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MAJOR ARTICLE

Risks of Opportunistic Infections in People With Human Immunodeficiency Virus With Cancers Treated With Chemotherapy

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Background. We ascertained incidence of opportunistic infections (OIs) in people with human immunodeficiency virus (PWH) with cancer undergoing chemotherapy with non-human immunodeficiency virus (HIV) comparators.

Methods. We identified 2106 PWH and 2981 uninfected Veterans with cancer who received at least 1 dose of chemotherapy between 1996 and 2017 from the Veterans Aging Cohort Study. We ascertained incident OIs within 6 months of chemotherapy amongst zoster, cytomegalovirus, tuberculosis, *Candida* esophagitis, *Pneumocystis jirovecii* pneumonia (PCP), toxoplasmosis, Cryptococcosis, atypical *Mycobacterium* infection, *Salmonella* bacteremia, histoplasmosis, coccidioidomycosis, or progressive multifocal leukoencephalopathy. We used Poisson methods to calculate OI incidence rates by HIV status, stratifying for hematological and nonhematological tumors. We compared OI rates by HIV status, using inverse probability weights of HIV status, further adjusting for PCP prophylaxis.

Results. We confirmed 106 OIs in 101 persons. Adjusted OI incidence rate ratios (IRRs) indicated higher risk in PWH for all cancers (IRR, 4.8; 95% confidence interval [CI], 2.8–8.2), hematological cancers (IRR, 8.2; 95% CI, 2.4–27.3), and nonhematological cancers (IRR, 3.9; 95% CI, 2.1–7.2). Incidence rate ratios were not significantly higher in those with CD4 >200 cells/mm^3 and viral load <500 copies/mL (IRR, 1.8; 95% CI, 0.9–3.2). All PCP cases (n = 11) occurred in PWH, with 2 microbiologically unconfirmed cases among 1467 PWH with nonhematological cancers, no PCP prophylaxis, and CD4 counts >200/mm^3.

Conclusions. Veterans with HIV undergoing chemotherapy had higher rates of OIs than uninfected Veterans, particularly those with hematological cancers, but not in PWH with HIV controlled disease. Our study does not support systematic PCP prophylaxis in solid tumors in PWH with HIV controlled disease.

Keywords. Cancer; chemotherapy; opportunistic infections; *Pneumocystis jirovecii* pneumonia; prophylaxis.

Since the advent of highly active combination antiretroviral therapy (ART), life expectancy has increased for persons with human immunodeficiency virus (PWH). Meanwhile, mortality and morbidity patterns for PWH have shifted away from acquired immune deficiency syndrome (AIDS)-related morbidity to noncommunicable diseases such as non-AIDS-defining malignancies [1, 2]. This change can be attributed to several factors including the aging of the PWH population [3], increased prevalence of cancer-causing coinfections and immunologic susceptibility to cancers [4–8], and increased carcinogenic exposures such as smoking [8]. With current demographic trends among PWH, it is expected that the burden of cancer in this group will continue to increase [9].

Despite a growing cancer prevalence among PWH, there is limited information regarding cancer treatment complications specific to this group. People with human immunodeficiency virus (HIV) may have unique harm profiles related to cancer therapies, particularly with those that impact the immune system. Chemotherapy, in particular, is a cornerstone of treatment for cancer patients, but little is known regarding the interaction of HIV disease and this treatment modality. For HIV-uninfected persons undergoing cytotoxic cancer chemotherapy, guidelines recommend *Pneumocystis jirovecii* pneumonia (PCP) and toxoplasmosis prophylaxis in persons with solid tumors and with a pneumocystis risk higher than 3.5% [10], or treated with a prednisone dose equivalent >20 mg/day for more than 1 month, or purine analogs [11]. Guidelines for hematological malignancies recommend PCP and toxoplasmosis primary prophylaxis for patients with hematopoietic stem

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cell transplantation, chronic lymphoid leukemia, alemtuzumab, or fludarabine-cyclophosphamide-rituximab use, administration of prednisone >20 mg for more than 1 month, or in subjects with primary immunodeficiencies [12], with optional prophylaxis for persons undergoing R-CHOP intensified treatment, the BEECOPP protocol for Hodgkin disease, or autologous bone marrow transplant. These varied recommendations have no guidance specificity for PWH leading to uncertainty related to prophylaxis in this growing and important group of patients.

