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Real-world use of antiretroviral therapy and risk of cancer among people with HIV in Texas

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Background: Combination antiretroviral therapy (cART) may reduce cancer risk among people with HIV (PWH), but cancer-specific associations are incompletely understood.

Methods: We linked HIV and cancer registries in Texas to a national prescription claims database. cART use was quantified as the proportion of days covered (PDC). Cox proportional hazards models assessed associations of cancer risk with cART usage, adjusting for demographic characteristics, AIDS status, and time since HIV report.

Results: We evaluated 63 694 PWH followed for 276 804 person-years. The median cART PDC was 21.4% (interquartile range: 0.0–59.8%). cART use was associated with reduced risk of Kaposi sarcoma [adjusted hazard ratio (aHR) 0.48, 95% confidence interval (CI) 0.34–0.68 relative to unexposed status] and non-Hodgkin lymphoma (aHR 0.41, 95% CI 0.31–0.53), liver cancer (aHR 0.61, 95% CI 0.39–0.96), anal cancer (aHR 0.65, 95% CI 0.46–0.92), and a miscellaneous group of 'other' cancers (aHR 0.80, 95% CI 0.66–0.98). In contrast, cART-exposed status was not associated with risk for cervical, lung, colorectal, prostate or breast cancers.

Conclusion: In a large HIV cohort incorporating data from prescription claims, cART was associated with greatly reduced risks of Kaposi sarcoma and non-Hodgkin lymphoma, and to a lesser degree, reduced risks of liver and anal cancers. These associations likely reflect the beneficial effects of HIV suppression and improved immune control of oncogenic viruses. Efforts to increase cART use and adherence may further decrease cancer incidence among PWH.

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Introduction

Combination antiretroviral therapy (cART) enables long-term suppression of HIV, improves immunity, and extends life expectancy of people with HIV (PWH) [1]. Incidence of Kaposi sarcoma and non-Hodgkin lymphoma (NHL), which are common AIDS-defining cancers among PWH caused by viruses, declined dramatically in the cART era [2–4]. Incidence rates of other virus-associated cancers (e.g. anal and liver cancers and Hodgkin lymphoma) and of lung cancer, which are also elevated among PWH, have similarly declined over time [5].

HIV viral suppression and immune reconstitution through cART are central to cancer prevention among PWH and may account for declines in cancer incidence. Observational studies and randomized trials have

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demonstrated that early uninterrupted cART reduces the risk of virus-related cancers, although associations with virus-unrelated cancers have been mixed [6–13]. However, prior investigations have been limited by short follow-up or a small number of cancer cases, which has hindered analyses of specific cancer sites. Few large studies encompassing a diverse population of PWH, reflecting real-world patterns of access to medical care and adherence to cART, have addressed this question [7,10–12].

In this study, we evaluated the risk of specific virus-related and virus-unrelated cancers associated with cART use among PWH. As state HIV registries do not routinely collect treatment information, we augmented a large observational cohort of PWH within the HIV/AIDS Cancer Match Study with a data linkage to longitudinal prescription claims [5,14]. Our study cohort is comprised of an ethnically diverse population of PWH residing in Texas who engaged in care through public or private insurance.

Methods

Study cohort

The study used linked HIV surveillance and cancer registry data from the HIV/AIDS Cancer Match (HACM) Study in Texas [5] and data from Symphony Health, ICON plc, an aggregator of Medicaid, Medicare, and private insurance claims. The Symphony Health Integrated Dataverse covers over 93% of prescriptions dispensed in the United States [14]. We identified all individuals in Symphony Health who had an International Classification of Disease 9 or 10 diagnosis code for HIV infection (042; B20) or an HIV antiretroviral (ARV) medication prescription between 1 January 2008 and 31 May 2019. Population-based HIV data from the Texas HIV registry included PWH resident in Texas and alive on 1 January 2008 as well as new HIV cases diagnosed during 2008–2015.

We constructed a cohort of PWH in Texas by linking these two data sources based on privacy-preserving hash algorithms of encrypted personal identifiers. The Synoma encryption engine, which utilizes the SHA-256 hash algorithm recommended by the US National Security Agency, was provided to Texas HIV registry staff who used it locally to create anonymized tokens (i.e. hashed text strings) for PWH in their registry. Similarly, Symphony Health only possessed tokenized information shared by providers across the United States. These two sets of tokens were then matched using a deterministic linkage. No personally identifying information on PWH was exchanged or disclosed during the linkage process. As shown in Supplemental Figure 1, http://links.lww.com/QAD/D24, we excluded individuals for whom the matches appeared invalid and individuals with an HIV report date after December 2015. We further restricted the analytic cohort to PWH who matched to at least one prescription claim of any type.

