TITLE: Comparing trends in infection-related and infection-unrelated cancer incidence among people with and without HIV: a population-based matched cohort study using administrative health data in Ontario, Canada, 1996-2020

Authors: Ioana A. Nicolau[1,4] MSc, Rahim Moineddin[2,3] PhD, Tony Antoniou [4,3,2] PhD, Jennifer D. Brooks[1] PhD, Jennifer L. Gillis[7] PhD, Claire E. Kendall[8,9,10,11,3] MD PhD, Curtis Cooper[5] MD MSc, Michelle Cotterchio[1,6] PhD, Kate Salters[14] PhD, Marek Smieja[15] MD PhD, Abigail E. Kroch[12] PhD MPH, Joanne D. Lindsay[4] MES, Colleen Price[13] BA BSS, Anthony Mohamed[4] MES, Ann N. Burchell[2,4,3] PhD

Affiliations:
[1]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[2]Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada
[3]ICES, Toronto, Ontario, Canada
[4]Li Ka Shing Knowledge Institute, St Michael's Hospital, Unity Health Toronto, Toronto, Ontario, Canada
[5]Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[6]Ontario Health (Cancer Care Ontario), Toronto, Ontario, Canada
[7] Canadian Cancer Society, Toronto, Ontario, Canada
[8]Bruyère Research Institute, Ottawa Ontario, Canada
[9]Department of Family Medicine, University of Ottawa, Ottawa, Ontario, Canada
[10]Institut du Savoir Montfort, Ottawa, Ontario, Canada
[11]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ottawa, Ontario, Canada
[12]Ontario HIV Treatment Network, Toronto, Ontario, Canada
[13] Canadian HIV/AIDS and Chronic Pain Society
[14]British Columbia Centre for Excellence in HIV/AIDS, Vancouver, British Columbia, Canada
[15]McMaster University, Hamilton, Ontario, Canada

Conflict of interest: Marek Smieja reports funding from the Canadian Institutes of Health Research, Air Canada and the Greater Toronto Airports Authority. No other competing interests were declared.

Corresponding Author:
Ann N. Burchell, PhD
Scientist, Department of Family and Community Medicine and MAP Centre for Urban Health Solutions, Li Ka Shing Knowledge Institute, St. Michael's Hospital
Associate Professor, Department of Family and Community Medicine, Faculty of Medicine, and Dalla Lana School of Public Health, University of Toronto
30 Bond Street, Toronto, ON Canada M5B 1X1
Email: ann.burchell@unityhealth.to

Funding: This study received funding from Ontario HIV Treatment Network Endgame Game Changer Grant (No. EFP-1104-GC). Ioana Nicolau was funded by a Canadian Institutes of Health Research Doctoral Award (No. 201710MDR) and the Canadian HIV Observational Cohort Scholar Award (No. 711352). Ann Burchell is a Canada Research Chair in Sexually Transmitted Infection Prevention (Tier 2). During the study, Ann Burchell received support from an Ontario HIV Treatment Network (OHTN) Endgame Leader award and a Non-Clinician Researcher award from the Department of Family and Community Medicine, Faculty of Medicine, University of Toronto. Jennifer Gillis received support from the OHTN Endgame Student Leadership Award. Claire Kendall was supported by CIHR New Investigator award and Clinical Research Chair Award from the Faculty of Medicine University of Ottawa.

Data sharing: The data set from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are therefore either inaccessible or may require modification.

Acknowledgements: The authors thank members of the community engagement committee, and co-chairs Joanne D. Lindsay and Anthony Mohamed, as well as their community partner agencies. The authors thank Karl Everett at ICES Central for his contributions to data preparation.

Contributors: ANB (principal investigator) and IAN were involved in the study concept and design. IAN conducted the analysis with supervision from ANB, TA, JDB, and RM. All authors interpreted the data. IAN drafted the manuscript. All authors revised it critically for important intellectual content, approving the final version to be published, and agreeing to be accountable for all aspects of the work.

Disclaimer: Parts of this material are based on data and/or information compiled and provided by the Canadian Institute for Health Information; Immigration, Refugees and Citizenship Canada (IRCC) current to March 2020; and Ontario Health (Cancer Care Ontario). The analyses, results, conclusions, opinion, views and statements expressed herein are solely those of the authors and do not reflect those of the funding and data sources; no endorsement is intended or should be inferred. This study was supported by ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). The opinions, results and conclusions reported in this article are those of the authors and are independent from the funding sources. No endorsement by ICES or the Ontario MOH and MLTC is intended or should be inferred.

ABSTRACT

Background: People with HIV are at higher risk of certain cancers than the general population. We compared trends of infection-related and -unrelated cancers among people with and without HIV.

Methods: We conducted a retrospective population-based matched cohort study of adults with and without HIV using linked health administrative databases in Ontario, Canada. Incident cancers identified from Jan. 1, 1996 to Nov. 1, 2020 were categorized as infection-related or -unrelated. We used competing risk analyses to examine trends in cumulative incidence and cause-specific hazard rates.

Results: We matched 20304 people with HIV and 20304 without HIV (N=40608). There were 1534 cancers diagnosed among people with HIV and 903 cancers among people without HIV. The risk of infection-related cancer by age 65 for people with HIV decreased from 19.0% (95% Confidence Interval [CI] 15.6–22.3) in 1996–2011 to 10.0% (95% CI 7.9–12.1) in 2012–2020. Compared with people without HIV, people with HIV had similar hazard rates of infection-unrelated cancer but had increased rates of infection-related cancer, particularly at younger age groups (18.0 [95% CI 9.4–34.2] vs. 1.9 [95% CI 1.0-3.6] for age 18–39 years vs. 70+ years). These trends were consistent for males and females with HIV.

Interpretation: We observed significantly higher rates of infection-related, but not infection-unrelated cancer, among people with HIV. The elevated rate of infection-related cancer in 2012-2020 highlights the importance of early and sustained antiretroviral therapy along with cancer screening and prevention measures.

INTRODUCTION

People with HIV on combination antiretroviral therapy (cART) have on average two times higher risk of cancer than the general population(1-3). Before the introduction cART in 1996, the most common cancers among people with HIV were Kaposi sarcoma, non-Hodgkin lymphoma, and invasive cervical cancer, classified as AIDS-defining cancers (ADC).(2, 4, 5) In recent years, non-AIDS defining cancers (NADC) have become increasingly common(2, 4, 5) given the success of cART bringing life expectancy near that of the general population.(6) Cancer risks reflect the interaction of multiple component causes, including HIV-related immunosuppression and decreased immune surveillance of oncogenic infections, and a higher prevalence of known cancer risk factors such as tobacco and alcohol use, obesity, viral hepatitis, and human papillomavirus (HPV) infection(3, 7).

Most studies comparing cancer incidence among people with and without HIV have been conducted in Europe and United States(1-5, 8-15) with comparatively few studies in Canada(16-18). Ontario is the province with the highest number of annual new HIV infections and the largest population of people living with HIV nationally.(19, 20) We previously documented a substantial decline in ADC incidence from 403 to 104 per 100000 person-years between 1997 and 2020 in Ontario, but little to no decrease in the incidence of infection-unrelated cancer.(21) Our objective was to extend this work to compare calendar and age-related trends in the incidence of infection-related and -unrelated cancers among people with HIV to a matched cohort of people without HIV from 1996 to 2020.

METHODS

Study design and setting

We conducted a retrospective population-based matched cohort study in Ontario, Canada, from Jan. 1, 1996 and Nov. 1, 2020 using linked administrative health datasets housed at ICES (formerly known as the Institute for Clinical Evaluative Sciences). ICES is an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. We used the Reporting of Studies Conducted Using Observational Routinely-Collected Health Data (RECORD) checklist.(22) This study also incorporated insights from Ontarians living with both HIV and cancer through a Community Advisory Board.

Participants

We identified Ontario residents aged 18 years or over with a diagnosed HIV infection according to a validated case-finding algorithm described previously.(21, 23) We defined cohort entry as the earliest record of an HIV-related diagnostic code in the case-finding algorithm. We excluded individuals who were missing age or sex information, or who at cohort entry were not residing in Ontario or who had a previous cancer diagnosis. Each person with HIV was matched 1:1 with an individual without a diagnosis of HIV as of the cohort entry date (within one year). Individuals were matched on birth year (within one year), sex, census division, neighbourhood income quintile, and region of birth (i.e., Canadian born or immigrated prior to 1986, born outside of Canada in a country with low HIV prevalence, or born outside of Canada in regions with high HIV prevalence).(24) We followed participants from cohort entry until the earliest date of cancer diagnosis, date of death, Nov. 1, 2020, or the date of loss-to follow-up defined as no record of death and no contact with the health care system for at least 5 years; we censored individuals 5 years after the date of last contact.(25-28)

Data sources

We ascertained cancer diagnoses using the Ontario Cancer Registry, which records information for all primary incident cancers (except for basal cell and squamous cell skin cancers) using the International Classification of Diseases for Oncology (ICD-O-3).(29, 30) We used the Registered Persons Database, a registry of all Ontario residents with health insurance, for demographic and date of death information. We used the Canadian Institute for Health Information's Discharge Abstract Database and the Ontario Health Insurance Plan database to identify hospital admissions, claims for physician services, and comorbidity burden. We used the Immigration, Refugees and Citizenship Canada Permanent Residents Database to identify immigration status and region of birth. Finally, we used postal code information to obtain neighbourhood-level income and rurality. The data sets were linked using unique encoded identifiers and analyzed at ICES.(31-33)

Outcomes and covariates

As we had done previously, (21) our primary outcomes were infection-unrelated and infection-related cancers (Appendix 1, Supplementary Table A1).(34) In secondary analyses, we examined the incidence of ADC, infection-related NADC, and the three most commonly observed NADCs in our study.

