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Racial differences in prostate cancer risk in young HIV-positive and HIV-negative men: a prospective cohort study

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Abstract

Purpose—African American men have the highest incidence of prostate cancer among ethnic groups, and racial disparity is highest in younger men. Prostate cancer prevalence is rising in HIV-infected men due to improved survival on antiretroviral therapies, yet little is known about racial differences in prostate cancer risk by HIV-infection status and age.

Methods—Prospective cohort study of prostate cancer risk in 2800 HIV-infected and -uninfected men who have sex with men (MSM) ages 40–70 (22% African American) in the Multicenter AIDS Cohort Study from 1996–2010. Poisson regression models were used to examine associations between race or HIV-infection status and prostate cancer risk among men ages 40–70, 40–55, and 56–70.

Results—Among men ages 40–70, incidence rates (IR) per 100,000 person years were 169 among all men and 276 among African American HIV-infected men. Prostate cancer risk was similar by HIV-infection status (IRR 1.0, 95% CI 0.55–1.82), but nearly 3-fold higher in African Americans compared to non-African Americans in adjusted models (IRRs 2.66 and 3.22, 95% CIs 1.36–5.18 and 1.27–8.16 for all or HIV-infected men, respectively). Racial disparity in prostate cancer risk was greatest in African American men ages 40–55 (adjusted IRR 3.31, 95% CI 1.19–9.22). Prostate cancer risk showed associations with family history of prostate cancer (p =0.001), but not heavy smoking, androgen supplement use, or HIV-related factors.

Conclusions—Among MSM, African American HIV-positive and HIV-negative men ages 40–55 have nearly a 3-fold increased risk of young-onset prostate cancer compared to non-African American men, highlighting the need to make informed decisions about screening in this population.

Keywords

HIV-1; prostate cancer; cancer risk; cancer epidemiology; cancer racial disparity

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Introduction

Prostate cancer is the most common non-cutaneous cancer among men (1), and incidence rates have been rising over time among HIV-infected men due to improved survival on newer antiretroviral therapies (ART) (2). Prostate cancer presents some unique challenges in HIV-infected populations, including higher cancer-specific mortality rates in comparison to HIV-uninfected populations (3) and lower rates of prostate-specific antigen (PSA) screening in subpopulations, including racial and sexual minorities (4–6). Major established risk factors in the general population are older age, African American race, and family history of prostate cancer (7, 8); modifiable risk factors include androgen supplement use and obesity (9, 10). The influence of HIV-related factors on prostate cancer risk remains poorly defined (11).

Previous studies report contradictory findings regarding the incidence rates of prostate cancer in HIV-infected compared to uninfected men. Several studies have reported lower incidence rates of prostate cancer among men with HIV infection and/or AIDS compared to the general population (9, 12–14). Proposed explanations for the lower prostate cancer incidence rates in HIV-infected men in these studies include lower PSA screening rates, competing risks from HIV-related comorbidities and mortality, and androgen deficiency, which is common in HIV-infected populations (12). However, other studies found similar or slightly higher incidence rates of prostate cancer in HIV-infected compared to uninfected men (15–18). Given these contradictory results, the effect of HIV infection on prostate cancer risk remains unclear in the highly active antiretroviral therapy (HAART) era.

Several studies have reported trends toward a younger age at prostate cancer diagnosis in HIV-infected compared to uninfected men (5, 19, 20). A recent study in the largest HIV cohort in North America found that while age at prostate cancer diagnosis was younger among HIV-infected subjects, the difference was not statistically significant (21); findings were inconclusive with respect to young-onset prostate cancer in groups by HIV status because age was examined in 10-year bins rather than comparing age of young-onset prostate cancer cases by HIV status. Young-onset prostate cancers diagnosed before age 55 are biologically and genetically distinct compared to prostate cancers diagnosed in older men (8, 22). Moreover, high-grade prostate cancers occurring before age 55 have a higher risk of cancer-specific mortality (23). PSA screenings have greatly improved early detection of prostate cancers (7, 24), and detection rates of young-onset prostate cancer have increased from 2.3% of total prostate cancers diagnosed in the early-PSA era (1988 to early 1990s) to 9–10% in the post-PSA era (8, 25). American Cancer Society (ACS) guidelines suggest screening at age 40 for men with multiple first-degree relatives with prostate cancer, age 45 for African Americans and men with a single first-degree relative diagnosed with prostate cancer at age < 65, and age 50 for men at average risk. With exception of a study by Riedel et al. (5), little is known about young-onset prostate cancer among HIV-infected men in the HAART era. Given the evolving epidemiology of prostate cancer risk in HIV-infected men on newer ART regimens, further study is needed to understand if subpopulations of people living with HIV or AIDS (PLWHA) may be at heightened risk at an earlier age.

