PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Cohort Profile: l'Actuel Pre-Exposure Prophylaxis (PrEP) Cohort Study in Montreal, Canada
AUTHORS	Greenwald, Zoë; Maheu-Giroux, Mathieu; Szabo, Jason; Robin, Judith Alexia; Boissonnault, Michel; Nguyen, Vinh-Kim; Thomas, Rejean

VERSION 1 – REVIEW

REVIEWER	Stefanie Vaccher Kirby Institute, UNSW Sydney, Australia
REVIEW RETURNED	25-Jan-2019

GENERAL COMMENTS	This cohort profile on PrEP users at one clinic in Montreal, Canada is interesting and timely. However, I would like to see fewer descriptive analyses and more detailed presentation of new results, even if only baseline data or a short follow-up period is included. Many of the included data seem to have already been published at different times, leading to inconsistent numbers of people being included in the reported results without making this clear to the reader. Considering the broader context of PrEP implementation and applicability of this study to PrEP in Canada and internationally would strengthen the findings. Specific recommendations are presented by section of the paper below. Required changes Introduction - You explicitly state that the Clinique medicale l'Actuel sought to target PrEP to "individuals at substantial risk for HIV acquisition" (line 25), yet contradict this statement in lines 44-5 saying that in contrast to this high-risk targeted approach, more diverse risk profiles will be included in your study - consider revising Participants - Please include specific eligibility criteria, perhaps as a table or figure? Also clarify if informed consent is oral or written. Participant characteristics should be reported in the results section - clearer explanation of methods of data collection required first (eg. sexual partners, see below) as per author guidelines Can you be sure that the 504 participants who did not initiate PrEP and return for a visit did not initiate PrEP elsewhere? A further comment about the availability and accessibility of PrEP in Canada would help international readers understand the broader context within which this research was conducted. Measurements - Further information about the baseline questionnaire required - was it online/anonymous/interviewer-administrated/incentivised etc?

	Missing data - line 26-7 "it occurs that responses to questions are undocumented" is unclear. Please revise. Incident HIV infections - The number of people or PY of follow-up included in the incidence calculation should be mentioned. Were efforts made to link data to HIV notifications or other records to determine if any seroconversions occurred in participants deemed lost to follow up? Risk compensation - How was 'risky behaviour' defined and measured? Have these data been updated from the cited report in 2015 to include all new participants? Incident STI risk - Was the frequency of testing prior to PrEP initiation controlled for? Increased testing has lead to artificially-inflated STI positivity rates in other PrEP studies. If a different time period and thus cohort were used once again when reporting these results compared to previous sections, please make this clearer or consider revising so data are presented on the same individuals in each section of the paper. Patterns of PrEP use - Without results of a multivariate model being presented, limited conclusions can be drawn about factors associated with PrEP regimen. Suggested changes Introduction - When discussing previous PrEP RCTs, consider: the low/no efficacy shown in women, differentiating between studies testing TDF alone or TDF/FTC, differences between daily and intermittent PrEP studies The iPrEx study results were published in 2010, not 2011 (line 15) Explanation of a 'notice of compliance' (line 17) would be helpful for non-Canadian readers Cohort description - Are you referring to a specific PrEP cascade in line 55? Patient and public involvement - What % of participants were word-of-mouth referrals from the first survey? A comment about how recruitment of people previously attending an HIV rapid testing site may have affected results may also be warranted here. Patterns of PrEP use - Did people switch regimens multiple times? Mean number of switches? What does used PrEP 'episodically' mean? (line 35) Very high rate of loss to follow up - consider a comment about 'seasons of PrEP use' or how fluctuating risk may affect PrEP adherence and continuity of engagement in care Where there any other costs to the individual for accessing PrEP (eg. STI testing, doctor's appointments?) How did the median income in this study compare to the median Canadian income? Limitations - Consider a clearer emphasis on the large proportion of missing data (15-20%?) and how representative this one clinic population is in terms of PrEP implementation in Canada or more broadly. Table 1 - How do college and university education differ? No definitions of regular or occasional sexual partners in text. Table 2 - Comment on issues comparing 2018 follow-up to other years given uneven period of follow-up (especially in regards to lack of PrEP follow-up >6 months, as this cut-off may not have been reached for all participants). Why was the % of people who did not initiate PrEP so much higher in recent years? No corresponding ** in the table, just the notes Table 3 - Specify time periods of data collection e.g. STI history Table 4- Did intermittent PrEP prescriptions vary by year/period of enrollment (IPERGAY findings not released until 2015)? Is the mean number of sexual partners normally distributed? Consider

	reporting the median and IQR instead. How is the prescribing doctor's years of practice relevant to individual sociodemographic and behavioural profiles? Figure 2 - Make it clearer which questions appeared in which sections of the questionnaire

REVIEWER	Liza Coyer Public Health Service of Amsterdam, the Netherlands
REVIEW RETURNED	26-Feb-2019