We ascertained the following information on covariates at cohort entry: age, sex, rurality, neighborhood income quintile, region of birth, immigration status, comorbidity using the Johns Hopkins Adjusted Clinical Group System based on type of illness using diagnosis codes in the two years preceding cohort entry(35, 36), and expected health care use(36). We classified calendar periods 1996–2003, 2004–2011 and 2012–2020, corresponding to the early cART, established cART, and contemporary cART eras, respectively(37, 38). We classified attained age (time-varying) as early adulthood (18–39), early and late middle adulthood (40–49 and 50–59), and early and late old adulthood (60–69 and 70+)(39-43).

Statistical analysis

We used descriptive statistics to summarize categorial (n, %) and continuous variables (median, interquartile range [IQR]) at cohort entry. We used standardized differences to compare characteristics at cohort entry between people with and without HIV, with a difference of less than 0.1 indicating good intergroup balance.(44)

We plotted unadjusted non-parametric cumulative incidence curves for the primary and secondary outcomes and estimated cumulative cancer risk by age 65.(10) We used cause-specific hazards models to compare cancer incidence among people with and without HIV, stratified by calendar period, attained age, and sex (for primary outcomes only), with all-cause mortality as a competing event and censoring at loss to follow-up and end of follow-up.

When examining infection-related cancers, we considered infection-unrelated cancers as a competing event in addition to all-cause mortality since, by definition, being diagnosed with an infection-unrelated first primary cancer precludes diagnosis of an infection-related first primary cancer. Similarly, for infection-unrelated cancers we considered infection-related cancer as a competing risk. We used cause-specific hazard ratios (HRs) to estimate the relative effect of HIV status on the hazard function(45) and estimated 95% confidence intervals (CIs) using the robust sandwich covariance estimate(46). We adjusted all models for comorbidity, expected resource utilization, and immigration status. We assessed the proportionality of hazards assumption by interaction terms between HIV status and time and weighted Schoenfeld residuals. In sensitivity analysis, we calculated the E-value to examine the amount of confounding bias needed to completely explain away the observed HRs.(47, 48)

We used the prodlim package in RStudio (Version 0.98.1091, 2009-2014 RStudio Inc.) to estimate cumulative incidence functions and to plot cumulative incidence curves. All other analyses were conducted using SAS Enterprise Guide (Version 7.15, Cary, NC, USA).

Ethics approval

This study was approved by the research ethics boards of St. Michael's Hospital (REB# 19-113), Toronto, and University of Toronto (REB# 00038757).

RESULTS

We matched 20304 people with HIV to 20304 individuals without HIV, for a total sample of 40608 study participants (Figure 1). Most were male, born in Canada or long-term residents, who lived in urban centers and in the lowest neighbourhood income quintile (Table 1). The median age at cohort entry was 37 (IQR 30–45) years. Compared with people without HIV, people with HIV at cohort entry were more likely to have a higher comorbidity burden and high expected resource use (Table 1).

There were 2437 incident first primary cancers over 449975 person-years of observation (median 10 [IQR 5–17] years), of which 1534 (62.9%) were diagnosed among people with HIV and 903 (37.1%) among people without HIV (see Appendix 1, Supplementary Table A2 for site-specific cancers). Compared with people without HIV, people with HIV had a greater proportion of ADC and infection-related NADC diagnoses (e.g., anal cancer) and a lower proportion of infection-unrelated cancers (Table 2).

Calendar trends in incidence

The probability of infection-related cancer for people with HIV declined between the early (1996–2003) to the contemporary (2012–2020) cART eras (Figure 2, Panel A), with the cumulative risk of being diagnosed with an infection-related cancer by age 65 declining from 19.0% (95% CI 15.6%–22.3%) to 10.0% (95% CI 7.9%–12.1%) during this period (Table 3). This decrease was driven largely by a decline in ADCs, with a smaller decrease in the probability of infection-related NADCs (Table 3). Conversely, we saw no change in trends for infection-related cancer among people without HIV (Figure 2, Panel B). However, among people with HIV the burden of cancer shifted from infection-related to infection-unrelated cancer in late adulthood (Appendix 1, Supplementary Figure A1). We observed similar findings when examining trends by sex (Appendix 1, Supplementary Figure A2).

Among people with and without HIV, we observed no calendar trends for the three most common NADCs, prostate, lung, and colorectal cancer (Appendix 1, Supplementary Figure A2). However, the risk of a diagnosis of anal and liver cancer by age 65 was higher among people living with HIV compared to HIV-negative people and this was consistent over time (Table 3).

Age-specific trends

People with HIV had a 7.9 (95% CI 6.2–10.1) times higher hazard rate of infection-related cancer at any age compared with people without HIV, averaged across all ages and time periods. However, the magnitude of the heightened risk decreased with age and time, such that the HR of infection-related cancer was 25.1 (95% CI 13.2–47.7) for those aged 18 to 39 and 1.9 (95% CI 1.0–3.7) for individuals over 70 years of age (Table 4 and Figure 3). An E-value of 15.3 would completely explain away an HR of 7.9 and E-values of 49.7 and 3.2 for HRs of 25.1 and 1.9, respectively. We found comparable infection-related cancer trends in analyses stratified by sex (Table 4) and calendar period (Appendix 1, Supplementary Table A3).

When examining trends in infection-unrelated cancer, people with HIV had the same hazard rate of infection-unrelated cancer as people without HIV (Table 4). We observed that older females with HIV had a greater hazard rate of infection-unrelated cancer than older females without HIV, although the difference was not statistically significant. In contrast, males with HIV who were 60–69 years of age had a lower hazard of infection-unrelated cancer than males without HIV, likely reflecting the increased hazard of mortality (Table 4).

INTERPRETATION

In our matched population-based study of people with and without HIV in Ontario, Canada from 1996 to 2020, we observed that the hazard of infection-related cancer was 7.9 times higher among people with HIV than without HIV. However, the risk of having a diagnosis of infection-related cancer by age 65 dropped from 19% in the early cART era (1996–2011) to 10% in the contemporary cART era (2012–2020) for people with HIV, a decline that was driven primarily by a decrease in ADC. We attribute this finding to improvements in antiretroviral therapies over time and earlier entry into HIV care, strategies which improve immune function and decrease the risk of persistent oncogenic infections.(7) Nevertheless, we observed a consistently heightened risk for infection-related NADCs among people living with HIV, particularly for anal and liver cancers. Vaccination against pathogens that cause such cancers, notably HPV and hepatitis B virus, are recommended for people living with HIV.(49) Moreover, there is strong evidence that anal cancer can be prevented through screening and subsequent treatment of high-grade squamous intraepithelial lesions, highlighting the need for optimized screening and treatment of cancer precursors.(50, 51) Likewise, prevention of liver cancer includes treatment of hepatitis B virus and hepatitis C virus infection, as well as efforts tackling metabolic risk factors (e.g., diabetes, hypertension, cardiovascular disease) associated with non-alcoholic fatty liver disease-related liver cancer(52). We did not observe differences by HIV status in the risk for infection-unrelated cancers, consistent with others (18, 53).

When we examined age-specific trends, we found that relative to people without HIV, people with HIV had a greater hazard of infection-related cancer at younger ages with a 25 (95% CI 13–48) times higher hazard rate for the 18-39 age group. This is consistent with other studies that observed an earlier age at cancer diagnosis for people with compared to people without HIV for certain cancers including anal, lung, prostate, oropharyngeal, and myeloma cancer(54-56). However, the higher relative difference at younger ages compared with older is partially due to the fact that the incidence in the background population increases with age(57). No major differences were noted when examining trends in infection-related and -unrelated cancer by sex.

Strengths of our analysis include use of a population-based matched cohort of people with and without HIV in a setting with publicly funded healthcare. Given our large study sample and long follow-up, we were able to capture many events and examine sex and age-specific trends over time. Our competing risk approach using age as the time scale to obtain a measure of lifetime cancer risk(60) and reporting cumulative cancer risk by age 65 has both clinical and public health utility.

Limitations

People with undiagnosed HIV or those who do not access care would have been excluded from our analyses. For those included but subsequently lost-to-follow-up in administrative databases, our assumptions regarding end of follow-up time may have resulted in over-estimation of person-time at risk, and thus an under-estimate of cancer incidence. Although we had many cancer events, we lacked precision to estimate cancer risks for certain age- and sex- groups, as well as for specific cancer sites beyond the most common ones. Finally, known cancer risk factors were unavailable, including lifestyle factors (e.g., smoking, alcohol), family history, and clinical data (e.g., CD4, coinfection with hepatitis B or C, antiretrovirals), precluding their examination in our analysis. However, in our sensitivity analysis we explored the magnitude of confounding bias that would explain away the observed association between HIV status and infection-related cancer and found that an extremely strong confounder would be required; one

that is a very strong risk factor for cancer and strongly associated with HIV status. The E-value we calculated of 15.3 suggests that the confounder needed is 15.3 times more likely to occur in people with than without HIV and increases the risk of cancer by a factor of 15.3. Smoking is an example of a risk factor that most aligns with this, however, it is unlikely to explain away the association in younger age groups (E-value 49.7).

