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Title: The burden of cancer among people living with HIV in Ontario, Canada, 1997–2020: a retrospective population-based cohort study using administrative health data

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Reviewer 1

General comments (author response in bold)

This study is important in that there are few Canadian studies looking at cancer incidence in people living with HIV. The absence of data on HIV viral load/CD4 at enrollment/ART status/smoking status/alcohol use is unfortunate and these data would have been additive, but this does not detract from the value of this study and what it adds to the existing literature.

We thank Reviewer 1 for their insightful feedback and agree that data on HIV viral load/CD4 at enrollment/ART status/smoking status/alcohol would have been a nice addition. This is the first manuscript of a planned series of manuscripts examining the burden of cancer. This manuscript is intended as a population-wide descriptive study to give an overall larger picture of the burden of cancer among people with HIV in Ontario, which has not been described to date. We will have the opportunity to look at individual-level correlates of cancer using an Ontario HIV cohort (Ontario HIV Treatment Network Study) which has been recently linked at ICES and which has rich questionnaire and laboratory data.

Please note: page numbers refer to the submitted 46 page PDF proof

Major comments

Page 5, 23. The term monotonic is used several times. I assume by this that you mean that the trend was consistently downward (monotonic decrease) rather than fluctuating over the course of the time period in question. However, this is not a term which is particularly commonplace in medical literature and I would encourage you to expand on this or define it, if not in the abstract then at least in the body of the text

Page 18, first paragraph. Throughout the paper, the acronym ICES is used but never further elaborated/defined. Here you also use a sentence which ends “analyzed at ICES based”. Is this a typo/incomplete sentence? If not, it’s not totally clear to me what is meant by this.

Page 19, first paragraph. I wonder what the impact of the pandemic on cancer diagnosis may have been, given that last date of entry into the cohort was March 31, 2020. This is not touched on in the discussion but I suspect that cancers where screening/earlier detection is sometimes important such as cervical/anal cancers and hepatocellular carcinoma may have been impacted by reduced access to care or a shift in care from in-person to virtual. It would be interesting to see a sensitivity analysis with the pandemic excluded to see whether this has any discernable impact on cancer incidence trends in this population.

Page 24. Cancer rates in this study were 1.2 to 1.3 times higher than the national and provincial general population estimates. How does this compare to incidence rate ratios elsewhere or to Canadian estimates from other studies? Suggest specifically comparing your findings to existing population estimates.

Page 25. You acknowledge the inability to identify individuals with undiagnosed HIV or those not accessing care, which I agree is an important limitation but one that is difficult

to overcome. I'd add to this the potential impacts of the current COVID-19 pandemic on care as above.

Page 25. You acknowledge the limitation of not having access to cancer risk factors. I'd agree that this is another important limitation of your study. I'd suggest specifically acknowledging the absence of HIV viral load information and CD4 percentages as well. Additionally, substance use data such as smoking patterns (current/former/never and amount) as well as alcohol use patterns are absent. We know that these are important drivers of morbidity and mortality in all patients but also that substance use tends to be higher among people living with HIV than with the general population. I think exploring in your discussion how these variables relate to cancer incidence in people living with HIV outside your study population may be additive, including any estimates of potential effect size. You also do not have ethnicity (although region of birth was included) and I suspect that ethnicity was not available as a baseline variable. This limits ability to look at potentially informative comparisons such as malignancy rates in Indigenous people living with HIV versus Canadian-born non-indigenous versus foreign born people living with HIV.

Page 38. The table on the left has cut-off text and cannot be read, and the formatting within the table is inconsistent in terms of defining the cells. There is no caption defining what the numbers in the table on the left or the tables on the right are. The tables on the right do not have labeled rows. The table does not have a title/table name.

The figures are not named and no figure captions are included, although the figures are referenced in the text.

Minor comments (stylistic/grammar)

Page 16, first paragraph – suggest eliminating “, and increased survival”. It is redundant to say that an intervention both decreased mortality and increased survival. It is sufficient to say that it “led to decreased morbidity and mortality in people with HIV.”

Page 16, second paragraph, third line – I believe the comma after cervical cancer is unnecessary

Page 37 – this page is blank. Is this intentional?

Page 47 – this page is blank. Is this intentional?

