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To T or not to T: Differences in Testosterone Use and Discontinuation by HIV Serostatus among Men who Have Sex with Men

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Abstract

Objectives: To characterize contemporary patterns and correlates of testosterone therapy (TTh) use and discontinuation by HIV serostatus among men in the Multicenter AIDS Cohort Study (MACS).

Methods: Self-reported testosterone use was collected semiannually from 2400 (1286 HIV-infected/1114 HIV-uninfected) men who have sex with men. Multivariable Poisson regression estimated prevalence ratios for TTh use and predictors of TTh discontinuation (2012–2015).

Results: Use was higher among HIV-infected compared to HIV-uninfected men in all age strata, with an age-adjusted prevalence of 17% versus 5%, respectively (adjusted prevalence ratio=3.7, $p<0.001$). Correlates of use in the multivariable model were similar by HIV serostatus: white race, the LA site, >1 recent sexual partner, non-smoking, and higher AHA/ACC CVD risk score category (approximately 70% of testosterone users were in the high risk category). Compared to HIV-uninfected men, HIV-infected men more frequently reported building muscle mass as a motivation for testosterone use. The TTh discontinuation rate was 20.9/100 person years (CI 17.3, 25.0). Relative to HIV-uninfected men, HIV-infected men were half as likely to discontinue

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(adjusted incidence rate ratio: 0.4, $p<0.001$). Discontinuation was 40 percent higher in the period after the FDA safety communication for testosterone in 2014, independent of co-factors ($p=0.06$).

Conclusions: Given the high prevalence of both TTh use and CVD risk among HIV-infected men, the benefits and risks of TTh should be examined in future studies of aging HIV-infected men and monitored routinely in clinical practice.

Keywords

Testosterone; discontinuation, HIV; men who have sex with men; cardiovascular disease risk

Introduction

The rising use of testosterone therapy (TTh) in the United States over the past decade (1–3) has elicited concerns regarding both the appropriateness of its use and uncertainty over its benefits and risks. The recent randomized placebo-controlled T Trials demonstrated several potential benefits among older men including for bone density, sexual desire and function, mood, and depressive symptoms (4, 5). However, the association of TTh with cardiovascular outcomes remains inconclusive (6). The U.S. Federal Drug Administration (FDA) released a safety communication for testosterone products in January 2014 (7, 8), following the publication of two studies that reported elevated risks of heart attack and stroke associated with TTh use (9–11). Yet other studies have not confirmed these findings (12–16), and new data continue to conflict. For example, TTh was associated with a higher risk of coronary artery noncalcified plaque progression in the T Trial (17) while a large observational study found that TTh use was associated with a lower risk of cardiovascular events (16).

The ongoing uncertainty over potential cardiovascular risks associated with TTh is salient for HIV-infected men, who have an elevated burden of cardiovascular disease (18, 19) and may be more likely to have an indication for TTh use. Testosterone was often prescribed for AIDS-related wasting prior to the availability of effective combination antiretroviral therapy (cART), and HIV-related wasting is an indication for short-term testosterone use in the Endocrine Society Guidelines (20). Moreover, hypogonadism has been found to be prevalent among men with HIV (21–25), and aging-related testosterone decline will further contribute to hypogonadism as the HIV-infected population ages (26).

Despite these linkages, epidemiologic and clinical data regarding TTh use among men with HIV are limited. To the best of our knowledge, there is only one published estimate of TTh use among HIV-infected men in the cART era, documenting a TTh initiation rate of 19.7/1000 person-years from 1996–2011 (27) more than twice the rate reported among a commercially-insured US population in 2011 (1). Without an HIV-uninfected control group, the investigators were unable to compare differences between testosterone users with and without HIV. Furthermore, the rates and predictors of TTh discontinuation among men with HIV have not been described, and it is unknown whether they are represented by rates reported from overall populations of TTh users. We sought to characterize contemporary patterns and correlates of TTh use and discontinuation by HIV serostatus among men in the Multicenter AIDS Cohort Study (MACS) from 2012–2015. We also compared the

cardiovascular risk profiles among TTh users with and without HIV and evaluated whether the rate of discontinuation increased after the FDA safety communication.