GENERAL COMMENTS	Thank you for the opportunity to review this study profile about an open, prospective cohort of daily and intermittent PrEP users in a community setting in Montreal, Canada. This cohort will be an important and useful source of real-world data on PrEP use, monitoring and care. Since enrolment started in 2013, this cohort captures early as well as later PrEP implementation and adoption, which could provide very interesting insights into PrEP uptake, care retention and discontinuation over time. Moreover, data on the use of daily and/versus intermittent regimens is particularly welcome, especially given relative scarcity of data on intermittent PrEP. It's rationale and research aims are clearly described. Major comments: 1. In the introduction, I would suggest to elaborate on how PrEP provision is organized in Canada/Quebec and who can prescribe PrEP. It is mentioned that l'Actuel is a top referral site in Montreal for HIV and STI testing and treatment, but what proportion of PrEP users (in Montreal) obtain their PrEP through this site? All? If there are other local PrEP providers (other clinics, general practitioners, etc.), which is suggested by bullet point 3 under strengths and limitations of this study, it would not be correct to state that results are representative of local PrEP users, as this would depend on user characteristics/ preferences across providers. 2. Most summarized findings to date refer to conference abstracts. This in itself is not problematic, but it is important to be clear on the sample sizes of these analyses and which time spans these data cover, given these may be interim/unfinished analyses and are not all updated until June/July 2018. In addition, I do find it problematic that the authors do not address nor incorporate the serious concerns raised about their research group's analysis of STI incidence pre-PrEP compared to post-PrEP (Marcus et al. Concerns about a study on sexually transmitted infections after initiation of HIV preexposure prophylaxis, AIDS 2018). Specific comments: Abstract: 1. Please specify all sample sizes and denominators throughout the abstract (same comments apply to the 'cohort description' section): - it is unclear whether the median age given is about the 2385 'participants' with an initial consultation or those (n=2156) with a PrEP description at baseline (who are referred to as being 'included in the cohort' in the participants section and are described in table 1).

	- I assume median PrEP duration and person-years of follow-up were calculated among all those who initiated PrEP care (n=1551)? Please clarify. - Please specify the sample size and effect estimates of the before and after PrEP initiation analysis. 2. Could you confirm that enrolment took place up to and including June 2018 and that follow-up took place up to and including July 2018? If this is correct, why was there no enrolment in July 2018? It should then also be 'through' instead of 'to' July 2018. 3. The sentence "The l'Actuel PrEP cohort [..] in North America" may fit better under 'participants'. 4. Are there any specific analyses planned for the future? Certain areas of concern (such as PrEP discontinuation) have been highlighted elsewhere in the paper, so I was wondering if you will be looking into these specifically? Strengths and limitations: 5. Bullet point 1: typo "effectiveness" 6. Bullet point 2: typo "strengths" Introduction: 7. Are the Canadian guidelines for PrEP indicators identical to those used by l'Actuel? Do these guidelines also include the use of intermittent PrEP? I'm missing some detail on the use of intermittent PrEP in the Canadian setting. Cohort description: 8. As the authors mention that the cohort is integrated into, and supported through, routine clinical care, does it mean all mentioned outcomes will be monitored in 'indefinite' time? Or would this depend on future funding? (i.e. please confirm there is no end date). 9. Second paragraph of the 'participants' section: should be 229, not 228 (according to Fig. 1) 10. Related to my questions about sample size from the abstract, it is unclear when someone is considered a participant in this cohort. In the abstract, all those with a PrEP consultation are considered participants, but later only those with a prescription at baseline are considered as being included in the cohort and are later referred to as the participants ("Table 1 outlines characteristics of participants [..]"). Moreover, the summary characteristics as stated in paragraph 3 of the 'participants' section are different from those given in table 1. I think all relevant details have been given in-text about those with an initial consult, those who actually obtained PrEP and those who eventually used PrEP, but it's a bit of a puzzle, so I would suggest improving the readability of this section. 11. It would be interesting to know the duration of PrEP use prior to being lost-to-follow-up/discontinuing PrEP of those no longer retained in care. Are there any participants who discontinued PrEP for some time and then restarted? Or are these planned analyses? 12. Please confirm table 2 is the situation as per July 2018. 13. Is the choice between daily and intermittent PrEP mainly provider- or user-driven? (i.e. do providers steer those with lower risk profiles towards intermittent PrEP?) Are regimen switches also documented? 14. Clear paragraph on missing data and why this occurs. In table 1, I would prefer calling missing data 'missing' instead of 'unknown'. Moreover, please also provide sample sizes for the regular partners and occasional partners in table 1 as these are currently missing.

	Findings to date: 15. I would suggest something along the lines of “following PrEP discontinuation” after the sentence “[…] translating to an HIV incidence of 3.9 cases per 100 person-years”. 16. Although I do not disagree with the rejection of the perception that all PrEP users engage in CAS with multiple partners, I do not think the conclusion “The results of this analysis suggest that […] not grounded in reality” immediately follows from the reported observation that some PrEP users report a change or remain stable in their risk behaviour after initiating PrEP, as this depends on their specific behaviors before and during PrEP. It would be useful to elaborate a little more detail on the specific behaviors reported. 17. Reference 20 does not refer to a strictly observational study, as iPrEX is a trial. Please provide some references to observational studies. 18. As with any real-world study, loss-to-follow-up could be an issue. Loss-to-follow-up is 39% in this cohort (606/1551). Whether this results in bias depends on mechanism of missingness: if loss-to-follow-up is missing not a random, bias is likely introduced. Do you have any information on this?