People with HIV with malignancies treated with chemotherapy may be at enhanced risk of opportunistic infections (OIs) due to the combined immunologic impairment of chemotherapy and disturbances caused by chronic HIV infection, which, despite good viremic control, is still associated with adverse immune effects [13]. Several studies have also suggested that PWH may have persistently depressed CD4 counts after treatment with chemotherapy and/or radiotherapy [14–16], but most analyses had limited power to determine whether this impacts the clinical risk for major OI complications.

In this study, we used contemporary data from a large, national cohort of Veterans to (1) clarify types and risks for OIs in PWH undergoing chemotherapy and (2) compare OI incidence with uninfected comparators.

METHODS

Population

We used data from the Veterans Aging Cohort Study (VACS), a large cohort of PWH who, upon enrollment, are matched by age, race/ethnicity, sex, and Veterans Affairs clinical site to 2 uninfected comparators assembled from Veterans Affairs clinical and administrative data. To be included in this study, PWH and uninfected comparators had to be diagnosed with a malignancy between January 1, 1996 and November 1, 2017, and undergo at least 1 administration of systemic chemotherapy as defined by the Surveillance, Epidemiology and End-Results Antineoplastic Drugs Database (seer.cancer.gov).

Study Outcomes and Variables

The VA databases were used to identify baseline sociodemographic variables at cancer diagnosis, clinical and oncological variables, and chemotherapy administered. We recorded the following demographics: age at cancer diagnosis, year of cancer diagnosis, sex, race/ethnicity, VA site, HIV status and smoking status (current, former, never), presence of alcohol use disorder, and a modified Charlson comorbidity index (CCI) at time of cancer diagnosis (removing both cancer and HIV/AIDS from the score to avoid bias) and hepatitis C virus status [17]. Antimicrobial prophylaxis was identified using pharmacy data and defined by any agent prophylactically active against pneumocystis or toxoplasmosis: cotrimoxazole, dapsone, atovaquone, inhaled or intravenous pentamidine, or pyrimethamine.

Tumor anatomic site was collected from linked cancer registry data; we analyzed hematological and nonhematological malignancies separately, because intrinsic risk of OIs for hematological malignancies is greater, and guidelines recommend systematic prophylaxis for pneumocystis and toxoplasmosis for most hematological malignancies [11, 12] and in some cases for cytomegalovirus (CMV) reactivation [18]. We also excluded Kaposi sarcoma, because any incident OI might reflect underlying immunodeficiency in PWH and/or HIV-uncontrolled viremia. Cutaneous cancers other than melanoma were also excluded, because these would be prone to differential diagnosis biases between veterans with HIV or not, and not be treated with systemic chemotherapy. The following malignancies were considered hematological: non-Hodgkin lymphoma, Hodgkin disease, acute nonlymphocytic leukemia, acute lymphocytic leukemia, chronic lymphocytic leukemia, chronic myelocytic leukemia, plasma cell disorders, and other hematological/reticuloendothelial cancers.

Our primary outcome was incidence of OI within 6 months of chemotherapy initiation and occurring at least 14 days after first chemotherapy administration. We defined the following infections for our outcome: zoster, CMV, tuberculosis, *Candida* esophagitis, PCP, toxoplasmosis, Cryptococcosis, atypical *Mycobacterium* infection, *Salmonella* bacteremia, histoplasmosis, coccidioidomycosis, cryptosporidiosis, isosporiasis, and/or progressive multifocal leukoencephalopathy. We used diagnostic codes to identify OIs. All OIs were then confirmed by an infectious diseases physician by chart review (see Supplement for OI diagnostic criteria).

Statistical Analysis

We first compared baseline patient characteristics by HIV status, testing for differences using the χ^2 test for categorical variables and the Wilcoxon test for continuous variables. We then performed similar comparisons by HIV status, stratified by hematological versus nonhematological malignancy. Next, we compared the proportions of cancer anatomic site and OI type by HIV status.