Exposure and outcome assessment

We used US HIV treatment guidelines to identify cART regimens as those combinations considered first-line treatments or appropriate regimens for treatment optimization (Supplemental Tables 1 and 2, http://links.lww.com/QAD/D24) [15]. The start date for each antiretroviral medication was the prescription fill date for the claim. The stop date was calculated as the start date plus the days' supply plus a 7-day grace period. If the first day of a calendar month fell between antiretroviral drug start and stop dates, then the entire month was considered exposed to the antiretroviral drug. cART exposure was then defined on a monthly scale for intervals of concomitant antiretroviral drug use, based on the above cART definition.

We made two assumptions about antiretroviral drug use. First, we assumed that antiretroviral drugs were taken as prescribed, that is, the dispensed prescription was taken for the numbers of days prescribed, antiretroviral drugs were not obtained from outside sources, and gaps between refills represented time that a person ran out of supply or discontinued the drug. Second, we ignored 'carry-over' of oversupply from prior or duplicate prescriptions. If multiple antiretroviral drugs in the same class were prescribed concurrently, we assumed that the person took the minimum combination consistent with the cART definition. Months meeting the criteria of the cART algorithm were considered 'exposed'. Months with antiretroviral drug claims that did not meet the criteria for cART (i.e. incomplete regimens) and months with prescriptions only for nonantiretroviral drug medications were considered 'unexposed'. Months with no prescriptions of any type were considered to have 'unknown' exposure status (i.e. possible gap in claims data).

Invasive cancer diagnoses were ascertained through linkage to the Texas cancer registry [5]. Cancers were coded using the International Classification of Diseases for Oncology third edition [16], and we present results for the following cancer sites: Kaposi sarcoma, NHL, cervix, anus, liver, Hodgkin lymphoma, lung, female breast, prostate, and colorectum.

Statistical analysis

The start of each person's follow-up was the latest of HIV report date; 1 January 2008; first prescription claim of any type; or age 18 years. Follow-up ended at the earliest of age at death, last date of complete Texas cancer registry data (31 December 2015), or 6 months after the person's last prescription's stop date.

We quantified overall prescription usage by measuring the proportion of days covered (PDC) by any medication, as the sum of months covered by prescriptions of any type divided by the number of months between the first and last claims during the study period [17]. We similarly measured cART PDC as the sum of cART-exposed months divided by the number of months between first and last prescription claims of any type [17]. Months with unknown cART exposure are included in the PDC denominator. Any-drug PDC measures utilization of prescription medication coverage. cART PDC is a measure of utilization of cART, assuming that the claims accurately capture PWH medication coverage. We also calculated the ratio of cART PDC to any-drug PDC, which reflects the proportion of months with known medication status that a person was on cART. A ratio of cART PDC to any-drug PDC equal to 1 would indicate full adherence, while a ratio less than 0.5, for example, would indicate poor adherence (i.e. use of cART <50% of the time covered by prescription claims) or that the person obtained cART medications from an outside source not covered by Symphony Health claims.

We used the above definitions of cART exposure in our analyses of cancer risk, except that a person was considered 'exposed' for every month starting with the first month that their antiretroviral medications met the criteria of the cART algorithm, regardless of subsequent prescription claims. This approach was necessary in the cancer risk analyses because of substantial gaps in the pharmacy claims data that we observed in our descriptive assessment (see Results section). This alternative classification of cART exposure assumes that the patient and clinician intended to use cART and that any gaps represented short lapses and/or incomplete capture of prescriptions in the claims data (it is analogous to an intent-to-treat analysis). We used Cox regression models to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) for the associations between this time-varying cART exposure variable and incidence of the specified cancers, adjusted for demographic and HIV risk factors.

Statistical analyses were performed using SAS version 9.4 (SAS Institute, North Carolina, USA). The Texas Department of State Health Services Institutional Review Board approved the study protocol and granted a waiver of informed consent.

Results

We conducted a linkage of 104 049 PWH in the Texas HIV registry with 2 500 178 eligible patients in the Symphony Health database, yielding 71 047 matches. After exclusions and restricting follow-up to 2008–2015, the analytic cohort comprised 63 694 PWH with at least one prescription claim (61.2% of PWH in Texas, Supplemental Figure 1, http://links.lww.com/QAD/D24).

Most PWH who matched to prescription claims had more than one payer type (85%). Of the 13 244 361 prescription claims among included PWH, 48.1% were covered by private insurance, 31.1% by Medicare, 16.9% by Medicaid, and 4% through direct cash payment to pharmacies. Non-Hispanic white individuals and MSM were overrepresented among matches (Supplemental Table 3, http://links.lww.com/QAD/D24). Median HIV report date among matches was 2007.