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1
Reviewer Name: Stefanie Vaccher
Institution and Country: Kirby Institute, UNSW Sydney, Australia

1. This cohort profile on PrEP users at one clinic in Montreal, Canada is interesting and timely. However, I would like to see fewer descriptive analyses and more detailed presentation of new results, even if only baseline data or a short follow-up period is included.
Author response: We thank the reviewer for their comments and we share their eagerness in having new results presented as rapidly as possible. However, our goal with publishing this cohort profile paper was to provide detailed data on the establishment of the l’Actuel PrEP cohort. As such, this article primarily serves to lay a descriptive foundation of the cohort, beyond what can generally be described in the methods section of a research paper. A second objective of our cohort profile is to advise other researchers of existing datasets and collaboration opportunities. For these reasons, we are keen to keep the descriptive analyses and we can assure the reviewer that new results will be published as stand-alone papers in a timely fashion.

2. Many of the included data seem to have already been published at different times, leading to inconsistent numbers of people being included in the reported results without making this clear to the reader.
Author response: We agree that our previous wording around this issue may cause confusion for readers. The nature of the cohort profile paper is such that data from previous reports is cited which we understand can be confusing. In order to ameliorate this issue, we have improved reporting of the sample sizes/timelines present at each sets of results presented in the “findings to date” section.

3. Considering the broader context of PrEP implementation and applicability of this study to PrEP in Canada and internationally would strengthen the findings.

Author response: We have substantially revised the introduction and discussion by providing further details on the context of PrEP offering in Canada and the applicability to PrEP implementation in other settings (page 2, page 12).

Required changes
4. Introduction - You explicitly state that the Clinique medicale l'Actuel sought to target PrEP to "individuals at substantial risk for HIV acquisition" (line 25), yet contradict this statement in lines 44-5 saying that in contrast to this high-risk targeted approach, more diverse risk profiles will be included in your study - consider revising
Author response: Thank you for noting that these two statements seem to be in discrepancy. Indeed, the PrEP clinic was initially opened to “promote PrEP uptake directly to individuals at substantial risk for HIV acquisition”. However, in the l’Actuel PrEP Cohort, we do not implement strict PrEP eligibility criteria in order to qualify for PrEP as is the case in PrEP trials. Ours is a clinical cohort where decisions for PrEP initiation are based on a dialogue between clinicians and their patients rather than a fulfillment of a strict set of criteria. We removed the word “substantial” from the earlier sentence, so these statements do not appear to be in direct contrast.

5. Participants - Please include specific eligibility criteria, perhaps as a table or figure? Also clarify if informed consent is oral or written.
Author response: Informed consent is written, and the text has been updated to note this (page 5). As described above, we do not have specific PrEP indication-based eligibility criteria which participants must meet in order to be prescribed PrEP. The PrEP cohort inclusion criteria (seronegative at baseline PrEP visit, recommended or prescribed PrEP, consenting to research use of data) are now noted in the text (page 6), and are also outlined in the cohort flow chart in Figure 1.

6. Participant characteristics should be reported in the results section - clearer explanation of methods of data collection required first (eg. sexual partners, see below) as per author guidelines
Author response: Indeed, we agree that it is rather counter-intuitive not to present participant characteristics in the results section. These are presented in the “cohort description” section, following the guidelines laid out by BMJ Open for the Cohort Profile section. Unless the editor agrees for these to be presented in the results, we will follow the journal’s guidelines (Accessible here: https://bmjopen.bmj.com/pages/authors/#cohort_profiles.)

We have clarified the distinction between regular vs occasional partners (see page 6, table 3). The remaining methods of data collection have been described in the measurements section and refer to table 3, which provides a detailed description of measurements. We revised both for improved clarity.

7. Can you be sure that the 504 participants who did not initiate PrEP and return for a visit did not initiate PrEP elsewhere? A further comment about the availability and accessibility of PrEP in Canada would help international readers understand the broader context within which this research was conducted.
Author response: We have added extra contextual information on the landscape of PrEP offering in Montreal and in Canada (page 4). It is indeed possible that patients who did not initiate PrEP at l’Actuel chose to initiate PrEP elsewhere, though the landscape of PrEP offering in Montreal was very limited up until 2016. At this time, there were only a handful of other dedicated centers in Montreal that offer PrEP. Since all clinics belong to the public sector and with the same co-payment, the likelihood that some participants initiated PrEP elsewhere is probably low. We have included further detail on the offer of PrEP outside of Actuel (see page 12). In the Engage survey of MSM in Montreal, 78% reported receiving PrEP at a speciality clinic. We have cited this finding in the text. Unfortunately, no other specialized clinics have reported any data on numbers of patients on PrEP, so we cannot quantify to what extent PrEP is accessed at clinics other than Actuel.

