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Prostate Cancer Screening and Incidence Among Aging Persons Living with HIV

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Abstract

Introduction: The risk of prostate cancer among persons living with HIV (PWH) is not well understood and may be obscured by different opportunities for detection.

Methods: We identified 123,472 (37,819 PWH and 85,653 comparators) men enrolled in the Veterans Aging Cohort Study, a prospective national cohort of PWH and demographically-matched, uninfected comparators in 2000–2015. We calculated rates of PSA testing by HIV status and fit multivariable Poisson models comparing the rates of PSA testing, prostate biopsy, and cancer incidence.

Results: The mean age at enrollment was 52 years. Rates of PSA testing were lower in PWH versus uninfected comparators (0.58 versus 0.63 tests per person-year, respectively). Adjusted rates of PSA screening and prostate biopsy were lower among PWH (incidence rate ratio

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[IRR] 0.87, 95% CI 0.75–0.84) and IRR 0.79 (0.74–0.83), respectively. The crude IRR for prostate cancer was lower in PWH versus controls (IRR 0.90, 95% CI 0.83–0.97). However, in a multivariable model adjusting for PSA testing, cancer incidence was similar by HIV status (IRR=0.93, 95% CI 0.86–1.01, p=0.08). Among patients who received a prostate biopsy, incidence of prostate cancer did not differ significantly by HIV status (IRR 1.06, 95% CI 0.98–1.15, p=0.15). Among incident cancers, there were significant differences in the distributions of Gleason Grade (p=0.05), but not cancer stage (p=0.14) by HIV status.

Conclusions: When accounting for less PSA testing among PWH, the incidence of prostate cancer was similar by HIV status. These findings suggest that less screening contributed to lower observed incidence of prostate cancer in PWH.

Keywords

Prostate Cancer; HIV; Veterans; PSA; prostate cancer screening

Introduction

Antiretroviral therapy (ART) has transformed the length and quality of life for persons with HIV (PWH), a group encompassing 36.9 million people worldwide.[1,2] As the expanding population of PWH ages, secondary illnesses including non-AIDS defining cancers are increasingly important contributors to overall health and survival.[3–5] HIV infection is associated with greater risk of non-AIDS defining cancers such as Hodgkin lymphoma, oropharyngeal, anal, and lung cancer.[6,7] Prostate cancer, a common disease without clear immunologic or infectious etiology, is a notable exception as previous studies have reported lower risk among PWH.[8–10] Registry and population-based studies, including those from our national cohort study, have found that lower incidence rates for PWH have persisted even when adjusting for age, comorbidity and viral suppression.[11–13] Etiologic hypotheses related to the effects of HIV infection or its treatment have been proposed but lack validation and, together, drive continued debate about the utility or optimal manner of early detection practices for PWH.[14–17] As a result, prostate cancer risk among men with HIV remains incompletely characterized, but has growing relevance for guiding early detection approaches in the aging population of PWH.

A gap in the evidence addressing the association between HIV infection and prostate cancer is the absence of rigorous adjustment for differential screening between PWH and uninfected patients. Yet, there are reasons to examine HIV-related differences in screening practices. Shorter perceived life expectancy for PWH could lead to less testing and thereby less detection. This premise is supported by evidence that the incidence of prostate cancer paradoxically increases with improved viral suppression, a trend unique to prostate cancer that could result from more intense detection practices.[13] There may also be differences contributed by stigma and patient preference that further confound the use of PSA testing in PWH.[18] To date, no studies with sufficient sample size, age representation, or longitudinal follow-up have defined screening practices among PWH and the potential effects on cancer incidence, or other factors that may limit detection.[3,5,11,12,19]

As a growing number of PWH enter their fifth and sixth decades of life, opportunities for prostate cancer detection are likely to increase. Therefore, we aimed to characterize PSA screening practices among PWH and estimate standardized prostate cancer risk by HIV status while accounting for PSA testing. Using a large, national cohort of PWH and demographically matched controls in the United States' Veterans Health Administration (VHA), we assessed the association between HIV infection and prostate cancer screening and detection. We specifically sought to account for potential confounding, previously unmeasured in the VHA and other nationally-representative cohorts, relating to differential use of PSA-based screening.

