

## Research Article

## Are HIV-Infected Men Vulnerable to Prostate Cancer Treatment Disparities?

Adam B. Murphy<sup>1</sup>, Ramona Bhatia<sup>2</sup>, Iman K. Martin<sup>3</sup>, David A. Klein<sup>4</sup>, Courtney M.P. Hollowell<sup>5</sup>, Yaw Nyame<sup>6</sup>, Elodi Dielubanza<sup>1</sup>, Chad Achenbach<sup>7</sup>, and Rick A. Kittles<sup>8</sup>

## Abstract

**Background:** HIV-infected (HIV<sup>+</sup>) men face cancer treatment disparities that impact outcome. Prostate cancer treatment and treatment appropriateness in HIV<sup>+</sup> men are unknown.

**Methods:** We used electronic chart review to conduct a retrospective cohort study of 43 HIV<sup>+</sup> cases with prostate cancer and 86 age- and race-matched HIV-uninfected (HIV<sup>-</sup>) controls with prostate cancer, ages 40 to 79 years, from 2001 to 2012. We defined treatment appropriateness using National Comprehensive Cancer Network guidelines and the Charlson comorbidity index (CCI) to estimate life expectancy.

**Results:** Median age was 59.5 years at prostate cancer diagnosis. Median CD4<sup>+</sup> T-cell count was 459.5 cells/mm<sup>3</sup>, 95.3% received antiretroviral therapy, and 87.1% were virally suppressed. Radical prostatectomy was the primary treatment for 39.5% of HIV<sup>+</sup> and 71.0% of HIV<sup>-</sup> men ( $P = 0.004$ ). Only 16.3% of HIV<sup>+</sup> versus 57.0% of HIV<sup>-</sup> men received open radical prostatectomy ( $P < 0.001$ ). HIV<sup>+</sup> men received more radiotherapy (25.6% vs. 16.3%,  $P = 0.13$ ). HIV was negatively associated with open radical prostatectomy (OR = 0.03,  $P = 0.007$ ), adjusting for insurance and CCI. No men were undertreated. Fewer HIV<sup>+</sup> men received appropriate treatment (89.2% vs. 100%,  $P = 0.003$ ), due to four overtreated HIV<sup>+</sup> men. Excluding AIDS from the CCI still resulted in fewer HIV<sup>+</sup> men receiving appropriate treatment (94.6% vs. 100%,  $P = 0.03$ ).

**Conclusion:** Prostate cancer in HIV<sup>+</sup> men is largely appropriately treated. Under- or overtreatment may occur from difficulties in life expectancy estimation. HIV<sup>+</sup> men may receive more radiotherapy and fewer radical prostatectomies, specifically open radical prostatectomies.

**Impact:** Research on HIV/AIDS survival indices and etiologies and outcomes of this prostate cancer treatment disparity in HIV<sup>+</sup> men are needed. *Cancer Epidemiol Biomarkers Prev*; 23(10); 2009–18. ©2014 AACR.

## Introduction

With the advent of highly active antiretroviral therapy (HAART), the risk of progression from HIV infection to AIDS and from AIDS to death has decreased, and survival has increased dramatically (1). By 2015, approximately

half of treated HIV-infected (HIV<sup>+</sup>) persons will be older than 50 years and at risk for age-associated conditions, such as prostate cancer (2, 3). The literature demonstrates that HIV<sup>+</sup> men may be at reduced risk for prostate cancer compared with seronegative men (4) even when controlling for prostate cancer screening (5). However, the burden of disease in men with HIV is still substantial (5), and prostate cancer rates are expected to rise as the HIV<sup>+</sup> population continues to age (6).

HIV<sup>+</sup> patients with lung cancer, another highly prevalent non-AIDS-defining cancer, experience disparities in cancer treatment and outcome (7). They are less likely to receive standard-of-care treatment or any treatment for localized non-small cell lung cancer (7), despite evidence that they have equivalent outcomes as uninfected patients when treated for early stage disease (8). These treatment disparities may contribute to the increased mortality in HIV<sup>+</sup> patients with lung cancer (7). HIV<sup>+</sup> patients may be at risk for cancer undertreatment due to a variety of etiologies, including provider reluctance, ethnic minority status, lack of insurance, poverty, and poor social support (7, 9).