For analyses of OI incidence, we included patients if they had received at least 1 dose of chemotherapy after their cancer diagnosis. Using Poisson methods, we calculated the incidence rate of OIs and 95% confidence intervals (CIs) using the binomial distribution, stratified by HIV status and hematological versus nonhematological malignancy type. To compare OI risk by HIV status, we used inverse probability weighting (IPW) of HIV status to account for differences between PWH and controls potentially influencing OI risk. To generate inverse probability weights, we first calculated estimated probabilities by fitting logistic regression models predicting HIV status based on baseline characteristics of age, sex, tumor site, race/ethnicity, year of cancer diagnosis, smoking status, and alcohol use disorder. These probabilities were then used to directly calculate inverse

probability of HIV status weights [19]. We then fitted IPW Poisson models to evaluate the association between HIV and OI risk overall, stratified by hematological and nonhematological malignancies, adjusting for OI prophylaxis use. To assess differences in OI incidence over time, we divided the overall study period into 4 intervals (1996–2000, 2001–2006, 2007–2012, and 2013–2017) and calculated overall OI incidence for cohort subjects in each period by HIV status. We also recalculated the adjusted incidence rate ratio (IRR) for each period and compared age at cancer diagnosis, CD4 count, proportion of hematological cancers, and prevalence of HIV virologic suppression at the time of cancer diagnosis.

We then fitted a separate Poisson regression model of PWH to explore factors associated with incidence of OI among PWH, analyzing the association with age at cancer diagnosis, sex, race/ethnicity, hematological versus nonhematological malignancy, smoking status, CCI, CD4 count, presence of HIV virologic control (HIV viral load ≤500 copies/mL), and use of PCP prophylaxis. We used Stata version 15 for statistical analyses.

Patient Consent Statement

This research was approved by the Yale University School of Medicine Institutional Review Board, which granted a waiver of informed consent.

RESULTS

During the study period we identified 2106 PWH and 2981 uninfected comparators with cancer treated with at least 1 administration of chemotherapy. Compared with uninfected Veterans, PWH were slightly younger (55 versus 59 years), had lower alcohol use disorder (14.0% versus 19.4%) (Table 1), had more hematological malignancies (30.3% versus 15.7% of all malignancies in PWH and uninfected persons, respectively), and were more likely to be prescribed PCP prophylaxis (30.3% versus 4.2%). Although gender, race, and smoking status differed statistically between populations. The CCI scores were similar in both populations. Baseline characteristics according to HIV status and hematological versus nonhematological cancer are shown in Supplemental Table S1. In PWH with a CD4 count >200/mm^3, 261 of 1443 (18%) were prescribed prophylaxis (26.5% and 15.0% in PWH with hematological cancers and nonhematological cancers, respectively).

Lung cancer was the most common nonhematological cancer type (19.0% of cancers among PWH, 29.5% of uninfected Veterans). The next most frequent were anal, liver, colorectal, pharynx, and pancreas in PWH and colorectal, liver, pharynx, and esophagus in uninfected Veterans (Supplemental Table S2). For hematological cancers, lymphomas were the most frequent, with higher proportions in PWH (24.4%), followed by acute lymphocytic and nonlymphocytic leukemia, and plasma cell disorders.

Table 1. Baseline Characteristics by HIV Status for Patients With Cancer Treated With Chemotherapy

Characteristics	PWH (n = 2106)	Uninfected Veterans (n = 2981)	*P*
Age (median, IQR)	55 (49–62)	59 (54–64)	<.001
Male, n (%)	2077 (98.6)	2913 (97.7%)	.02
Race/Ethnicity, n (%)			<.001
Non-Hispanic white	944 (44.8)	1183 (39.7)	
Non-Hispanic black	963 (45.7)	1537 (51.6)	
Hispanic	147 (7.0)	211 (7.1)	
Other	52 (2.5)	50 (1.7)	
Smoking, n (%)			<.001
Never	389 (18.5)	451 (15.1)	
Current	1127 (53.5)	1723 (57.8)	
Former	324 (15.4)	545 (18.3)	
Unknown	266 (12.6)	262 (8.8)	
CCI (median, IQR)[a]	1 (0–2)	1 (0–2)	.8
Alcohol Use Disorder, n (%)	295 (14.0)	577 (19.4)	<.001
Malignancies, n (%)			<.001
Hematological	639 (30.3)	469 (15.7)	
Nonhematological	1467 (69.7)	2512 (84.3)	
PCP prophylaxis use, n (%)	638 (30.3)	124 (4.2)	<.001
HIV-related characteristics		NA	
Recent CD4, cells/mm^3, median (IQR)	287 (140–506)	NA	
Controlled viremia (<500 copies/mL) (%)	1302 (68.7)	NA	
CD4 count >200 cells/mm^3 (%)	1441 (68.4)	NA	
CD4 count >200 cells/mm^3 and controlled viremia (%)	909 (43.2)	NA	
CD4 count >200 cells/mm^3 and controlled viremia and PCP prophylaxis (%)	161 (7.6)	NA	

