PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: the LHIV-Manitoba clinical cohort of people living with HIV in Manitoba, Canada
AUTHORS	McClarty, Leigh; Cheuk, Eve; Ireland, Laurie; Kendall, Claire; Bibeau, Christine; Loeppky, Carla; Kasper, Ken; Keynan, Yoav; Blanchard, james; Becker, Marissa

VERSION 1 – REVIEW

REVIEWER	Seble Kassaye Georgetown University
REVIEW RETURNED	25-Nov-2019

GENERAL COMMENTS	This is a well written manuscript that describes the establishment of a clinical cohort of adults living with HIV in Manitoba, Canada. The authors indicate the need for establishment of this clinic-based cohort in this region, highlighting distinct characteristics of the regional HIV epidemic that includes a higher proportion of individuals with injection drug use and heterosexual transmission as the modes of exposure to HIV relative to other parts of Canada where most cases of HIV are attributed to contact between men. They also report the higher rates of new diagnoses in this part of Canada, and propose that establishment of this cohort is important to identify and address any deficiencies in the care and treatment continuum as the cohort would allow for patient-level analysis rather than the aggregate reports received from the provincial administrative data sources. The Cohort has several distinct features that I believe will add to the existing literature and there is a benefit to publication to ensure that information related to these unique attributes and approaches are shared with the scientific committee. There are numerous strengths to the establishment of this cohort, and a particular strength is the excellent description and framework upon which the consent process has been elaborated. The group has taken particular attention to describe this component in great detail, highlighting the recognition of the sensitivities that exist for individuals who commit to participate in such cohorts. The consent process allows for potential enrollees to consent to different components and demonstrates high standard and consideration for individual autonomy and respect for participants – linkage to administrative health information requires specific approval, and the detailed explanation of this quells any reservation a reader may have about linkage of clinical and administrative surveillance data. In addition, the authors address the representativeness of the cohort that is enrolled relative to those served by the programs in which the cohort is based. There are differences by gender and ethnicity that the authors address directly with including plans to attempt to

	improve enrollment of unrepresented groups. There are various limitations and weaknesses, some inherent to clinical cohorts, that the authors should address. My specific recommendations and comments that could further strengthen this manuscript are as follows: 1. What was the logic for posthumous enrollment? Though there may be no ethical issue, what will be gleaned from this information, and could it generate mistrust within the community? 2. Is there active engagement of the community by way of a community advisory group to ensure that the activities that are in place do not alienate the community given that it is fairly small? This is often an important component of any research related to sensitive subjects, and should be considered for this cohort. 3. Please correct page 4 line 53 “next clinic appointment on in a year’s time…” – please remove the <u>on</u> 4. Data are manually abstracted from the EMR – please report QA procedures to ensure data accuracy 5. Page 5 lines 28 – awkward statement “For deceased clients and participants who provide consent to data linkage…” – it is impossible for deceased persons to provide consent. Please reword this to reflect what the author is trying to express – for example “ for individuals who die after providing consent for…” 6. Please describe how chronic and mental health diagnoses were coded – was this using [ICD-9/10 or other internationally accepted diagnostic coding] performed by the clinicians? Or was there a separate adjudication process? This information should be explicitly stated. 7. The authors include risk categories as a variable that is collected. Are these risk categories captured using structured or unstructured fields from the clinical records? For those individuals who agree to use of their surveillance data, how often are the data collected from the two data sources

	concordant? In table 3, how was the "main" risk category selected from the other possible exposures for those with multiple risk factors? How this was conducted should be described in further detail in the methods section. Also, please provide an explanation for "possible exposure in an HIV-endemic country" – what kind of exposure is this alluding to? 8. The authors report that their program is embedded within a unique care model. Additional information in the methods section regarding the how this program is structure would be helpful. Do all three of the outpatient clinic sites, the hospital-based clinic site, the community health center, and the nurse-run health access center all follow the same model? If not, does this provide an opportunity to compare different care models that are in place? 9. In table 1, the authors have a variable category "drugs", and indicate that this could be prescription or legal. It would be helpful to include the types of drugs that data are collected on, and also provide some reasoning in the text why they have selected to include prescription medications in this category. 10. Alcohol use should also be broken down by amount using established categories. 11. Including a breakdown of viral subtype in Table 2 would be helpful given the population diversity and discussion of possible acquisition of HIV outside of Canada. 12. Please define CKD stage in table 2.

