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Immune Status and Associated Mortality After Cancer Treatment Among Individuals With HIV in the Antiretroviral Therapy Era

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IMPORTANCE Immunologic decline associated with cancer treatment in people with HIV is not well characterized. Quantifying excess mortality associated with cancer treatment–related immunosuppression may help inform cancer treatment guidelines for persons with HIV.

OBJECTIVE To estimate the association between cancer treatment and CD4 count and HIV RNA level in persons with HIV and between posttreatment CD4 count and HIV RNA trajectories and all-cause mortality.

DESIGN, SETTING, AND PARTICIPANTS This observational cohort study included 196 adults with HIV who had an incident first cancer and available cancer treatment data while in the care of The Johns Hopkins HIV Clinic from January 1, 1997, through March 1, 2016. The study hypothesized that chemotherapy and/or radiotherapy in people with HIV would increase HIV RNA levels owing to treatment tolerability issues and would be associated with a larger initial decline in CD4 count and slower CD4 recovery compared with surgery or other treatment. An additional hypothesis was that these CD4 count declines would be associated with higher mortality independent of baseline CD4 count, antiretroviral therapy use, and risk due to the underlying cancer. Data were analyzed from December 1, 2017, through April 1, 2018.

EXPOSURES Initial cancer treatment category (chemotherapy and/or radiotherapy vs surgery or other treatment).

MAIN OUTCOMES AND MEASURES Post–cancer treatment longitudinal CD4 count, longitudinal HIV RNA level, and all-cause mortality.

RESULTS Among the 196 participants (135 [68.9%] male; median age, 50 [interquartile range, 43-55] years), chemotherapy and/or radiotherapy decreased initial CD4 count by 203 cells/μL (95% CI, 92-306 cells/μL) among those with a baseline CD4 count of greater than 500 cells/μL. The decline for those with a baseline CD4 count of no greater than 350 cells/μL was 45 cells/μL (interaction estimate, 158 cells/μL; 95% CI, 31-276 cells/μL). Chemotherapy and/or radiotherapy had no detrimental association with HIV RNA levels. After initial cancer treatment, every 100 cells/μL decrease in CD4 count resulted in a 27% increase in mortality (hazard ratio, 1.27; 95% CI, 1.08-1.53), adjusting for HIV RNA level. No significant increase in mortality was associated with a unit increase in $\log_{10}$ HIV RNA after adjusting for CD4 count (hazard ratio, 1.24; 95% CI, 0.94-1.65).

CONCLUSIONS AND RELEVANCE In this study, chemotherapy and/or radiotherapy was associated with significantly reduced initial CD4 count in adults with HIV compared with surgery or other treatment. Lower CD4 count after cancer treatment was associated with an increased hazard of mortality. Further research is necessary on the immunosuppressive effects of cancer treatment in adults with HIV and whether health care professionals must consider the balance of cancer treatment efficacy against the potential cost of further immunosuppression. Monitoring of immune status may also be helpful given the decrease in CD4 count after treatment and the already immunocompromised state of patients with HIV.

Invited Commentary

Supplemental content

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Malignant neoplasms are a leading cause of death among people with HIV in the era of antiretroviral therapy (ART).[1-5] Historically, there were concerns about immunosuppressive effects of certain cancer treatments in people with HIV[6-10] and drug-drug interactions with ART.[11,12] As ART efficacy has improved and life expectancy in people with HIV has increased,[13] the use of standard cancer treatment in this population is becoming common in clinical practice. Prior studies have shown that people with HIV can successfully undergo standard cancer treatments for a variety of malignant neoplasms, including lung cancer,[14,15] anal cancer,[16,17] non-Hodgkin lymphoma,[18,19] and breast cancer,[20] among others.[21,22] Although toxic effects of systemic cancer treatment are still possible, ART is often used during cancer treatment to avoid complications associated with HIV progression.[1,14,23,24] Despite these advancements, cancer treatment recommendations specific to people with HIV are limited.[25] Questions about long-term effects and individual factors affecting cancer treatment tolerability remain.[26]

A question of particular importance is the effect of different cancer treatments on HIV RNA and CD4 levels. Both CD4 and HIV RNA are important clinical biomarkers for morbidity and mortality in people with HIV.[27,28] Use of ART may be interrupted owing to tolerability issues during certain cancer treatments, with a resulting loss of HIV RNA suppression.[29] Whether owing to ART interruption or a direct effect of cancer treatments, a pronounced period of immunosuppression in people with HIV has been observed after various chemotherapy and radiotherapy regimens.[7,16,29-31] However, these declines have not been consistent.[18,32] It is also unclear whether potential declines in CD4 count or increases in HIV RNA level due to cancer treatment will increase the risk of a poor outcome among people with HIV.[29,31,33] In this study, we used a joint longitudinal survival model to compare longitudinal changes in CD4 count and HIV RNA level by cancer treatment type and to quantify the association between these biomarkers and all-cause mortality risk after cancer treatment in a clinical cohort of adults with HIV and an incident first cancer. We hypothesized that a decline in CD4 count after cancer treatment is independently associated with higher mortality.

Key Points

Question What is the association between cancer treatment and CD4 count and HIV RNA level, and how are these markers associated with all-cause mortality among people with HIV?

Findings In a clinical cohort study of 196 adults with HIV and cancer, chemotherapy and/or radiotherapy resulted in a decline in CD4 count of 203 cells/μL shortly after treatment compared with other cancer treatments but did not increase HIV RNA level. Every decline in CD4 count of 100 cells/μL was associated with a 27% increase in mortality.

Meaning These results suggest that the immunosuppressive effects of cancer treatments should be considered in the development of cancer treatment recommendations specific to people with HIV.

Methods

Data Sources

We identified incident first cancer cases among enrollees in the Johns Hopkins HIV Clinical Cohort (JHHCC) from January 1, 1997, to September 30, 2014. This longitudinal clinical cohort of adults with HIV has been previously described.[34] The JHHCC study was approved by the Johns Hopkins Medicine institutional review board. All participants provided written informed consent prior to enrollment. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Information on cancer treatment and stage at diagnosis was available for 296 of the 382 cases (77.5%) identified during the study period via linkage to the Maryland Cancer Registry. Cases without longitudinal data were excluded, yielding a final study sample of 196 participants. Cancer type, defined using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program Site Groups for Primary Site,[35] and date of diagnosis were validated via a medical record review. Staging at diagnosis followed the SEER Summary Staging 2000 guidelines.[36] The Maryland Cancer Registry collected data on the type and date of initiation of the first course of cancer treatment, using the following categories: chemotherapy, radiotherapy, surgery, hormone therapy, immunotherapy, and other.