Methods

Study Population

The MACS is a prospective cohort study of HIV infection among men who have sex with men (MSM). Since 1984, a total of 7343 HIV-infected and -uninfected men were enrolled in four sites: Baltimore/Washington D.C., Chicago, Pittsburgh, and Los Angeles. Details of the design and methods have been published (28, 29); briefly, men attend semi-annual study visits that include structured questionnaires, physical examination, and the collection of blood samples (forms available: www.aidscohortstudy.org/researchers). The primary analyses of TTh use included data from the 2400 (1286 HIV+, 1114 HIV-) participants under active follow-up from 2012–2015. Study procedures were approved by Institutional Review Boards at each site and all participants provided informed consent.

Outcome and Exposure Variables

Self-reported testosterone use was obtained through an interviewer-administered questionnaire. HIV serostatus was measured using enzyme-linked immunosorbent assay [ELISA] and confirmed using Western blot. AIDS was confirmed through medical records and cART use was assessed using structured questionnaires; we dichotomized the time period of cART initiation using the year 2000, before which TTh was commonly prescribed in conjunction with cART for HIV-infected men with hypogonadism and wasting.(30) Participants self-reported date of birth, race, education, health insurance coverage, use of medications including erectile dysfunction drugs, number of sexual partners, smoking, recreational drug use, and alcohol use in the preceding 6 months. Recreational drug use was categorized as no drug use, use of marijuana only, or use of 1 the following substances: inhaled nitrates, cocaine or crack, opiates, uppers, downers, phencyclidine, and gamma-hydroxybutyric acid. Body mass index (BMI) was measured using weight and height (kg/m²), and classified as low (<20.5), normal (20.5–24.9), overweight (25–29.9), and obese (≥ 30). The frailty phenotype was defined as the simultaneous presence of 3 of 5 components: 1) weakness (grip strength); 2) slowness (timed walk); 3) self-reported unintentional weight loss ≥ 10 pounds, 4) self-reported exhaustion, and 5) self-reported limitation in physical activity; men meeting 1–2 components were classified as Pre-Frail (31, 32). The American Heart Association/American College of Cardiology 10-year CVD risk score was calculated, and categorized into low, moderate and high risk using established cutpoints (33).

Statistical Analysis

TTh Prevalence and Correlates—TTh prevalence at most recent study visit was stratified by HIV serostatus and age. Overall prevalence by HIV serostatus was age-adjusted using direct standardization, with the age distribution of the total cohort as the standard population. We compared the reasons for TTh use, mode of administration, and prescription status by HIV serostatus using Chi-square tests.

We evaluated the following correlates: demographic (age, race, study site, college education), behavioral (sexual partners in the past six months, alcohol use, recreational drug use, and smoking status), and health-related factors (HIV serostatus, BMI, frailty phenotype, CVD risk category, and erectile dysfunction medication use). After carrying forward values from 2011, missing values for specific covariates ranged from 0.3% for cholesterol medication use to 26% for CVD risk category (due to missing fasting glucose, cholesterol, or blood pressure measurements among men who did not complete a full study visit or participated by phone). Missing data was addressed using multiple imputation iterative chained equations (10 datasets). We estimated prevalence ratios (PR) for TTh use using Poisson regression models with robust variance on multiple imputation datasets. All demographic factors and other factors that correlated with TTh in unadjusted models (p -value <0.15) were included in multivariable analyses. We repeated the analysis stratified by HIV serostatus to evaluate whether the correlates of TTh differed by HIV serostatus.

TTh Discontinuation—The analytic sample for the longitudinal analysis of TTh discontinuation included participants who used TTh at a visit and completed at least one subsequent study visit during 2012–2015. Multiple visits per participant were included; visits were censored after discontinuation or the participant's last visit through 2015. The discontinuation date was defined as the midpoint between the last visit date at which TTh use was reported and the first subsequent visit when use was not reported. An indicator variable determined whether the visit occurred after January 31, 2014, the date of the first FDA safety communication on testosterone. We carried an individual's values forward and backward from before and after the visit with the missing covariate, respectively (missing data ranged from $<1\%$ for behavioral variables to 15% for BMI). We used multiple imputation with iterative chained equations to impute missing baseline values (10 datasets). Imputed values were carried forward for subsequent visits. We assessed the incidence rate ratios for discontinuation using multiple imputation estimates and multivariable Poisson regression models accounting for multiple observations per individual. Predictors were assessed at the most recent visit at which TTh use was reported and included the previously defined covariates and testosterone mode (transdermal versus injection). The multivariable model included demographics, whether the time was pre/post the FDA safety communication, and CVD risk category; remaining health and behavioral covariates were included if $p<0.15$ for the unadjusted association with TTh discontinuation. We evaluated whether the association between the FDA warning and discontinuation was modified by HIV serostatus or CVD risk score category. Statistical significance was determined by a two-sided p -value <0.05 . Analyses used Stata 13.1 (StataCorp, College Station, TX).