Abbreviations: CCI, Charlson comorbidity index; HIV, human immunodeficiency virus; IQR, interquartile range; NA, not applicable; PCP, *Pneumocystis jirovecii* pneumonia; PWH, people with HIV.

[a]Our modified CCI omits acquired immune deficiency syndrome and solid or nonsolid cancer diagnoses.

We confirmed a total of 106 incident OIs in 101 persons. Eighty-four occurred in PWH, and 22 occurred in uninfected Veterans (Supplemental Table S3). Of the 47 OIs occurring in patients with hematological malignancies, 43 occurred in PWH; of the 59 OIs occurring in patients with nonhematological malignancies, 41 occurred in PWH. The predominant OI was *Candida* esophagitis (n = 43), mostly in PWH (n = 33), followed by herpes zoster (n = 30), also mostly in PWH (n = 21). Ten zoster cases occurred in persons with lymphomas, 9 of whom were PWH, and 5 in persons with anal cancer, all PWH. Only 1 zoster case occurred in a PWH who had an indication for systematic valacyclovir prophylaxis (ie, a plasma cell disorder). All PCP cases (n = 11), 10 of the 11 CMV cases, all *Cryptococcus* cases (n = 3), and 5 of the 6 nontuberculous mycobacterial infection occurred in PWH. Toxoplasmosis diagnosed after chemotherapy was not identified in the cohort. Among PWH with CD4 counts >200/mm^3, nonhematological cancers at diagnosis, and not taking PCP prophylaxis, 2 (0.1%) were treated for possible but microbiologically unconfirmed PCP. Interstitial carcinomatosis

was suspected for both cases; one case was virologically suppressed, whereas the HIV viral load was 72 000 copies/mL for the second case.

Incidence rates for OIs were 89.0/1000 person-years in PWH and 17.8/1000 person-years in uninfected Veterans (Table 2). Rates were 142.4/1000 person-years and 19.0/1000 person-years in patients with hematological cancers and 66.6/1000 person-years and 17.6/1000 person-years in patients with nonhematological malignancies in PWH and uninfected Veterans, respectively. The OI incidence rates were higher in PWH for all cancers (IRR, 4.8; 95% CI, 2.8–8.2), hematological cancers (IRR, 8.2; 95% CI, 2.4–27.3), and nonhematological cancers (IRR, 3.9; 95% CI, 2.1–7.2), after accounting for IPW and adjusting for prophylaxis use (Table 2). We also explored OI incidence in subgroups of PWH; those with CD4 >200 cells/mm^3 still had increased risk of OIs during chemotherapy (IRR, 4.1; 95% CI, 2.3–7.2) compared with uninfected persons, but those with CD4 >200 cells/mm^3 and viral load <500 copies/mL did not have statistically significantly increased adjusted risk overall (IRR, 1.8; 95% CI, 0.9–3.2) or when stratifying by nonhematological or hematological cancers (both $P > .05$; results not shown).

In our analyses exploring OI incidence over time, we found that incidence was highest for PWH in 2001–2006 (136.0/1000 person-years for PWH) with a successive decline over the subsequent 2 periods (2007–2012 and 2013–2017) (Figure 1). Adjusted IRRs significantly declined over time, with an IRR of 3.0 (95% CI, 1.1–8.4) in the most recent time period. During the same periods, we found systematic and significant increase in age, median CD4 count, and proportions of PWH with HIV viremia <500 copies/mL at cancer diagnosis, as well as a significant decrease of proportions of hematological cancer diagnosis ($P < .001$ for all trends) (Figure 2). In analyses of predictive factors for OIs only among PWH, uncontrolled HIV viremia (IRR, 11.8; 95% CI, 6.3–22.4) and CCI score (IRR, 1.2; 95% CI, 1.0–1.4) were independently associated with OI risk (Table 3).