African American men have a higher risk of prostate cancer in comparison to non-African men, including a higher incidence of young-onset prostate cancer (26). African American men are also at higher risk for more aggressive tumors, and higher prostate cancer-related mortality. Management of prostate cancer risk and outcomes in African American men is influenced by racial disparities in health care access, surveillance, treatment, and survival (5, 6, 8, 26, 27). African American men are disproportionately represented among HIV-infected men, a population more vulnerable to health care disparities in comparison to uninfected men (5, 27, 28). A recent study in the HAART era found that HIV-infected men were largely appropriately treated in comparison to HIV-uninfected men, though under- or over-treatment sometimes occurred due to difficulty estimating life expectancy (27); disparities by HIV status remained for some treatment options such as radical prostatectomy, which was performed less frequently in those with HIV-infection. Although prostate cancer is becoming more prevalent among HIV-infected men in the HAART era, the effect of race on prostate cancer incidence in HIV-infected populations remains unknown. Considering these disparities by race and HIV-infection status, together with evidence of increased prostate cancer mortality (3) and lower rates of PSA screening in some HIV-infected cohorts (12), a better understanding of prostate cancer risk in HIV-infected men is needed to optimize cancer surveillance and health outcomes overall, and among sexual and racial minority groups. A retrospective study of prostate cancer outcomes in a predominantly African American HIV-infected urban cohort cited a high prevalence of intravenous drug use (IDU) and hepatitis C virus (HCV) infection in the study cohort as confounding factors, since these factors often influence linkage to care, comorbidities, and survival (5). Prospective cohort studies controlling for these and other confounding factors will provide more accurate estimates of prostate cancer risk by age and race in HIV-infected men.

The Multicenter AIDS Cohort Study (MACS), an observational cohort study based in four urban areas in the United States, offers important advantages because HIV-infected and uninfected populations are similar for demographics and lifestyle, which serves as an internal control. Here, we investigate the association between African American race, HIV-infection status, and prostate cancer risk in HIV-infected and uninfected men who have sex with men using longitudinal data from the MACS.

Methods

Study cohort

This is a nested prospective study in the MACS, an ongoing cohort study of men who report sex with men (MSM). Established in 1984, the MACS has enrolled 6972 HIV-infected and HIV-uninfected MSM over 3 recruitment waves (1984–85 (n=4957), 1987–91 (n=665), 2001–03 (n=1350)) at 4 study sites (Los Angeles, Chicago, Baltimore, and Pittsburgh) as described in (29), with a focus on recruitment of racial and ethnic minorities during the third wave. Behavioral, clinical, and laboratory data were collected at semi-annual visits as described (30). Eligible participants were 2800 HIV-infected and HIV-uninfected men over age 40 with least one study visit between 1996–2010 and no prior prostate cancer diagnosis at the beginning of follow-up (recruitment waves 1984–85 (n= 1766), 1987–91 (n= 212), 2001–03 (n= 822)). Follow-up began in 1996 at the earliest visit between ages 40–70.

Institutional Review Boards at each study site approved the research and written informed consent was obtained from all individual participants included in the study.

Data collection and covariates

The MACS public dataset (P23 release) was translated into a local SQL database and used for the analyses. HIV-infection status was coded as a time-invariant covariate based on seroconversion before study entry. Early HAART (1996–2000) vs. late HAART (2001–2010) era was treated as a time-varying covariate. HBV and HCV infection status, heavy smoking, and BMI values were summarized using data nearest to end of follow-up. Subjects were classified as intravenous drug users (IDU) if injection drug use was self-reported for at least year during follow-up. The follow-up period for each subject was defined as the first visit after age 40 in 1996 or later until first instance of incident prostate cancer, loss to follow-up, or last visit in 2010. Androgen supplement use and family history of prostate cancer were evaluated between enrollment and end of follow-up. HIV-related variables such as ART use, protease inhibitor (PI) use, plasma viral load, CD4 cell count, CD4:CD8 ratio, and AIDS diagnosis were summarized using data nearest to end of follow-up in HIV-positive subjects.

Cancer outcomes

A total of 47 incident prostate adenocarcinomas diagnosed during the study period were identified using International Classification of Diseases for Oncology, third edition (ICD-O-3) codes. Incident cancers were ascertained continuously during follow-up using cancer registry linkage data, available medical records and death certificates, and self-reported cancer diagnoses (30).

Statistical Analysis

Incidence rates (IR) per 100,000 person-years were calculated by dividing the total number of incident cancers by cumulative years of follow-up. Follow-up was defined by last visit, death, or first instance of the incident cancer. Poisson regression models adjusted for age (> age 55 vs. <=55 years), race (African American vs. non-African American), HIV-infection status, and calendar period (early vs. late HAART era) were used to examine risk of prostate cancer; incidence rate ratios (IRR) and 95% confidence intervals (CI) were estimated. Subgroup analyses by age (<= age 55 and >55 years) were conducted. Post-hoc analysis examined clinical characteristics in age-stratified groups by prostate cancer diagnosis. Statistical analysis was performed using the ‘stats’ package of R version 3.2.1.