Results

Characteristics of the study population are shown in Table 1. HIV-infected men were younger, less likely to be white, and less likely to have a college degree compared to HIV-uninfected men. Overall, 94% of men had health insurance coverage, without difference by HIV serostatus. HIV-infected men had lower BMI and were less likely to be in the 10-year CVD high risk category (53.4% vs. 64.4%), but were more likely to be current smokers (26.3% vs. 17.6%). Among the HIV-infected men, 88.7% were currently on cART, with a

median CD4+ T-cell count of 641 cells/ μ L (IQR: 466, 841) and 83.3% had plasma HIV RNA levels below the limit of detection (50 copies/mL); 55% of the men started cART before 2000, and 12.2% had a history of clinical AIDS.

Prevalence and Reasons for Testosterone Use

More HIV-infected men reported TTh use compared to the HIV-uninfected men in all age strata, with an overall age-standardized prevalence of 17% (95% CI 14.9%, 19.2%) versus 5% (CI 4.1%, 6.6%), respectively (Figure 1). Prevalence of testosterone use increased with age among HIV-infected men, ranging from 5% of men <50 years to 17.2% among men aged 50–59, and 25% among men 60.

Nearly all TTh users reported receiving a prescription from a healthcare provider (99%). Transdermal TTh (gels or patches) was the most popular formulation, used by 69% of men, followed by injection (27%). Low serum testosterone level was the most common reason for TTh use (90%). Other reasons included the desire for more strength or energy (37%), fatigue (36%), low libido (29%), and erectile dysfunction (16%). Among men taking TTh, those with HIV were half as likely to currently take medication for erectile dysfunction as HIV-uninfected men (10% vs. 20.2%, $p=0.02$). Only 8% of men reported using TTh to improve athletic performance. HIV-infected men were significantly more likely than HIV-uninfected men to report using TTh to build muscle (32.1% vs. 6.5%, $p<0.001$) and combat wasting (15.3% vs. 1.6%, $p<0.01$). Among the 30 HIV-infected men who used TTh to combat wasting, 97% had initiated cART prior to 2000, and 36% had a history of clinical AIDS. Among the 63 HIV-infected men who used TTh to build muscle, 84% began cART prior to 2000 and 27% had an AIDS diagnosis.

Correlates of Testosterone Use

After adjusting for demographic and behavioral factors, HIV-infected men were more than 3 times as likely to use testosterone as HIV-uninfected men (aPR 3.71, CI 2.79, 4.92; Table 2). TTh prevalence was significantly lower among black men compared with white men (4.6% v 13.5%, PR=0.34), and higher among men with compared to without college degrees (13.1% v 8.4%, PR=1.56) and among men in LA and Baltimore, relative to Pittsburgh (16.7%, 9.4% v. 6.1%, PRs=2.75, 1.54). TTh use increased 34% with each decade of age in unadjusted analysis (PR 0.34, CI 1.24, 1.45). Race and site remained significant correlates of TTh use in multivariable models, while the associations with age and education were attenuated. Testosterone use was higher among men in the highest compared to the lowest CVD risk score category in the multivariable model (13.4% v 5.2%, aPR 2.21, CI 1.15, 4.28). TTh use was not significantly associated with BMI or contemporaneous frailty status. TTh use was not statistically significantly associated with the concurrent use of erectile dysfunction medication but was positively associated with 2 recent sexual partners (13% v 8.4%, aPR: 1.62, CI 1.22, 2.15). In unadjusted analyses, TTh use was 45% higher among men who used recreational drugs but half as frequent among smokers compared to non-smokers and was not associated with alcohol use; only smoking remained significantly inversely associated in the adjusted analysis. The analyses stratified by HIV serostatus demonstrated that the correlates of TTh use were generally consistent for both HIV-infected and uninfected men, though associations with race were more pronounced among the HIV-

infected men (p for interaction=0.05, Supplemental Table 1). Additionally, the inverse association observed between TTh use and current smoking was stronger among HIV-uninfected men (p for interaction=0.07).