Little is known about prostate cancer treatment in HIV<sup>+</sup> men. The literature is largely limited to case series describing similar outcomes or tolerability of standard prostate

<sup>1</sup>Department of Urology, Northwestern University, Chicago, Illinois. <sup>2</sup>Institute for Public Health and Medicine, Northwestern University, Chicago, Illinois. <sup>3</sup>Neuropsychiatry Section, Department of Psychiatry, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania. <sup>4</sup>Feinberg School of Medicine, Northwestern University, Chicago, Illinois. <sup>5</sup>Division of Urology, Department of Surgery, Cook County Health and Hospitals System, Chicago, Illinois. <sup>6</sup>Glickman Urologic and Kidney Institute, Cleveland Clinic Foundation, Cleveland, Ohio. <sup>7</sup>Division of Infectious Diseases, Department of Medicine, Northwestern University, Chicago, Illinois. <sup>8</sup>Institute of Human Genetics, University of Illinois at Chicago, Chicago, Illinois.

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A.B. Murphy and R. Bhatia share first authorship and have contributed equally to this article.

**Corresponding Author:** Adam B. Murphy, Department of Urology, Northwestern University Feinberg School of Medicine, 303 E. Chicago Ave., 16-703, Chicago, IL 60611. Phone: 312-908-2002; Fax: 312-908-7275; E-mail: a-murphy2@northwestern.edu

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cancer treatments in men with HIV as the general population (10–16). In one of the largest reports, Pantanowitz and colleagues (17) described prostate cancer treatment in 17 HIV<sup>+</sup> patients; however, there was no assessment of treatment appropriateness or a seronegative group, limiting the ability to assess for potential disparities. Assessing for prostate cancer treatment disparities is important given emerging evidence that curative therapy with radical prostatectomy may be superior to other modalities like radiotherapy for clinically localized (nonmetastatic) disease (18–22). In this study, we compare primary prostate cancer treatments received and appropriateness of prostate cancer treatments between HIV<sup>+</sup> and HIV-uninfected (HIV<sup>-</sup>) men using the widely utilized National Comprehensive Cancer Network (NCCN) prostate cancer treatment guidelines (ref. 23; Supplementary Table S1).

## Materials and Methods

### Study design

We conducted a retrospective cohort study of 43 HIV<sup>+</sup> cases and 86 HIV<sup>-</sup> controls with prostate cancer seen at Northwestern Memorial Hospital, an academic medical center in Chicago, IL, from 2001 to 2012. We queried the electronic data warehouse (EDW), an integrated electronic medical record of all inpatient and outpatient encounters at Northwestern and affiliates, for data on diagnoses, comorbidities, primary prostate cancer treatments, medications, and laboratory values. We first identified all men with International Classification of Diseases (ICD)-9 codes indicating both HIV infection (codes V08, 042, or 795.71) and prostate cancer (codes 185.0, V10.46, or 233.4) and then age- and race-matched them to HIV seronegative men with prostate cancer. We race-matched to avoid potential confounding by African American race, given its known associations with HIV (24) and prostate cancer treatment disparities (25–27). To confirm HIV infection in the cases, we conducted a chart review assessing for positive HIV viral load, positive antibody testing (ELISA or Western blot analysis), documented history of HIV on provider notes, and/or receipt of HAART. HIV<sup>-</sup> controls were identified on the basis of presence of negative HIV antibody testing. Prostate cancer diagnoses were verified through chart review assessing for prostate cancer on any pathology reports and/or history of prostate cancer on provider notes. For both groups, we excluded men with relative contraindications to prostate cancer treatment: age above 79 years, history of morbid obesity, and/or presence of Current Procedural Terminology (CPT) billing codes indicating history of pelvic radiation therapy for non-prostate cancer malignancies. We also selected men with prostate cancer diagnosis that came at least 6 months after HIV diagnosis.

### HIV data

HIV data were extracted from the EDW clinician notes, billing records, scanned outside medical records, and laboratory records and validated by a HIV specialist. CD4<sup>+</sup> T-lymphocyte cell count (CD4) nadir was explicit

in notes or identified on the basis of the lowest value in the laboratory data. The nearest CD4 and HIV viral load preceding the prostate cancer diagnosis was ascertained. Viral suppression was defined as <500 copies/mL. HAART therapy was defined by prescription of any HIV antiretroviral medications preceding the prostate cancer diagnosis. We conducted manual chart review to confirm that HAART was being given to treat HIV infection.