8. Measurements - Further information about the baseline questionnaire required - was it online/anonymous/interviewer-administrated/incentivised etc?
Author response: Additional information on the baseline questionnaire has been included (page 7). Participation is not incentivized and this has been noted along with the statement on informed consent (Page 6).

9. Missing data - line 26-7 "it occurs that responses to questions are undocumented" is unclear. Please revise.
Author response: By “undocumented” we meant that certain issues may be discussed during a clinical consultation, but a clinician or nurse may fail to document the data on the questionnaire, leading to missing data. Following the reviewer’s suggestion, we have revised the missing data section for clarity (page 8).

10. Incident HIV infections - The number of people or PY of follow-up included in the incidence calculation should be mentioned. Were efforts made to link data to HIV notifications or other records to determine if any seroconversions occurred in participants deemed lost to follow up?
Author response: This calculation was based upon 203 individuals who discontinued PrEP, but returned to l’Actuel for HIV testing after discontinuation. Person-time was measured from date of PrEP discontinuation to the most recent HIV test on record. In total 75 person-years of follow-up were included in the analysis. We did not link data to HIV notifications, as this is not feasible due to privacy laws, the HIV notifications to public health are de-identified and not available for research outside of surveillance reporting by governmental agencies. We were therefore not able to validate the presence of seroconversions among individuals discontinuing PrEP at Actuel but potentially testing HIV positive elsewhere. This was a limitation of the study, which has now been described in the text (page 9).

11. Risk compensation - How was 'risky behaviour' defined and measured? Have these data been updated from the cited report in 2015 to include all new participants?
Author response: Risky behaviour was measured by increases in sexual partners and decreases in condom use within the first three months of PrEP use, as compared to the reported baseline data. The results presented are based on a 2015 study, which included data on 355 PrEP users from January 2011 – August 2015. These details have been added to the manuscript (page 9).

12. Incident STI risk - Was the frequency of testing prior to PrEP initiation controlled for? Increased testing has lead to artificially-inflated STI positivity rates in other PrEP studies.
Author response: This is an astute observation and we agree that recommendations for PrEP users to attend quarterly screening may contribute to apparently inflated estimates in PrEP studies. We did control for frequency of STI testing in the year prior and following PrEP initiation in this study. We have added this detail into the manuscript and also provided greater specificity to the reporting of our results of this study in line with your query and a comment from Reviewer #2 (page 10).

13. If a different time period and thus cohort were used once again when reporting these results compared to previous sections, please make this clearer or consider revising so data are presented on the same individuals in each section of the paper.
Author response: Thank you for noting the need for increased clarity. We have revised the text to be more specific about the timelines included in the STI study and for each result reported in the text.

14. Patterns of PrEP use - Without results of a multivariate model being presented, limited conclusions can be drawn about factors associated with PrEP regimen.
Author response: We have chosen to present descriptive results only in this cohort profile.

Suggested changes

15. Introduction - When discussing previous PrEP RCTs, consider: the low/no efficacy shown in women, differentiating between studies testing TDF alone or TDF/FTC, differences between daily and intermittent PrEP studies
Author response: We have added extra details to the background section regarding evidence to support daily and intermittent PrEP from RCTs, as these results informed our clinical practices and are directly applicable to the cohort. PrEP as a single ARV therapy of TDF was never recommended in Canada nor implemented in our clinic, therefore discussing the impact of TDF alone is not applicable to our setting.

16. The iPrEx study results were published in 2010, not 2011 (line 15)
Author response: Thank you for noting this error. The reporting has been updated to specify 2010 (page 4).

17. Explanation of a 'notice of compliance' (line 17) would be helpful for non-Canadian readers
Author response: Once Health Canada approves a drug for a specific use, they issue an official “notice of compliance”. We have reworded the section to state “approval” rather than “notice of compliance” for clarity (page 4).

18. Cohort description - Are you referring to a specific PrEP cascade in line 55?
Author response: For improved clarity, we have revised this section to say “throughout PrEP care” rather than referring to a cascade (Page 5).

19. Patient and public involvement - What % of participants were word-of-mouth referrals from the first survey? A comment about how recruitment of people previously attending an HIV rapid testing site may have affected results may also be warranted here.
Author response: Regrettably, by design, these two studies were not possible to link. The survey was conducted at a site outside of Actuel and had the objective of assessing PrEP interest, not linking participants to PrEP care and measuring uptake rates.

20. Patterns of PrEP use - Did people switch regimens multiple times? Mean number of switches
Author response: The majority of PrEP users do not switch regimens. We found that 14% of individuals who initiated PrEP daily switched to on-demand PrEP over the course of follow-up, and conversely that 14% of individuals who initiated on-demand PrEP switched to daily PrEP over the course of follow-up (now reported in the patterns of PrEP use section). Therefore, the mean number of switches is 0. A small minority of patients switch back and forth between regimens, however a more detailed description of PrEP regimen patterns will be reported in separate work.

21. What does used PrEP 'episodically' mean? (line 35)
Author response: Episodic PrEP use is defined as temporary discontinuations in their PrEP use of 6 months or longer. We clarified our definition (see page 11).