Testosterone Discontinuation

Overall 316 TTh users contributed 556 person-years of follow-up from 2012–2015; 71% were HIV-infected (Table 3). The median ages were 55.8 and 60.9 years for HIV-infected and uninfected men, respectively. Approximately 70% of the testosterone users were in the highest CVD risk category, with no difference by HIV serostatus; the median 10-year risk score was 9% and 11.6% for HIV-infected and uninfected men, respectively. Dyslipidemia was highly prevalent among TTh users, irrespective of HIV serostatus, followed by hypertension and diabetes. Compared to HIV-uninfected TTh users, HIV-infected men had a higher prevalence of smoking and a lower prevalence of obesity. (See Supplemental Table 2 for levels of these characteristics among TTh non-users.)

Among TTh users, 116 discontinued use, yielding a discontinuation rate of 20.9 per 100 person years (CI 17.4, 25.0). Discontinuation was significantly lower among HIV-infected men (18.1 per 100 person-years, CI 14.4, 22.6) than HIV-uninfected men (29.2 per 100 person-years, CI 21.5, 39.7). These differences persisted after adjusting for demographic, health, and behavioral characteristics, with discontinuation less likely among HIV-infected men compared to HIV-uninfected men (aIR 0.44, CI 0.29, 0.65) (Table 4). After adjusting for covariates, discontinuation was 40% higher after the release of the FDA safety communication regarding testosterone use (aIR 1.40, CI 0.99, 1.98), which approached statistical significance (p=0.06), consistent with higher observed quarterly discontinuation rates (Supplemental Figure 1). The association between the post-FDA safety communication period and discontinuation did not differ by HIV serostatus, though it differed marginally by CVD risk category. Discontinuation was 1.6 times higher in the period after compared to before the FDA communication among those with high CVD risk, and 2.1 times higher among those with moderate risk, but was not higher among those with low CVD risk (p-values for interactions=0.06 and 0.07; data not shown). Black and Hispanic men discontinued TTh at approximately twice the rate of white men. Current smokers were twice as likely to discontinue compared to non-smokers, while men with the heaviest alcohol consumption were less likely to discontinue (aIR 0.34, CI 0.12, 0.94). Discontinuation was higher among men who used transdermal TTh compared to injection, though the difference did not reach statistical significance (p=0.10). Discontinuation was not associated with age, study site, education, BMI, frailty status, CVD risk category, erectile dysfunction medication use, recent sexual activity, or recreational drug use.

Discussion

In this large, well-characterized and prospectively-followed cohort, HIV-infected men were more than three times more likely to use TTh and half as likely to discontinue TTh compared to uninfected men, independent of relevant co-factors. Testosterone utilization was highest in the oldest age group, with 1 in 4 HIV-infected men 60 years old using TTh. Our findings are consistent with the high TTh initiation rates reported in the few existing studies

among HIV-infected men (27, 34), and are enhanced by the comparison group of uninfected men which enabled us to quantify the difference in TTh use between HIV-infected and uninfected men. To our knowledge, this is the first study to document a significantly lower rate of TTh discontinuation among HIV-infected men.

Despite the markedly higher TTh use among men with HIV, many of the self-reported reasons for use were similar for HIV-infected and uninfected men. Low testosterone levels were the main reasons cited for TTh use regardless of HIV serostatus, cited by 90% of men, and in this population, symptoms regarding energy and fatigue were more common than those related to sexual dysfunction. Athletic performance was reported as a reason for TTh by just 8% of men, though physical performance motivations could contribute to other response categories, like strength and energy or building muscle. However, HIV-infected men were significantly more likely than uninfected men to use TTh to combat weight loss and build muscle. We hypothesized that HIV-infected men using TTh for these reasons were more likely to have a history of AIDS-related weight loss, and this was supported by the finding that the prevalence of AIDS among these men was 36% and 27%, respectively, more than 2 times the level among the total sample of HIV-infected men (12%). The 2010 Endocrine Society guidelines recommend the consideration of short-course testosterone therapy for HIV-infected men with low testosterone levels and weight loss (20), based on evidence from studies conducted in the 1990s and early 2000s, when significant HIV-related weight loss and delays in initiation of effective HIV treatment were more common. Although the prevalence of HIV wasting has decreased dramatically since potent cART regimens became available, our findings may suggest that men who were infected early in the HIV epidemic continue to be concerned about the effects of HIV infection on muscle mass and perceive that TTh may have a role in muscle mass preservation as they age. This may contribute to the higher prevalence of use and lower discontinuation rate observed among HIV-infected compared to uninfected men.