The cohort of 63 694 PWH was followed during 2008–2015 for 276 804 person-years (Table 1). Median follow-up was 6.3 years (interquartile range: 4.5–6.9). Most follow-up time accrued among the MSM HIV transmission group (61.1%), non-Hispanic Black and (39.4%) non-Hispanic White (34.3%) individuals, and PWH ages 30–49 years at cohort entry (56.3%). Overall, 32 415 (50.9%) PWH were diagnosed with AIDS before or during the follow-up period (59.6% of follow-up time was after an AIDS diagnosis). Of the total follow-up time, 93 300 person-years (33.7%) were cART-exposed, 64 594 (23.3%) were unexposed, and 118 910 (43.0%) had unknown exposure. Thus, of the total follow-up time with known cART status, 59.1% was cART-exposed.

Half of individuals had prescription claims covering at least 60% of their follow-up time [median any-drug PDC: 59.5%; interquartile range (IQR): 22.5–91.6%], and half had cART claims covering at least 21% of their follow-up time (median cART PDC: 21.4%; IQR: 0.0–59.8%). Prescriptions for cART were present for a median of 55% of months with known medication status (cART: any-drug PDC ratio, median 54.5%; IQR 0.0–87.5%). Among people with at least 1 month of cART exposure, the median proportion of follow-up covered by cART was 42.2% (IQR: 17.6–73.9%) and the median cART : any-drug PDC ratio was 74.3% (IQR: 45.5–92.9%).

During follow-up, 2137 PWH were diagnosed with cancer, including 1570 cancers at the 10 sites of interest. The most common cancers were NHL ($N = 388$), Kaposi sarcoma ($N = 244$), lung cancer ($N = 192$) and anal cancer ($N = 187$). As described above in the Methods, we analyzed cancer risk using an alternative time-dependent variable for cART exposure that assumed that a person was exposed to cART in all months after an initial cART-exposed month. Using this approach (Table 2), cART exposure was associated with significantly reduced risks for Kaposi sarcoma (aHR 0.48, 95% CI 0.34–0.68, compared to unexposed follow-up time), NHL (aHR 0.41, 95% CI 0.31–0.53), liver cancer (aHR 0.61, 95% CI 0.39–0.96), anal cancer (aHR 0.65, 95% CI 0.46–0.92), and the miscellaneous group of 'other' cancers (aHR 0.80, 95% CI 0.66–0.98). In contrast,

Table 1. Baseline characteristics of 63 694 people with HIV in Texas linked to prescription claims and followed from 2008 to 2015.

Characteristic	*N*	%	Person-years of follow-up	%
Total	63 694	100.0	276 804	100.0
Sex-HIV transmission risk group				
MSM (including MSM who inject drugs)	38 891	61.1	171 928	62.1
Male PWID (excluding MSM)	2940	4.6	12 852	4.6
Male heterosexual	2956	4.6	12 836	4.6
Male other/unknown	5666	8.9	22 061	8.0
Female PWID	2204	3.5	10 061	3.6
Female heterosexual	6968	10.9	31 317	11.3
Female other/unknown	4069	6.4	15 749	5.7
Race/ethnicity				
Non-Hispanic White	21 858	34.3	103 840	37.5
Non-Hispanic Black	25 124	39.4	104 876	37.9
Hispanic	15 521	24.4	63 469	22.9
Other/unknown	1191	1.9	4619	1.7
Age at entry (years)				
18–29	12 267	19.3	43 702	15.8
30–49	35 883	56.3	165 157	59.7
50–64	14 101	22.1	62 310	22.5
65+	1443	2.3	5635	2.0
Time from HIV report to entry (years)				
<0.25	22 476	35.3	67 334	24.3
0.25 to < 1	2557	4.0	12 027	4.3
1 to <3	6169	9.7	31 017	11.2
3 to <8	16 254	25.5	86 982	31.4
8+	16 238	25.5	79 444	28.7

MSM, men who have sex with men; PWID, people who inject drugs.

cART-exposed status was not associated with risk for cervical, lung, colorectal, prostate or breast cancers. Finally, there was reduced cancer risk associated with unknown cART exposure status for Kaposi Sarcoma, NHL, lung cancer, anal cancer and 'other' cancers.