Exposure and Outcomes

The main exposure in this study was initial cancer treatment type. We hypothesized that chemotherapy and/or radiotherapy might result in distinct patterns of CD4 count trajectories compared with surgery alone, other treatment, or no treatment.[29,31,37,38] A complete list of the available cancer treatment data are provided in eTable 1 in the Supplement. Based on exploratory analyses, cancer treatment was categorized into those receiving any chemotherapy and/or radiotherapy vs those receiving surgery or other treatment. Baseline was the earliest date of any cancer treatment initiation or the cancer diagnosis date, if untreated. The outcomes of interest are longitudinal CD4 count, longitudinal HIV RNA level, and all-cause mortality. Follow-up data were available through March 1, 2016, when individuals were administratively censored. CD4 count and HIV RNA level were collected through routine clinical care. All laboratory measurements drawn within the Johns Hopkins Hospital system and at the 2 largest commercial laboratories serving patients in the JHHCC were available.[34] Vital status and date of death were obtained through medical record review and linkage to the Social Security Death Index and National Death Index.

Covariates

Covariates were collected via a semiannual medical record review and laboratory tests. Race/ethnicity was categorized as non-Hispanic black or other. Calendar period, based on date of cancer diagnosis, was categorized into 1997 to 2002, 2003 to 2008, and 2009 to 2014. Injection drug use was based on self-reported HIV acquisition risk group. Hepatitis C virus status was determined by a positive antibody test result while

enrolled. We used the closest measurement before cancer diagnosis for baseline CD4 count and HIV RNA level, measured at a median of 33 cells/μL (interquartile range [IQR], 12-63 cells/μL) days before. Baseline CD4 count was categorized into 350 cells/μL or less, 351 cells/μL to 500 cells/μL, and greater than 500 cells/μL (to convert CD4 count to $\times 10^9$ per liter, multiply by 0.001). Individuals were considered virally suppressed if baseline HIV RNA level was 400 copies/mL or less. Other covariates included a prior AIDS diagnosis, not including the current AIDS-related cancer diagnosis, and ART use at baseline. To isolate mortality associated with an individual's CD4 and HIV RNA trajectories, we sought to adjust for the effect of each individual's cancer severity. To do this, we used age-adjusted SEER estimates of 5-year mortality for each individual's particular cancer type and stage.[39-44]

Longitudinal Models

The changes in CD4 count and HIV RNA load trajectories associated with initial cancer treatment category were examined using linear mixed-effects models.[45] We chose to model absolute CD4 count to compare with similar analyses[29-31] and because it is a clinically meaningful measurement. A $\log_{10}$ transformation of HIV RNA level was used. Models were selected based on Akaike information criteria and an examination of the residuals.[45] The candidate models included the various hierarchical interactions among time, baseline CD4 count or $\log_{10}$ HIV RNA level, and initial cancer treatment category (listed in eTables 2 and 3 in the Supplement). The propensity score was used in both models to account for confounding; the score represented the conditional probability of receiving chemotherapy and/or radiotherapy based on age, sex, race/ethnicity, injection drug use, baseline ART, calendar period, hepatitis C virus infection, previous AIDS diagnosis, and baseline CD4 count and was modeled using natural cubic splines with knots at the 20th, 40th, 60th, and 80th percentiles. Exploratory analyses supported the use of chemotherapy and/or radiotherapy as the fixed effect at baseline given that an almost immediate decline in CD4 count was observed after treatment initiation (eFigure 1 in the Supplement). The first measures of posttreatment CD4 count and HIV RNA level were collected at a median of 42 cells/μL (IQR, 21-91 cells/μL) days after the start of cancer treatment.

The final models for CD4 count and HIV RNA level included a random intercept, random effects for the slopes, and the following fixed effects: (1) time, modeled using natural cubic splines with a knot at the 50th percentile; (2) the propensity score modeled with natural cubic splines with knots at the 25th, 50th, and 75th percentiles; and (3) an indicator for chemotherapy and/or radiotherapy. The longitudinal CD4 model also included fixed effects for (1) categorical baseline CD4 count, (2) an interaction between baseline CD4 count and chemotherapy and/or radiotherapy, (3) an interaction between baseline CD4 count and time, (4) an interaction between chemotherapy and/or radiotherapy and time, and (5) an interaction among baseline CD4 count, chemotherapy and/or radiotherapy, and time. The additional fixed effects included in the longitudinal $\log_{10}$ HIV RNA model were (1) an indicator for the unsuppressed baseline HIV RNA level, (2) an interaction between chemotherapy and/or radiotherapy and an unsuppressed baseline HIV RNA level, (3) an interaction between chemotherapy and/or radiotherapy and time, and (4) an interaction among chemotherapy and/or radiotherapy, an unsuppressed HIV RNA level, and time.

Joint Longitudinal Survival Model

The joint longitudinal survival model simultaneously estimated the CD4 and HIV RNA longitudinal processes and a proportional hazards model for all-cause mortality. Joint models are useful to address measurement error in the longitudinal process and censoring for the longitudinal process due to a survival event.[46] The expected value of the CD4 count, scaled by 100 cells/μL, and $\log_{10}$ HIV RNA level were incorporated as linear estimators in the survival model.[47] The survival model also included SEER-estimated 5-year mortality tercile categories, age, race/ethnicity, sex, injection drug use, no cancer treatment, no baseline ART, hepatitis C virus infection, baseline CD4 count category, calendar period, and chemotherapy and/or radiotherapy to account for confounding. We used a Markov chain Monte Carlo algorithm to estimate the parameters, where the baseline hazard was approximated using penalized B splines.[47,48] The 95% credible intervals were calculated for each of the parameters.[47]

Data were analyzed from December 1, 2017, through April 1, 2018. All analyses were performed using the JMbayes package in R, version 3.4.2 (R Project for Statistical Computing).[47-50]

Sensitivity Analyses

We conducted a sensitivity analysis among the subset of individuals deemed to have a good cancer prognosis, defined as those with a baseline CD4 count of greater than 200 cells/μL and a SEER-estimated 5-year mortality of less than 50% (n = 101). This restriction was intended to isolate the association between various cancer treatments on CD4 count, HIV RNA level, and mortality among individuals for whom treatment-related decisions are not solely dictated by poor cancer prognosis or immune status. Given the limited information on cancer treatment type, dose, and duration, we also sought to reduce heterogeneity by conducting a sensitivity analysis among those with solid tumors (n = 144) and among those with lymphoma (n = 48).

