PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	CTN 328: Immunogenicity outcomes in people living with HIV in Canada following vaccination for COVID-19 (HIV-COV)-Protocol for an observational cohort study
AUTHORS	Costiniuk, Cecilia T.; Singer, Joel; Langlois, Marc-Andre; Kulic, Iva; Needham, Judy; Burchell, Ann; Jenabian, Mohammad-Ali; Walmsley, Sharon; Ostrowski, Mario; Kovacs, Colin; Tan, Darrell; Harris, Marianne; Hull, Mark; Brumme, Zabrina; Brockman, Mark; Margolese, Shari; Mandarino, Enrico; Angel, Jonathan; Routy, Jean-Pierre; Anis, Aslam; Cooper, Curtis

VERSION 1 – REVIEW

REVIEWER	AbdulAzeez Anjorin Lagos State University, Microbiology (Virology research)
REVIEW RETURNED	16-Aug-2021

GENERAL COMMENTS	Good protocol paper. Please work on the suggestions as attached including the references. The reviewer provided a marked copy with additional comments. Please contact the publisher for full details.

REVIEWER	Claire Deleage Frederick National Laboratory for Cancer Research, ACVP
REVIEW RETURNED	03-Sep-2021

GENERAL COMMENTS	In this manuscript, the authors are detailing the protocol they will follow to set up an observational cohort study to assess the immunogenicity outcomes in HIV positive participants following COVID-19 vaccination. As the authors mentioned this cohort comes a little late looking at the current situation of the pandemic and its impact on immunosuppressed patients. However, this type of cohort is still essential to understand how HIV infected people built up specific immune response to SARS-CoV-2 post vaccination and if any additional immune boost would be needed to keep this population safe. The main goals, general methodology, recruitment, Subpopulation of interest and timeline for participants are clearly presented and were specifically designed to answer key questions. The different parameters listed to assess the humoral and cellular immunity is clearly based on recent literature on SARS-CoV-2 and should be able to answer a lot of questions regarding the magnitude, specificity and durability of the immune response of the participants. My only question is did the authors considered enrolling PLWH who didn't receive the vaccines but did get infected to compare the specificity, durability and type of immune response in patients who

	have been in direct contact replicating the virus compare to people who have been vaccinated. Adding such a subgroup to this cohort can also provide key information regarding the impact of HIV and SASRS-CoV-2 infection.

VERSION 1 – AUTHOR RESPONSE

bmjopen-2021-054208 - "CTN 328: Immunogenicity outcomes in people living with HIV in Canada following vaccination for COVID-19 (HIV-COV)-Protocol for an observational cohort study."

Thank you for the opportunity to revise and re-submit our manuscript.

1. We note that your trial registration does not currently contain a data sharing statement. BMJ Open adheres to the ICMJE guidelines on the registration of clinical trials, which states:
"clinical trials that begin enrolling participants on or after 1 January 2019 must include a data sharing plan in the trial's registration". See: http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html
Please update your registration to include a data sharing statement.

Authors' Response: Data will be shared with Canada's COVID-19 Immunity Task Force (CITF) in accordance with the CITF data sharing agreement. Coded participant data (core data elements: demographics, COVID-19 infection history, health conditions, vaccination, blood testing results) will be deposited into the CITF database every two months for future research concerning COVID-19 and related health outcomes. To request coded centralized data, researchers apply to the CITF Data Access Committee (DAC). The DAC will ask researchers to confirm their intended research activities have received necessary ethics approvals. Our registration has been updated to include a data sharing statement and we have also included this information in our manuscript (p.20-21). We also indicate in the main document that data sharing agreements will be obtained between CTN sites to use data not sent to the CITF (p.21).

2. Please ensure that all acronyms are defined on first mention, including those in the Abstract.

Authors' Response: All acronyms are now defined on first mention, including those in the abstract.

3. Please revise the Ethics and Dissemination section of the Abstract to include statements on the ethics and consent of this study.

Authors' Response: This has been revised as requested: "Research ethics boards at all participating institutions have granted ethics approval for this study." (Page 4). Written informed consent will be obtained from all study participants prior to enrolment.

The sentence "Both the protocol and informed consent form were reviewed and approved by the CTN Community Advisory Committee added to the Ethics and Dissemination section of the main text (p.20).

4. Please include a dissemination statement in the Ethics and Dissemination section of the main text.

Authors' Response: A dissemination statement has been added under the Knowledge Translation (KT) & Dissemination Plan sub-section of Ethics and Dissemination: "A first manuscript outlining the results of the primary objective will be submitted for publication within 6 months of participants completing the 6-month post 2nd vaccine dose study visit. A second manuscript outlining the durability results will be submitted for publication within 6 months of participants completing the 12-month post 2nd dose study visit. Data will also be shared with CTN members at the semiannual meetings and through conference abstracts (Page 21).