22. Very high rate of loss to follow up - consider a comment about 'seasons of PrEP use' or how fluctuating risk may affect PrEP adherence and continuity of engagement in care
Author response: This is an excellent recommendation and a comment and citation of the Elsesser et al. study which first proposed the “seasons of risk” hypothesis has been added to the findings to date section (page 11).

23. Where there any other costs to the individual for accessing PrEP (eg. STI testing, doctor's appointments?) How did the median income in this study compare to the median Canadian income?
Author response: We have provided extra data on the fees associated with accessing PrEP (page 11) and on the median income in Quebec during the study period (page 6).

24. Limitations - Consider a clearer emphasis on the large proportion of missing data (15-20%?) and how representative this one clinic population is in terms of PrEP implementation in Canada or more broadly.
Author response: We followed the reviewer's suggestion and put greater emphasis on missing data in the limitations section (page 12). The proportion of missing data should also be weighed against the real-world nature of our cohort. We may lack full control over data collection procedures but the real-world nature of this cohort entails that results are likely more relevant to clinical practice. Further information was also added regarding the potential for non-generalizability to national/international settings (page 12).

25. Table 1 - How do college and university education differ? No definitions of regular or occasional sexual partners in text.
Author response: We have revised our definition to regroup college and university education together into a "post-secondary education" category in the text as we do not feel that college as compared with university education will have a major impact on health literacy/knowledge and interest in staying on PrEP. This is an idiosyncrasy of the Quebec education system, where college typically comprises two years of school "CEGEP" between secondary school and university.

26. Table 2 - Comment on issues comparing 2018 follow-up to other years given uneven period of follow-up (especially in regards to lack of PrEP follow-up >6 months, as this cut-off may not have been reached for all participants). Why was the % of people who did not initiate PrEP so much higher in recent years? No corresponding ** in the table, just the notes
Author response: We are not trying to compare 2018 to other years, as this is evidently not a full year of follow-up. The reason we have provided table 2 and stratified follow-up time by year is to show readers the variance in follow-up time by year of initiation. The proportion of people who did not initiate PrEP did increase in recent years and this may be due to trends in the type of individuals who sought PrEP in the early implementation period "early initiators" versus individuals seeking PrEP once it became mainstream who may have been at lower risk, and therefore less inclined to take PrEP once detailed information on this prevention measure are provided. A comment regarding this has been added to the text in the clinical visits section (page 7). Thank you for noting the omission of a corresponding ** symbol in table 2, this has now been added in.

27. Table 3 - Specify time periods of data collection e.g. STI history
Author response: We have updated table 3 to include periods of data included in questionnaire items.

28. Table 4- Did intermittent PrEP prescriptions vary by year/period of enrollment (IPERGAY findings not released until 2015)? Is the mean number of sexual partners normally distributed? Consider reporting the median and IQR instead. How is the prescribing doctor's years of practice relevant to individual sociodemographic and behavioural profiles?
Author response:
On-demand PrEP prescriptions were stable from March 2015 onwards with about 20% of individuals receiving on-demand PrEP at baseline.
The number of sexual partners is not normally distributed it is skewed to the right. We agree with the reviewer that presenting median and IQR is more appropriate than presenting the mean for non-normally distributed data. After consideration, we decided the best way to show this variable is in categories, as this demonstrates most clearly that the proportion of PrEP users who have a high number of sexual partners (over 30 partners within 12 months of baseline) is higher among daily PrEP users than on-demand users (see table 4). We chose to combine regular and occasional partners into a single variable (total partners) for the sake of presenting more concise information for readers to digest and because trends were similar between groups for regular and occasional partners.
We initially included the prescribing MD's years of practice as we hypothesized this may be relevant to the PrEP prescription as a greater experience in clinical practice may contribute to a physician's

ease in prescribing a more complex therapeutic regimen. However, given that we have not provided a detailed overview of factors associated with PrEP regimen prescriptions in this paper, we have decided to exclude this variable from the descriptive table in the revised manuscript.

Figure 2 - Make it clearer which questions appeared in which sections of the questionnaire
Author response: We have revised the text in the measurement section to describe which types of questions were included in the self-administered section, and the sections administered by nurses and clinicians (Page 7). In reality, there is overlap in the questions/sections as the nurses and clinicians review the self-administered portion of the questionnaires and some questions are asked in repetition. For this reason, we do not feel it is appropriate to revise figure 2 and group question types into discrete categories by patient/nurse/clinician section.

Response to Reviewer 2
Reviewer Name: Liza Coyer
Institution and Country: Public Health Service of Amsterdam, the Netherlands

Thank you for the opportunity to review this study profile about an open, prospective cohort of daily and intermittent PrEP users in a community setting in Montreal, Canada. This cohort will be an important and useful source of real-world data on PrEP use, monitoring and care. Since enrolment started in 2013, this cohort captures early as well as later PrEP implementation and adoption, which could provide very interesting insights into PrEP uptake, care retention and discontinuation over time. Moreover, data on the use of daily and/versus intermittent regimens is particularly welcome, especially given relative scarcity of data on intermittent PrEP. It's rationale and research aims are clearly described.