We identified several factors associated with TTh use and discontinuation that were salient for both HIV-infected and uninfected men. TTh use, but not discontinuation, varied significantly by study site, with use markedly higher in Los Angeles after adjusting for other factors. This difference in use may be driven by regional variation in both demand and supply side factors, such as the prevalence of direct-to-consumer advertising, community norms and preferences, and physician knowledge and attitudes. Interestingly, the regional variation was strongest among the HIV-infected men, possibly reflecting differing approaches to TTh within the HIV care setting. Other demographic factors were linked to TTh use; black men were less likely to use and more likely to discontinue TTh, compared to white men. Testosterone utilization was higher in the older age groups, though age was not independently associated after adjustment for co-factors, many of which are age-related conditions. TTh use was also positively correlated with having a high 10-year CVD risk, and TTh users in our cohort had a high prevalence of dyslipidemia, hypertension, and diabetes. Smoking was the sole CVD risk factor that was strongly inversely associated with TTh use; current smokers were much less likely to use TTh, and smokers who used TTh discontinued at twice the rate of nonsmokers.

Among TTh users, discontinuation rates were fairly high; 20.9 per 100 person-years overall, and 29.2 per 100 person-years among HIV-uninfected men. Though the sample was small to investigate trends over time, the data suggest that the discontinuation rate may have increased in the period after the FDA safety communication, particularly among men in the moderate or high CVD risk groups. While we cannot attribute the reasons for discontinuation, it is possible that media coverage about the potential risk of heart attack and stroke after the FDA communication (35–38) influenced the behavior of participants, 70% of whom were in the AHA/ACC high risk category, and their prescribing physicians.

Limitations of our study include the self-reported ascertainment of TTh use; in particular, participants may have under-reported TTh use without a prescription. However, participants' self-reported reasons for TTh use revealed motivations that are valuable complements to the observed correlates of TTh use, and may help to explain differences in the durability of TTh use by HIV serostatus. Lacking data on TTh use before 2012, our study was not able to characterize duration of TTh use, or avoid the potential for reverse-causality and bi-directionality in the cross-sectional associations with TTh use. In contrast, we were able to assess the effect upon TTh usage of characteristics measured prior to the discontinuation, albeit for a short period of follow-up and without accounting for the duration of use prior to 2012. Ninety percent of users self-reported a testosterone deficiency, but our study did not include data on serum testosterone level monitoring among men before or after TTh initiation, which several studies have documented to be sub-optimal (1, 27, 39, 40). The key strengths of our study are the standardized characterization of TTh use, including participant motivations for use; the large multi-city sample; and the prospective characterization of demographic, health and socio-behavioral factors of both HIV-infected and uninfected participants.

Our findings suggest that HIV-infected men, particularly those over 50 years old, constitute a significant group of TTh users. The present study has implications for practice and future research. HIV care providers should discuss the evidence on the potential benefits and risks of TTh with men currently taking TTh, to enable men to make informed choices regarding use. HIV-infected men choosing to continue or initiate TTh should be appropriately monitored and supported, including serum testosterone measurements per treatment guidelines. Men choosing to discontinue may benefit from therapeutic options to alleviate symptoms associated with discontinuation. These may include the short-term use of human chorionic gonadotropin or clomiphene citrate to facilitate the production of testosterone in men with secondary hypogonadism (neither are FDA-approved for this purpose), screening and treatment for anxiety or depression, anti-resorptive therapy for men with concomitant osteoporosis, and diet and physical activity programs for body composition, energy, and mood. In the research domain, our study found significantly lower rates of discontinuation among HIV-infected TTh users, and thus, it would be useful for reports on trends in testosterone use and appropriate monitoring to report these data also among the subgroup with HIV, when data sources include HIV serostatus. In addition, more evidence is needed regarding the relative benefits and risks of long-term TTh use among men with HIV. The extent to which the current evidence on TTh, conducted primarily among men without HIV, is generalizable to HIV-infected men remains unclear. HIV-infected men are an important