Conclusion

People with HIV remain at much greater risk of infection-related cancers than people without HIV across all age groups. Our findings emphasize the importance of promoting and encouraging early and routine cancer prevention strategies for people with HIV, such as early linkage to HIV care and treatment, screening for and treatment of viral hepatitis, HPV vaccination, and screening for HPV-related anal and cervical cancers. Although the risk of infection-unrelated cancers was similar between people with and without HIV, infection-unrelated cancers still contributed greatly to the overall cancer burden for people with HIV, especially at older ages. Consequently, clinicians are encouraged to have ongoing conversations about lifetime cancer risk with patients in HIV care, and encourage risk reduction such as smoking cessation, and breast and colorectal screening.

REFERENCES

1. Cobucci RNO, Lima PH, de Souza PC, Costa VV, Cornetta MdCdM, Fernandes JV, et al. Assessing the impact of HAART on the incidence of defining and non-defining AIDS cancers among patients with HIV/AIDS: a systematic review. Journal of infection and public health. 2015;8(1):1--10.
2. Shiels MS, Cole SR, Kirk GD, Poole C. A meta-analysis of the incidence of non-AIDS cancers in HIV-infected individuals. Journal of acquired immune deficiency syndromes (1999). 2009;52(5):611--22.
3. Park LS, Tate JP, Sigel K, Rimland D, Crothers K, Gibert C, et al. Time trends in cancer incidence in persons living with HIV/AIDS in the antiretroviral therapy era: 1997-2012. AIDS (London, England). 2016;30(11):1795-806.
4. Shiels MS, Engels EA. Evolving epidemiology of HIV-associated malignancies. Current Opinion in HIV and AIDS. 2017;12(1):6--11.
5. Shiels MS, Pfeiffer RM, Gail MH, Hall HI, Li J, Chaturvedi AK, et al. Cancer Burden in the HIV-Infected Population in the United States. JNCI Journal of the National Cancer Institute. 2011;103(9):753--62.
6. Marcus JL, Leyden WA, Alexeeff SE, Anderson AN, Hechter RC, Hu H, et al. Comparison of Overall and Comorbidity-Free Life Expectancy Between Insured Adults With and Without HIV Infection, 2000-2016. JAMA Netw Open. 2020;3(6):e207954.
7. Borges AH, Dubrow R, Silverberg MJ. Factors contributing to risk for cancer among HIV-infected individuals, and evidence that earlier combination antiretroviral therapy will alter this risk. Current opinion in HIV and AIDS. 2014;9(1):34--40.
8. Silverberg MJ, Abrams DI. AIDS-defining and non-AIDS-defining malignancies: cancer occurrence in the antiretroviral therapy era. Current Opinion in Internal Medicine. 2007;6(6):642--7.
9. Silverberg MJ, Chao C, Leyden WA, Xu L, Horberg MA, Klein D, et al. HIV infection, immunodeficiency, viral replication, and the risk of cancer. Cancer Epidemiology Biomarkers and Prevention. 2011;20(12):2551--9.
10. Silverberg MJ, Lau B, Achenbach CJ, Jing Y, Althoff KN, D'Souza G, et al. Cumulative Incidence of Cancer Among Persons With HIV in North America. Annals of Internal Medicine. 2015;163(7):507.
11. Hernández-Ramírez RU, Shiels MS, Dubrow R, Engels EA. Cancer risk in HIV-infected people in the USA from 1996 to 2012: a population-based, registry-linkage study. Lancet HIV. 2017;4(11):e495-e504.
12. Mahale P, Engels EA, Coghill AE, Kahn AR, Shiels MS. Cancer Risk in Older Persons Living With Human Immunodeficiency Virus Infection in the United States. Clin Infect Dis. 2018;67(1):50-7.
13. Robbins HA, Shiels MS, Pfeiffer RM, Engels EA. Epidemiologic contributions to recent cancer trends among HIV-infected people in the United States. Aids. 2014;28(6):881--90.
14. Park LS, Tate JP, Sigel K, Brown ST, Crothers K, Gibert C, et al. Association of Viral Suppression With Lower AIDS-Defining and Non–AIDS-Defining Cancer Incidence in HIV-Infected Veterans. Annals of Internal Medicine. 2018;169(2):87.
15. Patel P. Incidence of Types of Cancer among HIV-Infected Persons Compared with the General Population in the United States, 1992–2003. Annals of Internal Medicine. 2008;148(10):728.

16. Chiu CG, Smith D, Salters KA, Zhang W, Kanters S, Milan D, et al. Overview of cancer incidence and mortality among people living with HIV/AIDS in British Columbia, Canada: Implications for HAART use and NADM development. BMC cancer. 2017;17(1):270.
17. Salters KA, Cescon A, Zhang W, Ogilvie G, Murray MCM, Coldman A, et al. Cancer incidence among HIV-positive women in British Columbia, Canada: Heightened risk of virus-related malignancies. HIV Medicine. 2016;17(3):188--95.
18. Burchell A, Salters K, Eyawo O, Lindsay J, Chia J, Cotterchio M, et al. Cancer incidence among persons on modern suppressive antiretroviral therapy, 2000-12. Conference on Retroviruses and Opportunistic Infections (CROI). 2017.
19. PHAC. Estimates of HIV Incidence, Prevalence and Canada's Progress On Meeting The 90-90-90 HIV Targets, 2018. Ottawa, Ontario: Public Health Agency of Canada. ; 2020.
20. OHESI. Data and figures: Number of new HIV diagnoses, Ontario: Ontario HIV Epidemiology and Surveillance Initiative; 2017 [Available from: http://www.ohesi.ca/new-hiv-diagnoses-overall-2017/.
21. Nicolau IA, Antoniou T, Brooks JD, Moineddin R, Cooper C, Cotterchio M, et al. The burden of cancer among people living with HIV in Ontario, Canada, 1997-2020: a retrospective population-based cohort study using administrative health data. CMAJ Open. 2022;10(3):E666-e74.
22. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12(10):e1001885.
23. Antoniou T, Zagorski B, Loutfy MR, Strike C, Glazier RH. Validation of case-finding algorithms derived from administrative data for identifying adults living with human immunodeficiency virus infection. PloS one. 2011;6(6):e21748.
24. Canada PHAo. HIV/AIDS Epi Updates: HIV/AIDS in Canada among people from countries where HIV is endemic, April 2012,. Ottawa, Canada: Centre for Communicable Diseases and Infection Control, Public Health Agency of Canada; 2012.
25. Gillis J, Loutfy M, Bayoumi AM, Antoniou T, Burchell AN, Walmsley S, et al. A Multi-State Model Examining Patterns of Transitioning Among States of Engagement in Care in HIV-Positive Individuals Initiating Combination Antiretroviral Therapy. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2016;73(5):531--9.
26. Burchell AN, Gardner S, Light L, Ellis BM, Antoniou T, Bacon J, et al. Implementation and Operational Research: Engagement in HIV Care Among Persons Enrolled in a Clinical HIV Cohort in Ontario, Canada, 2001-2011. J Acquir Immune Defic Syndr. 2015;70(1):e10-9.
27. Wilton J, Liu JA-O, Sullivan A, Rachlis B, Marchand-Austin AA-O, Giles M, et al. Trends in HIV care cascade engagement among diagnosed people living with HIV in Ontario, Canada: A retrospective, population-based cohort study. PLoS One. 2019;14(1):e0210096.
28. Nicolau I, Antoniou T, Brooks JD, Moineddin R, Cooper C, Cotterchio M, et al. Cancer Among People Living with HIV in Ontario, Canada, 1997-2018. Canadian Association for HIV Research (CAHR) Conference2021.
29. How We Collect Cancer Registry Data – Cancer Care Ontario [Available from: https://www.cancercareontario.ca/en/data-research/accessing-data/technical-information/cancer-registry-data-collection.
30. Ontario Cancer Registry - CQCO [Available from: http://www.cqco.ca/cms/One.aspx?portalId=89613&pageId=121939.