Methods

Study Population

The study population was derived from the Veterans Aging Cohort Study (VACS), a longitudinal study of PWH and uninfected comparator subjects receiving care within the Veterans Health Affairs system (VHA).[20] VACS includes PWH enrolled at the initiation of HIV care, and HIV uninfected comparators demographically matched 1:3 on the basis of age, race/ethnicity, and site of care delivery based on electronic health record (EHR) data. VACS includes a high level of clinical detail extracted from national VHA databases, based on diagnosis codes, laboratory results, and demographic information that allow for ascertainment of longitudinal health outcomes in Veterans with and without HIV.[21–23] We included male patients without a baseline diagnosis of prostate cancer, who were 45 years and older at enrollment in VACS from 2000–2015. This study was approved by the VHA Connecticut Healthcare System and Yale University's Institutional Review Board.

Study Variables

We identified PSA tests using both VHA laboratory data files and Common Procedure Terminology (CPT) codes for outpatient claims. To distinguish PSA screening from testing performed for cause, we excluded tests that may occur in the setting of known or suspected prostate cancer using relevant diagnostic codes.[24] We identified prostate biopsy by CPT and ICD procedure codes. We compiled the number of PSA tests received by each patient and calculated the temporal density of PSA testing (number of PSA tests divided by person-time follow up).

We extracted clinical and demographic characteristics including age, race/ethnicity, geographic region, length of follow-up, substance abuse history, smoking history, and medical comorbidities. Among PWH we collected HIV disease characteristics at diagnosis and at the time nearest to a patient's first PSA test. We calculated the VACS index, a widely-validated instrument that predicts all-cause mortality in both PWH and controls. This tool incorporates: age, race, CD4, HIV-1, hemoglobin, platelet count, AST, ALT, FIB-4, creatinine, and hepatitis C status.[22,25] Lower scores reflect lower risks of HIV-specific and all-cause mortality. We identified prostate cancer cases from linked VA cancer registry data and compiled cancer characteristics including Gleason grade, PSA value (ng/mL) and cancer stage.[26]

Statistical Analysis

The primary study objectives were to determine the adjusted incidence rate ratio (IRR) for PSA testing and prostate cancer diagnosis between PWH and controls. The secondary study objectives were to compare the incidence of prostate biopsy by HIV status, and distributions of Gleason grade and clinical stage by HIV status.

We used descriptive statistics to compare baseline clinico-demographic characteristics, VACS index, and HIV biomarkers between PWH and controls. We compared the overall proportion of subjects receiving at least one PSA test, by HIV status, during the follow-up period. To compare the rates of testing, biopsy and cancer diagnosis, we fit unadjusted Poisson regression models to determine the IRRs of these endpoints by HIV status. We evaluated the associations clinical and demographic characteristics and rates of PSA testing, including an interaction term reflecting the differential effects of HIV infection status on each variable of interest. We then fit Poisson models with robust standard errors for PSA testing, biopsy and cancer diagnosis by HIV status, adjusting for age, race/ethnicity and smoking status, incorporating an exposure time offset. To understand the relationship between PSA testing practices and prostate cancer detection we fit additional models of cancer incidence, first adjusting by temporal density of PSA testing and subsequently fit a model only among patients who received a prostate biopsy, adjusting additionally by PSA level at the time of biopsy.

We used descriptive statistics to compare PSA levels at the time of prostate biopsy, and among incident cases compared distributions of clinical stage, Gleason grade, and PSA. Statistical significance was assessed using two-sided tests, at an alpha level of 0.05. All analyses were performed using SAS version 9.4 (SAS Institute).

Results

We identified 123,472 eligible patients in VACS, including 37,819 PWH and 85,653 HIV-uninfected (Figure 1). The median observation period was 7 years for PWH (IQR 3–12) and 9 years (IQR 4–13) for uninfected comparators. Most (99%) PWH initiated ART during their follow-up. The study cohort was racially diverse: 48.0% of PWH participants were Black, as were 47.5% of comparators. PWH and HIV-uninfected controls were similarly matched based on age, race, and region, however there were differences in the nature and degree of medical comorbidity between the groups (Table 1). PWH had more VA clinical visits per year compared to uninfected persons (mean of 7.5 versus 3.9).