sub-group of testosterone users, and should be adequately represented in the research agenda addressing testosterone therapy, including participation in clinical trials.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Testosterone Therapy Use Prevalence, by HIV Serostatus and Age Category. Total prevalence is age-standardized using the age distribution of the total study population. The denominators for each age-serostatus category from left to right were 463 HIV+ <50 years; 210 HIV- <50 years; 482 HIV+ 50–59 years; 356 HIV- 50–59 years; 341 HIV+ ≥60; and 548 HIV- ≥60.

Table 1:

Demographic, Behavioral, and Clinical Characteristics of 2,400 MACS Participants at Most Recent Study Visit 2012–2015, by HIV Status

	HIV+ n=1286	HIV– n=1114	Total n=2400
Age, years, median (IQR)	53.9 (45.5, 60.4)	59.8 (52.9, 66.4)	56.4 (48.7, 63.3)
Race			
White	52.6	71.9	61.5
Black	29.7	18.7	24.6
Hispanic/Other	17.7	9.4	13.9
Study Site			
Pittsburgh	23.3	27.6	25.3
Baltimore	25.0	24.9	24.9
Chicago	22.8	13.3	18.4
Los Angeles	28.9	34.2	31.4
College Graduate	43.5	60.7	51.5
Health Insurance ^(a)	94.4	94.3	94.4
Body Mass Index Category ^(b)			
Low Weight	8.0	5.8	7.0
Normal	36.9	29.7	33.6
Overweight	36.0	38.6	37.2
Obese	19.1	25.8	22.2
Frailty ^(c)			
No Frailty	35.9	34.5	35.3
Prefrail	51.7	55.1	53.2
Frailty Phenotype	12.3	10.4	11.5
AHA/ACC CVD Risk Category ^(d)			
<5% risk	33.9	21.9	28.3
5%-7.4% risk	12.7	13.7	13.2
7.5% risk	53.4	64.4	58.5
Erectile Dysfunction Medication Use	9.0	8.4	8.7
Sexual Partners in Last 6 Months			
None	37.9	38.8	38.3
One Monogamous	11.5	8.3	10.0
One Casual	10.8	16.4	13.4
Two or More	39.8	36.5	38.3
Current Smoker	26.3	17.6	22.3
Alcohol Use			
None	23.2	18.8	21.2
1–21 Drinks/Week	68.8	70.3	69.5
>21 Drinks/Week	7.9	11.0	9.3
Recreational Drug Use			

	HIV+ n=1286	HIV- n=1114	Total n=2400
None	47.9	60.5	53.7
Marijuana Only	18.8	14.7	16.9
1 Drug Other than Marijuana	33.3	24.7	29.3
Currently on cART	88.7		
ART prior to 2000	55.0		
HIV viral load <50 copies/mL	83.3		
CD4+ T cell count, cells/ μ L, median (IQR)	641 (466,841)		
Nadir CD4+ T cell count, cells/ μ L, median (IQR)	310 (198,444)		
History of AIDS	12.2		

Percentage, unless otherwise specified. IQR intraquartile range. cART combination antiretroviral therapy.

(a) Self-report of any medical coverage public or private since last semiannual MACS visit

(b) BMI was calculated as weight in kilograms divided by height in meters squared.

(c) Pre-Frailty includes 1–2 and frailty phenotype includes 3 or more of the 5 components: (1) weakness (grip strength); (2) slowness (timed walk); (3) self-reported unintentional weight loss of 10 pounds or more, (4) self-reported exhaustion, and (5) self-reported limitation in physical activity.

(d) The AHA/ACC pooled cohort equation includes age, race, systolic blood pressure, hypertension treatment, smoking status, diabetes. Total and high-density lipoprotein cholesterol (HDL) were measured from blood samples.