### Life expectancy estimation

The age-unadjusted Charlson comorbidity index (CCI; ref. 28) was utilized to estimate 10-year life expectancy and subsequent NCCN classification. The CCI is a validated instrument for predicting comorbidity and mortality (28, 29) and has been widely utilized in prostate cancer research (30, 31). The index can predict long-term non-prostate cancer mortality in patients with prostate cancer at the time of cancer treatment decision making (30, 31). Given the high 10-year prostate cancer-specific survival in the United States, prostate cancer diagnosis was not considered in the score. HIV was not considered a comorbidity in the CCI; however, history of opportunistic illness and/or CD4 < 200 cells/mm<sup>3</sup> was counted in the CCI as a prior diagnosis of AIDS, which added 6 points to the index. Although data from the current HAART era suggest that increased immune compromise continues to predict decreased life expectancy (32–34), we also conducted an additional analysis excluding AIDS diagnosis as a comorbidity from the CCI to assess its impact on defining risk-appropriate therapy. To calculate the score, each comorbidity was weighted accordingly and summed. A Charlson score of  $\geq 3$  predicts approximately 70% non-prostate mortality at 10 years and has been considered an appropriate cut-point for treatment decision making in patients with prostate cancer (30, 31), for whom benefits of prostate cancer treatment are not often seen for 8 to 10 years (35). In this study, patients with a CCI of 0 to 2 were considered to have  $\geq 10$  year life expectancy; those with scores  $\geq 3$  were considered to have <10 year life expectancy.

### Prostate cancer treatment data

Prostate cancer treatments were determined on the basis of ICD-9, CPT, and J code searches of the EDW health and billing records (Supplementary Table S2). We also conducted chart reviews to confirm treatments and to evaluate medical/surgical histories in provider notes for treatments that may not have occurred at our institution.

### Treatment definitions and appropriateness

We defined treatments as radical prostatectomy and nonradical prostatectomy treatments (Supplementary Table S2). The definition of radical prostatectomy encompassed both open (retropubic and perineal) and minimally invasive radical prostatectomy (MIRP), which included laparoscopic and robotic-assisted laparoscopic radical prostatectomy approaches. Radical prostatectomy included procedures performed with or without pelvic lymph

node dissection. Nonradical prostatectomy treatments were categorically defined as radiation therapy [brachytherapy, external beam radiation therapy (EBRT), proton beam radiation therapy, combined brachytherapy/EBRT], cryotherapy, high intensity focused ultrasound, primary androgen deprivation therapy (medical and surgical castration), expectant management (watchful waiting and active surveillance), and their combinations. Proton beam and EBRT were considered equivalent in the analysis of appropriate treatment. Regarding expectant management, active surveillance was considered a distinct treatment modality from watchful waiting; evidence of a follow-up appointment for prostate biopsy within 18 months after initial diagnosis and explicit phrasing was used to define receipt of active surveillance as primary therapy. Patients for whom we could not ascertain treatment were categorized as unknown.

We conducted a chart review for prostate biopsy pathology reports, provider notes, and radiologic reports to assess prostate biopsy Gleason score and clinical stage per American Joint Committee on Cancer guidelines (36). We used the PSA value immediately before the prostate biopsy or prostate cancer diagnosis. NCCN guidelines were used to assign a prostate cancer risk group to each patient based on serum PSA, Gleason score, and clinical stage (ref. 23; Supplementary Table S1). The guidelines recommend treatments that are adjusted on the basis of life expectancy for low and intermediate risk prostate cancer. We utilized predicted life expectancy based on CCI to subcategorize patients within risk groups (<10 years vs.  $\geq 10$  years life expectancy) to determine appropriate therapy. If treatment received aligned with the NCCN recommendations for the given risk stratum and predicted life expectancy, the patient was considered appropriately treated. A patient who actually received more aggressive management than recommended for his risk group was overtreated (e.g., <10 years life expectancy in the low-risk group undergoing radical prostatectomy). Conversely, undertreatment described a patient who received a less aggressive treatment regimen than was recommended for his risk stratum and life expectancy (e.g.,  $\geq 10$  years life expectancy in the intermediate-risk group treated with watchful waiting).

### Statistical analysis

Baseline characteristics are reported as medians for continuous and percentages for categorical variables in HIV<sup>+</sup> and HIV<sup>-</sup> participants. For significance testing, we used  $\chi^2$  tests for categorical variables and two sided *t* tests for continuous variables.

We compared the overall distribution of primary treatments received by HIV<sup>+</sup> and HIV<sup>-</sup> men with all prostate cancer stages using  $\chi^2$  trend tests. Similarly, we compared the proportion of HIV<sup>+</sup> and HIV<sup>-</sup> men who received NCCN risk-appropriate treatment (yes/no) using  $\chi^2$  tests.