Results

The 196 participants in the study sample included 135 (68.9%) men and 61 (31.1%) women; 151 (77.0%) were non-Hispanic black. Median baseline CD4 count was 297 cells/μL (IQR, 164-464 cells/μL). The median age at cancer treatment initiation was 50 (IQR, 43-55) years. A median of 8.5 (IQR, 3.0-16.0) longitudinal measures were available per individual. The distribution of baseline covariates, stratified by initial cancer treatment, is presented in **Table 1**. Seventy-two participants (36.7%) had no viral suppression at baseline, and 23 (11.7%) were ART naive. A full list of the cancer types and stage distributions are provided in eTable 4 in the Supplement. Most participants (118 [60.2%]) received chemotherapy and/or radiotherapy. There

Table 1. Baseline Characteristics of Individuals With an Incident Diagnosis of a First Cancer in JHHCC From 1997-2014 by Initial Cancer Treatment Category

Characteristic	Treatment Group[a]	
	Surgery or Other (n = 78)	Chemotherapy and/or Radiotherapy (n = 118)
Age, median (IQR), y	51 (44-56)	49 (42-55)
Female	25 (32.1)	36 (30.5)
Non-Hispanic black	58 (74.4)	93 (78.8)
Diagnosis year		
1997-2002	15 (19.2)	23 (19.5)
2003-2008	35 (44.9)	51 (43.2)
2009-2014	28 (35.9)	44 (37.3)
Hepatitis C virus infection	48 (61.5)	63 (53.4)
No ART at baseline	12 (15.4)	11 (9.3)
Prior AIDS	37 (47.4)	65 (55.1)
IDU	24 (30.8)	37 (31.4)
Baseline CD4 count		
≤350 cells/μL	45 (57.7)	67 (56.8)
351-500 cells/μL	20 (25.6)	25 (21.2)
>500 cells/μL	13 (16.7)	26 (22.0)
Baseline $\log_{10}$ HIV RNA level		
Median (IQR), copies/mL	2.0 (1.7-4.5)	2.0 (1.7-3.5)
Unsuppressed[b]	30 (38.5)	42 (35.6)
5-y Mortality risk, median (IQR)[c]	0.24 (0.07-0.44)	0.37 (0.22-0.69)

Abbreviations: ART, antiretroviral therapy; IDU, injection drug use; IQR, interquartile range; JHHCC, Johns Hopkins HIV Clinical Cohort.

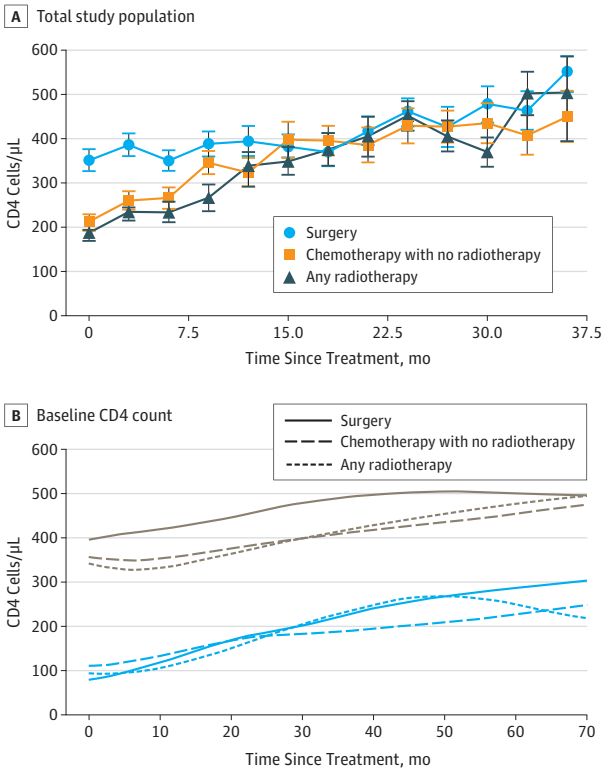
SI conversion factor: To convert CD4 count to $\times 10^9$ per liter, multiply by 0.001.

[a] Unless otherwise indicated, data are expressed as number (percentage) of patients.

[b] Indicates HIV RNA level of greater than 400 copies/mL.

[c] Based on the Surveillance, Epidemiology, and End Results estimates for an individual's particular cancer type and stage.

Figure 1. Exploratory Analysis of Unadjusted CD4 Values After Cancer Diagnosis Stratified by Cancer Treatment Type



A, Results are shown for the total population. Error bars indicate plus or minus 1 SD. B, Results are shown by baseline CD4 count, stratified at 200 cells/μL or less (blue lines) and greater than 200 cells/μL (brown lines).

was a higher 5-year SEER estimated mortality risk among those undergoing chemotherapy and/or radiotherapy compared with those undergoing surgery or other treatment (probability difference, 0.09; 95% CI, 0.02-0.18). The overall 5-year cumulative incidence of mortality was 45.1% (95% CI, 37.5%-51.7%). The crude survival curves and numbers under follow-up for each treatment group are available in eFigure 2 in the Supplement. Exploratory analyses used to categorize initial cancer treatment type are presented in **Figure 1**. Figure 1A shows that the mean and variance of CD4 count after cancer treatment is similar for those with chemotherapy or radiotherapy. In Figure 1B, lowess curves of CD4 count after cancer treatment show no difference in CD4 response at baseline CD4 count of 200 cells/μL or less and similar declines in CD4 count for those receiving chemotherapy without radiotherapy and those receiving any radiotherapy at a baseline CD4 count of greater than 200 cells/μL.