31. Chiu M, Lebenbaum M, Lam K, Chong N, Azimaee M, Iron K, et al. Describing the linkages of the immigration, refugees and citizenship Canada permanent resident data and vital statistics death registry to Ontario's administrative health database. BMC Med Inform Decis Mak. 2016;16(1):135.
32. Williams JIY, W. A summary of studies on the quality of health care administrative databases in Canada. Ottawa: Canadian Medical Association 1996.
33. Schull MJ, Azimaee M, Marra M, Cartagena RG, Vermeulen MJ, Ho M, et al. ICES: Data, Discovery, Better Health. Int J Popul Data Sci. 2020;4(2):1135.
34. Bouvard V, Baan R, Straif K, Grosse Y, Secretan Ba. A review of human carcinogens--Part B: biological agents. The Lancet Oncology. 2009;10(4):321--2.
35. Austin PC, van Walraven C, Wodchis WP, Newman A, Anderson GM. Using the Johns Hopkins Aggregated Diagnosis Groups (ADGs) to Predict Mortality in a General Adult Population Cohort in Ontario, Canada. Medical Care. 2011;49(10):932--9.
36. Health JHBSoP. The John Hopkins ACG System: State of the art technology and a tradition of excellence in one integrated solution Baltimore: Bloomberg School of Public Health; 2012.
37. Arts EJ, Hazuda DJ. HIV-1 antiretroviral drug therapy. Cold Spring Harb Perspect Med. 2012;2(4):a007161.
38. Tseng A, Seet J, Phillips EJ. The evolution of three decades of antiretroviral therapy: challenges, triumphs and the promise of the future. Br J Clin Pharmacol. 2015;79(2):182-94.
39. Medley ML. Life Satisfaction across Four Stages of Adult Life. The International Journal of Aging and Human Development. 1980;11(3):193-209.
40. Ory MG, Anderson LA, Friedman DB, Pulczinski JC, Eugene N, Satariano WA. Cancer prevention among adults aged 45-64 years: setting the stage. Am J Prev Med. 2014;46(3 Suppl 1):S1-6.
41. White MC, Holman DM, Boehm JE, Peipins LA, Grossman M, Henley SJ. Age and cancer risk: a potentially modifiable relationship. Am J Prev Med. 2014;46(3 Suppl 1):S7-15.
42. Harden J, Northouse L, Cimprich B, Pohl JM, Liang J, Kershaw T. The influence of developmental life stage on quality of life in survivors of prostate cancer and their partners. J Cancer Surviv. 2008;2(2):84-94.
43. Little W. Chapter 13: Aging and Elderly. Introduction to Sociology - 2nd Canadian Edition. Victoria, British Columbia: BCcampus; 2016.
44. Austin PC. Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research. Communications in Statistics - Simulation and Computation. 2009;38(6):1228-34.
45. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. Stat Med. 2017;36(27):4391-400.
46. Wei LJ, Lin DY, Weissfeld L. Regression Analysis of Multivariate Incomplete Failure Time Data by Modeling Marginal Distributions. Journal of the American Statistical Association. 1989;84(408):1065-73.
47. Fox MP, MacLehose RF, Lash TL. Uncontrolled confounders: the E-Value and G-Value. Applying Quantitative Bias Analysis to Epidemiologic Data Second Edition. Switzerland: Springer New York; 2021. p. 131-5.
48. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268-74.

49. Adolescents PoGftPaToOIiAa, HIV. w. Guidelines for the Prevention and Treatment of Opportunistic Infections in Adults and Adolescents
with HIV. .
50. Palefsky JM, Lee JY, Jay N, Goldstone SE, Darragh TM, Dunlevy HA, et al. Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer. N Engl J Med. 2022;386(24):2273-82.
51. Bouvard V, Wentzensen N, Mackie A, Berkhof J, Brotherton J, Giorgi-Rossi P, et al. The IARC Perspective on Cervical Cancer Screening. N Engl J Med. 2021;385(20):1908-18.
52. Tan DJH, Ng CH, Lin SY, Pan XH, Tay P, Lim WH, et al. Clinical characteristics, surveillance, treatment allocation, and outcomes of non-alcoholic fatty liver disease-related hepatocellular carcinoma: a systematic review and meta-analysis. The Lancet Oncology. 2022;23(4):521-30.
53. Grulich AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet. 2007;370(9581):59--67.
54. Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. Annals of internal medicine. 2010;153(7):452--60.
55. Jin F, Vajdic CM, Law M, Amin J, van Leeuwen M, McGregor S, et al. Incidence and time trends of anal cancer among people living with HIV in Australia. Aids. 2019;33(8):1361-8.
56. Shiels MS, Althoff KN, Pfeiffer RM, Achenbach CJ, Abraham AG, Castilho J, et al. HIV infection, immunosuppression, and age at diagnosis of non-AIDS-defining cancers. Clinical Infectious Diseases. 2017;64(4):468--75.
57. Biggar RJ, Kirby KA, Atkinson J, McNeel TS, Engels E. Cancer Risk in Elderly Persons With HIV/AIDS. JAIDS Journal of Acquired Immune Deficiency Syndromes. 2004;36(3):861--8.
58. Kaufman HW, Chen Z, Niles J, Fesko Y. Changes in the Number of US Patients With Newly Identified Cancer Before and During the Coronavirus Disease 2019 (COVID-19) Pandemic. JAMA Network Open. 2020;3(8):e2017267.
59. Glazier RH, Green ME, Wu FC, Frymire E, Kopp A, Kiran T. Shifts in office and virtual primary care during the early COVID-19 pandemic in Ontario, Canada. Cmaj. 2021;193(6):E200-e10.
60. Vyas MV, Fang J, Kapral MK, Austin PC. Choice of time-scale in time-to-event analysis: evaluating age-dependent associations. Annals of Epidemiology. 2021;62:69-76.

Table 1. Characteristics of people with and without HIV at cohort entry, from Ontario, Canada,1996–2020

Characteristic	People with HIV (N=20304)	People without HIV (N=20304)	Std. Diff.[1]
Age, median (IQR)	37 (30–45)	37 (30–45)	0.00
Age categories, n(%)			
18-29	4878 (24.0)	4875 (24.0)	0.00
30-39	7372 (36.3)	7338 (36.1)	0.00
40-49	4937 (24.3)	4959 (24.4)	0.00
50-59	2079 (10.2)	2094 (10.3)	0.00
60-69	660 (3.3)	672 (3.3)	0.00
70-79	243 (1.2)	230 (1.1)	0.01
80+	135 (0.7)	136 (0.7)	0.00
Sex, n (%)			
Female	4396 (21.7)	4396 (21.7)	0.00
Male	15908 (78.3)	15908 (78.3)	0.00
Period of cohort entry, n (%)			
1996-1999	3532 (17.4)	3534 (17.4)	0.00
2000-2003	3071 (15.1)	3074 (15.1)	0.00
2004-2007	3314 (16.3)	3305 (16.3)	0.00
2008-2011	3305 (16.3)	3305 (16.3)	0.00
2012-2015	3330 (16.4)	3338 (16.4)	0.00
2016-2020	3752 (18.5)	3748 (18.5)	0.00
Neighbourhood income quintile, n (%)	6872 (33.8)	6872 (33.8)	0.00
1 (Lowest)	4486 (22.1)	4486 (22.1)	0.00
2	3372 (16.6)	3372 (16.6)	0.00
3	2789 (13.7)	2789 (13.7)	0.00
4	2785 (13.7)	2785 (13.7)	0.00
5 (Highest)			
Rurality, n (%)			
Urban	19550 (96.3)	19420 (95.6)	0.03
Rural	754 (3.7)	884 (4.4)	0.03
Comorbidity burden[2], n (%)			
No comorbid conditions	0	2405 (11.8)	**0.52**
Low	7902 (38.9)	10191 (50.2)	**0.23**
Moderate	4013 (19.8)	1109 (5.5)	**0.44**
High	8389 (41.3)	6599 (32.5)	**0.18**
Resource Utilization Band (RUB)[3], n (%)	1–5	2399–2403	**0.52**
0 (Lowest expected resource use)	1–5	1581–1585	**0.41**
1	16 (0.1)	4356 (21.5)	**0.73**
2	11273 (55.5)	9548 (47.0)	**0.17**
3	6025 (29.7)	2027 (10.0)	**0.51**
4	2985 (14.7)	388 (1.9)	**0.48**
5 (Highest expected resource use)			
Immigration status duration[5], n (%)	15273 (75.2)	15273 (75.2)	0.00
Long term resident	1337 (6.6)	2413 (11.9)	**0.18**

Characteristic	People with HIV (N=20304)	People without HIV (N=20304)	Std. Diff.[1]
Long term immigrant	2471 (12.2)	2475 (12.2)	0.00
Recent immigrant to Canada	1223 (6.0)	143 (0.7)	**0.30**
Immigrated after index date[4]			
Region of birth, n (%)			
Canadian born	15273 (75.2)	15273 (75.2)	0.00
Born outside of Canada in a country with low HIV prevalence	2738 (13.5)	2738 (13.5)	0.00
Born outside of Canada in a country with high HIV prevalence[6]	2293 (11.3)	2293 (11.3)	0.00

Note: Ranges are shown to suppress a small cell count

Abbreviations: IQR, interquartile range; std. diff., standardized difference

[1]Standardized difference > 0.1 indicate a significant difference

[2]Comorbidity burden classification on based on the type of illness in the two years preceding cohort entry assessed using the Johns Hopkins Adjusted Clinical Group System collapsed Aggregated Diagnosis Groups (CADGs) with 0 CADG indicating no burden, 1-4 CADGs indicating low burden, 5-9 CADGs medium burden and 10-12 CADGs high burden.

[3]Expected health care use was assessed using the Johns Hopkins Adjusted Clinical Groups Resource Utilization Bands (RUB) based on 6 categories, with 0 being no health care use and 5 being the highest expected use

[4]Index date refers to the date of entry into the study defined as the earliest record of an HIV-related diagnostic code for people with HIV and used in the matching process as the same date (within 1 year) for individuals without HIV.