The majority of subjects received at least one screening PSA test during the observation period, including 76% of PWH and 84% among uninfected individuals ($p<0.001$). The rate of PSA testing in PWH was 0.58 tests per person-year (95% CI 0.75–0.58) compared with 0.63 (95% CI 0.626–0.63), per person-year among uninfected comparators. Figure 2 depicts the proportion of patients screened in each year by HIV status. Older age was associated with increased PSA testing, and this effect was more pronounced for PWH ($p<0.0001$ for interaction). Virally suppressed patients were more likely to be PSA-tested compared to unsupressed PWH (IRR 1.11, 95% CI 1.10–1.13). Substance abuse and hepatitis C infection was associated with less PSA testing for all patients (Table 2). Virally suppressed patients

had fewer visits (0.6 per year fewer, p<0.001) but more frequent PSA tests (0.66 tests per person-year [95% CI 0.65–0.67]) compared with non-virally suppressed (0.59 tests per person-year [95% CI: 0.58–0.60; p<0.001]).

In unadjusted analyses, PWH were less likely to be PSA-tested (IRR 0.92, 95% CI 0.91–0.92), undergo prostate biopsy (IRR 0.79, 95% CI 0.75–0.84), and diagnosed with prostate cancer (IRR 0.90, 95% CI 0.83–0.97, Table 3). These associations remained significant in the base adjusted model incorporating age, race/ethnicity, and smoking status. However, the risk of prostate cancer was not significantly different by HIV status when accounting for the rate of PSA testing (IRR 0.93, 95% CI 0.86–1.01). Further, among patients receiving a prostate biopsy, rates of prostate cancer detection were similar by HIV status, (IRR 1.06, 95% CI 0.98–1.2, p=0.15).

Rates of prostate biopsy were lower in PWH (0.0064 per person-year, 95% CI 0.0061–0.0067) compared with uninfected comparators (0.0081 per person-year, 95% CI 0.0078–0.0083) The median PSA level at the time of biopsy was higher among PWH (6.5 versus 5.9 ng/mL, p<0.001). Among incident prostate cancer cases, the median PSA at diagnosis was higher among PWH (6.70 ng/mL versus 6.18, p=0.003). There were differences of the distribution of Gleason Grade among incident cacers (p=0.05), but no significant differences in cancer stage (p=0.14),Table 3.

Discussion

Examining a longitudinal national cohort of PWH and matched uninfected comparators in the VHA, we found that PWH were significantly less likely to receive PSA testing and diagnostic procedures for prostate cancer including prostate biopsy. When accounting for less PSA screening in PWH, HIV status was not associated with a markedly different risk of prostate cancer. Although there was less PSA-based screening among PWH than among uninfected controls, overall rates of screening remained high in both groups in the entire observation period, including among men with high degrees of comorbidity or indicators of poor all-cause survival. Furthermore, among incident prostate cancer cases we identified similar distributions of prostate cancer grade and stage. By accounting for differential rates of screening, the central means for prostate cancer detection, this study challenges prior estimates that have reported decreased prostate cancer risk among PWH. Furthermore, this work proposes that less use of screening tests is one mechanism for observed differences in prostate cancer incidence by HIV status.

Our findings suggest that less PSA screening, at least in part, contributes to lower crude incidence rates among PWH. In VACS, the largest US cohort of PWH and demographically matched controls, PWH had lower rates of PSA screening despite more frequent clinical care. When adjusting for rates of PSA testing, HIV status was not associated with significantly different risk of prostate cancer. However, some uncertainty in the IRR parameter estimates maintains the possibility that HIV infection, or its treatment, are associated with lower risks of prostate cancer. Reduced opportunities for detection contributed by HIV infection should contextualize prior studies which have routinely identified lower incidence rates of prostate cancer among PWH.[3,5,11,12,19,27] Only one

previous study, comprised predominately of younger patients, accounted for the effects of PSA testing. In that study, which included 74 incident prostate cancers, the adjusted incidence of prostate cancer remained lower for PWH.[28] In contrast, the VACS cohort is distinguished by its size (over 3,000 incident cases), age representation, and racial/ethnic diversity and therefore may more accurately represent risk among patients likely to undergo screening. Moreover, the VACS data is further enriched by PSA laboratory values, and the ability to account for the temporal density of PSA testing.