As a *posthoc* analysis among those with clinically localized disease, we tested the association between radical prostatectomy and HIV status stratified by NCCN risk

group using  $\chi^2$  test. We then selected best-fit models using conditional binary logistic regression to analyze the association of HIV infection with radical prostatectomy treatment for men with clinically localized disease. We used a binary variable that represented radical prostatectomy versus nonradical prostatectomy treatments. We tested the associations for HIV status and radical prostatectomy with other covariates, including CCI (continuous and binary variable: CCI  $\geq 3$  vs. <3), body mass index (BMI; binary variable: BMI > 35 kg/m<sup>2</sup> vs.  $\leq 35$  kg/m<sup>2</sup>), private insurance status (private vs. public/self pay), nadir CD4 (continuous variable), CD4 at prostate cancer diagnosis (continuous variable), and HIV viral load (binary variable:  $\geq 500$  copies/ml vs. <500 copies/mL). Age and race were excluded from the regression models. The preferred model was selected on the basis of -2log likelihood scores; the best-fit regression model contained HIV status, CCI, and insurance status.

We tested the association between HIV infection and receiving open radical prostatectomy and MIRP as additional *posthoc* analyses among clinically localized patients with prostate cancer. We created binary variables that divided radical prostatectomy into open radical prostatectomy and MIRP. Open radical prostatectomy versus HIV status was analyzed using binary conditional logistic regression in a model controlled for CCI and insurance status. MIRP versus HIV was analyzed using binary conditional logistic regression in an unadjusted model due to sample size constraints.

Finally, we calculated all-cause mortality rate as the number of deaths per 1,000 person-years of follow-up since prostate cancer diagnosis. Deaths were verified using the Social Security death index.

Matching 1 HIV<sup>+</sup> prostate cancer patient to 2 HIV<sup>-</sup> prostate cancer patients provided 80% power to detect an OR  $\geq 2.5$  for receiving radical prostatectomy, assuming a 55% rate of radical prostatectomy in the HIV<sup>-</sup> population with an alpha of 0.05 (37). Statistical analyses were performed using SPSS 21 (IBM). The study was approved by the Northwestern University Institutional Review Board.

## Results

### Baseline characteristics

The median age of our study population at prostate cancer diagnosis was 59.5 years, with equal follow-up time of 7.5 years for both HIV<sup>+</sup> and HIV<sup>-</sup> men. Overall, 58% were Caucasian and 29% were African American, and the majority were insured (Table 1). Among HIV<sup>+</sup> men, nearly 40% had a prior AIDS-defining illness, with median nadir CD4 of 276.4 cells/mm<sup>3</sup>. At the time of prostate cancer diagnosis, the median CD4 was 459.5 cells/mm<sup>3</sup>, 95.3% were on HAART, and 87.1% were virally suppressed. Notably, the HIV<sup>+</sup> men had a higher median CCI (1 vs. 0,  $P < 0.001$ ). Median PSA levels were similar between groups ( $P = 0.17$ ). Overall, 62.5% of HIV<sup>+</sup> and 54.8% of HIV<sup>-</sup> men ( $P = 0.30$ ) had NCCN-defined low-risk prostate cancer. The distributions of risk categories were also similar ( $P = 0.68$ ), though there appeared to be a

**Table 1.** Subject characteristics at time of prostate cancer diagnosis

	HIV <sup>+</sup> (N = 43)	HIV <sup>-</sup> (N = 86)	P
<b>Continuous variables</b>			
	<b>Median (SD)</b>	<b>Median (SD)</b>	
Age, y	59.2 (8.4)	58.9 (8.3)	0.14
BMI, kg/m <sup>2</sup>	26.7 (5.7)	28.6 (5.9)	0.20
PSA, ng/mL	5.9 (92.6)	5.1 (32.7)	0.17
CCI	1.0 (3.6)	0.0 (1.15)	<0.001
CD4, cells/mm <sup>3</sup>	459.5 (298.2)	—	
Nadir CD4, cells/mm <sup>3</sup>	276.4 (242)	—	
<b>Categorical variables</b>			
	<b>%</b>	<b>%</b>	<b>P</b>
<b>Ethnicity</b>			
			0.78 <sup>a</sup>
<i>Caucasian</i>	56.8	59.3	
<i>African American</i>	34.1	25.6	
<i>Other</i>	9.0	15.1	
Uninsured	4.7	2.3	0.57
Smoker (current or former)	40.9	37.2	0.66
Alcohol use (current or former)	54.6	49.0	0.29
<b>Cancer variables</b>			
Clinical tumor stage			0.15 <sup>a</sup>
T1a	0	4.5	
T1c	57.1	65.2	
T2a	28.6	19.7	
T2b	0	6.1	
T2c	5.7	4.5	
T3a	5.7	0	
T3b	2.9	0	
<b>CCI ≥ 3</b>	39.5	8.1	<0.001
<b>NCCN risk classification</b>			
			0.68 <sup>a</sup>
Low	62.5	54.8	0.43
Intermediate	20.0	28.8	0.31
High/very high	7.5	12.3	0.43
Metastatic	10.0	4.1	0.21
<b>HIV variables</b>			
HAART Use	95.3	—	
<i>NRTI</i>	88.4	—	
<i>NNRTI</i>	41.9	—	
<i>PI</i>	18.6	—	
<i>INT</i>	18.6	—	
HIV viral load <500 copies/mL	87.1	—	
AIDS diagnosis	39.5	—	

NOTE: Student *t* tests were performed for continuous variables and  $\chi^2$  tests were performed for categorical variables. The bolded values are those with statistical tests where the *P* value was less than 0.05.