Longitudinal Results

Table 2 provides the results of the longitudinal CD4 submodel and the longitudinal $\log_{10}$ HIV RNA submodel. The mean CD4 count at the initiation of surgery or other treatment among those with a baseline CD4 count of greater than 500 cells/μL adjusted for their conditional probability of receiving chemotherapy and/or radiotherapy was 691 cells/μL (95% CI, 494-891 cells/μL). The initial decline in CD4 count associated with chemotherapy and/or radiotherapy among those with baseline CD4 count of greater than 500 cells/μL was 203 cells/μL (95% CI, 92-306 cells/μL). There was a significant interaction between the baseline CD4 count of 350 cells/μL or less and chemotherapy and/or radiotherapy on longitudinal CD4 count, where the decline in CD4 count among those receiving chemotherapy and/or radiotherapy vs surgery or other treatment was attenuated by 158 cells/μL (95% CI, 31-276 cells/μL), resulting in a mean decline of 45 cells/μL. **Figure 2** shows the estimated initial decline and 5-year CD4 trajectories stratified by baseline CD4 count category and cancer treatment category. For those in higher baseline CD4 count categories, the expected decline in CD4 count for the chemotherapy and/or radiotherapy group remained during 5 years of follow-up. Those with a low baseline CD4 count have a mean persistently low CD4 count regardless of cancer treatment category.

The intercept of the longitudinal $\log_{10}$ HIV RNA submodel is 1.68 (95% CI, 1.20-2.19), corresponding to a mean HIV RNA level of 48 copies/mL at the initiation of cancer treatment among those who are virally suppressed at baseline and

Table 2. Changes in Longitudinal CD4 Count and Log_{10} HIV RNA Level Associated With Initial Cancer Treatment Category in the Total Population Joint Longitudinal Survival Model[a]

Longitudinal Model by Covariate	Estimate (95% CI)[b]
CD4 cells/μL	
Intercept	691 (494 to 891)
Initial cancer treatment category	
Surgery or other	1 [Reference]
Chemotherapy and/or radiotherapy	−203 (−306 to −92)
Baseline CD4 count	
≤350 cells/μL	−400 (−499 to −308)
351-500 cells/μL	−151 (−262 to −45)
>500 cells/μL	1 [Reference]
Chemotherapy and/or radiotherapy and baseline CD4 interaction	
× CD4 count ≤350 cells/μL	158 (31 to 276)
× CD4 351-500 cells/μL	32 (−105 to 171)
Log_{10} HIV RNA	
Intercept	1.68 (1.20 to 2.19)
Initial cancer treatment category	
Surgery or other	1 [Reference]
Chemotherapy and/or radiotherapy	0.24 (−0.11 to 0.58)
Baseline HIV RNA level, copies/mL	
≤400 (suppressed)	1 [Reference]
>400 (unsuppressed)	1.84 (1.45 to 2.26)
Chemotherapy and/or radiotherapy and unsuppressed HIV RNA interaction	−0.53 (−1.09 to −0.02)

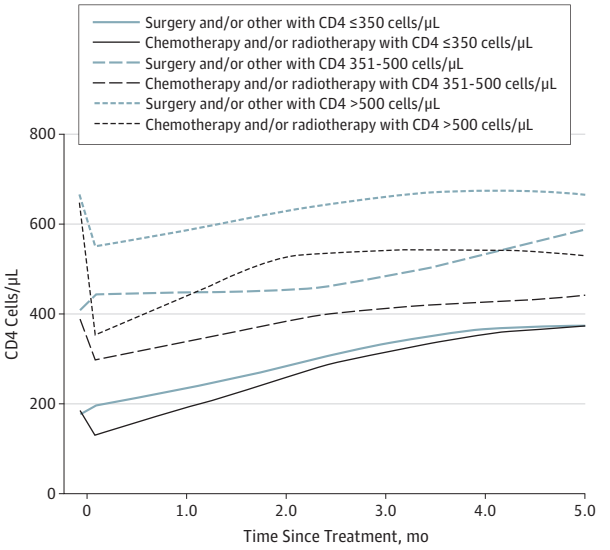
Abbreviation: CI, credible interval.

SI conversion factor: To convert CD4 count to $\times 10^9$ per liter, multiply by 0.001.

[a] Results exclude time splines, interactions with time splines, and propensity score results for brevity.

[b] Calculated using Markov chain Monte Carlo methods.

Figure 2. CD4 Count Response to Initial Cancer Treatment Category by Baseline CD4 Category



Initial cancer treatment categories included chemotherapy and/or radiotherapy vs surgery and/or other treatment.

did not receive chemotherapy and/or radiotherapy, adjusted for the propensity score. For those who were virally suppressed, chemotherapy and/or radiotherapy did not change their HIV RNA level compared with surgery or other treatment (immediate change in log_{10} HIV RNA level, 0.24; 95% CI, −0.11 to 0.58). There was a significant interaction between having an unsuppressed baseline HIV viral load and the receipt of chemotherapy and/or radiotherapy vs surgery or other treatment on longitudinal HIV viral load (interaction estimate, 184; 95% CI, 1.45-2.26). Those who were unsuppressed had a greater than expected decline in HIV RNA level associated with receipt of chemotherapy and/or radiotherapy (interaction estimate, −0.53; 95% CI, −1.09 to −0.02), resulting in a decline from a mean of 3311 copies/mL to a mean 1698 copies/mL. The covariance between the random intercepts for baseline CD4 count and baseline HIV RNA level was −0.33, and the covariance between the random slopes of the first-time spline segments of CD4 count and HIV RNA level was −0.55. The negative covariances indicate that higher levels of HIV RNA are associated with lower CD4 counts immediately before and after cancer treatment.

Survival Results

The all-cause mortality submodel results are presented in **Table 3**, including the sensitivity analyses. Among the total population, for every 100 cells/μL decline in CD4 count at any given time during follow-up, the hazard of mortality was increased by 27% (HR, 1.27; 95% CI, 1.08-1.53) with adjusting for confounders, including longitudinal log_{10} HIV RNA level and cancer severity, as approximated by the SEER-estimated 5-year mortality. Every unit increase in longitudinal log_{10} HIV RNA level was not significantly associated with mortality (HR, 1.24; 95% CI, 0.94-1.65) after adjusting for confounders, including longitudinal CD4 count. In the good prognosis sensitivity analysis, we observed a higher increase in the hazard of mortality associated with a 100 cells/μL decline in CD4 count (HR, 1.43; 95% CI, 1.05-2.01). In lymphoma sensitivity analysis, there was a 110% increase in the hazard of mortality associated with a 100 cells/μL decline in longitudinal CD4 count (HR, 2.10; 95% CI, 1.20-3.96) and no significant effect of longitudinal HIV RNA level. There was no significant association in the solid tumor sensitivity analysis.