[5]Immigration status categorized as: long term resident if Canadian born or immigrated prior to 1986; long term immigrant if residing in Canada for 10 or more years; and recent immigrant to Canada if residing in Canada for less than 10 years.

[6]Regions of Africa and the Caribbean were considered regions with high HIV prevalence

Table 2. Incident first primary cancers diagnosed among people with and without HIV, Ontario, Canada,1996–2020

Cancer group N (%)	Cancers among people with HIV (N=1534)	Cancers among people without HIV (N=903)	Total (N=2437)	Std. diff.[1]
Infection-unrelated cancer	696 (45.4)	784 (86.8)	1480 (60.7)	**0.97**
Infection-related cancer	838 (54.6)	119 (13.2)	957 (39.3)	**0.97**
ADC	559 (36.4)	45 (5.0)	604 (24.8)	**0.84**
Infection-related NADC	279 (18.2)	74 (8.2)	353 (14.5)	**0.30**
Most common site-specific NADCs among people with HIV				
Prostate	116 (7.6)	186 (20.6)	302 (12.4)	**0.38**
Lung	121 (7.9)	98 (10.9)	219 (9.0)	0.10
Colorectal	80 (5.2)	106 (11.7)	186 (7.6)	**0.24**
Anal	106–112 (6.9–7.3)	<6	112 (4.6)	**0.36**
Liver	49 (3.2)	19 (2.1)	68 (2.8)	0.07

Abbreviations: ADC, AIDS-defining cancer; NADC, non-AIDS defining cancers; std. diff., standardized difference.
[1]Standardized difference > 0.1 indicate a significant difference (in bold)
Note: Ranges are shown to supress a small cell count. Column percentages do not sum to 100% as cancers can be in more than 1 category.

Table 3. Crude cumulative incidence risk (%) by age 65 for people with and without HIV by calendar period, Ontario, Canada, 1996–2020

	People with HIV % (95% CI)			People without HIV % (95% CI)		
	Calendar periods			Calendar periods		
Cancer group	**1996–2003**	**2004–2011**	**2012–2020**	**1996–2003**	**2004–2011**	**2012–2020**
All cancers	25.3 (21.6–29.1)	25.6 (22.5–28.8)	18.3 (16.1–20.5)	11.0 (5.9–10.1)	14.2 (9.3–9.3)	13.9 (12.5–15.2)
Infection-unrelated cancer	7.0 (4.8-9.3)	9.4 (7.4-11.4)	8.7 (7.6-9.7)	10.8 (5.7-15.9)	12.4 (10.2-14.6)	11.8 (10.5-13.1)
Infection-related cancer	19.0 (15.6-22.3)	17.0 (14.1-19.9)	10.0 (7.9-12.1)	0.2 (0.0-0.4)	2.0 (0.9 -2.9)	2.2 (1.6-2.8)
ADC	14.8 (11.9-17.7)	12.0 (9.2-14.8)	6.0 (4.0-8.1)	0.2 (0.0-0.4)	0.5 (0.01-1.1)	0.8 (0.5-1.2)
Infection-related NADC	5.1 (2.7-7.5)	5.8 (4.3-7.2)	4.2 (3.4-5.0)	0.0 (0.0-0.0)	1.4 (0.5-2.2)	1.4 (0.9-1.8)
Most common site-specific NADCs among people with HIV						
Prostate[1]	1.7 (0.3-3.1)	1.2 (0.5-2.0)	2.1 (1.5-2.8)	5.9 (1.2-10.6)	5.5 (3.6-7.3)	3.4 (2.6-4.2)
Lung	0.9 (0.2-1.6)	2.6 (1.6-3.6)	1.5 (1.0-1.9)	1.7 (0.0-3.6)	1.0 (0.3-1.7)	1.4 (0.9-1.9)
Colorectal	1.3 (0.4-2.3)	0.9 (0.3-1.6)	1.0 (0.7-1.4)	2.0 (0.0-4.0)	1.3 (0.5-2.1)	1.4 (1.0-1.8)
Anal	1.9 (0.6-3.1)	1.3 (0.7-2.0)	1.8 (1.3-2.3)	0.0 (0.0-0.0)	0.03 (0.0-0.1)	0.02 (0.0-0.1)
Liver	1.1 (0.0-2.3)	0.7 (0.3-1.2)	0.6 (0.3-0.9)	0.0 (0.0-0.0)	0.4 (0.0-0.9)	0.3 (0.1-0.5)

[1]Restricted to males

Note: ADC= AIDS-defining cancer, NADC= non-AIDS defining cancer.

Table 4. Cause-specific hazard ratios (HR) and 95% confidence intervals (CI) for infection-related and infection-unrelated cancers comparing people with and without HIV, by age group and sex, Ontario, Canada. 1996-2020

	HR (95% CI)				
Outcome	**Age 18-39 years**	**Age 40-49 years**	**Age 50-59 years**	**Age 60-69 years**	**Age 70+**
	Both sexes combined				
Death	6.9 (5.0-9.5)*	4.1 (3.3-5.0)*	3.0 (2.4-3.6)*	2.1 (1.7-2.7)*	1.4 (1.1-1.7)*
Infection-related cancer	25.1 (13.2-47.7)*	15.1 (9.6-23.7)*	6.8 (4.7-9.9)*	3.1 (2.0-4.9)*	1.9 (1.0-3.7)
Infection-unrelated cancer	1.3 (0.9-1.9)	1.0 (0.8-1.3)	1.0 (0.8-1.2)	0.7 (0.6-0.9)	1.3 (1.0-1.6)
	Females				
Death	11.6 (5.7-23.8)*	15.9 (7.9-32.3)*	9.3 (4.7-18.5)*	2.8 (1.6-5.2)*	1.7 (1.2-2.4)*
Infection-related cancer	22.2 (5.7-87.5)*	6.4 (2.4-17.2)*	35.6 (4.9-259.5)*	4.5 (1.2-16.9)*	3.7 (0.9-16.1)
Infection-unrelated cancer	1.1 (0.6-2.0)	1.0 (0.6-1.5)	1.5 (1.0-2.4)	1.3 (0.8-2.1)	1.9 (1.0-3.4)
	Males				
Death	5.6 (3.9-8.1)*	3.1 (2.5-3.9)*	2.5 (2.0-3.0)*	2.0 (1.5-2.6)*	1.2 (0.9-1.5)
Infection-related cancer	25.7 (12.2-54.0)*	18.3 (10.8-31.1)*	5.7 (3.9-8.4)*	2.9 (1.9-4.6)*	1.6 (0.8-3.2)
Infection-unrelated cancer	1.5 (0.9-2.4)	1.0 (0.8-1.4)	0.9 (0.8-1.2)	0.7 (0.5-0.8)*	1.1 (0.8-1.6)

* Indicates statistical significance with the confidence interval excluding the null value of 1.
Abbreviations: HR cause-specific hazard rate ratios; CI, confidence interval.
Models were adjusted for calendar period, comorbidity, expected resource utilization and immigration status and included attained age at follow-up (categorical) and HIV status interaction term.