Results

We identified a cohort of 2800 men between ages 40–70 enrolled in the MACS from between 1996–2010, contributing 24,016 person-years (n=1448 HIV-uninfected and n=1352 HIV-infected men with median follow-up of 14 and 8 person-years, respectively) (Table 1). Comparing prostate cancer risk factors in groups by HIV status, HIV-infected compared to uninfected subjects were younger at baseline, median age (IQR), 42 (40–47) vs. 45 (40–50) years, respectively, and had a lower proportion with BMI>30 kg/m^2 and higher proportion of African Americans, heavy smokers, and exogenous androgen supplement use (testosterone,

dehydroepiandosterone (DHEA), Oxandrolone, or Nandralone) during follow-up compared to uninfected subjects (27.9% compared to 1.1%, respectively). Additionally, a higher proportion of HIV-infected subjects were HBV- or HCV-infected. Among HIV-infected subjects at follow-up, mean CD4 cell count was 516 cells/μl, 90.2 % reported ART use, and 29.4% had plasma viral load > 400 RNA copies/ml (at or above the limit of detection of the available test at some earlier visits); 40.6% had CD4 nadir <200 cells/ μl and 27.5 % had an AIDS diagnosis before study endpoint (Table 1). In groups by race, African Americans were significantly younger at baseline and had shorter follow-up in comparison to non-African Americans; median (IQR) age and duration within study for African Americans vs. non-African Americans was 42 (40–46) vs. 44 (40–49) years and 7 (7–8) vs. 14 (7–14) years. In comparison to non-African Americans, a lower proportion of African Americans were heavy smokers and reported androgen supplement use, while a higher propotion had BMI>30 kg/m^2 and HIV- or HCV-infection. HIV-infected African American subjects reported less ART use (84.3% vs. 92.4%), had a higher proportion with unsuppressed viral load > 400 copies/ml (35% vs. 24.1%), and lower proportion with an AIDS diagnosis before study endpoint (16.9% vs. 31.4%) in comparison to HIV-infected non-African Americans. The proportion of subjects reporting a positive family history of prostate cancer was similar between groups by HIV-infection status and race.

A total of 47 incident prostate cancer diagnoses were identified among the participants: 45 with prostate cancer as the first cancer diagnosis, and 2 with Kaposi sarcoma or Non-Hodgkin lymphoma diagnoses preceding the prostate cancer diagnosis. The crude IRs of prostate cancer among all, HIV-positive, and HIV-negative subjects were 169, 185, and 150 per 100,000 person-years, respectively (Table 2). Prostate cancer had nearly two-fold higher crude IRs among African-American compared to non-African American subjects ages 40–70 (267 and 148 per 100,000 person-years, respectively). Among groups by race and HIV status, HIV-infected African Americans had the highest crude IR relative to other groups (crude IR 276 per 100,000 person-years). Among subjects age 40–55, crude IRs were more than 3-fold higher in African Americans compared to non-African Americans (crude IR 200 vs. 60 per 100,000 person-years, respectively).

In Poisson regression models adjusted for age, race, and HAART era, there was no significant association between HIV-infection status and prostate cancer risk among subjects age 40–70 (IRR 1.0, 95% CI 0.55–1.82) (Table 3). By contrast, prostate cancer incidence rates were significantly higher among African American compared to non-African American subjects age 40–70 in adjusted models for all subjects (IRR 2.66, 95% CI 1.36–5.18) or only HIV-infected subjects (IRR 3.22, 95% CI 1.27–8.16). As expected, the incidence rate was significantly higher in subjects > age 55 compared to age < =55 in adjusted models for all subjects (IRR 6.08, 95% CI 3.24–11.41) or only HIV-infected subjects (IRR 6.98, 95% CI 2.74–17.78).

Sixteen subjects met criteria for young-onset prostate cancer, with diagnoses by age 55; the age ranges at time of young-onset prostate cancer diagnosis were 41–50 years in HIV-positive compared to 50–54 years in HIV-negative subjects, a difference that was not statistically significant (p=0.11). To investigate risk of young- and older-onset prostate cancer in African American compared to non-African American subjects, we evaluated

Poisson regression models stratified by age (Table 3). When stratifying by age, prostate cancer incidence rates were similar in HIV-infected vs. uninfected subjects ages 40–55 and 56–70 in adjusted analyses (IRRs 0.89 and 1.07; 95% CIs 0.33–2.41 and 0.51–2.26, respectively). By contrast, African American subjects had a significantly increased risk of young-onset prostate cancer in adjusted analyses (IRR 3.31, 95% CI 1.19–9.22); the risk of older-onset prostate cancer was also elevated (IRR 2.29, 95% CI 0.92–5.67).