Table 2:

Correlates of testosterone therapy use at most recent study visit among 2400 men who have sex with men in the MACS, 2012–2015

	TTh Prevalence	Unadjusted Models		Multivariable Model	
		Prevalence Ratio	95% CI	Adjusted Prevalence Ratio	95% CI
HIV serostatus					
HIV-uninfected	5.7	1[ref]		1[ref]	
HIV-infected	22.2	3.86***	(2.93,5.07)	3.71***	(2.79,4.92)
Race					
White	13.5	1[ref]		1[ref]	
Black	4.6	0.34***	(0.23,0.50)	0.40***	(0.26,0.62)
Hispanic/Other	10.2	0.76	(0.54,1.07)	0.86	(0.57,1.28)
Age (per 10 years)		1.34***	(1.24,1.45)	1.18	(0.97,1.44)
Study Site					
Pittsburgh	6.1	1[ref]		1[ref]	
Baltimore	9.4	1.54*	(1.03,2.29)	1.48	(0.99,2.22)
Chicago	9.3	1.53	(1.00,2.34)	1.29	(0.85,1.98)
Los Angeles	16.7	2.75***	(1.94,3.90)	2.62***	(1.84,3.73)
College Graduate					
No	8.4	1[ref]		1[ref]	
Yes	13.1	1.56***	(1.23,1.98)	1.15	(0.89,1.48)
Health Insurance					
No	5.4	1[ref]			
Yes	10.6	1.96	(0.94,4.07)		
Body Mass Index Category					
Low Weight	10.7	1.18	(0.73,1.90)		
Normal	9.0	1[ref]			
Overweight	10.4	1.09	(0.83,1.43)		
Obese	9.2	0.98	(0.69,1.39)		
Frailty					
No Frailty	12.6	1[ref]		1[ref]	
Prefrail	8.8	0.79	(0.58,1.08)	0.77	(0.57,1.04)
Frailty Phenotype	14.3	1.29	(0.93,1.79)	1.12	(0.80,1.56)
AHA/ACC CVD Risk Category					
<5% risk	5.2	1[ref]		1[ref]	
5%-7.4% risk	7.7	1.56	(0.86,2.84)	1.56	(0.78,3.12)
7.5% risk	13.4	2.31***	(1.54,3.46)	2.21*	(1.15,4.28)
Erectile Dysfunction Medication Use					
No	10.3	1[ref]			
Yes	13.2	1.31	(0.90,1.90)		
Sexual Partners in Last 6 Months					

	Unadjusted Models			Multivariable Model	
	TTh Prevalence	Prevalence Ratio	95% CI	Adjusted Prevalence Ratio	95% CI
None	8.4	1[ref]		1[ref]	
One Monogamous	9.6	1.16	(0.77,1.74)	1.22	(0.82,1.79)
One Casual	11.1	1.32	(0.87,2.02)	1.44	(0.96,2.16)
Two or More	13.0	1.57**	(1.19,2.07)	1.62***	(1.22,2.15)
Current Smoker					
No	12.1	1[ref]		1[ref]	
Yes	5.9	0.49***	(0.34,0.71)	0.65*	(0.44,0.95)
Alcohol Use					
None	9.7	1[ref]			
1–21 Drinks/Week	10.5	1.08	(0.80,1.46)		
>21 Drinks/Week	12.8	1.29	(0.83,1.99)		
Recreational Drug Use					
None	8.8	1[ref]		1[ref]	
Marijuana Only	11.3	1.27	(0.90,1.80)	1.22	(0.89,1.68)
1 Drug Other than Marijuana	12.9	1.45**	(1.11,1.90)	1.25	(0.94,1.65)

*
 $p < 0.05$

**
 $p < 0.01$

 $p < 0.001$.

Prevalence ratios from the multivariable model adjust for all covariates shown. BMI, ED medication use, and alcohol use were not included due to their lack of associations with TTh in unadjusted models.

Table 3:

Sociodemographic and Cardiovascular Profile of Testosterone Therapy Users by HIV Status, n=316, 2012–2015

	HIV-infected n=225	HIV-uninfected n=91
Age, years, median (IQR)	55.8 (50.9, 61.0)	60.9 (54.4,66.3)
Race		
White	68.4	82.4
Black	16.0	9.9
Hispanic/Other	15.6	7.7
AHA/ACC CVD Risk Score, median (IQR)	9.0 (4.7,17.4)	11.6 (5.3, 21.0)
AHA/ACC CVD High Risk Category ^(a)	71.9	70.1
Hypertension ^(b)	64.6	63.6
Diabetes ^(c)	21.4	24.3
Dyslipidemia ^(d)	86.7	79.5
Current Smoker	19.8	7.1
Body Mass Index 30 kg/m ²	17.9	36.7

^(a) The sample of testosterone users are the 316 men included in the discontinuation analysis. The AHA/ACC pooled cohort equation includes age, race, systolic blood pressure, hypertension treatment, smoking status, diabetes. The high risk category includes those with $\geq 7.5\%$ 10 year risk scores.