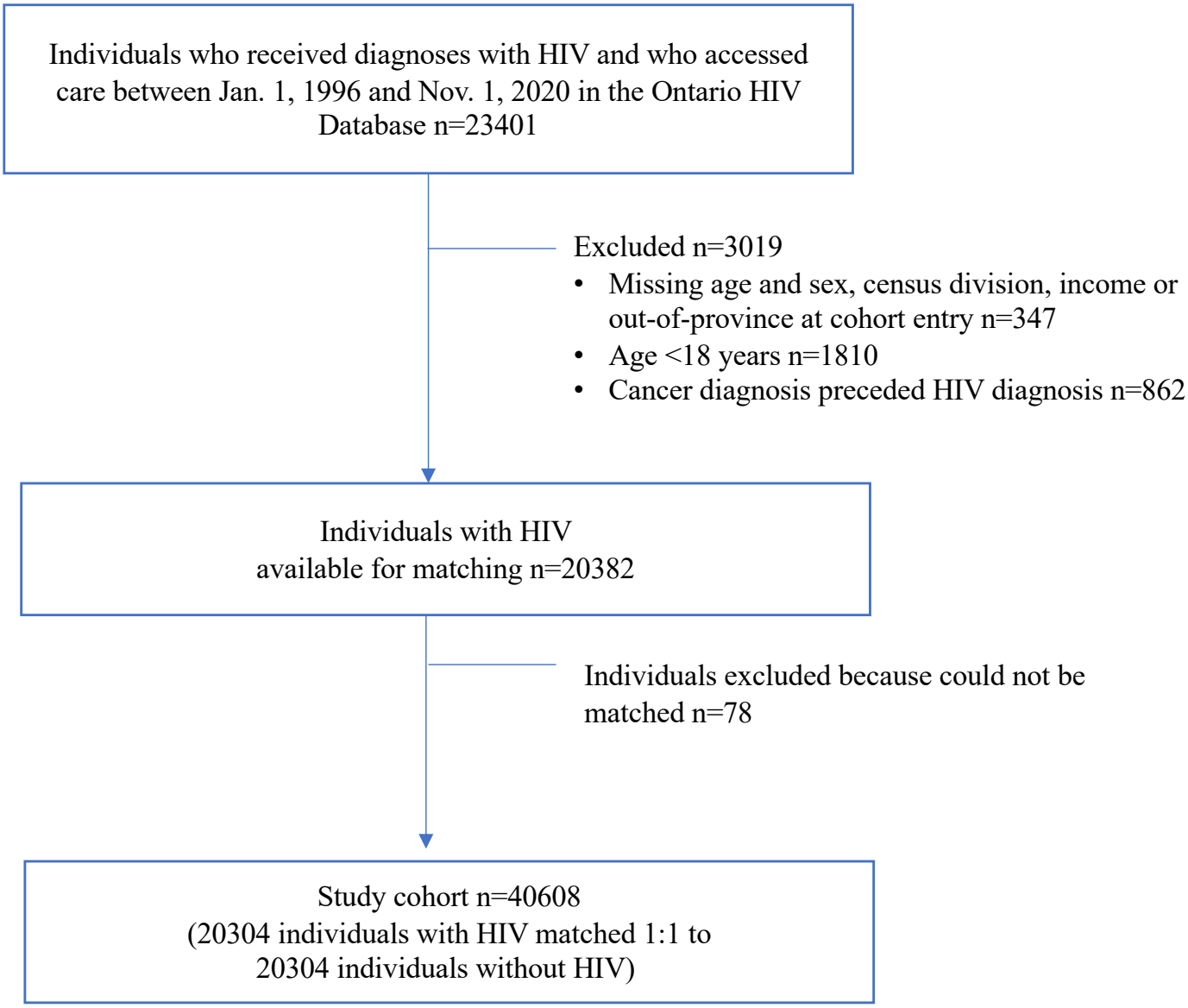


Figure 1. Study flow chart

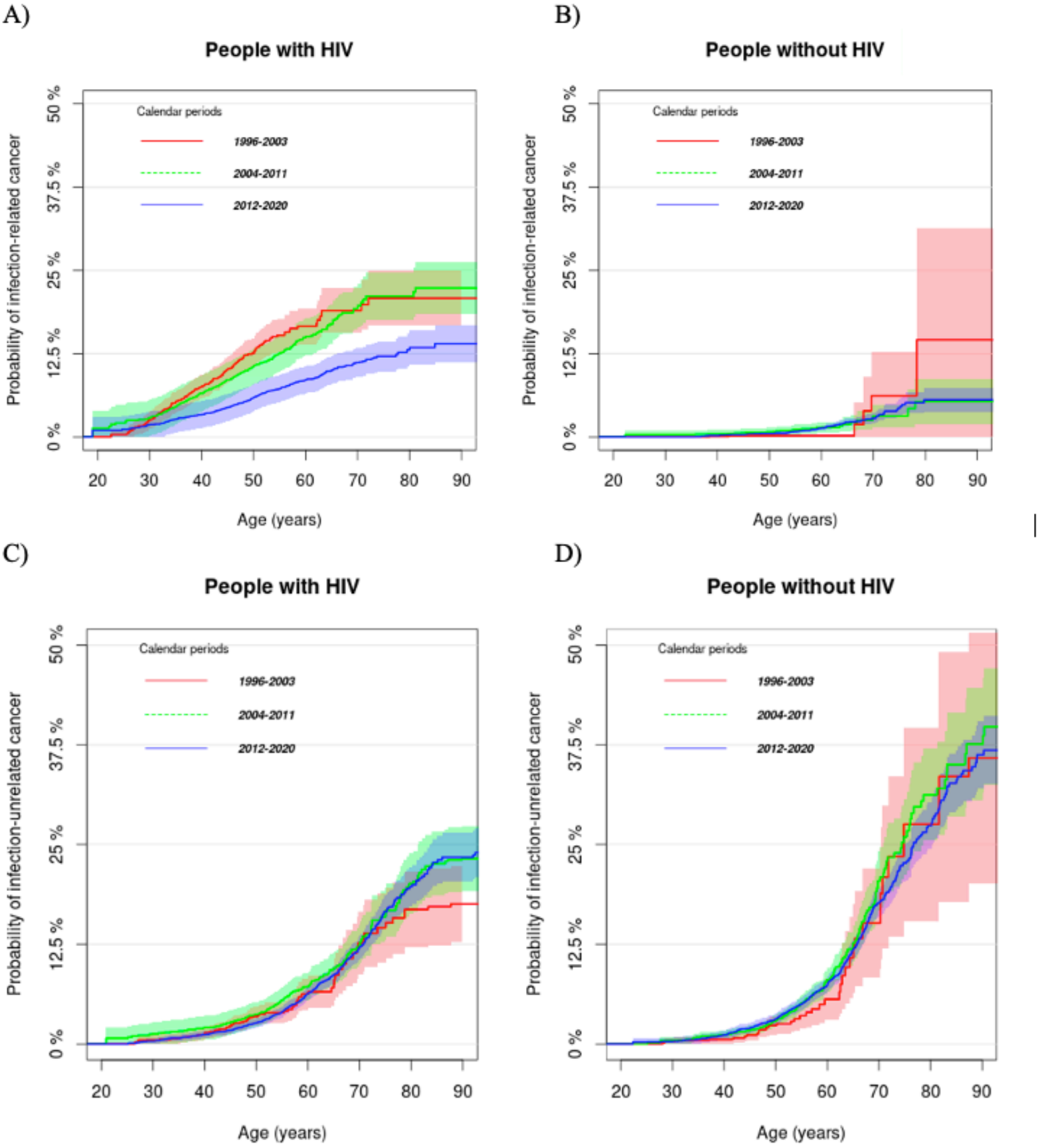


Figure 2. Cumulative incidence of infection-related cancer (Panels A and B) and infection-unrelated cancers (Panels C and D) for people with and without HIV by calendar period with age as the time scale, Ontario, Canada

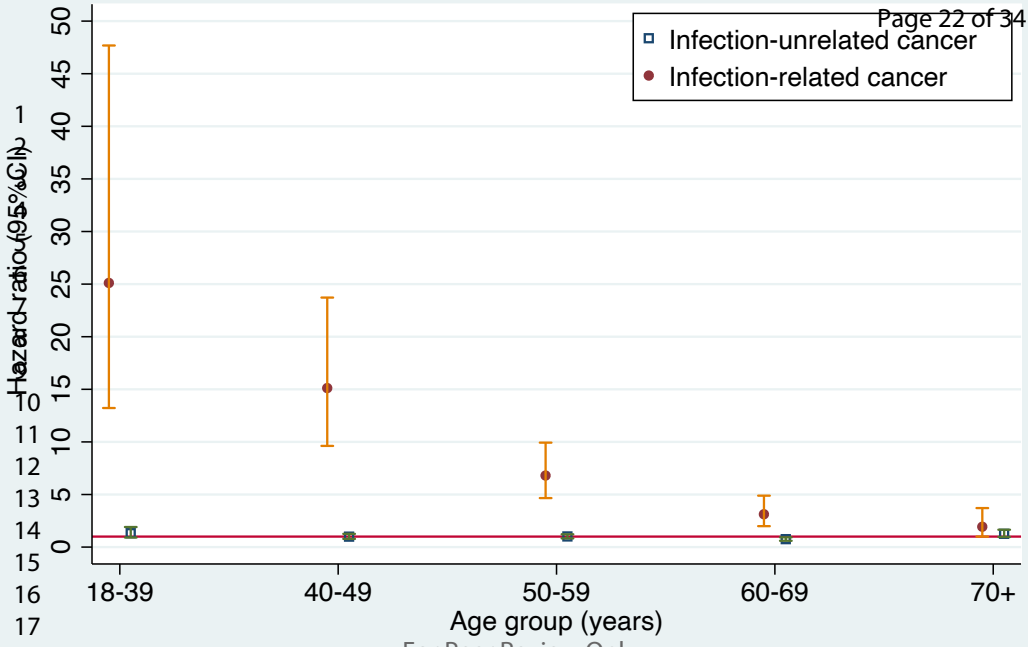


Figure 3. Cause-specific hazard rate ratios (HR) of infection-related and infection-unrelated cancer comparing people with and without HIV by age-group, Ontario, Canada

Associated 95% confidence intervals (CI) are represented by whiskers. Red line represents null value of HR=1.