DISCUSSION

In this study, we compared the incidence rates of OIs in PWH and uninfected veterans undergoing chemotherapy for cancer. We found that OI incidence was significantly higher in PWH for both hematological and nonhematological malignancies, even after accounting for imbalances in risk factors in both populations. Increased risk of OIs for PWH with cancer receiving chemotherapy persisted through recent years despite population-level improvements in HIV disease control, although there was a decrease in adjusted risk ratios.

Table 2. Comparison of Incidence Rates and Adjusted Rate Ratios of First Opportunistic Infection in All Cancers, and According to Hematological and Nonhematological Cancers in PWH and Uninfected Veterans

Incidence Rates and Ratios of First OI in All Cancers					
Number of Events (Persons With First OI)		OI Incidence Rate/1000 p-y (95% CI)			
PWH (n = 2106)	Uninfected (n = 2981)	PWH	Uninfected	IRR for PWH[b]	95% CI
78 (3.7%)[a]	23 (0.8%)[a]	89.0 (71.3–111.2)	17.8 (11.9–26.9)	4.8	2.8–8.2
Incidence Rates and Ratios of First OI in Hematological Cancers					
PWH (n = 639)	Uninfected (n = 469)	PWH	Uninfected	IRR for PWH[b]	95% CI
37 (5.8%)	4 (0.9%)	142.4 (103.2–196.5)	19.0 (7.1–50.6)	8.2	2.4–27.3
Incidence Rates and ratios of First OI in Nonhematological Cancers					
PWH (n = 1467)	Uninfected (n = 2512)	PWH	Uninfected	IRR for PWH[b]	95% CI
41 (2.8%)	219 (8.7%)	66.6 (49.1–90.4)	17.6 (11.2–27.6)	3.9	2.1–7.2
Incidence Rates and Ratios of First OI in All Cancers for PLHIV With CD4 >200 Cells/mm^3 Compared With All Uninfected Patients					
PWH (n = 1441)	Uninfected (n = 2981)	PWH	Uninfected	IRR for PWH[b]	95% CI
48 (3.3%)	23 (0.8%)	80.0 (60.3–106.2)	17.8 (11.9–26.9)	4.1	2.3–7.2
Incidence Rates and Ratios of First OI in All Cancers for PWH With CD4 >200 cells/mm^3 and HIV RNA <500 Copies/mL Compared With All Uninfected Patients					
PWH (n = 909)	Uninfected (n = 2981)	PWH	Uninfected	IRR for PWH[b]	95% CI
13 (1.4%)	23 (0.8%)	33.5 (19.4–57.6)	17.8 (11.9–26.9)	1.82	0.86–3.90

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; IRR, incidence rate ratio; OI, opportunistic infection; P-y, person-year; PWH, people with HIV; RNA, ribonucleic acid.

[a]A total 106 OIs in 101 persons, because some patients had multiple events.

[b]Inverse probability weighted and adjusted for *Pneumocystis jirovecii* pneumonia prophylaxis use.

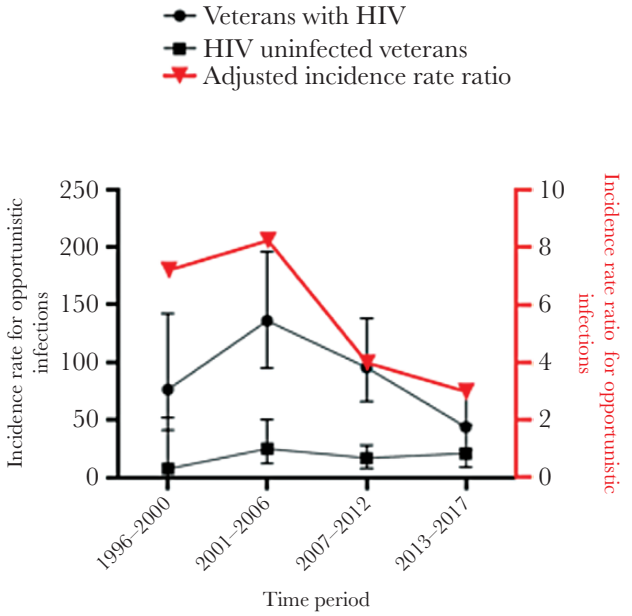

Figure 1. Incidence of opportunistic infections (OIs) after cancer chemotherapy by human immunodeficiency virus (HIV) status during 4 time periods: 1996–2000, 2001–2006, 2007–2012, and 2013–2017. Incidence was highest for people with HIV (PWH) in 2001–2006 and then declined. Adjusted incidence rate ratios (inverse probability weighted and adjusted for *Pneumocystis jirovecii* pneumonia prophylaxis use) for OIs for PWH versus uninfected also shown (red triangles) and was highest in 2001–2006, with a decline for subsequent periods (see main text for further details).