Abbreviations: NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor; INT, integrase inhibitor.

<sup>a</sup> $\chi^2$  test of trend.

preponderance of metastatic cases in the HIV<sup>+</sup> group (10.0% in HIV<sup>+</sup> vs. 4.1% in HIV<sup>-</sup>, *P* = 0.21; Table 1).

### Treatment distribution

Next, we looked at the distribution of prostate cancer treatments between HIV<sup>+</sup> and HIV<sup>-</sup> men (Table 2). Radical prostatectomy was the primary treatment for 39.5% of HIV<sup>+</sup> men and 71.0% of HIV<sup>-</sup> men (*P* = 0.004). The

difference in radical prostatectomy persisted when analyzing the subset of men with CCI < 3 as a marker of high estimated 10-year life expectancy (38.6% in HIV<sup>+</sup> men vs. 70.9% in HIV<sup>-</sup> men, *P* < 0.001, data not shown). Limiting the analysis to open radical prostatectomy, we found that 16.3% of HIV<sup>+</sup> men versus 57.0% of HIV<sup>-</sup> men were treated by open radical prostatectomy (*P* < 0.001). There were nonsignificant trends for increased receipt of MRP

**Table 2.** Prostate cancer treatment patterns, treatment appropriateness, and HIV serostatus

	HIV <sup>+</sup> (N = 43)	HIV <sup>-</sup> (N = 86)	P
	%	%	
Primary treatment			0.09 <sup>a</sup>
Active surveillance	9.3	4.7	0.13
Watchful waiting	2.3	1.2	0.57
Radiation therapy	25.6	16.3	0.13
ADT	7.0	2.3	0.23
Cryotherapy	2.3	0	0.99
Unknown	14.0	4.5	0.06
Radical prostatectomy	39.5	71.0	<b>0.004</b>
Open	16.3	57.0	<b>0.0009</b>
MIRP	23.2	14.0	0.11
Treatment relative to NCCN guidelines <sup>b</sup>			<b>0.008<sup>a</sup></b> (0.10 <sup>a</sup> )
Undertreatment	0 (2.7)	0 (0)	1.00 (0.13)
Appropriate	89.2 (94.6)	100 (100)	<b>0.003 (0.03)</b>
Overtreatment	11 (2.7)	0 (0)	<b>0.003 (0.13)</b>

NOTE:  $\chi^2$  tests were performed. The bolded values are those with statistical tests where the *P* value was less than 0.05.

Abbreviation: ADT, androgen deprivation therapy.

<sup>a</sup> $\chi^2$  test of trend.

<sup>b</sup>Analysis including AIDS diagnosis in the Charlson Co-morbidity Index calculation (analysis excluding AIDS diagnosis in the CCI calculation).

(23.2% vs. 14.0%; *P* = 0.11) and radiation therapy (25.6% vs. 16.3%, *P* = 0.13) in the HIV<sup>+</sup> group.

### Risk appropriate treatment

We then assessed for discordance between the NCCN guideline recommendations and actual treatments received (Table 2). Overall, fewer HIV<sup>+</sup> men (89.2%) were treated appropriately compared with HIV<sup>-</sup> men (100%; *P* = 0.003). There was no evidence of prostate cancer undertreatment in any of the HIV<sup>+</sup> or HIV<sup>-</sup> men. However, overtreatment occurred in four HIV<sup>+</sup> men with prior AIDS diagnoses. When recalculating CCI excluding prior AIDS diagnoses and reexamining treatment appropriateness, 3 of the 4 overtreated men were reclassified as appropriately treated, and only one man remained overtreated because of multiple other comorbid conditions limiting life expectancy. Excluding AIDS diagnosis from the CCI calculation also resulted in reclassifying one man who had prior AIDS diagnosis and received watchful waiting from appropriately treated to undertreated. Overall, 94.6% of HIV<sup>+</sup> men and 100% of HIV<sup>-</sup> men with known treatment were appropriately treated after excluding the AIDS diagnosis (*P* = 0.03).