Next, we compared clinical characteristics by presence or absence of a prostate cancer diagnosis for subjects ages 40–70 and younger (ages 40–55) and older (ages 56–70) age strata (Table 4). Among men ages 40–70, subjects with a prostate cancer diagnosis were significantly older than non-outcome subjects at age of diagnosis or end of follow-up (median age 58 vs. 53 years; p=.004) and a higher proportion had a positive family history of prostate cancer in comparison to non-outcome subjects (25.5% vs. 12.1%, p=0.001); other variables showed no significant difference. Among men age 40–55, subjects with a prostate cancer diagnosis had a greater proportion of African Americans (43.7% vs. 22.8%; p=0.047) or family history of prostate cancer (18.8% vs. 12.3%; p=0.43). HIV-related covariates, including CD4 cell count s, HIV viral load s, ART use, and PI use, were generally balanced between groups by prostate cancer diagnosis, excepting a lower proportion with AIDS diagnoses among outcome versus non-outcome subjects ages 40–70 (10.5% vs. 27.8%; p=0.066) and ages 56–70 (0% vs. 28.7%; p=.053), which most likely explains the difference in CD4:CD8 ratios between groups. Androgen supplementation, which is common among young gay and bisexual men (31), was not higher in younger compared to older HIV-positive subjects (22.4% vs. 40.6%, respectively). Similarly, androgen supplementation was not higher in younger vs. older HIV-infected African Americans (9.6% vs. 19.5%). Furthermore, no prostate cancer cases among African Americans reported androgen supplement use. Three subjects with prostate cancer diagnoses died while being followed in the MACS, one due to prostate cancer-related causes and two from causes unrelated to prostate cancer.

Discussion

In this prospective cohort study of HIV-infected and uninfected men who have sex with men ages 40–70, African American race was associated with a 2.7-fold increase in prostate cancer risk overall. African American race was associated with more than 3-fold increase in prostate cancer risk among younger men ages 40–55. This is the first unbiased measure of young-onset prostate cancer risk by race among HIV-infected and uninfected men, irrespective of a positive family history of prostate cancer. As expected, increasing age was significantly associated with elevated prostate cancer risk overall and in models restricted to HIV-infected men. While a null association was observed between HIV-infection and prostate cancer risk in groups by age, a suggestion of increasing prostate cancer incidence among HIV-infected men ages 40–70 in the late HAART era was supported by a trend toward a negative association between early HAART era and prostate cancer risk.

Prostate cancer incidence rates by race and HIV-infection status were highest among HIV-infected African American men relative to other groups (crude IR 276 per 100,000 person-years). The racial differences in prostate cancer risk we detected are largely consistent with findings in the general population (9); in our cohort, the greatest racial disparity in incidence

rate was in younger men ages 40–55. The association of African American race with nearly a 3-fold higher risk of prostate cancer in HIV-infected and uninfected men ages 40 to 70 was not attenuated in adjusted models restricted to subjects ages 40–55. As the HIV-infected population grows in the HAART era, identifying high-risk groups and optimizing their linkage to care will help to reduce disparities in prostate cancer diagnosis, treatment, and survival. The trend of increased risk of prostate cancer diagnosis among young HIV-infected and uninfected men in our cohort is also consistent with studies reporting a 1.5- to 3-fold increased risk of young-onset prostate cancer in African Americans compared to Caucasians in the general population (8, 25, 26).

Several studies reported a deficit in risk of prostate cancer among HIV-infected men (9, 12–14). However, we found similar risk of prostate cancer in HIV-infected compared to uninfected men who have sex with men, ages 40–70, 40–55, and 56–70. Our finding that prostate cancer incidence rates are similar by HIV-infection status is consistent with other studies (15), (18) and earlier study in the MACS (30). Differences in prostate cancer incidence rates reported here compared to studies reporting a deficit of prostate cancer risk in HIV-infected populations may be explained by several factors (9, 12–14). The lower prevalence of AIDS and AIDS-related deaths in our study and reported by Seaberg et al. (30) compared to some earlier studies (9, 12, 13, 18) reduces bias from competing risks. Additionally, calendar period adjustment for early vs. late HAART era in our study adjusts for competing risks due to immunodeficiency and AIDS-related deaths, which were more prevalent in the early HAART era. The higher incidence of prostate cancer among HIV-infected populations in the HAART compared to pre-HAART era is also consistent with this scenario (32). These observations suggest that differences in screening rates, ascertainment, and/or survivorship bias, which may be largely attributable to the success of widespread HAART use, probably explain discordant results for prostate cancer risk between studies of HIV-infected populations.