However, the increased risk of OIs in PWH was no longer statistically significant when selecting individuals with CD4 levels >200 cells/mm^3 and controlled viremia, irrespective of cancer types. The majority of OIs were *Candida* esophagitis or herpes zoster, and we found no toxoplasmosis infections nor definite PCP in PWH with nonhematological malignancies and a CD4 count >200 cells/mm^3. Uncontrolled HIV viremia and comorbidity burden were linked to OI risk for PWH.

To our knowledge, this is the first study assessing incidence of OIs in PWH undergoing chemotherapy as a primary outcome with an uninfected comparison group. Series in PWH have largely focused on the effect of cancer treatments on CD4 counts, and highlighted the risk of CD4 count transient depletion after chemotherapy, and of more severe and prolonged depletion after radiotherapy [14, 16, 20]. In these studies, OIs were described in PWH with AIDS-defining cancers: 8 (12%) and 10 (14%) OIs in non-Hodgkin lymphoma series of 68 and 74 patients, respectively [20, 21]. Recent cohorts of PWH with nonhematological malignancies undergoing chemotherapy showed no OIs [16, 22, 23], although these results may simply be due to the limited numbers of PWH analyzed. Although our cohort spanned the early and more recent periods of the ART era, we found continued elevated risk of OIs associated with HIV infection. This may relate to incomplete immune recovery in addition to the immunosuppressive effect of chemotherapy present in some PWH with cancer, despite the increasing median levels of CD4 counts at cancer diagnosis. It is interesting to note that this risk seems to be substantially lower in PWH with CD4 levels >200/mm^3 and HIV virologic suppression, because adjusted incidence rate ratios of OIs in this subgroup were not significantly different from uninfected Veterans.

Our decrease in IRR of OIs with calendar time may have several underlying explanations. Chemotherapy protocols may have been modified with time and accumulated experience in the oncologic care of PWH, inducing less immune toxicities and interactions. However, the most substantial contributor is likely to be the increased proportion of PWH with virologic control over time and increases in median CD4 levels at cancer diagnosis. Our findings reflect broader trends in OI incidence as illustrated by a large study using data from the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) that found decreased incidence of OIs during 2000–2010 era in PWH without cancer, which correlated with increasing CD4 values and better virologic control with time [24]. It is notable that incidence rates for OIs among all cancer patients in our study were substantially higher than OIs among the general PWH population during the most recent period for NA-ACCORD (2008–2010; 14.5 cases per 1000/person-years; 95% CI, 13.7–15.4) but were broadly similar to cancer patients in our cohort with good HIV disease control.

Candida esophagitis and herpes zoster represented approximately three quarters of OIs and disproportionally affected PWH. *Candida* esophagitis can result in pain, dysgeusia, anorexia, and malnutrition, reducing tolerance to cancer therapies. Herpes zoster can lead to severe neuralgia as well as more serious sequelae such as blindness or encephalitis. Herpes zoster in PWH undergoing chemotherapy may have resulted from combined effects of HIV-related immune disturbances and added immunosuppression from chemotherapeutics [25, 26]. European Conference on Infections in Leukaemia (ECIL) guidelines recommend acyclovir or valacyclovir prophylaxis administered after allogeneic or autologous hematopoietic stem cell transplants [27] and as optional prophylaxis in persons with plasma cell disorders or chronic lymphocytic leukemia. How much these recommendations were applied in our study for patients with plasma cell disorders is unknown, but herpes zoster cases generally occurred in patients without these cancers. Our study supports evaluations of preventive herpes zoster strategies specifically in PWH with malignancies, particularly lymphomas and anal cancer, as previously evaluated in persons with nonhematological malignancies in the general population [28]. Increased coverage with inactivated zoster vaccine may decrease the risk for herpes zoster in this population.