Discussion

Although some prior studies have examined the effect of different cancer treatments on CD4 count among people with HIV after cancer treatment,[29-31] we believe our analysis was novel in the following 2 regards: (1) we were able to more fully characterize the expected clinical course of 2 key HIV biomarkers—CD4 count and HIV RNA level—among persons with HIV undergoing cancer treatment, and (2) we determined the association between these biomarker trajectories and mortality risk using a model that simultaneously incorporated longitudinal CD4 count and HIV RNA level. The estimated initial decline in CD4 count of 203 cells/μL after chemotherapy and/or radiotherapy is similar to what has been

Table 3. Survival Submodels of the Joint Longitudinal Survival Models for the Total Population, Good Prognosis Population, and Solid Tumor Population[a]

Covariate	Population, HR (95% CI)			
	Total[b]	Good Prognosis	Solid Tumor	Lymphoma
5-y SEER mortality risk[c]				
Low	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Moderate	1.90 (1.07-3.35)	4.00 (1.10-14.9)	2.15 (1.09-4.23)	1.43 (0.05-28.4)
High	6.03 (3.35-11.5)	2.82 (1.04-7.91)	6.54 (3.33-13.5)	NA
Baseline CD4 cell count category[d]				
Lowest	1.19 (0.57-2.45)	4.21 (1.00-19.6)	1.18 (0.54-2.49)	1.61 (0.13-19.3)
Middle	1.29 (0.61-2.80)	4.11 (1.04-17.9)	1.22 (0.56-2.72)	0.40 (0.05-3.45)
Highest	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Initial cancer treatment category				
Surgery or other	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Chemotherapy and/or radiotherapy	1.81 (1.10-3.28)	0.70 (0.28-1.84)	2.04 (1.10-3.91)	0.07 (0.02-0.33)
Calendar period				
1997-2002	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
2003-2008	1.15 (0.62-2.02)	0.96 (0.31-3.35)	1.18 (0.60-2.37)	0.86 (0.18-4.27)
2009-2014	0.74 (0.36-1.54)	0.53 (0.10-2.69)	0.65 (0.27-1.47)	1.80 (0.23-12.5)
Longitudinal CD4 count decline[e]	1.27 (1.08-1.53)	1.43 (1.05-2.01)	1.17 (0.98-1.46)	2.10 (1.20-3.96)
Longitudinal HIV RNA level increase[f]	1.24 (0.94-1.65)	1.10 (0.61-1.96)	1.32 (0.94-1.83)	0.95 (0.48-1.80)

Abbreviations: ART, antiretroviral therapy; CI, credible interval; HR, hazard ratio; IDU, injection drug use; NA, not applicable; SEER, Surveillance, Epidemiology, and End Results.

[a] Models adjusted for listed covariates and age, sex, race/ethnicity, IDU, baseline ART use, baseline hepatitis C, and use of no initial cancer treatment. Lymphoma model also adjusted for AIDS vs non-AIDS defining lymphoma.

[b] Calculated using Markov chain Monte Carlo methods.

[c] Based on SEER estimates for an individual's particular cancer type and stage. For total population and those with solid tumor, low risk indicates 0.0 to 0.323; moderate risk, 0.324 to 0.648; and high risk, 0.649 to 0.973. For the population with good prognosis, low risk indicates 0.0 to 0.147 (reference category); moderate risk, 0.148 to 0.296; and high risk, 0.297 to 0.444. For the population with lymphoma, low risk indicates 0.0-0.236; moderate risk, 0.237 to 0.394.

[d] For total population and those with good prognosis and solid tumor populations, lowest category baseline CD4 counts are 350/μL or less; middle category, 351/μL to 500/μL; and highest category, greater than 500/μL. For the lymphoma population, lowest category baseline CD4 counts are 200/μL or less; middle category, 201/μL to 350/μL; and highest category, greater than 350/μL (to convert CD4 count to $\times 10^9$ per liter, multiply by 0.001).

[e] Longitudinal decline in CD4 count is incorporated as a linear estimator from the longitudinal model and is scaled by 100/μL (ie, HR reflects a 100/μL decrease in estimated CD4 count).

[f] Longitudinal $\log_{10}$ HIV RNA level is incorporated as a linear estimator from the longitudinal model and is scaled by $\log_{10}$ (ie, HR reflects a 1-U increase in the $\log_{10}$ estimated HIV RNA level).

previously observed.[38,51-58] However, we also found that CD4 count decline after chemotherapy and/or radiotherapy was attenuated for those with a low pretreatment CD4 count. Intuitively, a very low CD4 count can only decline by a certain amount. At baseline, 36.7% of individuals were virally unsuppressed and 11.7% were ART naive, yet we found no increase in HIV RNA level associated with chemotherapy and/or radiotherapy. Conversely, for those who were virally unsuppressed before cancer treatment, HIV RNA level declined more among those who underwent chemotherapy and/or radiotherapy than among those who underwent surgery or other treatment. This finding suggests that perhaps the monitoring and engagement in health care associated with ongoing chemotherapy and/or radiotherapy may improve ART uptake or ART adherence and rejects the concern that more intensive cancer treatment regimens may negatively affect ART adherence.[23,59-61]

We believe the association between lower CD4 count after cancer treatment and higher mortality supports the hypothesis that immune status in persons with HIV can influence mortality after cancer diagnosis. Previous analyses have not incorporated CD4 count measurements, particularly time-varying CD4 counts, as a test of this hypothesis.[33] Therefore, this analysis explicitly ties together changes in longitudinal CD4 count due to cancer treatment and the subsequent association with mortality. Our study did not assess the cause of death, and death among persons with HIV after cancer diagnosis may be due to noncancer causes. Insights into the specific drivers of morbidity and mortality in persons with HIV and cancer (ie, AIDS events or non-AIDS events) can better inform clinical care for these patients. Regardless, immunosuppression appears to drive poor outcomes after cancer diagnosis in persons with HIV. The study results are likely generalizable to adults enrolled in HIV clinical care in the ART era.