Major comments:

1. In the introduction, I would suggest to elaborate on how PrEP provision is organized in Canada/Quebec and who can prescribe PrEP. It is mentioned that l'Actuel is a top referral site in Montreal for HIV and STI testing and treatment, but what proportion of PrEP users (in Montreal) obtain their PrEP through this site? All? If there are other local PrEP providers (other clinics, general practitioners, etc.), which is suggested by bullet point 3 under strengths and limitations of this study, it would not be correct to state that results are representative of local PrEP users, as this would depend on user characteristics/ preferences across providers.

Author response: Thank you drawing attention to the need to provide further context regarding the landscape of PrEP offering in Canada and specifically in Montreal. We have added additional information regarding PrEP provision in Quebec to the introduction (page 4). Unfortunately, we are not able to state what proportion of PrEP users in Montreal obtain PrEP through this site, as there is currently no way to measure the total number of PrEP users in Montreal. However, we can confirm that Actuel was the first sexual health centre to publicly promote the availability of PrEP in Montreal in 2013. Individual clinicians working within sexual health practices or family medicine clinics have been able to provide PrEP during the study period as well. A recent random-driven sample of gay men in Montreal found that 78% of PrEP users in their sample received PrEP from a specialty clinic, such as Actuel (page 12). Unfortunately, this survey did not ask PrEP users which specific clinic they received their prescription through.

2. Most summarized findings to date refer to conference abstracts. This in itself is not problematic, but it is important to be clear on the sample sizes of these analyses and which time spans these data cover, given these may be interim/unfinished analyses and are not all updated until June/July 2018. In addition, I do find it problematic that the authors do not address nor incorporate the serious concerns raised about their research group's analysis of STI incidence pre-PrEP compared to post-PrEP

(Marcus et al. Concerns about a study on sexually transmitted infections after initiation of HIV preexposure prophylaxis, AIDS 2018).

Author response: We have revised the manuscript by including a mention of the timelines and sample sizes for each study highlighted. Some of the concerns raised by Marcus et al. (which has been cited) in their critique of our paper have now been mentioned as study limitations following the description of this study (page 10).

Specific comments:

Abstract:
1. Please specify all sample sizes and denominators throughout the abstract (same comments apply to the 'cohort description' section):
- it is unclear whether the median age given is about the 2385 'participants' with an initial consultation or those (n=2156) with a PrEP description at baseline (who are referred to as being 'included in the cohort' in the participants section and are described in table 1).
Author response: We have revised the abstract and cohort description sections by providing sample sizes, accordingly. The median age was provided for the N=2156 participants who were prescribed PrEP at baseline and consented to contribute their data for research use. We have removed a mention of the total number of participants consulting for PrEP (N=2385) from the abstract in order streamline the reporting of key results in the abstract.

- I assume median PrEP duration and person-years of follow-up were calculated among all those who initiated PrEP care (n=1551)? Please clarify.
Author response: Yes, median PrEP duration and person-years of follow-up are calculated for the 1551 individuals who initiated PrEP care. This detail has been added to the abstract.

- Please specify the sample size and effect estimates of the before and after PrEP initiation analysis.
Author response: The sample size this study (N=109) has been added to the abstract.

2. Could you confirm that enrolment took place up to and including June 2018 and that follow-up took place up to and including July 2018? If this is correct, why was there no enrolment in July 2018? It should then also be 'through' instead of 'to' July 2018.
Author response: Yes, the follow-up time was lagged one-month later than enrolment so that we could report data on treatment initiation at the first follow-up (1 month after baseline) for all those with baseline consults up to June 30, 2018. We have added this detail on the justification of different end dates for cohort enrolment and follow-up to the manuscript for improved clarity (page 6)

3. The sentence "The l'Actuel PrEP cohort [..] in North America" may fit better under 'participants'.
Author response: Thank you for this suggestion. We have shifted this sentence into the 'participants' section accordingly.

4. Are there any specific analyses planned for the future? Certain areas of concern (such as PrEP discontinuation) have been highlighted elsewhere in the paper, so I was wondering if you will be looking into these specifically?
Author response: Yes, indeed, PrEP discontinuation is an area of research which we have explored via preliminary analyses presented at various scientific conferences and which may be further elaborated into a research manuscript.

Strengths and limitations:
5. Bullet point 1: typo "effectiveness"

6. Bullet point 2: typo “strengths”
Author response: These typos have been corrected, thank you for noting them.

Introduction:
7. Are the Canadian guidelines for PrEP indicators identical to those used by l’Actuel? Do these guidelines also include the use of intermittent PrEP? I’m missing some detail on the use of intermittent PrEP in the Canadian setting.
Author response: Regarding PrEP guidelines, clinicians at Actuel are knowledgable regarding Canadian and Quebec guidelines for PrEP indication, but may use their clinical discretion in prescribing to patients who may not directly match these indications. For example, the PrEP guidelines do not indicate PrEP for MSM in serodiscordant partnerships if the HIV-positive partner has an undectable viral load. However, if a patient matching this profile wishes to initiate PrEP, the clinician may choose to prescribe to this patient. We have elaborated the description of use of PrEP guidelines by including mention of on-demand PrEP in the introduction (page 4).