Incidence of PCP in this study was low, and our analysis found no toxoplasmosis infections. These results may reflect

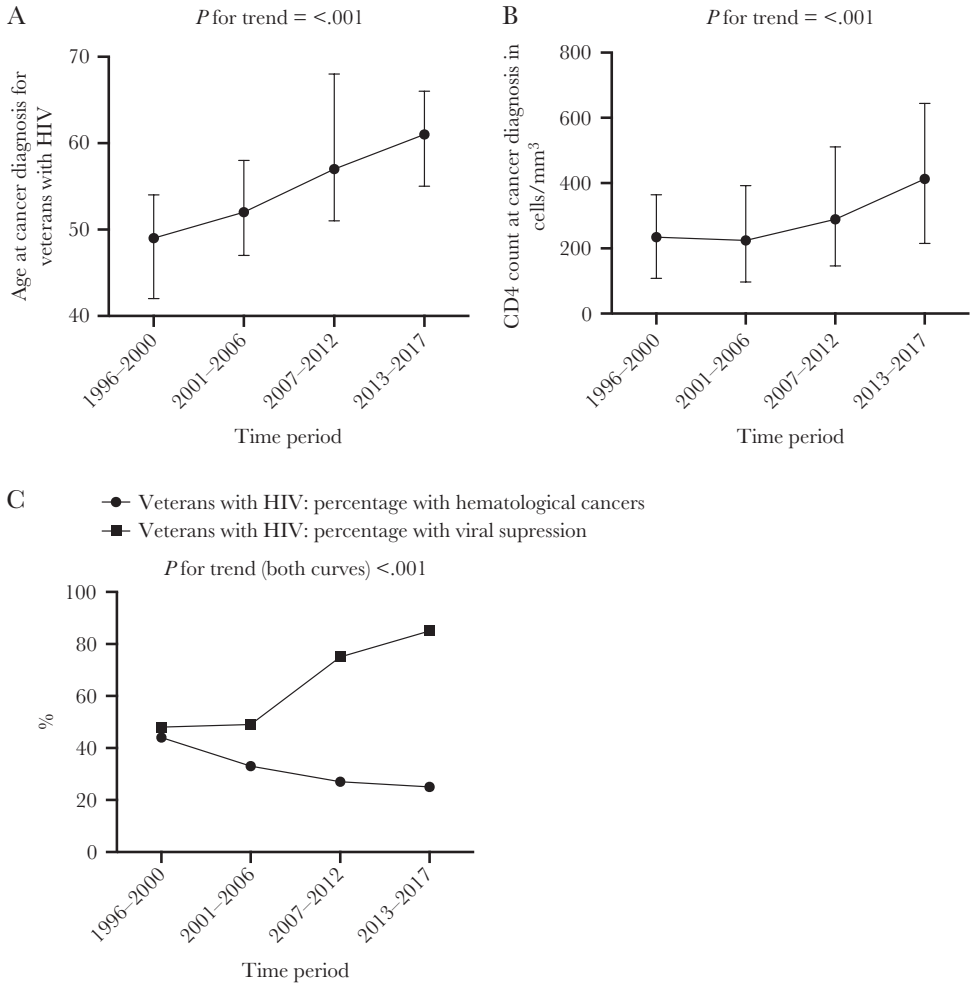

Figure 2. Trends in age (2a), median CD4 count (2b), proportion of hematological cancers and proportion with human immunodeficiency virus (HIV) control (HIV <500 copies/mL) (2c) during study time periods at cancer diagnosis for Veterans with HIV during study time periods.

adequate PCP prophylaxis in PWH with low CD4 levels in our study cohort, as recommended by the NCCN guidelines [29]. In addition, the 2 unconfirmed PCP in PWH >200/mm^3 CD4 cell counts without PCP prophylaxis, 1 of the 2 with uncontrolled viremia, provide evidence against systematic PCP prophylaxis in PWH with cancer and higher levels of CD4, particularly if there is controlled viremia. Our results conflict with the European AIDS Clinical Society (http://www.eacsociety.org) and the British HIV association guidelines [30], in which PCP prophylaxis is suggested in PWH with solid cancers, irrespective of CD4 counts. However, proven PCP in uninfected subjects with solid organ malignancies and chemotherapy have been published [31, 32], including a PWH with a CD4 count >500 cells/mm^3 who was not taking ART [33]. Thus, if prophylaxis is not used, clinicians should be aware of the possibility of PCP when confronted with interstitial lung disease, even in patients with high CD4 counts.