Virally-suppressed PWH were more likely to be screened with PSA. These findings suggest that beyond HIV status alone, measures of life expectancy may influence screening practices among PWH. These results complement recent work from VACS which indicated that prostate cancer is unique among non-AIDS defining cancers in that its incidence appears to increase following the initiation of viral suppression.[13] In this work, improved measures of viral suppression and HIV control including higher CD4 count, lower viral load, and lower VACS index were associated with greater likelihood of screening. We also found that the effects of clinical and demographic variables on PSA testing differed significantly by HIV status, underscoring complexity in the interactions of HIV infection and prostate cancer screening practices. Taken together, these observations suggest that differences in PSA testing related to improved control of HIV and other comorbidities could underlie greater detection of latent disease, but requires direct validation.

Although there were small differences in PSA levels among men who underwent prostate biopsy, most patients were diagnosed at localized stage and with low and intermediate grade cancers, findings which appear consistent with distributions of screened patients within screened populations. PWH had PSA levels at biopsy and diagnosis that were statistically higher, however the magnitude of difference appear to lack clinical significance, though cannot be entirely discounted. An analysis of patients in the National Cancer Database (NCDB) recently found greater odds of diagnosis with advanced stage cancer and increased mortality for PWH, even after accounting for healthcare-related factors.[29] Although the potential for more aggressive clinical behavior warrants validation, there are methodological limitations of hospital registry based studies such as the NCDB that may fail to account for measures of HIV control, or prior detection practices such as less PSA screening in PWH that may lead to later stage diagnosis.

Although the use of a large, matched cohort with detailed clinical data offers advantages for comparing disease incidence, there are several limitations that require attention. We ascertained PSA testing using VHA EHR data. Therefore, we are unable to account for the preferences of patients or physicians, or the effects of other factors such as family history that may lead to differential rates of screening. Analyses conducted among patients who received a prostate biopsy introduce the possibility of selection biases based on PSA level, digital rectal examination findings or other clinical indicators not fully captured through our approach. In addition, despite accounting for the influence of comorbidity on the decision to screen we cannot rule out the contribution of residual confounding or stigma associated with HIV diagnosis. The majority of incident cases were clinically localized cancers. Therefore, we are unable to characterize potential differences in disease biology and outcome occurring in the setting of locally advanced or metastatic disease, and cannot comment on recurrence-

free survival among treated patients. Lastly, differences in PSA screening between by HIV infection may be reduced in the VHA given consistent healthcare coverage among veterans and high historical rates of screening.[30] More pronounced gaps in PSA testing between PWH and outside of the VHA may explain larger differences in the observed incidence of prostate cancer.

Despite these limitations, the use of a national cohort with longitudinal follow-up provided the ability to rigorously account for prostate cancer screening and detection. Through this approach we were able to account not only for the laboratory-based PSA test results, but also use validated measures of comorbidity and prognosis such as the VACS index to account for screening and detection practices in a manner that has not been previously applied. Furthermore, this work is enhanced by robust follow-up, tracking patients into their fifth and sixth decades where prostate cancer is more commonly screened for and diagnosed. Lastly, longitudinal enrollment with substantial follow-up time in VACS allows for the consideration of the chronicity of HIV infection, further enriching the application of these findings to the aging population of PWH.