REVIEWER	Christopher Gill Boston U. School of Public Health, Boston MA, USA
REVIEW RETURNED	02-Dec-2019

GENERAL COMMENTS	The authors have provided a description of a newly created Cohort of patients living with HIV in Manitoba, Canada. However, the paper is not a scientific article in the sense that it does not seek to describe a specific analysis within this cohort, or to test a hypothesis. While the authors do provide some summary statistics (age, sex, race, risk factors) about the cohort with some comparisons between the cohort and the larger population of HIV positive patients in Manitoba, the data are still not presented in a way that asks and answers any

	scientific questions. I have no concerns about the construction of the cohort, which would be beyond the scope of a journal article review (it is not up to a reviewer to advise a PI about the design of a cohort study, my job is to review a scientific analysis that emerged from that cohort). But since this is not a hypothesis driven scientific analysis, but merely a description of a new cohort that in the future will very likely generate interesting scientific analyses, I'm not exactly sure what advice to offer. To me, whether to publish or not seems to be 100% an issue for the BMJ Open editors to decide: are you interested in publishing papers that merely describe a cohort under study, but do not actually present any analyses from that cohort? Or not? This does not seem to be my call to make.

REVIEWER	Juan E Losa Hospital Universitario Fundacion Alcorcon. Spain
REVIEW RETURNED	18-Jan-2020

GENERAL COMMENTS	In addition to the third 90 (viral suppression: 83,2 % in the cohort), I miss data on the first and second 90 of the HIV care cascade; that is, percentage of diagnosis and patients on ART.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Seble Kassaye
Institution and Country: Georgetown University
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
This is a well written manuscript that describes the establishment of a clinical cohort with data obtained from clinical and administrative sources. There are several unique characteristics that are important to share with the scientific community. Please see attached some specific recommendations on how to further strengthen the manuscript. I appreciate the opportunity to provide this review.

- *The authors thank reviewer 1 for her generous review and very helpful comments and recommendations. The specific comments and suggestions have been pasted below, with our responses in point-form below each item.*

This is a well written manuscript that describes the establishment of a clinical cohort of adults living with HIV in Manitoba, Canada. The authors indicate the need for establishment of this clinic-based cohort in this region, highlighting distinct characteristics of the regional HIV epidemic that includes a higher proportion of individuals with injection drug use and heterosexual transmission as the modes of exposure to HIV relative to other parts of Canada where most cases of HIV are attributed to contact between men. They also report the higher rates of new diagnoses in this part of Canada, and propose that establishment of this cohort is important to identify and address any deficiencies in the care and treatment continuum as the cohort would allow for patient-level analysis rather than the aggregate reports received from the provincial administrative data sources.

The Cohort has several distinct features that I believe will add to the existing literature and there is a benefit to publication to ensure that information related to these unique attributes and approaches are shared with the scientific committee. There are numerous strengths to the establishment of this cohort, and a particular strength is the excellent description and framework upon which the consent

process has been elaborated. The group has taken particular attention to describe this component in great detail, highlighting the recognition of the sensitivities that exist for individuals who commit to participate in such cohorts. The consent process allows for potential enrollees to consent to different components and demonstrates high standard and consideration for individual autonomy and respect for participants – linkage to administrative health information requires specific approval, and the detailed explanation of this quells any reservation a reader may have about linkage of clinical and administrative surveillance data. In addition, the authors address the representativeness of the cohort that is enrolled relative to those served by the programs in which the cohort is based. There are differences by gender and ethnicity that the authors address directly with including plans to attempt to improve enrollment of unrepresented groups.

- *Once again, we want to thank reviewer 1 for highlighting the importance and potential of the LHIV-Manitoba cohort.*

There are various limitations and weaknesses, some inherent to clinical cohorts, that the authors should address. My specific recommendations and comments that could further strengthen this manuscript are as follows:

1. What was the logic for posthumous enrollment? Though there may be no ethical issue, what will be gleaned from this information, and could it generate mistrust within the community?