The association between OIs and uncontrolled HIV viremia highlights the importance of continuing effective ART in all PWH with cancer, carefully selecting for antiretrovirals that minimize interactions with cytotoxic agents. Comorbidity burden was also independently associated with OI risk, and it may reflect PWH populations that may have ongoing immune dysfunction despite CD4 recovery, because these more subtle immune disturbances have also been associated with the risk of noncancer comorbidities [34].

Our study has some limitations. Underlying cancer risk differs among PWH and uninfected Veterans, justifying the use of IPW to account for non-HIV-related factors that may have contributed to imbalances in OI risk. Chemotherapy types were not accounted for in our adjustments, and there may have been differences in (1) frequencies and doses of administration and (2) number of cycles by HIV status. However, chemotherapy characteristics were indirectly accounted for by tumor type, age, and comorbidity burden, because these factors help guide cancer

Table 3. Adjusted Poisson Regression Model Predicting Opportunistic Infection Incidence in PWH

Characteristics	Incidence Rate Ratio	95% CI	*P*
Age	1.01	0.99–1.04	.30
Male	0.55	0.07–4.09	.55
Race/Ethnicity			
Non-Hispanic white	Reference	Reference	Reference
Non-Hispanic black	0.98	0.59–1.64	.95
Hispanic	1.43	0.67–3.05	.36
Other	1.22	0.28–5.31	.79
Smoking			
Never	Reference	Reference	Reference
Current	0.92	0.51–1.63	.77
Former	1.40	0.71–2.74	.33
Charlson comorbidity index	1.17	1.01–1.35	.04
Malignancy type			
Nonhematological	Reference	Reference	Reference
Hematological	1.35	0.83–2.20	.22
HIV-Related Characteristics			
Recent CD4, cells/mm^3			
>500	Reference	Reference	Reference
350–500	1.67	0.78–3.60	.19
200–349	0.95	0.44–2.10	.89
100–199	0.50	0.20–1.24	.13
50–100	0.44	0.14–1.31	.14
<50	1.21	0.53–2.76	.65
Uncontrolled viremia	11.82	6.25–22.35	<.001
PCP prophylaxis use	1.48	0.88–2.48	.13

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; PCP, *Pneumocystis jirovecii* pneumonia; PWH, people with HIV;

therapeutic strategies, and they were included in the calculation of the IPW scheme. Adjustment on PCP prophylaxis further accounted for chemotherapeutic-associated risk for PCP and toxoplasmosis infection [10, 11]. We did not assess for OI incidence beyond 6 months after chemotherapy administration, nor did we specifically evaluate the risk of OIs after radiotherapy. Studies on CD4 depletion postcancer treatments in PWH have shown a fast recovery of CD4 counts after chemotherapy interruption within 6 months but possible prolonged depletion particularly after radiotherapy [14–16]. Furthermore, cervical cancers were absent from our analysis, because almost all Veterans were men, and our conclusions may not be generalizable to all HIV populations. Last, we did not account for other sources of immunosuppression outside of HIV and cancer-related factors. The strengths of our study reside in its large, national, well characterized cohort of Veterans thanks to the different VA databases derived from extensive, long-standing electronic health record systems and the systematic chart review by an Infectious Diseases specialist of all OI cases in Veterans with cancer.

CONCLUSIONS

In conclusion, our study showed increased risk of incident OIs in the 6 months after chemotherapy in PWH with hematological and nonhematological malignancies compared with uninfected veterans. A statistically significant increased risk did not persist in PWH with CD4 counts >200/mm^3 and controlled viremia. Most OIs reported were esophagitis candida and herpes zoster. Our study does not support systematic PCP prophylaxis in solid tumors in PWH with CD4 >200 cells/mm^3 and controlled viremia.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Author contributions. A. M., J. S., and V. L. M. conceived the analysis and interpreted the findings. A. M. and K. M. S. drafted the manuscript project. A. M., and K. M. S. performed the statistical analysis. All other authors read and approved the final manuscript.

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