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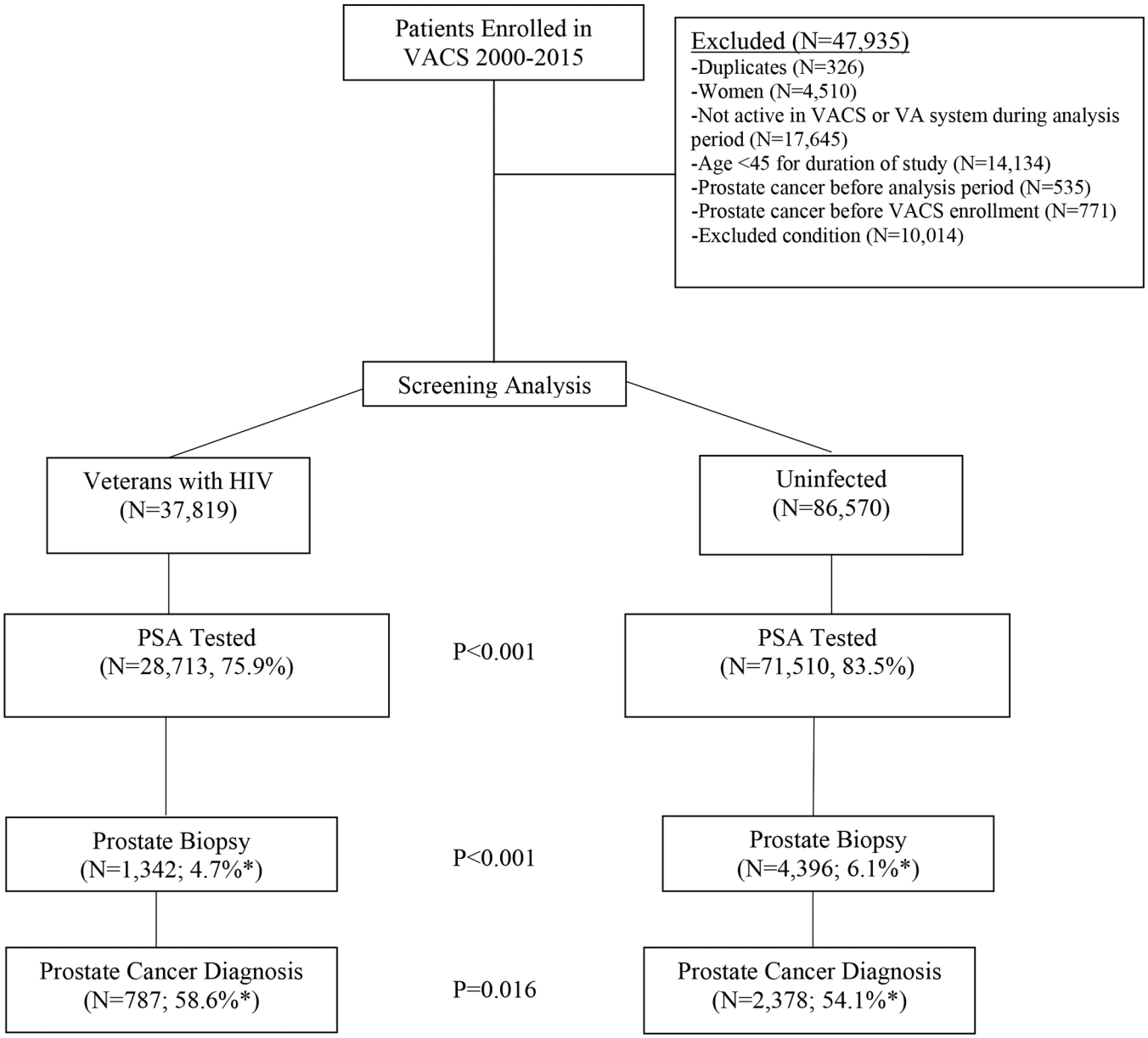

Figure 1.
Study schema
Abbreviations: VACS=Veterans Aging Cohort Study; PSA=prostate-specific antigen; HIV=Human immunodeficiency virus; VA=Veterans Affairs