### Association between HIV and radical prostatectomy by NCCN risk classification

Among men with clinically localized prostate cancer, we evaluated the association of HIV and radical prostatectomy stratified by NCCN risk classification (Supplementary Table S3). There were significantly fewer radical prostatectomies among HIV<sup>+</sup> men in the low-risk group (12.0% in HIV<sup>+</sup> men vs. 65.0% in HIV<sup>-</sup> men, *P* < 0.001) and

intermediate-risk group (12.5% in HIV<sup>+</sup> men vs. 61.9% in HIV<sup>-</sup> men, *P* = 0.02). The rates of radical prostatectomy were not significantly different in the high/very high risk group (66.7% in HIV<sup>+</sup> men vs. 55.6% in HIV<sup>-</sup> men, *P* = 0.73).

### Association between HIV and radical prostatectomy in the multivariate model

We next evaluated for factors associated with receiving radical prostatectomy as primary treatment for clinically localized prostate cancer (Table 3). In our best-fit conditional logistic regression, HIV infection was strongly negatively associated with radical prostatectomy (OR, 0.13; *P* = 0.01) when controlling for CCI and insurance status. In other models, BMI, CD4, and viral suppression were not associated with radical prostatectomy utilization (data not shown, all *P* > 0.20).

Given that the difference in radical prostatectomy utilization predominated in the open radical prostatectomies on univariate analysis, we then stratified by type of radical prostatectomy to compare open radical prostatectomy with the nonradical prostatectomy treatments using binary conditional logistic regression. HIV infection was strongly negatively associated with open radical prostatectomy (OR, 0.03; *P* = 0.007) when controlling for CCI and insurance. HIV was not associated with receipt of MIRP in the univariate conditional regression model (OR = 0.78; *P* = 0.77).

### All-cause mortality

Although cancer-specific survival could not be assessed, all-cause mortality was not statistically different between

**Table 3.** Binary logistic regressions for the association of HIV infection and radical prostatectomy in clinically localized prostate cancer

All RP ( <i>n</i> = 72) vs. other non-RP treatments <sup>a,b</sup> ( <i>n</i> = 49)	Open RP ( <i>n</i> = 50) vs. other non-RP treatments <sup>a,b</sup> ( <i>n</i> = 49)	MIRP ( <i>n</i> = 22) vs. other non-RP treatments <sup>a,c</sup> ( <i>n</i> = 49)
OR (95% CI)	OR (95% CI)	OR (95% CI)
HIV infection <b>0.13 (0.03–0.63)<sup>d</sup></b>	HIV infection <b>0.03 (0.003–0.39)<sup>e</sup></b>	HIV infection 0.78 (0.14–4.36)
CCI ≥ 3 0.54 (0.07–4.14)	CCI ≥ 3 1.29 (0.09–18.53)	—
Private insurance 1.10 (0.09–13.11)	Private insurance 2.03 (0.16–25.17)	—

NOTE: The bolded values are those with statistical tests where the *P* value was less than 0.05.

Abbreviation: RP, radical prostatectomy.

<sup>a</sup>Other non-RP treatments included: radiation therapy, cryotherapy, high-intensity frequency ultrasound, androgen deprivation therapy, and expectant management.

<sup>b</sup>HIV status, Charlson Co-morbidity Index, and insurance status included in the models.

<sup>c</sup>HIV status included in the model.

<sup>d</sup>*P* < 0.05.

<sup>e</sup>*P* < 0.01.

HIV<sup>+</sup> and HIV<sup>−</sup> men after prostate cancer diagnosis (11.9/1,000 vs. 7.4/1,000 person-years, *P* = 0.47).

## Discussion

In this single-center study of largely HAART-experienced, virally suppressed patients, HIV infection was not associated with significant differences in prostate cancer characteristics or undertreatment. However, we found that HIV<sup>+</sup> men were statistically less likely to receive appropriate prostate cancer treatment, which was driven by calculated life expectancy. The HIV<sup>+</sup> group also trended toward more radiotherapy and was significantly less likely to receive radical prostatectomy, especially open radical prostatectomy, compared with the seronegative group.

We found that the median age at prostate cancer diagnosis in HIV<sup>+</sup> men was 7 years earlier than the observed national median age (59.2 vs. 66.0 years; ref. 38), which likely reflects the younger age distribution of HIV<sup>+</sup> men (39). Consistent with prior reports, HIV does not seem to be associated with aggressive prostate cancer subtypes (17). However, we found that the frequency of metastatic disease at presentation in the HIV<sup>+</sup> cohort was 2.5 times the frequency of that observed in the seronegative cohort, though this failed to reach statistical significance. Lack of access to regular medical care and delayed presentation in a subset of HIV<sup>+</sup> men could be a contributing factor and should be examined in future studies.