- *Thank you for highlighting this as something that needs further explanation/rationale. We have added a few sentences around this in the second paragraph of our Study measures, data sources, and data collection sub-section, on page 5.*
- *Reviewer 1 raises an interesting point regarding the community perception of posthumous data collection from deceased clients of the Manitoba HIV Program. While we have not specifically started a discussion around posthumous data collection with community members, we have been completely transparent about the data collection process throughout the development of the cohort. As such, the ways in which data are collected have been clearly stated while we have presented about the progress of this study, and to this point, no concerns have been raised. Having said that, we thank reviewer 1 for sharing this concern – we take this notion seriously, and we will plan to have this conversation more explicitly moving forward.*
    - *In the meantime, the authors are confident that the measures we have taken to maintain confidentiality and anonymity for all participants – regardless of whether they were alive or deceased at enrolment – are adequate to protect their individual identities.*

2. Is there active engagement of the community by way of a community advisory group to ensure that the activities that are in place do not alienate the community given that it is fairly small? This is often an important component of any research related to sensitive subjects, and should be considered for this cohort.

- *We thank reviewer 1 for this note – we completely agree with this sentiment and we have added a Patient and Public Involvement section on page 4 of the paper to address this.*
    - *Briefly, the LHIV Study team has been engaging with stakeholders – including providers and staff within the Manitoba HIV Program and other community clinics, key decision-makers at Manitoba Health, Seniors and Active Living, members of the Manitoba First Nations AIDS Working Group, and community members through the LHIV Community Scholar Program – throughout the development of the cohort. Throughout the enrolment process, we have engaged key stakeholders via community forums and meetings with key stakeholders. As we move forward with our analyses, dissemination and knowledge*

translation activities (meetings, "one-pager" materials for providers, presentations to community groups through programming offered at Nine Circles Community Health Centre, "lunch and learn" events for providers and staff within clinical settings) will be organized and facilitated by study team members and Manitoba HIV Program staff.

3. Please correct page 4 line 53 "next clinic appointment on in a year's time..." – please remove the <u>on</u>

- *Thank you very much for bringing this to our attention. We have corrected this error in the updated version of our paper.*

4. Data are manually abstracted from the EMR – please report QA procedures to ensure data accuracy

- *We have included a few sentences in the first paragraph of the Study measures, data sources, and data collection section of our paper (page 5) on the QA procedures taken. The authors thanks reviewer 1 for noting this important omission.*

5. Page 5 lines 28 – awkward statement "For deceased clients and participants who provide consent to data linkage..." – it is impossible for deceased persons to provide consent. Please reword this to reflect what the author is trying to express – for example "for individuals who die after providing consent for..."

- *The authors very much appreciate reviewer 1's assistance in ensuring the clarity of our manuscript. We have changed the wording in the last paragraph of the Study measures, data sources, and data collection sub-section on page 5 of our paper and hope that our intended meaning is now clearer.*

6. Please describe how chronic and mental health diagnoses were coded – was this using [ICD-9/10 or other internationally accepted diagnostic coding] performed by the clinicians? Or was there a separate adjudication process? This information should be explicitly stated.

- *Thank you for this question. While have not included any data pertaining to the mental health conditions captured for cohort participants at this point, we acknowledge that it is important for us to note how those data are collected. Due to limited space in the paper, we will provide a more comprehensive description here for reviewer 1.*
    - *Information about participants' diagnosed mental health comorbidities are captured in our provincial administrative health databases. Specifically, the provincial medical claims (physician billings) dataset contains every diagnosis (ICD-9/10 coding) that a physician makes during a patient encounter (in- and outpatient).*
    - *Of note, we have also collected some limited data on mental health comorbidities through our clinical files (electronic or paper-based). We are currently exploring how this data compares to what we can capture through the provincial administrative health datasets. Pending this additional analyses, we have elected to hold on presenting that data.*
- *In the clinical files, providers have not consistently entered date on chronic comorbidities with ICD codes assigned to them. However, the authors, in consultation with providers at the Manitoba HIV Program, were selective in choosing to present data only for conditions for which providers could confidently diagnose. As we move forward with analyses, we will be able to*

verify these data by comparing clinical data to administrative data by using validated algorithms that have been used in Manitoba for numerous previous studies.

7. The authors include risk categories as a variable that is collected. Are these risk categories captured using structured or unstructured fields from the clinical records? For those individuals who agree to use of their surveillance data, how often are the data collected from the two data sources concordant? In table 3, how was the "main" risk category selected from the other possible exposures for those with multiple risk factors? How this was conducted should be described in further detail in the methods section. Also, please provide an explanation for "possible exposure in an HIV-endemic country" – what kind of exposure is this alluding to?

