men: 67 ng/dL (95% CI:65-71) v. HIV-uninfected men 72 ng/dL (95% CI: 69-74), p=0.037**
- **When measured in afternoon/evening samples, FT concentrations did not differ in HIV-infected and HIV-uninfected men**
  - **Baseline mean PM FT: 65 ng/dL (95% CI:62-69) v. 65 ng/dL (95% CI: 62-67), p= 0.728**

Summary & Conclusions

- **FT decreased similarly over a 6-year interval in older HIV infected and HIV-uninfected men.**
- **Morning FT levels were lower among HIV-infected men than HIV-uninfected men, but afternoon /evening FT levels did not differ by HIV-serostatus.**
- **Since free testosterone has its peak in the morning and nadir in the afternoon/evening, these data may suggest that, similar to aging, HIV-infection is associated with a loss of diurnal variation in FT.**
- **Further work is needed to confirm these findings by measuring FT in the morning and afternoon/evening in the same individual, to understand the mechanism, and to investigate the clinical significance**