TESTOSTERONE THERAPY AND SUBCLINICAL ATHEROSCLEROSIS PROGRESSION AMONG MEN WITH HIV

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BACKGROUND

- Testosterone therapy (TTh) use is high among older men with HIV (MWH) in the United States
- Long-term cardiovascular consequences of testosterone use are unclear, and none of the studies reported to date have included a defined sub-group of persons with HIV
- We assessed whether coronary atherosclerosis progression differs by testosterone use among MWH

METHODS

Source Population: Multicenter AISD Cohort Study (MACS) Established in 1984 & ongoing as MACS/WIHS Combined Cohort Study; men who have sex with men in 4 US metro areas

- MACS participants aged 40-70 years were evaluated for subclinical coronary plaque progression between baseline (2010-2013) and follow-up (2015-17) by cardiac CT angiogram (CCTA)
  - Median inter-scan interval=4.6 years
  - CCTA exclusion criteria: coronary revascularization, kidney disease, or contrast allergy

Testosterone Exposure

TTh use prospectively self-reported since 2000, categorized as:

TTh exposed in inter-scan period

- ONGOING users: TTh in prior & interscan period
- NEW users: TTh in interscan period only

TTh unexposed in inter-scan period

- FORMER users [REF]: TTh in prior period only
- NEVER users: TTh in neither period

Former users have a presumed indication for TTh; thus a better counterfactual comparison group than never users

Outcomes

- Dichotomous progression outcome (Y/N) for CAC and noncalcified plaque; defined as progression if:
  - If baseline=0: incident CAC/plaque
  - If baseline >0 & <100: ≥10/yr increase
  - If baseline ≥100: ≥10%/yr increase

Statistical Analysis

- We assessed the association of TTh exposure with CAC and plaque progression using robust Poisson regression
- Multivariable models adjusted for demographic, cardiovascular risk factors, and HIV-related factors over the inter-scan period
- Sequential model additionally adjusted for low total serum testosterone (<300 ng/dL) measured at baseline CT and assessed its association with coronary plaque progression

RESULTS

New testosterone users had *2x risk of CAC and plaque progression* vs. former users

Table 1. Baseline characteristics of 300 men with HIV in the MACS, by testosterone therapy exposure group

	Testosterone Therapy Exposure			
	Ongoing n=44	New n=21	Former n=24	Never n=211
Age, years, median	53	49	51	51
White	63.6%	42.9%	75.0%	42.7%
ASCVD high risk category (>7.5% 10-year risk)	50.0%	36.8%	38.1%	40.0%
Current smoker	22.7%	19.0%	16.7%	28.9%
Cholesterol-lowering medication	63.6%	52.4%	45.8%	43.1%
Suppressed viral load (<20 copies/mL)	84.1%	76.2%	75.0%	81.5%
CD4 cell count ≤350 cells/mm3	13.6%	19.0%	29.2%	15.6%
Total testosterone <300 ng/dL	6.8%	9.5%	12.5%	5.7%
% visits with TTh, before CCTA, median (IQR)	40% (20-60)	0% (0-0)	10% (10-20)	0% (0-0)
% visits with TTh, between CCTA, median (IQR)	80% (60-100)	40% (10-60)	0% (0-0)	0% (0-0)

30% MWH were current and/or past TTh users
*99% prescribed by clinician
74% gel/patch; 26% injection

Table 2. Crude baseline atherosclerosis levels, by TTh exposure

TTh Exposure	N	Baseline Atherosclerosis	Percent Progress
CAC		*Agatston units*	
Ongoing	44	11 (0, 113)	57%
New	21	4 (0, 103)	57%
Former	24	1 (0, 57)	29%
Never	211	0 (0, 51)	39%
Noncalcified Plaque, *mm³*			
Ongoing	44	45 (13, 180)	43%
New	21	30 (0, 73)	47%
Former	24	26 (6, 108)	29%
Never	211	23 (0, 79)	39%

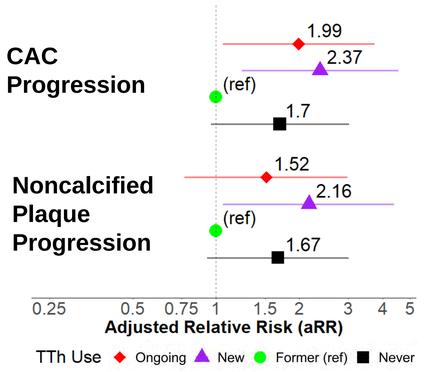


Figure 1. The adjusted relative risk of CAC and non-calcified plaque progression, by TTh exposure group.
Models are adjusted for age, race, pack-years smoking between scans, average SBP, fasting glucose, total and HDL cholesterol, and CD4 cell count between scans, reported use of antihypertensive, diabetes, or cholesterol medication ≥20% of interscan visits, viral suppression over interscan period, and history of AIDS diagnosis. *p<0.05,

Table 3. Low total testosterone and atherosclerosis progression

	CAC aRR (95% CI)	NCP aRR (95%CI)
Low total T (<300 ng/dL)	1.97*** (1.39,2.78)	0.97 (0.49,1.90)

Models are adjusted for age, race, pack-years smoking between scans, TTh exposure, average SBP, fasting glucose, total and HDL cholesterol, and CD4 cell count between scans, reported use of antihypertensive, diabetes, or cholesterol medication ≥20% of interscan visits, viral suppression over interscan period, and history of AIDS diagnosis. *** p < 0.001

RESULTS SUMMARY

- The risk of CAC and NCP progression was highest among new TTh users, followed by ongoing TTh users
- Findings are consistent with placebo-controlled interventional T Trial findings addressing plaque volume change
- Low total testosterone at baseline was also associated with progression of CAC, but not noncalcified plaque, independent of TTh exposure and other demographic and health co-factors
  - Stratified analyses will further explore once free T measures are available
- Limitations: Challenge of identifying an appropriate comparison group for men on TTh/ residual confounding; TTh use was self-reported and changed within time periods; reliance on total T levels can underestimates low T
- Strengths: Exposure ascertainment over 15 years; measurement of both calcified and noncalcified plaque progression over >4 years; controlled for prospectively-measured biologic, medication, and behavioral characteristics

CONCLUSION

- To our knowledge, this is the first HIV-specific data addressing testosterone therapy and subclinical CVD outcomes that can inform clinical decision-making for men with HIV
- Attention to CVD risk factors and guideline-driven implementation of CVD risk reduction strategies (eg statin use, BP control, smoking cessation, diabetes control) would be prudent among men on or considering testosterone therapy

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