- *Thank you to reviewer 1 for this question, and for pointing out that we have not explained this with adequate clarity in our paper. We have made some changes to the first paragraph in the subsection, "HIV exposures among cohort participants" in hopes of addressing this issue.*
- *To answer the first question, self (participant)-identified exposure categories are captured in unstructured fields in the clinical records.*
- *Information about risk or mode of acquisition are not captured in any administrative datasets. As the clinical records are our only source of data for these variables, we are unable to conduct any kind of comparative analyses to understand concordance/discordance.*
- *In Table 3 we used a "risk hierarchy" framework to identify "main" or primary exposure categories, and the table itself is organized according to the hierarchy (most "risky" category on top). The Public Health Agency of Canada (PHAC) and Manitoba Health, Seniors and Active Living both use variations of this evidence-based framework to categorize and organize risk exposure information from individuals who report more than one possible route of acquisition. For this paper, we followed the PHAC hierarchy, which has been referenced in our paper (reference no. 14).*
    - *As an example of how this would work - if a cohort participant's clinical file indicated potential exposure through condomless vaginal sex, condomless anal sex, and occupational exposure, in our analyses according to the hierarchy, their primary exposure category would be "Condomless anal sex between" with condomless vaginal sex as secondary.*
- *Finally, thank reviewer 1 for their question about the exposure category "potential exposure in an HIV-endemic country". We will try to provide a comprehensive explanation here, and we have added a footnote to Table 3, as well.*
    - *In participants' clinic files, there will often be a note or a check-box on a demographics sheet that simply says "endemic". During the data abstraction process, we had extensive conversations with providers who would have filled out clinic files to understand what would be meant by the "endemic" notation. When an client of the Manitoba HIV Program is eventually asked about the mechanism through which they believe they had acquired HIV, some would indicate that they had been born in, spent considerable time living/working in an HIV-endemic country, and during that time experienced an event that they considered "risky" for acquiring HIV. You will note that we do not assign the "endemic" category as a primary exposure category because, of course, as merely existing in an HIV-endemic country does not put one at risk of acquiring HIV. So, what we have tried to capture here is whether or not someone experiences a "risky" event in a country that has relatively high/endemic HIV prevalence.*

8. The authors report that their program is embedded within a unique care model. Additional information in the methods section regarding the how this program is structure would be helpful. Do all three of the outpatient clinic sites, the hospital-based clinic site, the community

health center, and the nurse-run health access center all follow the same model? If not, does this provide an opportunity to compare different care models that are in place?

- *Thank you for bringing up this important point. Indeed, the Manitoba HIV Program itself is unique because it brings together hospital-based specialist care with primary care-focused community-based clinics. We have added some additional text in the "Study setting" sub-section on page 4 to expand upon the care model employed within the Manitoba HIV Program.*
    - *In the future, we certainly hope to explore some analyses by clinic site.*
- *In the meantime, the authors would like to draw the reviewer's attention to an article that was published by the principal investigator of the LHIV study and co-author on this paper, Dr. Claire Kendall and colleagues, which we also cite in the present cohort profile paper:* Kendall, C. E., et al. (2019). Canadian HIV Care Settings as Patient-Centered Medical Homes (PCMHs). *J Am Board Fam Med, 32*(2), 158-167.
    - *The Manitoba HIV Program was one of a number of sites included in this paper's analyses.*

9. In table 1, the authors have a variable category "drugs", and indicate that this could be prescription or legal. It would be helpful to include the types of drugs that data are collected on, and also provide some reasoning in the text why they have selected to include prescription medications in this category.

- *Thank you for highlighting this. Based on this comment, we have decided to change the way we have categorized "drugs" in Table 1, such that we are now only referring to illegal or "street" drugs. We have changed the wording and associated data in Table 1 accordingly. We have also included a footnote to indicate which drugs are included in this category.*
- *At this point in our analysis, we have not yet been able to conduct analyses using the administrative dataset that would allow us to assess whether an individual's use of prescribed medication was outside of medical indication. Again, we thank Reviewer 1 for noting this, and the authors do intend to run analyses to better understand problematic substance use among cohort participants in the future. Unfortunately, given the limited analytical scope of the Cohort Profile paper format, and the early stages of our analyses, we are unable to include these data at this point.*