Receipt of appropriate treatment was high in both HIV<sup>+</sup> (89.2%) and HIV<sup>−</sup> (100%) groups, though HIV<sup>+</sup> men remained significantly less likely to be appropriately treated for prostate cancer, even when we excluded prior AIDS diagnoses from the life expectancy calculation

(94.6% vs. 100%, *P* = 0.03). This may be due to difficulty with estimating life expectancy in the HIV/AIDS population, resulting in undertreatment or overtreatment. Prior AIDS diagnosis weighs heavily in the CCI, which was devised in the pre-HAART era, and results in a low estimated 10-year life expectancy. In the HAART era, life expectancy of HIV<sup>+</sup> persons is approaching that of the general population (33, 40). Though survival may still be modulated by severity of immune compromise (32, 33) and prior AIDS diagnosis (34), it is unclear to what extent these should be factored into contemporary calculations of comorbidity or life expectancy in HIV<sup>+</sup> patients. As an increase in urologic referrals of HIV<sup>+</sup> men with prostate cancer is anticipated, revised HIV/AIDS survival indices are called for to assist in selecting appropriate prostate cancer treatments.

Analysis of individual categories of treatments revealed that HIV<sup>+</sup> cases received radical prostatectomy significantly less frequently and radiotherapy more frequently than HIV<sup>−</sup> controls. The same treatment pattern is well characterized in African American men (27, 41, 42). In African Americans, etiologies for treatment differences are multifactorial and include patient mistrust of physicians (43), general negative attitudes against surgery (44), and lack of access to care (26, 45–48). Potential provider factors may include bias from known poorer outcomes in national datasets (26, 46–53) and more challenging pelvic anatomy in African Americans (54, 55). In this study, we found that HIV infection was associated with decreased odds of receiving radical prostatectomy even after controlling for CCI, insurance status, and many known covariates associated with treatment choice that were not included in the final regression models. The observed difference in receipt of open radical prostatectomy was

also not explained by the timing of MIRP adoption at our institution (pre- and post-2007, data not shown).

Both patient and provider factors may contribute to the prostate cancer treatment differences we observed in HIV<sup>+</sup> men. Erectile dysfunction can be a devastating prostate cancer treatment complication (56) that is more frequent after radical prostatectomy compared with radiotherapy (57, 58), with between 30% and 90% of patients exhibiting postoperative sexual dysfunction (59). Furthermore, open radical prostatectomy may confer greater risk of erectile dysfunction compared with laparoscopic robotic radical prostatectomy (60). Although we were unable to ascertain specific HIV risk factors in this sample, men who have sex with men (MSM) comprise the largest risk category in Chicago (70%; ref. 61), similar to national trends. Sexual concerns are prominent in MSM diagnosed with prostate cancer (62), and in one small series, all MSM who had undergone radical prostatectomy reported postoperative sexual dysfunction, including erectile dysfunction (63). Anal insertion during sex requires a higher degree of erectile function than vaginal sex, thus the risk of erectile dysfunction may deter MSM away from radical prostatectomy and open radical prostatectomy in particular (64). Provider assessments of sexual preference and sexual concerns are frequently inadequate (64), and these should be prioritized to improve prostate cancer treatment decision making in HIV<sup>+</sup> and MSM populations.

Surgical considerations may have affected treatment received. Relative to the MIRPs, open radical prostatectomies are associated with higher average blood loss (65–67) and likely involve higher risk for needle stick and electrocautery injuries to the surgeons (68). It is possible that open radical prostatectomies are performed less frequently in HIV<sup>+</sup> men to limit risk of HIV transmission to the surgeon (17), though the rate of occupational HIV infection after a needle stick injury is relatively low (0.3%; refs. 69, 70). In the pre-HAART era, 74% of orthopedic surgeons reported at least moderate concern about occupational acquisition of HIV (71). Even in the era of widespread HAART in which there have been no documented cases of HIV transmission to surgeons (72, 73), concern over HIV acquisition during surgery persists in over half (54%) of trainees, in whom only a fraction (16%) is aware of the minimal risk conferred by needle stick injury (74). There may also be perceived increased risk of wound infections or other negative surgical outcomes associated with comorbid HIV infection. Silberstein and colleagues found a slight increase in transfusion and postoperative ileus in HIV<sup>+</sup> men relative to seronegative patients who underwent robotic radical prostatectomy. However, short-term oncologic outcomes were comparable, and the study lent credence to the safety and efficacy of robotic radical prostatectomy in HIV<sup>+</sup> men (12). Data from open radical prostatectomy series are limited, but suggest that it is safe in men with relative immune competence (e.g., CD4 >400/mm<sup>3</sup>) and viral suppression (11, 17), consis-

tent with reports on safety of other surgeries in patients with comorbid HIV (75).