Strengths and Limitations

Our study had several strengths, including the detailed demographic and clinical information available for a population of individuals with HIV and cancer. We had comprehensive longitudinal laboratory measures for our cohort. We were able to incorporate multiple complex processes, including CD4 and HIV RNA responses, into our analysis via the use of joint longitudinal survival models, addressing questions relevant for clinical care of persons with HIV who are diagnosed with cancer for which current guidelines are insufficient.[62]

This study was not without its limitations. As with many previous studies on cancer among persons with HIV, there is a trade-off between obtaining more granular data and sample size. We were limited to broad initial cancer treatment categories among a population of persons with HIV who were diagnosed with various cancers at various stages. Therefore, we must assume that the cancer treatment categorization will result in similar immune effects for these individuals, and individuals in both treatment categories may have received subsequent treatment. As a result, heterogeneity in cancer treatments likely increased the variance in the longitudinal CD4 count trajectories. However, by restricting to the initial treatment, we are essentially using an intention-to-treat strategy. A proper per-protocol analysis would therefore result in a larger association. We also had to assume that our SEER-estimated 5-year mortality adequately accounted for a patient's cancer severity to isolate the independent association between CD4 count and mortality. Those classified in the surgery or other treatment group may have had earlier-stage cancer at diagnosis, and thus residual confounding in the all-cause mortality analysis is possible. Another limitation was the lack of data on cancer response to the initial treatment regimen, which would be associated with subsequent mortality and receipt of additional treatment. Given the use of the SEER-estimated mortality and the lack of cancer response data, residual confounding is possible in the association between longitudinal CD4 count and mortality. We also conducted sensitivity analyses in subsets of the study population to address these limitations. Restricting to those expected to survive their cancer and those with lymphoma appeared to strengthen the association between longitudinal CD4 count and all-cause mortality; restricting to solid tumors yielded similar HRs to the total population but lost significance.

Conclusions

The results of this cohort study suggest that maintaining a high CD4 count after cancer diagnosis has clinically meaningful implications for survival. The results also suggest that CD4 count declines associated with cancer treatment are concerning for persons with HIV and establishes that immunosuppression in persons with HIV driven by cancer treatment rather than the HIV disease process can still result in an increased risk of mortality. Further consideration of the immunosuppressive effects of cancer treatment in persons with HIV appears to be needed. For example, we think a comparison of these outcomes among persons with HIV with locoregional solid tumors undergoing surgery alone or surgery and adjuvant chemotherapy and/or radiotherapy would be a reasonable clinical scenario in which to further explore these results.

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REFERENCES

1. Rubinstein PG, Aboulafia DM, Zloza A. Malignancies in HIV/AIDS: from epidemiology to therapeutic challenges. *AIDS*. 2014;28(4):453-465. doi:10.1097/QAD.0000000000000071

2. Goehringer F, Bonnet F, Salmon D, et al. Causes of death in HIV-infected individuals with immunovirologic success in a national prospective survey. *AIDS Res Hum Retroviruses*. 2017;33(2):187-193. doi:10.1089/aid.2016.0222

3. Schwarcz SK, Vu A, Hsu LC, Hessol NA. Changes in causes of death among persons with AIDS: San Francisco, California, 1996-2011. *AIDS Patient Care STDS*. 2014;28(10):517-523. doi:10.1089/apc.2014.0079

4. Antiretroviral Therapy Cohort Collaboration. Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996-2006: collaborative analysis of 13 HIV cohort studies. *Clin Infect Dis*. 2010;50(10):1387-1396. doi:10.1086/652283

5. Smith CJ, Ryom L, Weber R, et al; D:A:D Study Group. Trends in underlying causes of death in people with HIV from 1999 to 2011 (D:A:D): a multicohort collaboration. *Lancet*. 2014;384(9939):241-248. doi:10.1016/S0140-6736(14)60604-8

6. Parameswaran L, Taur Y, Shah MK, Traina TA, Seo SK. Tolerability of chemotherapy in HIV-infected women with breast cancer: are there prognostic implications? *AIDS Patient Care STDS*. 2014;28(7):358-364. doi:10.1089/apc.2013.0370

7. Le Moal G, Prazuck T, Saberan-Roncato M, et al. Immuno-virological and clinical impacts of treating cancer in patients living with HIV. *J Antimicrob Chemother*. 2015;70(1):249-256. doi:10.1093/jac/dku362

8. Grew D, Bitterman D, Leichman CG, et al. HIV infection is associated with poor outcomes for patients with anal cancer in the highly active antiretroviral therapy era. *Dis Colon Rectum*. 2015;58(12):1130-1136. doi:10.1097/DCR.0000000000000476

9. Albaran RG, Webber J, Steffes CP. CD4 cell counts as a prognostic factor of major abdominal surgery in patients infected with the human immunodeficiency virus. *Arch Surg*. 1998;133(6):626-631. doi:10.1001/archsurg.133.6.626

10. Hoffman R, Welton ML, Klencke B, Weinberg V, Krieg R. The significance of pretreatment CD4 count on the outcome and treatment tolerance of HIV-positive patients with anal cancer. *Int J Radiat Oncol Biol Phys*. 1999;44(1):127-131. doi:10.1016/S0360-3016(98)00528-8

11. Flepisi BT, Bouic P, Sissolak G, Rosenkranz B. Drug-drug interactions in HIV positive cancer

patients. *Biomed Pharmacother*. 2014;68(5):665-677. doi:10.1016/j.biopha.2014.04.010

12. Berretta M, Caraglia M, Martellotta F, et al. Drug-drug interactions based on pharmacogenetic profile between highly active antiretroviral therapy and antiblastic chemotherapy in cancer patients with HIV infection. *Front Pharmacol*. 2016;7:71. doi:10.3389/fphar.2016.00071

13. Samji H, Cescon A, Hogg RS, et al; North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) of IeDEA. Closing the gap: increases in life expectancy among treated HIV-positive individuals in the United States and Canada. *PLoS One*. 2013;8(12):e81355. doi:10.1371/journal.pone.0081355