HIV-related factors showed no significant difference among subjects with vs. without prostate cancer diagnosis in our study cohort, except CD4:CD8 ratio, which was higher among cases relative to non-cases within the cohort. However, the slightly higher CD4:CD8 ratio among outcome compared to non-outcome HIV-infected subjects age 40–70 was influenced by the lower proportion of outcome subjects with AIDS (5, 9, 12, 30). Protease inhibitors were used by the majority of HIV-infected subjects in our cohort. However, in contrast to reports suggesting that protease inhibitors may be associated with lower risk of prostate cancer (9, 33), we found no significant difference in protease inhibitor use by prostate cancer diagnosis.

We examined other risk factors, including family history of prostate cancer, exogenous androgen supplement exposure, and high BMI, for possible associations with young-onset prostate cancer (9, 10). A positive family history of prostate cancer was more common among all subjects with young-onset prostate cancer compared to controls of similar age (18.8% vs. 12.3%), consistent with previous studies (8). Androgen supplement use and proportions of subjects with BMI >30 kg/m2 were similar between men age 40–55 by young-onset prostate cancer diagnosis, while a non-significant increase was observed in the proportion of heavy smokers (31.2% vs. 20%). Thus, the only risk factors showing positive

associations with young-onset prostate cancer risk in our study were African American race, and positive family history.

Considering the elevated risk of prostate cancer among African Americans in the study cohort, we also examined cohort characteristics by race. Several prostate cancer risk factors, such as BMI, age, smoking, and androgen supplementation (34–36), differed between groups by HIV status and race. A positive family history of prostate cancer was reported by a higher proportion of African Americans with young-onset prostate cancer compared to all African Americans in the study cohort (28.6% vs. 12.0%). More African Americans were HIV- or HCV-infected, while fewer reported taking androgen supplements or heavy smoking. In contrast to a retrospective study on prostate cancer in an urban cohort of predominantly African American HIV-infected subjects with prevalent IDU (5), African Americans in our study cohort had a low prevalence of IDU (7.4%), lower rates of HCV infection (25.6%), and lower prevalence of heavy smoking (13.7%) than reported in a cross-sectional study examining the association of heavy smoking and prostate cancer (36). Given the nested study design, longitudinal cohort with data collected biannually, and fewer confounding factors compared to many prior studies, findings in our study are less likely to be confounded by sociodemographic differences, ascertainment bias, and competing risks. A notable finding among African Americans in our study was the difference in age of young-onset prostate cancer diagnoses by HIV-infection status: age 50–54 years in HIV-negative subjects vs. 41–50 years in HIV-positive subjects (p=0.11). Although this difference in age at diagnosis was not statistically significant, several other studies also noted a trend toward younger age at prostate cancer diagnosis in HIV-infected compared to uninfected African American men (5, 19–21). Further studies are warranted to evaluate whether HIV-infection status is associated with a younger age at prostate cancer diagnosis among men ages 40–55.

Given that African American men are disproportionately represented in HIV-infected populations, including our cohort, it is often difficult to disentangle the influence of racial composition on prostate cancer burden in HIV-infected populations. Other factors such as lower PSA screening rates in African American men (26), potentially resulting from competing risks related to comorbidities and mortality, or limited access to care, may contribute to decreased estimates of prostate cancer burden among African Americans in HIV-infected populations. Among studies reporting a deficit of prostate cancer risk in PLWHA (9, 13, 14), the proportion of African Americans ranged from 16 to 40%; these proportions overlap with those reported in studies that found a null association between HIV-infection and prostate cancer risk, such as (15, 30) and the present study. Due to uncertainty regarding the percentage of African Americans with follow-up past age 40 and length of follow-up in these other studies, some comprised of mixed gender and sexual orientation, the influence of racial composition on prostate cancer risk in these HIV-infected populations remains inconclusive. In our analyses of men ages 40–70, models stratified by HIV status aimed to examine differences in the association of race with prostate cancer risk between groups, but were underpowered in the HIV-uninfected group due to the lower proportion of African Americans (17.8%). Consistent with findings from an earlier report (17), the stronger racial disparity with respect to prostate cancer risk within the HIV-infected group may in part reflect earlier screening in younger African American subjects, allowing sufficient statistical power to detect a difference by race in the HIV-infected group. Whether

the association of race with prostate cancer risk is stronger in HIV-infected vs. uninfected populations remains unclear in our study, and warrants further study in larger cohorts.