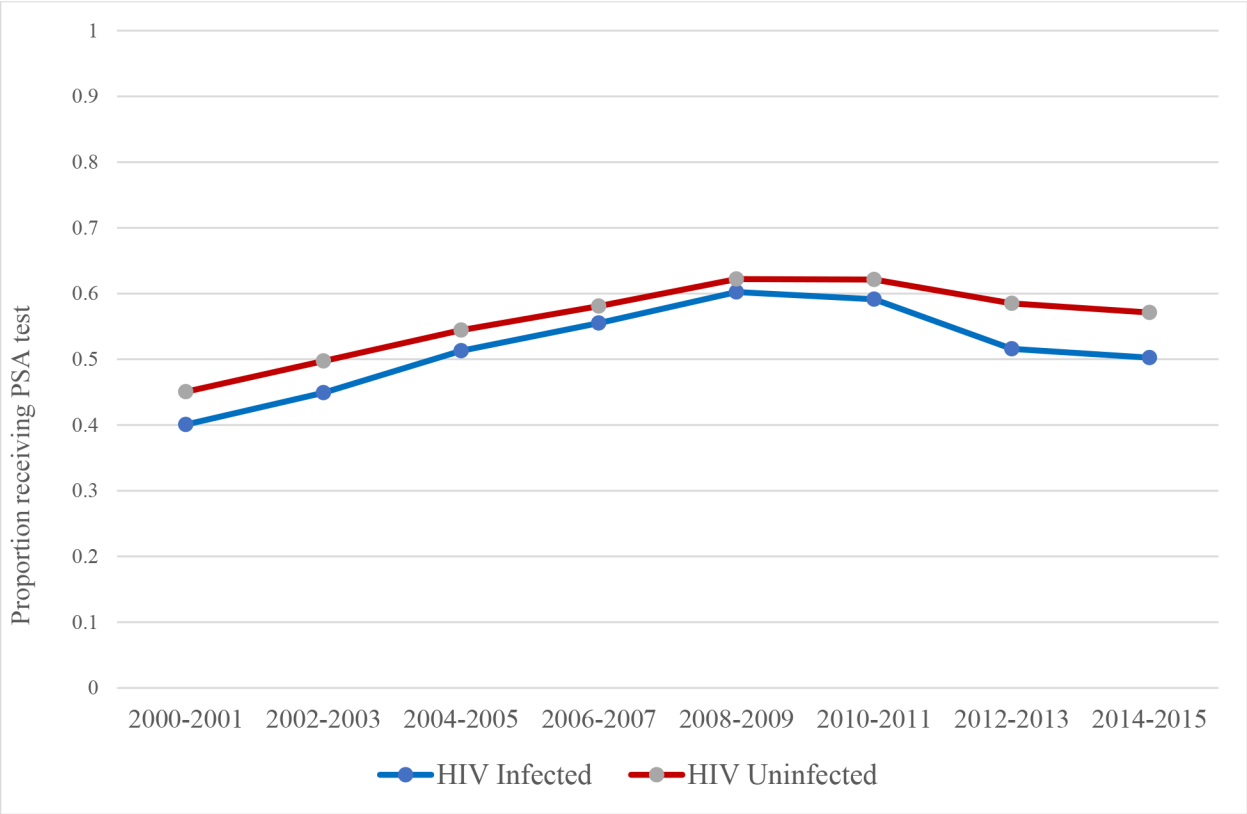

Figure 2.

Proportion of patients enrolled in the Veterans Aging Cohort Study receiving PSA testing by HIV status

Abbreviations: PSA=prostate-specific antigen; HIV=Human immunodeficiency virus

Table 1.

Baseline clinical and demographic characteristics of male patients in Veterans Aging Cohort Study.

Variable	Persons with HIV (N= 37,819)	Persons without HIV (N=85,653)
Age, mean (SD), years	52 (7.8)	52 (7.9)
Race, n (%)		
White	15,174 (40)	34,796 (41)
Black	18,152 (48)	40,662 (47)
Hispanic	2,951 (8)	7,042 (8)
Other	1,542 (4)	3,153 (4)
Region, n (%)		
Northeast	6,797 (18)	15,996 (19)
West	6,967 (18)	14,536 (17)
Midwest	4,570 (12)	9,861 (12)
South	17,490 (46)	40,381 (47)
Median follow up, years (IQR)	7 (3–12)	9 (4–13)
Number of PSA tests, mean (SD)	4.2 (4.7)	5.5 (5.2)
Visits per person year, mean (SD)	7.5 (9.6)	3.9 (4.1)
HIV-disease characteristics, n (%)		
CD4+ T-cell count (cells/mm^3), n (%)		
0–200	9,512 (25)	
200–500	13,312 (35)	
>500	10,343 (27)	
Receipt of ART at cohort entry, n (%)	32,140 (85)	
HIV RNA >500 copies/mL, n (%)	10,949 (29)	
VACS index, median (IQR)	59 (47–75)	31 (25–38)
Substance abuse, n (%)	6,790 (18)	10,848 (13)
Smoking status, n (%)		
Former Smoker	6,063 (18)	16,556 (21)
Current Smoker	19,333 (56)	4,1173 (51)
Comorbidity, n (%)		
Diabetes	8,818 (23)	30,856 (36)
Hyperlipidemia	4,095 (11)	17362 (20)
Hypertension	8,643 (23)	28,284 (33)
Renal impairment (eGFR<60)	1,520 (4)	1,613 (2)
Hepatitis C infection, n (%)	11,840 (31)	12,559 (15)

Abbreviations: PSA=Prostate specific antigen; VACS= Veterans Aging Cohort Study; eGFR=Estimated glomerular filtration rate; ART=Antiretroviral therapy

Table 2.

Rates of PSA testing according to different patient characteristics by HIV status, estimated through Poisson regression.