Discussion

We examined real-world cART use among 63 694 PWH in Texas in relation to the risk of developing common virus-related and virus-unrelated cancers. In our analysis, cART exposure was associated with an approximate 50–60% reduction in the risks for Kaposi sarcoma and NHL, two of the most common cancers in PWH. Risk was also approximately 30–40% lower with cART use for two other virus-related cancers, namely, liver and anal cancers. There was a 20% reduction in the risk of 'other' cancers, but this was a miscellaneous group, and none of the other specified cancers showed a decrease with cART use.

Although we identified strong protective associations between cART use and risk of virus-related cancers, our study faced challenges in complete ascertainment of antiretroviral prescriptions. Data from prescription claims may underestimate medication adherence, as has been described in other studies [18]. First, a substantial fraction of follow-up time was classified as having unknown cART exposure status, because there were gaps in prescription claims for any medication. It is likely that cART regimens were obtained during some of this time from sources not captured in our data, as Symphony Health does not collect prescription information from the Texas HIV Medication Program, which distributes antiretroviral drugs for qualifying low-income uninsured and under-insured PWH [19]. In 2015, approximately one in five PWH in Texas were HIV Medication Program clients [20], the majority of whom (>70%) had undetectable viral loads [19].

Second, we assigned cART exposure status based on claims indicating receipt of approved regimens, and some individuals whom we classified as unexposed appeared to be using less effective combinations. Specifically, among 64 594 person-years that we classified as cART-unexposed, 7.6% had claims for a single antiretroviral drug or an incomplete or unrecommended regimen (see Supplemental Table 4, http://links.lww.com/QAD/D24). A third issue is that many PWH started follow-up several years after their HIV infection was diagnosed and reported. Therefore, a formal evaluation of cancer risk in relation to the duration of cART use was precluded by the lack of prescription claims for the period prior to the start of follow-up. Combined, these effects likely resulted in some exposure misclassification (i.e. categorizing periods of cART exposure as unexposed or unknown status), which would have biased associations between cART and cancer risk toward the null, and made it impossible for us to assess the precise time course over which effective HIV treatment would begin to affect cancer risk.

Table 2. Associations of combination antiretroviral therapy use with cancer risk among people with HIV in Texas.

Cancer type and cART exposure status	Cancers (*N*)	Hazard ratio, unadjusted[a]	Lower 95%CI	Upper 95%CI	Hazard ratio, adjusted[a]	Lower 95% CI	Upper 95% CI
Kaposi sarcoma	244						
Unexposed	71	Reference			Reference		
Exposed	56	0.54	0.38	0.77	0.48	0.34	0.68
Unknown	117	0.73	0.54	0.99	0.70	0.52	0.95
Non-Hodgkin lymphoma	388						
Unexposed	140	Reference			Reference		
Exposed	87	0.43	0.33	0.56	0.41	0.31	0.53
Unknown	161	0.65	0.52	0.82	0.63	0.50	0.79
Cervix	32						
Unexposed	10	Reference					
Exposed	9	0.86	0.35	2.13	0.84	0.34	2.08
Unknown	13	0.82	0.36	1.89	0.84	0.37	1.93
Hodgkin lymphoma	97						
Unexposed	24	Reference			Reference		
Exposed	37	1.06	0.64	1.77	0.99	0.59	1.65
Unknown	36	0.83	0.49	1.41	0.79	0.47	1.34
Lung	192						
Unexposed	71	Reference			Reference		
Exposed	75	0.76	0.55	1.05	0.78	0.56	1.08
Unknown	46	0.57	0.39	0.82	0.58	0.40	0.84
Colon and Rectum	122						
Unexposed	38	Reference			Reference		
Exposed	45	0.84	0.54	1.29	0.83	0.54	1.28
Unknown	39	0.80	0.51	1.25	0.79	0.51	1.25
Liver	117						
Unexposed	42	Reference			Reference		
Exposed	36	0.62	0.40	0.97	0.61	0.39	0.96
Unknown	39	0.77	0.50	1.20	0.73	0.47	1.14
Prostate	130						
Unexposed	47	Reference			Reference		
Exposed	46	0.66	0.44	0.99	0.70	0.47	1.05
Unknown	37	0.72	0.47	1.11	0.70	0.45	1.08
Anus	187						
Unexposed	64	Reference			Reference		
Exposed	63	0.70	0.49	0.99	0.65	0.46	0.92
Unknown	60	0.61	0.43	0.87	0.65	0.46	0.93
Breast	61						
Unexposed	20	Reference			Reference	–	–
Exposed	20	0.93	0.50	1.73	0.93	0.50	1.73
Unknown	21	0.69	0.37	1.28	0.70	0.38	1.30
Other	570						
Unexposed	189	Reference			Reference		
Exposed	213	0.79	0.65	0.97	0.80	0.66	0.98
Unknown	168	0.65	0.53	0.80	0.65	0.53	0.81

cART, combination antiretroviral therapy, CI, confidence interval. Estimates that are statistically significant ($P < 0.05$) are underlined.
[a]Cox regression models use age as the time scale. The adjusted models are adjusted for sex-HIV transmission risk group, race/ethnicity, time-updated AIDS status, and years since HIV report at study entry (linear). The 'exposed' status in the time-dependent cART exposure variable captures current or prior exposure to cART, that is, a person is considered exposed in a given month of follow-up if prescription claims indicate exposure to cART in that month or any prior months.