A limitation of this study is that our findings are based on a cohort of MSM, and thus may not be generalizable to other HIV-infected populations for several reasons. For example, sociodemographic characteristics of the MACS are not representative of many lower income and less educated HIV-infected populations, which often correlate with reduced healthcare access and engagement. Conversely, overdiagnosis of prostate cancer is more likely to result from increased engagement with healthcare, particularly among men dealing with the burden of HIV-infection and associated comorbidities. However, as reported by Seaberg et al. (30), SIRs for prostate cancer in the MACS are below 1 for both HIV-infected and uninfected groups, arguing against overdiagnosis in our cohort. SIRs below 1 are also consistent with possible underascertainment of prostate cancer, which might stem from stigma associated with a prostate cancer diagnosis and consequences of treatment in MSM as discussed by Rosser et al. (28). Factors explored in other studies include compromised sexual function following treatment in MSM (37, 38) and poorer health outcomes potentially caused by the heteronormative slant of prostate cancer treatment options (39, 40). Nonetheless, other factors may heighten prostate cancer risk among MSM, particularly androgen use (35), which was higher among young gay and bisexual adolescents in comparison to heterosexual adolescents in a US study published in 2014 (39). While we found no significant enrichment of androgen supplement use in prostate cancer cases overall (10.6 % in cases vs. 14.1% in non-cases), or in subjects with young-onset prostate cancer (12.5% in cases vs.12.4% in non-cases), the higher prevalence of androgen supplement use among MSM is a distinguishing factor compared to many non-MSM populations. Other limitations of the study are similar to those of other cohort studies of this scale (30) in that statistical power was limited by the number of outcomes. Incident prostate cancer cases in the study, however, were comparable to those reported by other studies with a similar focus (5, 18, 19, 30). Gleason scores, PSA tests, digital rectal exams, and tumor stage were not available for the study cohort, and therefore analyses could not be stratified by these characteristics. Despite these limitations, through a nested study design and age-stratified analyses, we identified HIV-infected African American men ages 40–55 as an unrecognized subgroup among the growing HIV-infected population with elevated risk of prostate cancer (11).

Prostate cancer diagnosis and management are becoming increasingly important issues for aging populations with HIV infection (27). Overdiagnosis, overtreatment, and compromised quality of life are potential disadvantages of population-wide PSA screenings (24). In addition to cost, an important problem with wide-scale PSA screening is the difficulty in distinguishing between prostate cancers that are likely to become symptomatic versus those that do not. Accordingly, the risk/benefit ratio of PSA screening must be carefully considered (24) and informed decisions about screening should follow discussions with health care providers about uncertainties, risks, and benefits of screening. Our evaluation of prostate cancer risk in an HIV-infected and uninfected cohort suggest that ACS guidelines for the general population apply similarly to HIV-infected men with at least ten years life expectancy. Consistent with findings by Carter et al.(41), our study demonstrates the prognostic significance of positive family history of prostate cancer; it was the only risk factor we found to be associated with a young-onset prostate cancer diagnosis (41). This

finding in conjunction with other diagnostic parameters may help young HIV-infected and uninfected African Americans age 40–55 reach a balanced decision between screening and watchful waiting to avoid instances of overdiagnosis and overtreatment without compromising overall health outcomes.

In conclusion, we evaluated prostate cancer risk in a prospective cohort of HIV-infected and -uninfected MSM and found more than 3-fold increased risk of young-onset prostate cancer among African American compared to non-African American men. In view of the racial differences in young-onset prostate cancer risk detected in our study, we propose that HIV-infected African American men be informed of their prostate cancer risk and participate in making informed decisions about screening starting at age 45 for those with at least ten years life expectancy.

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Table 1

Demographic and clinical characteristics of groups by HIV status and race

	All (n=2800)	HIV-negative (n=1448)	HIV-positive (n=1352)	*p*	Non-African American (n=2181)	African American (n=619)	*p*
Cumulative person years							
Median (IQR)	11 (7–14)	14 (7–14)	**8 (7–14)**	<0.001	14 (7–14)	**7 (7–8)**	<0.001
Age at entry visit							
Median (IQR)	43 (40–49)	45 (40–50)	**42 (40–47)**	<0.001	44 (40–49)	**42 (40–46)**	<0.001
Race n (%)				<0.001			<0.001
Caucasian	1931 (69)	1090 (75.2)	**841 (62.2)**				
African-American	619 (22.1)	257 (17.8)	**362 (26.8)**				
Other	250 (8.9)	101 (7)	**149 (11)**				
Heavy smoking[a] n (%)				<0.001			<0.001
No	2229 (79.6)	1192 (82.3)	**1037 (76.7)**		1695 (77.8)	**534 (86.3)**	
Yes	571 (20.4)	256 (17.7)	**315 (23.3)**		486 (22.2)	**85 (13.7)**	
HIV infection[b]	1352 (48.3)				990 (45)	**362 (58.5)**	<0.001
Hepatitis C infection[c] n (%)	273 (9.7)	99 (6.8)	**174 (12.9)**	<0.001	115 (5.3)	**158 (25.6)**	<0.001
Hepatitis B infection[c] n (%)	193 (6.9)	67 (4.6)	**126 (9.3)**	<0.001	145 (6.6)	48 (7.8)	0.524
CD4 cell count (cells/μl)[d§] n (%)							0.637
< 200			196 (15.5)		135 (13.6)	61 (16.9)	
200–349			199 (15.7)		143 (14.5)	55 (15)	
350–499			254 (20.0)		189 (19.1)	65 (18)	
≥ 500			619 (48.8)		444 (44.8)	175 (48.3)	
Viral load > 400 copies/ml [d§] n (%)			367 (29.4)		231 (23.3)	**136 (38.4)**	<0.001
ART use [d§] n (%)			1220 (90.2)		915 (92.4)	**305 (84.3)**	<0.001
CD4+ nadir < 200 (cells/μl) [d] n (%)			549 (40.6)		413 (41.7)	136 (37.6)	0.189
AIDS diagnosis[c,d]			372 (27.5)		311 (31.4)	**61 (16.9)**	<0.001
BMI (kg/m^2) [§]				<0.001			
Mean (SD)	26.1 (4.6)	27.0 (5.1)	**25.2 (3.9)**		26.0 (4.9)	**26.4 (4.9)**	0.042
>30 n (%)	344 (12.3)	229 (15.8)	**115 (8.5)**		228 (10.5)	**116 (18.7)**	