Cohort description:
8. As the authors mention that the cohort is integrated into, and supported through, routine clinical care, does it mean all mentioned outcomes will be monitored in ‘indefinite’ time? Or would this depend on future funding? (i.e. please confirm there is no end date).
Author response: Yes, at present we plan to continue follow-up for active PrEP users indefinitely and there is no planned end date for the PrEP cohort. We have included this information in the manuscript (page 5).

9. Second paragraph of the ‘participants’ section: should be 229, not 228 (according to Fig. 1)
Author response: Thank you, we have updated the text accordingly.

10. Related to my questions about sample size from the abstract, it is unclear when someone is considered a participant in this cohort. In the abstract, all those with a PrEP consultation are considered participants, but later only those with a prescription at baseline are considered as being included in the cohort and are later referred to as the participants (“Table 1 outlines characteristics of participants [..]”). Moreover, the summary characteristics as stated in paragraph 3 of the ‘participants’ section are different from those given in table 1. I think all relevant details have been given in-text about those with an initial consult, those who actually obtained PrEP and those who eventually used PrEP, but it’s a bit of a puzzle, so I would suggest improving the readability of this section.
Author response: To improve the clarity of reporting we have revised the terminology to state “Consulted for PrEP” (N=2385), “PrEP cohort participants” (N=2156), “initiated PrEP care” (N=1551) – as is described in the flow chart (Figure 1). The differences in summary statistics between the participant section and table 1 have now been corrected.

11. It would be interesting to know the duration of PrEP use prior to being lost-to-follow-up/discontinuing PrEP of those no longer retained in care. Are there any participants who discontinued PrEP for some time and then restarted? Or are these planned analyses?
Author response: Thank you for this recommendation. We have reported on the numbers of individuals who discontinued PrEP for ≥6 months and then restarted, which we define as “episodic PrEP use”. In a poster presented at CROI 2018, we found that 9% of participants (N=114) had demonstrated episodic PrEP use with gaps in their care. These results are summarized in the Findings To Date “patterns of PrEP use” section.

12. Please confirm table 2 is the situation as per July 2018.
Author response: We confirm that follow-up took place up to and including July 2018.

13. Is the choice between daily and intermittent PrEP mainly provider- or user-driven? (i.e. do providers steer those with lower risk profiles towards intermittent PrEP?) Are regimen switches also documented?
Author response: The decision to take a PrEP regimens is both provider and user-driven as it is based upon a discussion between clinician and patient. This detail has been added to the clinical visits section (page 7). Regimen switches are documented and are reported in the findings to date "patterns of PrEP use" section (page 11).

14. Clear paragraph on missing data and why this occurs. In table 1, I would prefer calling missing data 'missing' instead of 'unknown'. Moreover, please also provide sample sizes for the regular partners and occasional partners in table 1 as these are currently missing.
Author response: We have revised the text in the missing data section (page 7-8) and table 1, according to the reviewer's suggestion. The sample sizes (or rather, number with missing data) for both the number of regular partners and occasional partners are now provided in Table 1.

Findings to date:
15. I would suggest something along the lines of "following PrEP discontinuation" after the sentence "[…] translating to an HIV incidence of 3.9 cases per 100 person-years".
Author response: We have integrated this suggestion into the text for improved clarity of reporting (page 9).

16. Although I do not disagree with the rejection of the perception that all PrEP users engage in CAS with multiple partners, I do not think the conclusion "The results of this analysis suggest that […] not grounded in reality" immediately follows from the reported observation that some PrEP users report a change or remain stable in their risk behaviour after initiating PrEP, as this depends on their specific behaviors before and during PrEP. It would be useful to elaborate a little more detail on the specific behaviors reported.
Author response: We agree that this sentence did not logically follow the previously reported results. We have revised the reporting in this section in lines with comments from both reviewers (page 10).

17. Reference 20 does not refer to a strictly observational study, as iPrEX is a trial. Please provide some references to observational studies.
Author response: Thanks for this recommendation. We have updated this section to refer to two recently published systematic reviews investigating STIs among PrEP users including both observational studies and RCTs (page 10).

18. As with any real-world study, loss-to-follow-up could be an issue. Loss-to-follow-up is 39% in this cohort (606/1551). Whether this results in bias depends on mechanism of missingness: if loss-to-follow-up is missing not a random, bias is likely introduced. Do you have any information on this?
Author response: We recently presented data on loss-to-follow-up from PrEP care at the 2018 Glasgow HIV drug therapy conference. This analysis found some predictors associated with greater travel distance from a patient's home to the clinic and among younger participants. We have added a brief overview of study results to the cohort profile (see page 11)

VERSION 2 – REVIEW

REVIEWER	Stefanie Vaccher Kirby Institute, UNSW Australia
REVIEW RETURNED	18-Apr-2019