^(b) Hypertension is defined by SBP ≥ 140 or DBP ≥ 90 or using antihypertensive medications

^(c) Diabetes is defined by fasting glucose ≥ 126 or use of diabetes medication.

^(d) Dyslipidemia is defined by fasting total cholesterol ≥ 200 mg/dl or LDL ≥ 130 mg/dl or HDL < 40 mg/dl or triglycerides ≥ 150 mg/dl or use of lipid-lowering medication

Table 4:

Predictors of discontinuation among 316 testosterone users in the MACS, 2012–2015

	Unadjusted Models		Multivariable Model	
	Incidence Rate Ratio	95% Confidence Interval	Incidence Rate Ratio	95% Confidence Interval
HIV-infected	0.62 *	(0.42,0.90)	0.44 ***	[0.29,0.65]
Post FDA safety communication	1.28	(0.90,1.81)	1.40	[0.99,1.98]
Testosterone type				
Injection or more than one method	1[ref]		1[ref]	
Transdermal (gel or patch) only	1.41	(0.88,2.25)	1.50	[0.92,2.44]
Age (per 10 years)	0.93	(0.73,1.19)	1.13	[0.79,1.62]
Race				
Caucasian	1[ref]		1[ref]	
Hispanic/Other	1.53	(0.92,2.54)	1.91 *	[1.06,3.46]
Black	2.09 **	(1.36,3.22)	2.23 ***	[1.39,3.55]
Study Site				
Pittsburgh	1[ref]		1[ref]	
Baltimore	1.23	(0.63,2.40)	1.40	[0.72,2.72]
Chicago	1.45	(0.75,2.80)	1.75	[0.89,3.43]
Los Angeles	1.16	(0.62,2.18)	1.12	[0.59,2.14]
College Graduate	0.71	(0.50,1.02)	0.87	[0.58,1.31]
Body Mass Index Category				
Low Weight	1.21	(0.54,2.71)		
Normal	1[ref]			
Overweight	1.15	(0.73,1.81)		
Obese	1.43	(0.86,2.39)		
Frailty				
No Frailty	1[ref]		1[ref]	
Prefrail	1.03	(0.70,1.52)	1.03	[0.70,1.52]
Frailty Phenotype	1.69	(0.98,2.91)	1.70	[0.96,3.02]
AHA/ACC CVD Risk Category				
<5% risk	1[ref]		1[ref]	
5%-7.4% risk	0.92	(0.49,1.72)	0.74	[0.39,1.41]
>=7.5% risk	0.89	(0.56,1.41)	0.62	[0.30,1.27]
Erectile Dysfunction Medication Use	0.92	(0.52,1.64)		
Sexual Partners in Last 6 Months				
None	1[ref]			
One Monogamous	0.75	(0.35,1.63)		
One Casual	0.67	(0.37,1.22)		
Two or More	0.85	(0.57,1.27)		

	Unadjusted Models		Multivariable Model	
	Incidence Rate Ratio	95% Confidence Interval	Incidence Rate Ratio	95% Confidence Interval
Current Smoker	1.87 **	(1.24,2.81)	2.11 **	[1.35,3.29]
Alcohol Use				
None	1[ref]		1[ref]	
1–21 Drinks/Week	0.99	(0.63,1.55)	0.96	[0.61,1.50]
>21 Drinks/Week	0.41	(0.15,1.11)	0.34 *	[0.12,0.94]
Recreational Drug Use				
None	1[ref]			
Marijuana Only	0.84	(0.51,1.40)		
1 Drug Other than Marijuana	0.77	(0.51,1.15)		

*
 $p < 0.05$

**
 $p < 0.01$

 $p < 0.001$

The multivariable regression model includes all listed covariates; BMI, use of erectile dysfunction medication, number of sexual partners, and recreational drug use were not included in the model due to lack of statistical significance in the unadjusted analyses.