Reviewer 2

General comments (author response in bold)

Thank you for this interesting work exploring cancer rates in persons with HIV over the last two decades within the Canadian context. I would agree that there is a lack of data within this specific context to inform providers and patients about their risk and care. The study is consistent with prior work in this area that notes decreasing ADCs since the use and availability of cART, but is able to offer a purely Canadian perspective. While this main point is highlighted in the abstract, it is unlikely to be surprising to any clinician familiar with the treatment of HIV. The study question is clear and methods seem appropriate for the question and data availability and quality.

1. The dates of participant inclusion and follow-up for cancer diagnosis are confusing as there is not a full year of time, yet the authors make mention that a 1-year lag was used for cancer detection (187-189). This would suggest that no patient would be included after the date Nov 30, 2019. Clarification on this would be ideal.

Yes, the reviewer is correct. We modified the methods section to reflect that. (p5)

2. Significant effort was used to describe patient characteristics (geography, socio-economic status, co-morbidity) but this offers little to the paper in terms of exploring the effects of these patient characteristics on cancer outcomes (incidence/prevalence) so I would suggest reducing the emphasis on this (in the methods) and/or excluding it from the paper unless further exploration relative to the outcomes is included.

We reduced the emphasis on patient characteristics by shortening the descriptions of the baseline variables in the methods section. We included a Table 1 summary of baseline characteristics to describe the population of people with HIV in Ontario and to allow others to compare this population to HIV populations in other jurisdictions and extrapolate findings to other contexts. (p6)

3. The limitations of this study are many using administrative data but the lack of viral load (suppression), immune status (CD4) and social factors (smoking, substance use) need to be more thoroughly discussed. These are highly important factors when discussing the incidence of any health issue, but in particular cancer, in persons with HIV and that needs to be stressed. However, the lack of this information, particular in a modern era with high rates of cART use (reference any recent publication), may NOT be as relevant to cancer incidence given the majority of persons have viral suppression and relatively normal immune function. I would also recommend the authors more clearly recognize and state the need for better understanding exactly what/why certain cancers are occurring at (?)higher incidence/prevalence in persons with HIV as this will have a more profound impact on the practice of clinicians through behavioural modification and/or screening. The information in this paper is necessary to drive the work that will truly impact clinical care and patients. Until then, we will just have to assume it's more of the same (?higher rates of common cancers... prostate, colon, lung, NHL...?).

We agree with the reviewer that the limitations of administrative data lack important cancer correlates such as lifestyle and social factors (e.g., smoking, alcohol, obesity) and immunologic markers (e.g., immune function, CD4). This manuscript is intended as a the first population-wide descriptive study in Ontario to give an overall picture of the burden of cancer among people with HIV and is the first study of a planned series of studies examining the burden of cancer. We will have the opportunity to look at individual-level correlates of cancer using an Ontario HIV cohort (Ontario HIV Treatment Network Study) which has been recently linked at ICES and which has rich questionnaire and laboratory data that will allow us to better understand why certain cancers are occurring at higher rates in people with HIV. We also have a future paper in progress that directly compares incidence in people with HIV and matched HIV negative controls and will be able to shed light on the incidence rates of the most common cancer rates. In this manuscript we were limited by the small numbers of site-specific cancers to show age-standardized rates for the most common cancers but we included crude rates in the Supplemental file Table 6-A. (p7 and supplemental file)

4. The figures outlining change in incidence over time are easy to understand and clearly drive home the point the authors are trying to make.

Overall, I believe that this paper is readable and will be of interest to many clinicians, in particular those who are interested in but less familiar with care of persons with HIV. Again, most experienced providers will know that rates of cancer, particularly ADC, have decreased since the uptake of cART.

Additional comments:

1. page 21 (231) - please include REB number

We included the REB numbers. (p6)

2. page 38 and 40 - it is unclear what UCL and LCL are referring to

The tables on pages 38 and 40 were removed as they were duplicates of the supplemental tables and were submitted by accident.

3. Table 1 - please bold what are considered significant standard differences between sexes

We marked in bold in Table 1 significant standard differences between sexes.

4. Table 2 - site-specific cancers could be placed in a supplement as it is a very busy table and offers little information for the bulk of these specific diagnoses.

We placed site-specific cancers in a supplemental table (Table 2-A).