GENERAL COMMENTS	Thank you for taking on board feedback provided previously. All suggested changes have been made, while keeping within the limitations of the cohort report. A few minor comments to add to your revisions below: - General comment: Using the term 'risk behaviour' to describe condomless sex etc by people taking PrEP portrays these individuals as taking risks when they aren't, because they are protected by PrEP. This is a recurring issue in the literature and something we are all grappling with, but something to be aware of. - Measurements: You mention 'criteria defined in the Quebec and Canadian PrEP guidelines' but do not state these. To save readers having to look them up, a brief summary of key criteria would be helpful. - Risk compensation: Typo - causaly - Strengths and Limitations: Lines 40-7 you say you cannot quantify the number of PrEP users in Montreal but the large majority of Montreal PrEP users are managed at Clinique l'Actuel. This statements seen contradictory. - References: Please check references e.g. #26 Traeger et al journal abbreviation incorrect; #35 Apelian et al author list too long - Table 1: Line 23, is this 'missing data' line cut off? Considering the very small number of individuals without missing data here, you may consider not reporting number of partners.

REVIEWER	Liza Coyer Public Health Service of Amsterdam, the Netherlands
REVIEW RETURNED	07-May-2019

GENERAL COMMENTS	The authors have adequately addressed all of my comments. I very much appreciate the the expanded introduction, which now includes more information on PrEP access and contexualises the Clinique médicale l'Actuel in terms of PrEP provision and care. In addition, the "findings to date" section has definitely improved with respect to clarity on the reporting of time periods and sample sizes of analyses and limitations to the findings thus far have been appropriately highlighted. I have no further comments, and recommend to accept this manuscript for publication.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Stefanie Vaccher

Institution and Country: Kirby Institute, UNSW Sydney, Australia

Thank you for taking on board feedback provided previously. All suggested changes have been made, while keeping within the limitations of the cohort report.

A few minor comments to add to your revisions below:

1. General comment: Using the term 'risk behaviour' to describe condomless sex etc by people taking PrEP portrays these individuals as taking risks when they aren't, because they are protected by PrEP. This is a recurring issue in the literature and something we are all grappling with, but something to be aware of.

Author response: We agree that the term ‘risk behaviour’ has a different connotation in the context of PrEP users, who are protected from HIV infection by PrEP. Given that PrEP users are still at risk of STI acquisition and transmission when engaging in condomless sex or sex with multiple partners, these practices do arguably remain forms of ‘risky behaviour’, though certainly lower risk behaviours as a result of the protection conferred by PrEP. To avoid any confusion or implied judgment about the associated risk of such behaviors, we now refer to them as sexual behaviors.

2. Measurements: You mention 'criteria defined in the Quebec and Canadian PrEP guidelines' but do not state these. To save readers having to look them up, a brief summary of key criteria would be helpful.

Author response: We agree that it will be helpful for readers to have a summary of the Quebec and Canadian PrEP guidelines in the text. We have added a brief overview of the indications for PrEP among MSM as outlined in the Canadian and Quebec PrEP guidelines (see introduction, paragraph 2).

3. Risk compensation: Typo - causaly

Author response: The typo has been corrected, thank you.

4. Strengths and Limitations: Lines 40-7 you say you cannot quantify the number of PrEP users in Montreal but the large majority of Montreal PrEP users are managed at Clinique l’Actuel. This statements seen contradictory.

Author response: We have reworded this sentence as follows to avoid the contradictory nature in which it was previously phrased. “However, we feel that the l’Actuel PrEP Cohort is broadly representative of PrEP users in Montreal given that Clinique l’Actuel is the largest PrEP provider in the city and was the first sexual health clinic to offer PrEP in Montreal. “

5. References: Please check references e.g. #26 Traeger et al journal abbreviation incorrect; #35 Apelian et al author list too long

Author response: Corrected, thank you.

6. Table 1: Line 23, is this 'missing data' line cut off? Considering the very small number of individuals without missing data here, you may consider not reporting number of partners.

Author response: The missing data line is accurately stated, however we have revised the table to specify that the statistic reported for missing data is N(%) for improved clarity when compared with the Median (IQR) reported among those with valid responses to the question regarding numbers of sexual partners within the past 12 months. The total number of participants with missing data for regular partners is 425 (19.7%), meaning that 1731 individuals (80.3%) reported their numbers of regular partners. Similarly for occasional partners, 417 participants (19.4%) had missing responses, meaning that 1739 individuals reported their numbers of occasional partners. This is a substantial number of participants who have no missing data for the number of partners variables, and it is an important descriptive factor include in the l'Actuel PrEP cohort profile, therefore we prefer to include these variables in the table.

Reviewer: 2

Reviewer Name: Liza Coyer

Institution and Country: Public Health Service of Amsterdam, the Netherlands

The authors have adequately addressed all of my comments. I very much appreciate

the expanded introduction, which now includes more information on PrEP access and contexualises the Clinique médicale l'Actuel in terms of PrEP provision and care. In addition, the "findings to date" section has definitely improved with respect to clarity on the reporting of time periods and sample sizes of analyses and limitations to the findings thus far have been appropriately highlighted. I have no further comments, and recommend to accept this manuscript for publication.

Author response: We are pleased to hear that our revisions have addressed the critiques initially raised by this reviewer. Again, we thank the reviewer for her constructive comments, which have improved the quality of reporting in our manuscript