Cancer risk is elevated among PWH [5], partly because of loss of immunologic control of oncogenic viruses, including Kaposi sarcoma-associated herpesvirus (etiologically relevant for Kaposi sarcoma), Epstein–Barr virus (NHL and Hodgkin lymphoma), human papillomavirus (cervical and anal cancers), and hepatitis B and C viruses (liver cancer). Risks of some of these cancers increase with higher HIV viral load and/or lower $CD4^+$ count [12]. Anal cancer risk increases among PWH with prolonged high-level HIV replication and low $CD4^+$ counts (especially after a lag of several years) [12], highlighting the importance of long-term immunosuppression [12,21]. Prior investigations have demonstrated that cART and sustained HIV viral suppression are associated with decreased risk of virus-associated cancers, including Kaposi sarcoma, NHL, and cervical cancer [7,12,13]. In a randomized controlled trial of sustained cART versus intermittent treatment guided by $CD4^+$ counts, the sustained cART group had lower rates of Kaposi sarcoma, NHL, and Hodgkin lymphoma [6]. Similarly, the reduced risks that we observed for Kaposi sarcoma and NHL with cART use plausibly reflect the effects of improved immune function. These reduced risks may also partly reflect other benefits of regular access to medical care.

We did not confirm the previously reported association between cART and decreased cervical cancer risk [12], and the protective effect for Kaposi sarcoma was more

modest than seen in Silverberg *et al.* [7] which may reflect exposure misclassification in our study, our lack of data on the timing of initiation and full duration of cART, or (for cervical cancer) the small number of cancer outcomes. Furthermore, half of the individuals in our study had prevalent HIV relative to the start of follow-up (i.e. diagnosed pre-2008) and most of the remaining individuals had incident HIV prior to the 2015 update in treatment guidelines to initiate cART earlier in the course of HIV disease irrespective of $CD4^+$ counts [22,23]. Together, these individuals would have received cART under the historical guidelines to initiate treatment at $CD4^+$ counts less than 350, when risk of certain cancers is higher and benefits of treatment may be attenuated.

cART adherence is recommended to manage HIV disease and prevent transmission, yet PWH face a variety of psychosocial, medical, financial, and provider-related barriers to care. In prior studies using insurance claims, approximately 40% of PWH in the United States, and 49% of PWH in Texas with Medicaid, had suboptimal cART adherence (defined as PDC <80%) [24,25]. Furthermore, only 57% of PWH in the United States achieved viral suppression in 2019 [26]. In our study, the median proportion of follow-up time on cART was 21.4%; this proportion increased to 54.5% when we considered only follow-up time with known exposure status, but this still represents only modest adherence. Real-world studies show that adherence is lower among people taking multitablet regimens [27]. Only 32% of people in our study who used cART were ever on single-tablet regimens (data not shown), which could also partly explain the modest adherence.

Our study linked the Texas HIV registry, a collaborating site in the HACM Study, to a database with high coverage (>93%) of US prescription claims [5,14]. Strengths of our study include its diverse group of participants from both private and public insurance plans, large sample size (more than 63 000 PWH) and duration of follow-up (median 76 months), which are advantages compared with prior studies [7,10,11]. We used the prescription data to quantify cART exposure based on recent HIV treatment guidelines [15]. Moreover, we incorporated data from the Texas cancer registry for population-based ascertainment of cancer. Our observational results are derived from real-word claims data and thus are generalizable to PWH receiving routine care in the United States. In addition, we analyzed associations for 10 cancer types.

In conclusion, in a large HIV cohort incorporating data from prescription claims, we found that cART use was associated with greatly reduced risks of Kaposi sarcoma and non-Hodgkin lymphoma, and to a lesser degree, reduced risks of liver and anal cancers. These associations likely reflect the beneficial effects of HIV suppression and improved immune control of oncogenic viruses. Despite major declines in cancer risk among PWH over the past 20 years, risk remains elevated compared with the general population [5]. More widespread cART use with sustained adherence offers an important opportunity to further reduce cancer incidence among PWH.

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Conflicts of interest

There are no conflicts of interest.

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