14. Moltó J, Moran T, Sirera G, Clotet B. Lung cancer in HIV-infected patients in the combination antiretroviral treatment era. *Transl Lung Cancer Res*. 2015;4(6):678-688. doi:10.3978/j.issn.2218-6751.2015.08.10

15. Hakimian R, Fang H, Thomas L, Edelman MJ. Lung cancer in HIV-infected patients in the era of highly active antiretroviral therapy. *J Thorac Oncol*. 2007;2(4):268-272. doi:10.1097/01.JTO.0000263707.31202.d7

16. Fraunholz IB, Haberl A, Klauke S, Gute P, Rödel CM. Long-term effects of chemoradiotherapy for anal cancer in patients with HIV infection: oncological outcomes, immunological status, and the clinical course of the HIV disease. *Dis Colon Rectum*. 2014;57(4):423-431. doi:10.1097/DCR.0000000000000057

17. Hauerstock D, Ennis RD, Grossbard M, Evans A. Efficacy and toxicity of chemoradiation in the treatment of HIV-associated anal cancer. *Clin Colorectal Cancer*. 2010;9(4):238-242. doi:10.3816/CCC.2010.n.035

18. Montoto S, Wilson J, Shaw K, et al. Excellent immunological recovery following CODOX-M/IVAC, an effective intensive chemotherapy for HIV-associated Burkitt's lymphoma. *AIDS*. 2010;24(6):851-856. doi:10.1097/QAD.0b013e3283301578

19. Coutinho R, Pria AD, Gandhi S, et al. HIV status does not impair the outcome of patients diagnosed with diffuse large B-cell lymphoma treated with R-CHOP in the cART era. *AIDS*. 2014;28(5):689-697. doi:10.1097/QAD.0000000000000133

20. Gomez A, Montero AJ, Hurley J. Clinical outcomes in breast cancer patients with HIV/AIDS: a retrospective study. *Breast Cancer Res Treat*. 2015;149(3):781-788. doi:10.1007/s10549-015-3275-9

21. Montoto S, Shaw K, Okosun J, et al. HIV status does not influence outcome in patients with classical Hodgkin lymphoma treated with chemotherapy using doxorubicin, bleomycin, vinblastine, and dacarbazine in the highly active antiretroviral therapy era. *J Clin Oncol*. 2012;30(33):4111-4116. doi:10.1200/JCO.2011.41.4193

22. Nguyen ML, Farrell KJ, Gunthel CJ. Non–AIDS-defining malignancies in patients with HIV in the HAART era. *Curr Infect Dis Rep*. 2010;12(1):46-55. doi:10.1007/s11908-009-0075-6

23. Carbone A, Vaccher E, Gloghini A, et al. Diagnosis and management of lymphomas and other cancers in HIV-infected patients. *Nat Rev Clin Oncol*. 2014;11(4):223-238. doi:10.1038/nrclinonc.2014.31

24. Barta SK, Xue X, Wang D, et al. Treatment factors affecting outcomes in HIV-associated non–Hodgkin lymphomas: a pooled analysis of 1546 patients. *Blood*. 2013;122(19):3251-3262. doi:10.1182/blood-2013-04-498964

25. Suneja G, Shiels MS, Angulo R, et al. Cancer treatment disparities in HIV-infected individuals in the United States. *J Clin Oncol*. 2014;32(22):2344-2350. doi:10.1200/JCO.2013.54.8644

26. Bryant AK, Huynh-Le M-P, Simpson DR, Gupta S, Sharabi AB, Murphy JD. Association of HIV status with outcomes of anal squamous cell carcinoma in the era of highly active antiretroviral therapy. *JAMA Oncol*. 2018;4(1):120-122. doi:10.1001/jamaoncol.2017.2844

27. Walker AS, Gibb DM. Monitoring of highly active antiretroviral therapy in HIV infection. *Curr Opin Infect Dis*. 2011;24(1):27-33. doi:10.1097/QCO.0b013e3283423e0e

28. Lundgren JD, Babiker AG, Gordin F, et al; INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med*. 2015;373(9):795-807. doi:10.1056/NEJMoa1506816

29. Alfa-Wali M, Allen-Mersh T, Antoniou A, et al. Chemoradiotherapy for anal cancer in HIV patients causes prolonged CD4 cell count suppression. *Ann Oncol*. 2012;23(1):141-147. doi:10.1093/annonc/mdr050

30. Sankatsing SUC, Hillebregt MMJ, Gras L, et al. Prolonged decrease of CD4+ T lymphocytes in HIV-1-infected patients after radiotherapy for a solid tumor. *J Acquir Immune Defic Syndr*. 2013;62(5):546-549. doi:10.1097/QAI.0b013e318285d934

31. Alfa-Wali M, Tait D, Allen-Mersh T, et al. Colorectal cancer in HIV positive individuals: the immunological effects of treatment. *Eur J Cancer*. 2011;47(16):2403-2407. doi:10.1016/j.ejca.2011.06.036

32. Lichterfeld M, Qurishi N, Hoffmann C, et al; German Clinical AIDS Working Group (KAAD). Treatment of HIV-1–associated Kaposi's sarcoma with pegylated liposomal doxorubicin and HAART simultaneously induces effective tumor remission and $CD4^+$ T cell recovery. *Infection*. 2005;33(3):140-147. doi:10.1007/s15010-005-4099-z

33. Coghill AE, Shiels MS, Suneja G, Engels EA. Elevated cancer-specific mortality among HIV-infected patients in the United States. *J Clin Oncol*. 2015;33(21):2376-2383. doi:10.1200/JCO.2014.59.5967

34. Moore RD. Understanding the clinical and economic outcomes of HIV therapy: the Johns Hopkins HIV Clinical Practice Cohort. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;17(suppl 1):S38-S41. doi:10.1097/00042560-199801001-00011

35. National Cancer Institute Surveillance, Epidemiology, and End Results Program. ICD-O-3/WHO 2008 Definition. https://seer.cancer.gov/siterecode/icdo3_dwhoheme/index.html. Updated January 20, 2017. Accessed September 14, 2017.

36. National Cancer Institute Surveillance, Epidemiology, and End Results Program. SEER Summary Staging Manual–2000 Codes and Coding Instructions. https://seer.cancer.gov/tools/ssm/ssm2000/SSSM2000-122012.pdf. Updated December 2012. Accessed September 14, 2017.