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	All (n=2800)	HIV-negative (n=1448)	HIV-positive (n=1352)	*p*	Non-African American (n=2181)	African American (n=619)	*p*
Androgen supplement use [c,e]	393 (14)	16 (1.1)	**377 (27.9)**	<0.001	349 (16)	**44 (7.1)**	<0.001
Family history of prostate cancer	344 (12.3)	190 (13.1)	154 (11.4)	0.181	270 (12.4)	74 (12)	0.830

Values in bold indicate significant (p<0.05) between-group differences in comparisons by HIV status or race

[a] Smoking reported at half pack per day or more for at least two years during follow-up

[b] Seroconversion prior to study entry

[c] Before study endpoint

[d] Includes only HIV-infected subjects with data

[e] Reported use of testosterone, DHEA, Oxandrin, or Nandralone at 2 or more visits between enrollment and study endpoint

[$] Time-updated values

Table 2

Crude incidence rates of prostate cancer by HIV status and race

Univariate Model	Incident Cancers (No.)	Person-Years	IR (95% CI)
All	47	27800	169.1 (124.2–224.8)
HIV-uninfected	28	15150	184.8 (122.8–267.1)
HIV-infected	19	12651	150.2 (90.4–234.5)
Race			
Non-African American	34	22937	148.2 (102.7–207.1)
African American	13	4863	267.3 (142.3–457.1)
HIV-negative			
Non-African American	23	13180	174.5 (110.6–2618)
African American	5	1970	253.8 (82.4–592.3)
HIV-positive			
Non-African American	11	9757	112.7 (56.3–201.7)
African American	8	2893	276.5 (119.4–544.9)
Age 40–55[a]			
Non-African American	9	14850	60.6 (27.7–115.0)
African American	7	3494	200.3 (80.5–412.8)

IR, incidence rate per 100,000 person-years

[a]Calculated for subjects with follow-up within the specified age range

Table 3

Univariate and Multivariate Analysis of Risk Factors for Prostate Cancer by age.

	Age 40–70 (n= 2800)		HIV+, Age 40–70 (n= 1352)		Age 40–55 (n=2584)		Age 56–70 (n=1157)	
Covariates	**IRR (95% CI)**	***p***	**IRR (95% CI)**	***p***	**IRR (95% CI)**	***p***	**IRR (95% CI)**	***p***
Univariate model								
HIV serostatus								
HIV-infected	0.85 (0.47, 1.52)	0.582	–		1.04 (0.39, 2.77)	0.938	1.21 (0.58, 2.52)	0.618
HIV-uninfected	Reference				Reference		Reference	
Race								
African American	**1.94 (1.03, 3.68)**	0.042	**2.56 (1.03, 6.34)**	0.043	**3.31 (1.23, 8.88)**	0.018	2.41 (0.99, 5.87)	0.053
non-African American	Reference		Reference		Reference		Reference	
HAART era								
Early HAART era	0.46 (0.21, 1.03)	0.058	0.56 (0.16, 1.92)	0.354	0.73 (0.23, 2.25)	0.577	0.55 (0.17, 1.81)	0.323
Late HAART era	Reference		Reference		Reference		Reference	
Age								
>55	**5.51 (3.01, 10.07)**	<0.001	**6.12 (2.46, 15.22)**	<0.001	–		–	
<=55	Reference		Reference					
Multivariate model								
HIV-infected	1 (0.55, 1.82)	0.993	–		0.89 (0.33, 2.41)	0.821	1.07 (0.51, 2.26)	0.861
African American	**2.66 (1.36, 5.18)**	0.004	**3.22 (1.27, 8.16)**	0.014	**3.31 (1.19, 9.22)**	0.022	2.29 (0.92, 5.67)	0.075
Early HAART era	0.72 (0.32, 1.63)	0.432	0.95 (0.27, 3.37)	0.939	0.92 (0.29, 2.96)	0.894	0.59 (0.18, 1.94)	0.382
Age>55	**6.08 (3.24, 11.41)**	<0.001	**6.98 (2.74, 17.78)**	<0.001	–		–	

IRR, incidence rate ratio

Values in bold indicate p<0.05

No. of incident cancers in groups by age: 40–70 (n=47), 40–55 (n=16), 56–70 (n=31)

Table 4

Demographic and clinical characteristics of groups by prostate cancer diagnosis and age.