APPENDIX 1 – Supplementary Materials

Supplementary Table A1. Cancer definitions using ICD-O-3

Cancer type	ICD-O-3 code
All cancers	C00.0–C80.9
Anus	C21
Bladder	C67
Brain	C70-C72
Breast	C50
Cervix	C53
Colorectal	C18–C20, C26.0
Esophagus	C15
Hodgkin lymphoma	Histologies 9650-9667
Kaposi sarcoma	Histology 91403
Kidney	C64 - C65
Larynx	C32
Leukemia	C42
Liver	C22
Lung	C34
Malignant neoplasm of other and unspecified male genital organs	C63
Melanoma of the skin	C44 with histologies 8720–8790
Multiple myeloma	Histologies 9731–9732, 9734
Non-Hodgkin lymphoma	Histologies 9590–9597, 967-972, 9735, 9737, 9738
Oral cavity & pharynx	C00–C00.9, C01.9-C02.9, C03-C11, C12.9, C13, C14.0, C14.2, C14.8
Ovary	C56.9
Pancreas	C25
Penis	C60
Prostate	C61.9
Stomach	C16
Testis	C62
Thyroid	C73.9
Uterus	C54-C55
Vagina	C52
Vulva	C51
Infection-related cancer groupings	
AIDS-defining cancers (ADC)	
Kaposi sarcoma	Histology 91403
Non-Hodgkin's lymphoma	Histologies 9590–9597, 967-972, 9735, 9737, 9738
Cervical cancer*	C53
Infection-related non-AIDS defining cancers (NADC)	
HPV-associated cancers*:	
Anogenital Anus Penis Unspecified male genital organs Vulva	 C21 C60 C63 C51

Vagina	C52
Oral cavity & pharynx	C01–C06, C09, C10, C14
H. Pylori-associated cancer:	
Stomach	C16
HBV/HCV-associated cancer:	
Liver	C22
EBV-associated cancer:	
Nasopharynx	C11
Hodgkin's lymphoma	Histologies 9650-9667

ICD-O-3=International Classification of Disease for Oncology, Third Edition ICD-10=International Statistical Classification of Diseases and Related Health Problems, Tenth Version 2016. All cancer types exclude basal cell and squamous cell skin cancers

Acronyms: HBV/HCV – hepatitis B and C viruses; HPV – human papillomavirus; EBV – Epstein-Barr virus

*Note: cervical cancer was not included in the infection-related NADC classification as it is part of the ADC classification.

Supplementary Table A2. Site-specific incident cancers diagnosed among people with and without HIV in Ontario, Canada, 1996-2020

Specific cancer site, n (%)	Cancers diagnosed among people with HIV (N=1,534)	Cancers diagnosed among people without HIV (N=903)	Total (N=2,437)
Non-Hodgkin's lymphoma[3]	305 (19.9)	37 (4.1)	342 (14.0)
Kaposi sarcoma[3]	235-241	<6	241 (9.9)
Lung	121 (7.9)	98 (10.8)	219 (9.0)
Prostate	116 (7.6)	186 (20.6)	302 (12.4)
Anus[3]	106-112	<6	112 (4.6)
Colorectal	80 (5.2)	106 (11.7)	186 (7.6)
Liver[3]	49 (3.2)	19 (2.1)	68 (2.8)
Hematopoietic and reticuloendothelial System (Leukemia)	49 (3.2)	46 (5.1)	95 (3.9)
Oral cavity and pharynx[3]	49 (3.2)	20 (2.2)	69 (2.8)
Hodgkin's lymphoma[3]	46-52	<6	52 (2.1)
Breast	45 (2.9)	47 (5.2)	92 (3.8)
Melanoma of the skin	38 (2.5)	45 (5.0)	83 (3.4)
Kidney and renal pelvis	36 (2.3)	36 (4.0)	72 (2.9)
Thyroid	33 (2.2)	53 (5.9)	86 (3.5)
Male genitalia (penis[3], testis)	19 (1.2)	12 (1.3)	31 (1.3)
Stomach[3]	18 (1.2)	23 (2.5)	41 (1.7)
Cervix[3]	15-21	<6	21 (0.9)
Brain/Central Nervous System	17 (1.1)	20 (2.2)	37 (1.5)
Female upper genital tract (corpus uteri, uterus, ovary, placenta)	17 (1.1)	14 (1.5)	31 (1.3)
Multiple myeloma	17 (1.1)	17 (1.9)	34 (1.4)
Bladder	16 (1.0)	21 (2.3)	37 (1.5)
Pancreas	15 (1.0)	18 (2.0)	33 (1.3)
Esophagus	13 (0.8)	9 (1.0)	22 (0.9)
Other connective and soft tissue[1]	10 (0.7)	8 (0.9)	18 (0.7)

Female lower genital tract (vulva, vagina)[3]	7-13	<6	13 (0.5)
Biliary tract	9 (0.6)	8 (0.9)	17 (0.7)
Larynx	9 (0.6)	8 (0.9)	17 (0.7)
Lymph nodes	3-9	<6	9 (0.4)
All other cancer sites[2]	16-33	22-40	55 (2.3)

[1] Includes blood vessel, bursa, cartilage, fascia, fat, ligament except uterine, lymphatic vessel, muscle, synovia, tendon (sheath). Excludes cartilage (of): articular (C40-C41), larynx (C32.3), nose (C30.0), connective tissue of breast (C50.-), Kaposi sarcoma (C46.-), mesothelioma (C45.-), peripheral nerves and autonomic nervous system (C47.-), peritoneum (C48.-), retroperitoneum (C48.0)

[2]All other sites include: larynx (C32.-), other and unspecified parts of biliary tract (C24.-), other malignant neoplasms of skin (C44-), lymph nodes (C77-), nasal cavity and middle ear (C30.-), urethra (C68.-), retroperitoneum and peritoneum (C48.-), small intestine (C17.-), gallbladder (C23.-), heart (C38.-), adrenal gland (C74.-).

[3]Indicates cancers that have a known infectious cause

Note: Ranges are shown to suppress a small cell count (less than 6)

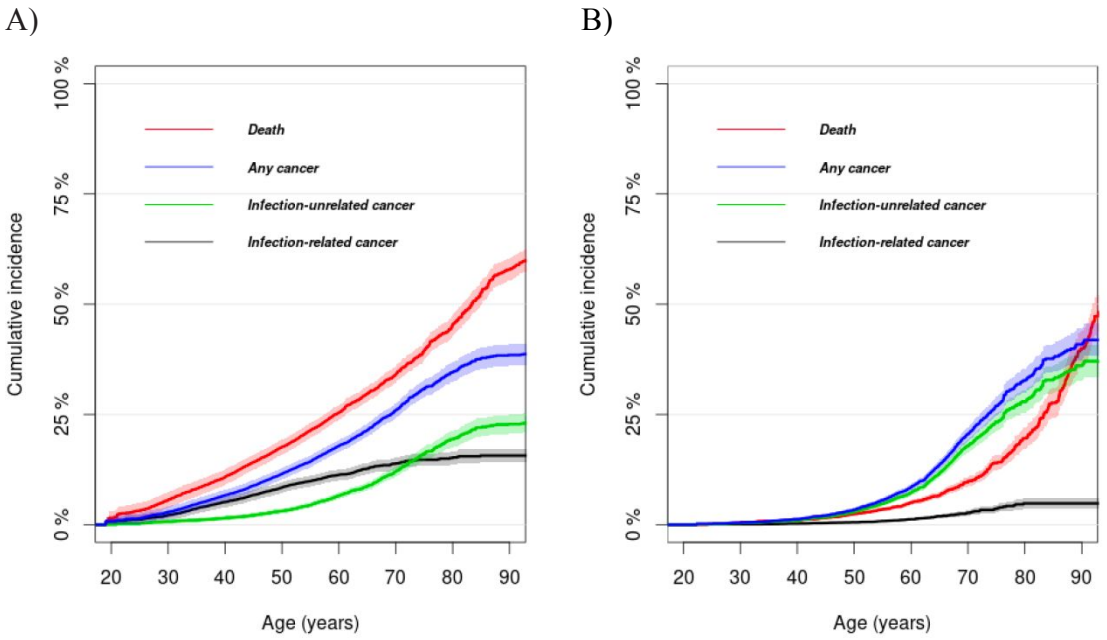
Supplementary Table A3. Hazard ratios and 95% confidence intervals (CI) from cause-specific models for noncancer death, any cancers, infection-related and infection-unrelated cancers comparing people with and without HIV, by age group and calendar period, Ontario, Canada. 1996-2020

	Hazard ratios (95% CI)			
Outcome	**Age 18-39 years**	**Age 40-59 years**	**Age 60-79 years**	**Age 80+ years[1]**
Calendar period (1996-2003)				
Death	11.20 (5.42-23.15)*	8.47 (4.95-14.50)*	8.89 (2.88-27.42)*	0.89 (0.36-2.16)
Any cancer	15.54 (6.76-35.69)*	5.31 (3.31-8.50)*	1.58 (0.82-3.04)	0.98 (0.12-7.79)
Infection-unrelated cancer	2.72 (0.98-7.53)	1.70 (0.99-2.93)	1.40 (0.65-2.98)	0.94 (0.12-7.54)
Infection-related cancer[1]	-	-	-	-
Calendar period (2004-2011)				
Death	6.09 (3.66-10.15)*	4.04 (3.16-5.17)*	1.87 (1.27-2.74)*	1.61 (0.97-2.69)
Any cancer	5.13 (3.29-7.99)*	2.57 (2.08-3.19)*	1.31 (0.94-1.81)	1.87 (0.76-4.61)
Infection-unrelated cancer	1.27 (0.70-2.29)	1.06 (0.81-1.39)	0.92 (0.63-1.33)	1.50 (0.58-3.84)
Infection-related cancer	27.52 (10.07-75.15)*	13.52 (8.08-22.63)*	5.24 (2.25-12.23)*	-
Calendar period (2012-2020)				
Death	5.68 (3.55-9.09)*	2.76 (2.29-3.33)*	1.64 (1.30-2.07)*	1.20 (0.85-1.70)
Any cancer	2.69 (1.79-4.05)*	1.70 (1.45-1.99)*	1.03 (0.85-1.25)	1.20 (0.66-2.17)
Infection-unrelated	1.09 (0.64-1.85)	0.96 (0.79-1.17)	0.87 (0.70-1.08)	0.98 (0.52-1.82)
Infection-related cancer	11.14 (4.68-26-49)*	6.84 (4.75-9.84)	2.08 (1.33-3.25)*	-