Surgical disparities are observed in HIV<sup>+</sup> persons with other malignancies. Amongst those with localized non-small cell lung cancer, HIV<sup>+</sup> patients are less likely to receive any cancer treatment, including surgical resection, even though such treatment could potentially be curative. This treatment disparity may contribute to poorer survival noted in patients with lung cancer with comorbid HIV infection (7). Though widely used prostate cancer guidelines (23) indicate that radical prostatectomy and radiotherapy are equally appropriate choices for a given risk stratification, emerging data suggest that radical prostatectomy results in improved survival over radiotherapy in men with clinically localized prostate cancer (18–22). In this study, significantly fewer radical prostatectomies occurred in HIV<sup>+</sup> men with intermediate-risk disease, which is the classification group most likely to benefit from surgery (22, 76). The survival benefit conferred by radical prostatectomy is also pronounced in men diagnosed with prostate cancer at younger ages (<65 years; refs. 20, 22), which includes many of the HIV<sup>+</sup> men in this study who were diagnosed at median age of 59.2 years. Thus, lower rates of radical prostatectomy may lead to excess mortality in HIV<sup>+</sup> men, which is consistent with a trend toward higher mortality among HIV<sup>+</sup> patients in our study. At this time, the source of the observed treatment differences in radical prostatectomy for HIV<sup>+</sup> men is unclear, but we believe that both patient and surgeon factors are important and should be further studied to optimize patient-centered cancer care (77).

A potential limitation of this study is the generalizability of our population. Most HIV patients in this cohort were on HAART with well-controlled infection. This study was also conducted at a large, urban referral center for radical prostatectomy. However, these factors would seem to promote the use of radical prostatectomy, raising concern that treatment differences seen here may be amplified in other circumstances (e.g., patients with untreated or uncontrolled HIV infection treated at centers with low radical prostatectomy volume). A second limitation of the study is the retrospective design that limited our ability to measure certain key variables, potentially leading to residual confounding. We were unable to assess the patients' perspective in the treatment decision-making process, which treatment options were presented and recommended by the physician, and which treatment was initially preferred and ultimately selected by the patient. A third limitation is that we may not have adequately captured treatments that were not undertaken at our institution, potentially resulting in underreporting radical prostatectomy for the HIV<sup>+</sup> group; however, we made efforts to thoroughly describe all treatments received by conducting chart reviews specifically looking for documentation of prostate cancer treatments in provider histories. Even if all HIV<sup>+</sup> men with unknown treatment had selected radical prostatectomy at another institution, there would

still be notably fewer radical prostatectomies in the HIV<sup>+</sup> group (53.5% vs. 71.0%,  $P < 0.001$ ). The strength of this study is that it is the first and largest report on the differences in rates of risk-appropriate prostate cancer treatment and patterns of prostate cancer treatment received between HIV<sup>+</sup> and HIV<sup>-</sup> men.

In conclusion, prostate cancer in HIV<sup>+</sup> men is largely appropriately treated. Under- or overtreatment may occur in HIV<sup>+</sup> men due to difficulties with life expectancy estimation. In HIV<sup>+</sup> men with adequate life expectancy, radical prostatectomy, specifically open radical prostatectomy, is utilized less and radiotherapy may be utilized more than in the general population, which may contribute to excess mortality. This treatment pattern should be confirmed in larger epidemiologic studies. Studies on etiologies and short- and long-term outcomes of decreased receipt of radical prostatectomy in HIV<sup>+</sup> men are warranted.

#### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

#### Authors' Contributions

**Conception and design:** A.B. Murphy, R. Bhatia, I.K. Martin, C.M.P. Hollowell, C. Achenbach

**Development of methodology:** A.B. Murphy, R. Bhatia, I.K. Martin, C.M.P. Hollowell

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** A.B. Murphy, R. Bhatia, E. Dielubanza

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** A.B. Murphy, R. Bhatia, I.K. Martin, D.A. Klein, Y. Nyame, C. Achenbach

**Writing, review, and/or revision of the manuscript:** A.B. Murphy, R. Bhatia, I.K. Martin, D.A. Klein, C.M.P. Hollowell, Y. Nyame, C. Achenbach, R.A. Kittles

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** A.B. Murphy, R. Bhatia, D.A. Klein

**Study supervision:** C.M.P. Hollowell

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# Cancer Epidemiology, Biomarkers & Prevention

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