Reviewer: 1
Dr. AbdulAzeez Anjorin, Lagos State University
Comments to the Author:
1. Good protocol paper. Please work on the suggestions as attached, including the references.

Authors' Response: Thank you for the positive feedback and the proposed edits. The changes requested, including to the references, have been implemented throughout the text.

2. Methods section: What informed the choice of each site, and 3 provinces out of 10 provinces and 3 territories?

Author's response: These sites were selected since they are 4 of the largest HIV clinics in Canada and have established research infrastructures to support the recruitment, enrolment and follow-up of a high volume of diverse study participants. These sites also have strong track records for rapid enrollment of participants in CTN studies. This text has been added to the Methods, Study design section (Page 10).

3. Sample size: The sample proportion here is better otherwise a standard formula like Kish Leslie sample formula or others may be used to better justify the sample population.

Author's response: We are aware that Kish published a book, "Survey Sampling" (not accessible to us), which discusses sample size calculation (referenced in another article by Israel in 1992). We are not clear about the reason why the reviewer has suggested this. However, we now reference that we used the UCSF sample size calculator (https://data.ucsf.edu/research/sample-size), which uses the typical normal distribution assumption with the continuity correction as an approximation to the binomial distribution. (Page 14).

4. References: Reference 5 was published in 2007. Please correct and verify other references.

Author's response: References 5 and 22-24 have been corrected, and the other references have been verified. Reference 55 has been removed since it is no longer relevant.

5. CITF CDE Baseline Questionnaire: Was the questionnaire pretested? It will interesting to include the Cronbach's alpha value as part of the statistical analyses?

To our knowledge, the CITF questionnaire has not been pretested in the general population or PLWH. Cronbach's alpha measures the internal consistency of responses. This is useful when one is asking questions which one believes all relate to a particular attribute, e.g., anxiety. In this instance, all of the questions should be correlated, and Cronbach's alpha would measure this.

Cronbach's alpha is also commonly used when there are multiple Likert questions in a survey/questionnaire that form a scale and one wishes to determine if the scale is reliable.

We can see applying Cronbach's alpha to, for example, questionnaire items 34 a-e, where all the questions purportedly measure the extent to which people adopted preventive measures (p.19).

6. What is the purpose of Question 6: "Are you an Indigenous person originating from North America?"

Author's response: It is important to determine the percentage of Indigenous persons participating in our study since they represent a vulnerable but often underrepresented group of PLWH. Due to systemic inequities and socio-economic marginalization, Indigenous peoples are at disproportionate risk of both HIV and COVID-19

Reviewer: 2
Dr. Claire Deleage, Frederick National Laboratory for Cancer Research
Comments to the Author:
In this manuscript, the authors are detailing the protocol they will follow to set up an observational cohort study to assess the immunogenicity outcomes in HIV positive participants following COVID-19 vaccination.
As the authors mentioned this cohort comes a little late looking at the current situation of the pandemic and its impact on immunosuppressed patients. However, this type of cohort is still essential to understand how HIV infected people built up specific immune response to SARS-CoV-2 post vaccination and if any additional immune boost would be needed to keep this population safe.
The main goals, general methodology, recruitment, Subpopulation of interest and timeline for participants are clearly presented and were specifically designed to answer key questions. The different parameters listed to assess the humoral and cellular immunity is clearly based on recent literature on SARS-CoV-2 and should be able to answer a lot of questions regarding the magnitude, specificity and durability of the immune response of the participants.

1. My only question is did the authors considered enrolling PLWH who didn't receive the vaccines but did get infected to compare the specificity, durability and type of immune response in patients who have been in direct contact replicating the virus compare to people who have been vaccinated. Adding such a subgroup to this cohort can also provide key information regarding the impact of HIV and SASRS-CoV-2 infection.

Authors' Response: Although we did discuss the possibility of enrolling unvaccinated PLWH infected with SARS-CoV-2 in the cohort, the availability of such participants would be insufficient. From our clinical experience, the number of PLWH refusing vaccination is relatively low given the tremendous efforts from advertising campaigns and health care providers encouraging vaccine uptake in Canada. Therefore, our power would likely be too low to draw conclusions between persons with immunity via natural infection vs vaccination. Furthermore, in our experience, individuals refusing vaccination may be less likely to participate in a longitudinal research study due to medical mistrust, further reducing the power.

VERSION 2 – REVIEW

REVIEWER	AbdulAzeez Anjorin Lagos State University, Microbiology (Virology research)
REVIEW RETURNED	28-Oct-2021

GENERAL COMMENTS	This piece is now a better update.