10. Alcohol use should also be broken down by amount using established categories.

- *The authors agree that this would be a very helpful attribute to be able include in our cohort. Currently, we have been collecting information about problematic drug and alcohol use from individual clinic files. Quantity of alcohol consumption is not consistently collected in clinic files, so we are unable to accurately ascertain this information. Alcohol consumption is also not captured in our administrative databases, unless someone is specifically diagnosed with alcoholism and a physician bills for a service pertaining to that diagnosis. Given all of these factors, we certainly recognize the limitations to this variable and will analyse and interpret our findings related to "problematic alcohol consumption" accordingly.*
- *We would also add that it is standard practice within the Manitoba HIV Program for providers to only record a client's alcohol use as problematic in their clinic file if, through their clinical interactions, it is evident that the client is consuming alcohol in "binges" (i.e. ≥4 or 5 drinks in a row over a 2 hour period – as defined by National Institute of Alcohol Abuse and Alcoholism) or if it is actively interfering in the person's daily life.*

11. Including a breakdown of viral subtype in Table 2 would be helpful given the population diversity and discussion of possible acquisition of HIV outside of Canada.

- *Thank you for this suggestion and helpful insight. Unfortunately, up to now, we have not collected information about viral subtype in this cohort, although it may be possible for us to do so in the future and we will explore this.*

12. Please define CKD stage in table 2.

- *We thank the reviewer for this suggestion. While the authors agree that including information on staging of chronic kidney disease would be helpful to contextualize our understanding of comorbidities within the clinical cohort, unfortunately, this information is not recorded in the clinical files and is inconsistently captured in administrative datasets.*
    - *Thanks to this comment, we recognize that we do not have enough information to report on this variable at this time. As such, the authors have opted to remove it from this paper.*
    - *In the long term, once we have managed to complete more in-depth analyses, the authors hope to focus on a more comprehensive analysis of mental health and chronic conditions comorbidities.*

Reviewer: 2
Reviewer Name: Christopher Gill
Institution and Country: Boston U. School of Public Health, Boston MA, USA
Please state any competing interests or state 'None declared': None decleared

Please leave your comments for the authors below
Review of McClarty et al BMJ Open 2019

The authors have provided a description of a newly created Cohort of patients living with HIV in Manitoba, Canada. However, the paper is not a scientific article in the sense that it does not seek to describe a specific analysis within this cohort, or to test a hypothesis. While the authors do provide some summary statistics (age, sex, race, risk factors) about the cohort with some comparisons between the cohort and the larger population of HIV positive patients in Manitoba, the data are still not presented in a way that asks and answers any scientific questions. I have no concerns about the construction of the cohort, which would be beyond the scope of a journal article review (it is not up to a reviewer to advise a PI about the design of a cohort study, my job is to review a scientific analysis that emerged from that cohort). But since this is not a hypothesis driven scientific analysis, but merely a description of a new cohort that in the future will very likely generate interesting scientific analyses, I'm not exactly sure what advice to offer. To me, whether to publish or not seems to be 100% an issue for the BMJ Open editors to decide: are you interested in publishing papers that merely describe a cohort under study, but do not actually present any analyses from that cohort? Or not? This does not seem to be my call to make.

- *We thank reviewer #2 for his comments and thoughts. We appreciate that he has recognized the potential of our cohort to meaningfully contribute to the literature.*
- *We have not made any changes to the document based on reviewer 2's comments it has not included specific recommendations/suggested edits for our paper.*
- *However, we can say that we have carefully followed the formatting and structure guidelines set out by BMJ Open for Cohort Profile papers.*

- *We do feel that this kind of publication provides valuable opportunities for academics to share their experiences with the broader research community. Indeed, as this cohort was being developed, we very much appreciated reading about the processes that other groups had followed in developing their own cohorts in this journal.*

Reviewer: 3

Reviewer Name: Juan E Losa

Institution and Country: Hospital Universitario Fundacion Alcorcon. Spain

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

In addition to the third 90 (viral suppression: 83,2 % in the cohort), I miss data on the first and second 90 of the HIV care cascade; that is, percentage of diagnosis and patients on ART.

- *The authors thank reviewer 3 for taking the time to review our paper.*
- *We certainly agree with him that the LHIV-Manitoba cohort provides a great opportunity for us to present information about the HIV care cascade and the 90-90-90 targets. In fact, a manuscript is currently in preparation that will present the data that reviewer 3 mentions in his comment.*
- *The authors decided that a cascade analysis based on LHIV-Manitoba cohort data warranted its own paper and so we have opted to leave out these analyses in this Cohort Profile paper.*
- *Finally, we want to highlight that this paper's purpose is primarily to highlight the processes involved in the development of the LHIV-Manitoba cohort, and to briefly highlight the characteristics of study participants. The authors have a number of papers with a results focus planned in the coming months.*