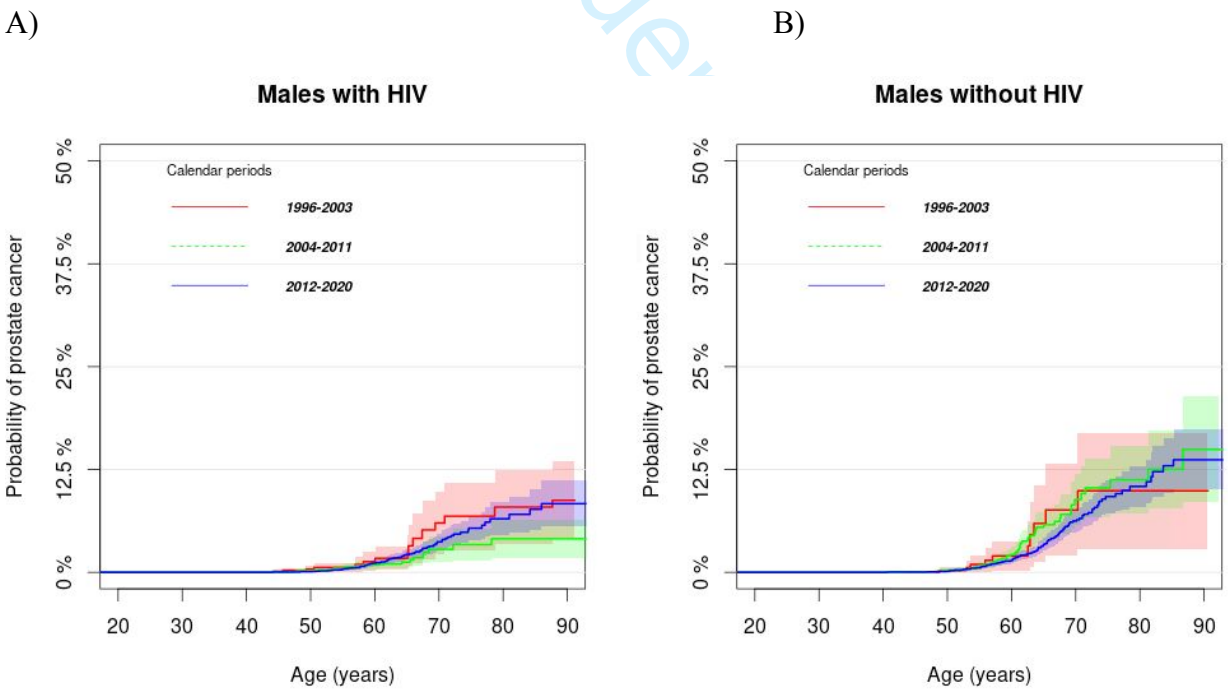
* Indicates statistical significance with the confidence interval excluding the null value of 1.

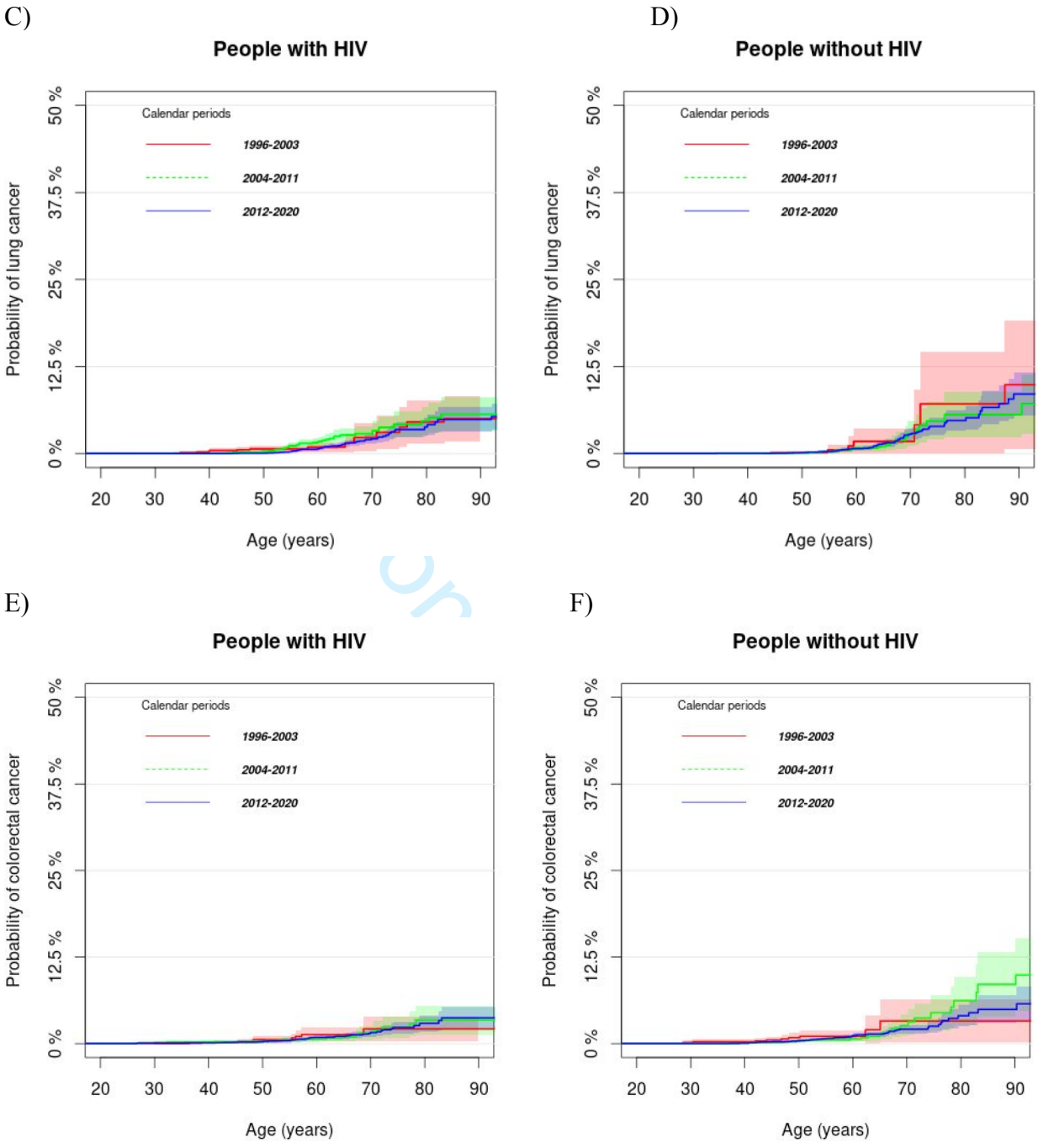
[1]Hazard ratios could not be estimated for infection-related cancers in 1996-2003 and for age 80+ across all calendar periods due to small number of events.

Models were stratified by calendar period and adjusted for comorbidity, expected resource utilization and immigration status and included age at follow-up (categorical) and HIV status interaction term.



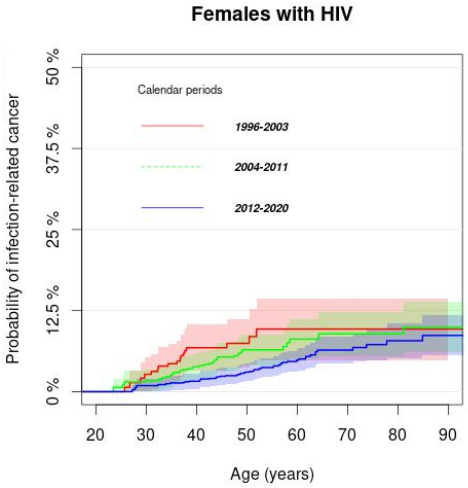
Supplementary Figure A1. Cumulative incidence of death, any cancer, infection-related and -unrelated cancer for people with HIV (Panel A) and without HIV (Panels B) with age as the time scale, Ontario, Canada



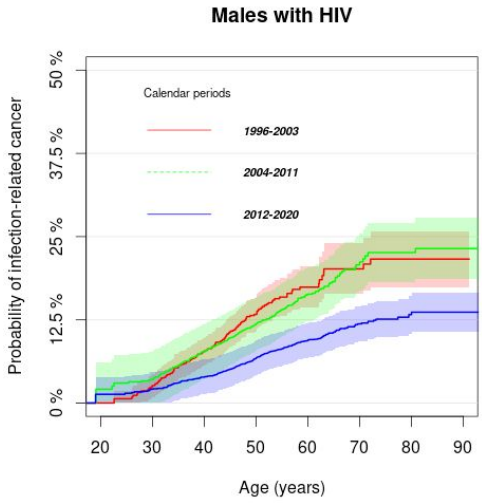


Supplementary Figure A2. Cumulative incidence of prostate (Panels A and B; restricted to males), lung (Panels C and D) and colorectal cancer (Panels E and F) for people with and without HIV by calendar period with age as the time scale, Ontario, Canada

A)



B)



Supplementary Figure A3. Sex-specific cumulative cancer incidence for infection-related cancers among people with HIV by calendar period with age as the time scale, Ontario, Canada