37. Horberg MA, Hurley LB, Klein DB, et al. Surgical outcomes in human immunodeficiency virus–infected patients in the era of highly active antiretroviral therapy. *Arch Surg*. 2006;141(12):1238-1245. doi:10.1001/archsurg.141.12.1238

38. Hakim FT, Cepeda R, Kaimei S, et al. Constraints on CD4 recovery postchemotherapy in adults: thymic insufficiency and apoptotic decline of expanded peripheral CD4 cells. *Blood*. 1997;90(9):3789-3798. doi:10.1182/blood.V90.9.3789

39. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Statistics Review (CSR) 1975-2014 SEER Statistics. https://seer.cancer.gov/archive/csr/1975_2014/. Updated April 2, 2018. Accessed February 28, 2018.

40. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Small Intestine Cancer. https://seer.cancer.gov/statfacts/html/smint.html. Updated January 20, 2017. Accessed February 28, 2018.

41. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Anal Cancer. https://seer.cancer.gov/statfacts/html/anus.html. Updated January 20, 2017. Accessed February 28, 2018.

42. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Stat Facts: Vulvar Cancer. https://seer.cancer.gov/statfacts/html/vulva.html. Updated January 18, 2017. Accessed February 28, 2018.

43. National Cancer Institute Surveillance, Epidemiology, and End Results Program. Cancer Query Systems. https://seer.cancer.gov/canques/index.html. Updated September 27, 2016. Accessed February 28, 2018.

44. American Cancer Society. Survival Rates for Penile Cancer. https://www.cancer.org/cancer/penile-cancer/detection-diagnosis-staging/survival-rates.html. Published August 3, 2017. Accessed February 28, 2018.

45. Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G, eds. *Longitudinal Data Analysis*. Boca Raton, FL: CRC Press; 2008. doi:10.1201/9781420011579

46. Bycott P, Taylor J. A comparison of smoothing techniques for CD4 data measured with error in a time-dependent Cox proportional hazards model. *Stat Med*. 1998;17(18):2061-2077. doi:10.1002/(SICI)1097-0258(19980930)17:18<2061::AID-SIM896>3.0.CO;2-O

47. Rizopoulos D. The R package JMbayes for fitting joint models for longitudinal and time-to-event data using MCMC. *J Stat Softw*. 2016;72(7):1-45. doi:10.18637/jss.v072.i07

48. Rizopoulos D, Ghosh P. A Bayesian semiparametric multivariate joint model for multiple longitudinal outcomes and a time-to-event. *Stat Med*. 2011;30(12):1366-1380. doi:10.1002/sim.4205

49. Rizopoulos D. *Joint Models for Longitudinal and Time-to-Event Data: With Applications in R*. Boca Raton, FL: CRC Press; 2012. doi:10.1201/b12208

50. R Core Team. R: A Language and Environment for Statistical Computing. Version 3.4.2. Vienna, Austria: R Foundation for Statistical Computing; September 28, 2017.

51. Mackall CL, Fleisher TA, Brown MR, et al. Distinctions between $CD8^+$ and $CD4^+$ T-cell regenerative pathways result in prolonged T-cell subset imbalance after intensive chemotherapy. *Blood*. 1997;89(10):3700-3707. doi:10.1182/blood.V89.10.3700

52. Louagie H, Van Eijkeren M, Philippe J, Thierens H, de Ridder L. Changes in peripheral blood lymphocyte subsets in patients undergoing radiotherapy. *Int J Radiat Biol*. 1999;75(6):767-771. doi:10.1080/095530099140113

53. De Ruysscher D, Waer M, Vandeputte M, Aerts R, Vantongelen K, van der Schueren E. Changes of lymphocyte subsets after local irradiation for early stage breast cancer and seminoma testis: long-term increase of activated (HLA-DR+) T cells and decrease of "naive" (CD4-CD45R) T lymphocytes. *Eur J Cancer*. 1992; 28A(10):1729-1734. doi:10.1016/0959-8049(92)90079-H

54. Haas GS, Halperin E, Doseretz D, et al. Differential recovery of circulating T cell subsets after nodal irradiation for Hodgkin's disease. *J Immunol*. 1984;132(2):1026-1030.

55. Nakayama Y, Makino S, Fukuda Y, et al. Varied effects of thoracic irradiation on peripheral lymphocyte subsets in lung cancer patients. *Intern Med*. 1995;34(10):959-965. doi:10.2169/internalmedicine.34.959

56. Yang SJ, Rafla S, Youssef E, Selim H, Salloum N, Chuang JY. Changes in T-cell subsets after radiation therapy. *Radiology*. 1988;168(2):537-540. doi:10.1148/radiology.168.2.3260678

57. Wichmann MWMD, Meyer G, Adam M, et al. Detrimental immunologic effects of preoperative chemoradiotherapy in advanced rectal cancer. *Dis Colon Rectum*. 2003;46(7):875-887. doi:10.1007/s10350-004-6677-z

58. Madu A, Ocheni S, Ibegbulam O, Aguwa E, Madu K. Pattern of CD4 T-lymphocyte values in cancer patients on cytotoxic therapy. *Ann Med Health Sci Res*. 2013;3(4):498-503. doi:10.4103/2141-9248.122054

59. Torres HA, Rallapalli V, Saxena A, et al. Efficacy and safety of antiretrovirals in HIV-infected patients with cancer. *Clin Microbiol Infect*. 2014;20(10):O672-O679. doi:10.1111/1469-0691.12589

60. Deeken JF, Pantanowitz L, Dezube BJ. Targeted therapies to treat non–AIDS-defining cancers in patients with HIV on HAART therapy: treatment considerations and research outlook. *Curr Opin Oncol*. 2009;21(5):445-454. doi:10.1097/CCO.0b013e32832f3e04

61. Antoniou T, Tseng AL. Interactions between antiretrovirals and antineoplastic drug therapy. *Clin Pharmacokinet*. 2005;44(2):111-145. doi:10.2165/00003088-200544020-00001

62. Suneja G, Boyer M, Yehia BR, et al. Cancer treatment in patients with HIV infection and non–AIDS-defining cancers: a survey of US oncologists. *J Oncol Pract*. 2015;11(3):e380-e387. doi:10.1200/JOP.2014.002709