	All participants (n=2800)		p	Age 40–55† (n= 2584)		p	Age 56–70† (n= 1157)		p
Prostate cancer	Non-cases (n=2753)	Cases (n=47)		Non-cases (n=2568)	Cases (n=16)		Non-cases (n=1126)	Cases (n=31)	
Age at prostate cancer diagnosis or endpoint			0.004			0.830			0.114
Median (IQR)	53 (47–59)	58 (53.5–63)		53 (47–55)	50 (47–53.5)		61 (58–65)	62 (59–65)	
Mean (SD)	53.7 (8.2)	57.8 (7.1)		50.8 (4.7)	49.7 (4.2)		61.8 (4.5)	62.2 (3.7)	
Race n (%)			0.355			0.047			0.209
Non-African American	2147 (78)	34 (72.3)		1982 (77.2)	9 (56.3)		992 (88.1)	25 (80.6)	
African American	606 (22)	13 (27.7)		586 (22.8)	7 (43.7)		134 (11.9)	6 (19.4)	
Heavy smoking[a] n (%)			0.879			0.261			0.819
No	2192 (79.6)	37 (78.7)		2055 (80)	11 (68.8)		889 (79)	26 (83.9)	
Yes	561 (20)	10 (21.3)		513 (20)	5 (31.2)		237 (21)	5 (16.1)	
Androgen supplement use [b]	388 (14.1)	5 (10.6)	0.499	301 (12.4)	2 (12.5)	0.923	182 (16.2)	3 (9.7)	0.331
Family history of prostate cancer	332 (12.1)	12 (25.5)	0.001	315 (12.3)	3 (18.8)	0.431	162 (14.4)	9 (29)	0.023
BMI >30 (kg/m^2)[§] n (%)	481 (18.7)	7 (14.9)	0.644	368 (17.9)	1 (6.2)	0.357	215 (20.6)	6 (19.4)	0.971
HIV infection[c] n (%)	1333 (48.3)	19 (40.4)	0.277	1282 (49.9)	8 (50)	0.995	425 (37.7)	11 (35.5)	0.798
CD4 count < 200 (cells/μl)[d§] n (%)	193 (15.5)	3 (15.8)	0.867	182 (15.1)	2 (25)	0.401	39 (10.2)	1 (9.1)	0.943
CD4+ nadir < 200 (cells/μl)[d§] n (%)	541 (40.6)	8 (42.1)	0.652	499 (38.9)	5 (62.5)	0.234	179 (42.1)	3 (27.3)	0.348
CD8 count< 180 (cells/μl) [d§] n (%)	20 (1.6)	1 (5.3)	0.27	20 (1.7)	1 (12.5)	0.015	3 (0.8)	0 (0)	0.774
CD4:CD8 ratio [d§] (median [IQR])	0.57 (0.03–1.1)	0.73 (0.3–1.2)	0.048	0.57 (0.04–1.1)	0.73 (0.4–1.0)	0.288	0.61 (0.09–1.1)	0.79 (0.4–1.2)	0.271
Viral load > 400 copies/ml [d§] n (%)	363 (29.6)	4 (22.2)	0.346	341 (28.8)	1 (14.3)	0.408	72 (18.9)	3 (27.3)	0.464
ART use [d§] n (%)	1203 (90.2)	17 (89.5)	0.302	1066 (88.4)	7 (87.5)	0.856	395 (93)	10 (91)	0.745
Protease inhibitor use [d§]	748 (56)	13 (68.4)	0.940	700 (58)	5 (62.5)	0.721	235 (55.3)	8 (72.3)	0.506
AIDS diagnosis[d,e]	370 (27.8)	2 (10.5)	0.066	293 (24.3)	2 (25)	0.891	122 (28.7)	0 (0)	0.053

[a]Smoking reported at half pack per day or more for at least two years during follow-up

[b]Reported use of testosterone, Oxandrin, DHEA, or Nandralone at 2 or more visits any time following enrollment to study endpoint

[c] Seroconversion prior to study entry

[d] For HIV-infected subjects only

[e] Before study endpoint

[§] Time-updated values

[†] Subjects counted with follow-up within corresponding age bins. Subjects with follow-up corresponding to ages in both age bins were counted for person-time within each age bin

P-values calculated using chi-square test for categorical measures and *t*-test for continuous measures