Variable	Persons with HIV IRR (CI)	Persons without HIV IRR (CI)	P-value*
Age (10 year increment)	1.21 (1.20–1.22)	1.15 (1.15–1.16)	<0.0001
Race/Ethnicity			
White	Reference	Reference	
Black	0.96 (0.95–0.97)	0.97 (0.97–0.98)	0.062
Hispanic	0.96 (0.94–0.97)	1.05 (1.04–1.06)	<0.0001
Other	0.81 (0.78–0.83)	0.78 (0.77–0.80)	0.13
Region			
Northeast	Reference	Reference	
West	1.01 (0.99–1.03)	0.91 (0.90–0.92)	<0.0001
Midwest	0.97 (0.95–0.99)	0.97 (0.96–0.98)	0.81
South	1.18 (1.16–1.20)	1.12 (1.11–1.13)	<0.0001
Duration of follow-up, years	1.02 (1.02–1.02)	1.01 (1.01–1.01)	<0.0001
CD4 Count			
<200 cells/mm^3	Reference		
200–500 cells/mm^3	1.06 (1.04–1.07)		<0.0001
>500 cells/mm^3	1.10 (1.08–1.11)		<0.0001
Receipt of ART,	1.11 (1.10–1.13)		<0.0001
HIV RNA >500 copies/mL	0.90 (0.88–0.92)		0.66
VACS Index (in 10-point increments)	1.00 (0.99–1.00)	0.99 (0.98–0.99)	0.017
Substance Abuse	0.90 (0.89–0.91)	0.87 (0.86–0.88)	<0.0001
Smoking Status			
Never Smoker	Reference	Reference	
Former Smoker	1.13 (1.11–1.14)	1.14 (1.13–1.15)	0.31
Current Smoker	1.14 (1.13–1.15)	1.12 (1.11–1.13)	0.009
Comorbidity			
Diabetes	1.23 (1.22–1.24)	1.31 (1.30–1.31)	<0.0001
Hyperlipidemia	1.30 (1.28–1.32)	1.32 (1.31–1.33)	0.12
Hypertension	1.22 (1.21–1.23)	1.30 (1.29–1.31)	<0.0001
Renal Impairment (eGFR<60)	1.08 (1.04–1.11)	1.08 (1.05–1.10)	0.99
Hepatitis C Infection	0.93 (0.92–0.94)	0.94 (0.94–0.95)	0.17

Abbreviations: HIV=Human Immunodeficiency Virus; IRR=Incidence Rate Ratio; CI=Confidence Interval; ART=Anti-retroviral therapy; VACS=Veterans Aging Cohort Study; CD4=Cluster of Differentiation 4; RNA=Ribonucleic Acid; GFR=Glomerular Filtration Rate

*p-value for test of interaction term of variable of interest with HIV status.

Table 3.

PSA screening and prostate cancer incidence among PWH and Controls

	Men With HIV (n=37, 819)	Men Without HIV (n=85,653)	p-value
PSA testing ever, n (%)	28,713 (76)	71,510 (84)	<0.001
UNADJUSTED MODELS	Incidence Rate Ratio (95% CI)		
Longitudinal PSA testing in PWH	0.92 (0.91–0.92)		<0.001
Prostate biopsy in PWH	0.79 (0.75–0.84)		<0.001
Prostate cancer in PWH	0.90 (0.83–0.97)		0.008
ADJUSTED MODELS*	Incidence Rate Ratio (95% CI)		
Longitudinal PSA testing in PWH	0.87 (0.75–0.84)		<0.001
Prostate biopsy in PWH	0.79 (0.74–0.83)		<0.001
Prostate cancer in PWH	0.89 (0.82–0.96)		0.0042
Prostate cancer in PWH, model including PSA testing density	0.93 (0.86–1.01)		0.08
Prostate cancer in PWH, biopsied patients only	1.06 (0.98–1.15)		0.15
PROSTATE CANCER CASES	Men With HIV (n=787)	Men Without HIV (n=2,379)	
Summary Stage, n (%)			
Localized	680 (86)	2116 (89)	0.14
Regional	46 (6)	137 (6)	
Metastatic	23 (3)	46 (2)	
Missing	38 (5)	80 (3)	
Gleason Grade (Sum), n (%)			
6 or Less	264 (34)	908 (38)	0.05
7	285 (36)	858 (36)	
8 or Higher	139 (18)	348 (15)	
Missing	99 (13)	265 (11)	

Abbreviations: PSA=prostate-specific antigen; PWH=persons with HIV; CI=Confidence interval

*Models adjusted for age, race/ethnicity and smoking status