

Effects of HIV Status and Vaccination on Long COVID Conditions Within an Integrated Health Care System

Corresponding Author: Ms Adrienne Deneal

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Brief summary of the manuscript

The study explores the incidence of long COVID in people living with HIV compared to people living without HIV using a matched population, controlling for previously diagnosed conditions.

Overall impression of the work

The time interval definitions do not meet the latest long COVID definitions, that set the cut-off score to experiencing symptoms for more than 120 days post infection. The authors chose 2 different time intervals, 0-29 days post infection and 30-180 days post infection and they do not report following any guideline or definition for this cut-off. However, the author used a large database, there is good representation of both sexes, the author included a wide demographic with regards to race, and reported a number of relevant factors such as the type of COVID-19 variant, the vaccination status and a number of comorbidities. The long COVID definition with regards to the symptoms was well developed and the analysis controlled for pre-existing conditions, which allows to assess the true prevalence of the disease, something that is currently missing from the literature. The authors also report the incidence of each individual symptom on top of the incidence of long COVID, which provides a more wide picture and helps better understanding the disease.

If the cut-off is adjusted according to the latest National Academies of Sciences, Engineering, and Medicine (NASEM) definition (<https://nap.nationalacademies.org/catalog/27768/a-long-covid-definition-a-chronic-systemic-disease-state-with>), this paper could offer a lot of valuable data and help better understand the risk of long COVID in people with HIV. It is suggested that the authors re-run the analysis using the 120 days cut-off and re-submit the manuscript.

Specific comments, with recommendations for addressing each comment

1. It is suggested that the authors use person-based language throughout the manuscript. For instance, use people living with HIV vs PWH.
2. It is also suggested that the authors use the term long COVID, which is the patient advocated term.
3. The Introduction is too long and needs to be shortened. It is unclear why the authors spend such an extended part of the text describing a previous study and even referring to a Table within that study in this paper.
4. It is suggested that the Methods are moved before the Results to improve the flow of the manuscript.
5. Lines 59-61: "However, the incidence of PCC among PWH compared to people without HIV (PWoH), or those who have not tested positive for HIV, has not been examined." The following article investigated whether adults living with HIV were associated with increased chance of developing Long COVID compared to adults living without HIV and found the current evidence limited and inconclusive. Please cite: 10.1016/j.eclim.2024.102993
6. It would be interesting to also report the incidence in the unmatched populations, and conduct an adjusted analysis, as the large sample size would allow for a large number of factors to be included in the model, including CD4 count and viral load.

Reviewer #2

Effects of HIV Status and Vaccination on Long COVID 2 Conditions Within an Integrated Health Care System

Authors: Michael A. Horberg, MD1 *, Celeena Jefferson, MIT1 , Eric Watson1 3 , Seohyun Kim, PhD1 , Adrienne N. Deneal, MS*1 , Kelly A. Gebo2 4 , Brenna C. Hogan, MPH2 , Elizabeth Humes2 , Keri N. Althoff, PhD, MPH2

Summary

Investigation of risk of PCC in KPMAS cohort, stratified by HIV and COVID vaccination status. KPMAS is an integrated closed healthcare system, and is well-suited for this investigation as KPMAS has high ascertainment of COVID-19 vaccination, testing and PCC-related diagnoses among both PWH and PWoH. PCC are subdivided in those that developed within 30 days of PCR-proven COVID-19 diagnosis ('persistent conditions'), and those that developed later ('post-acute incident conditions'). PWH were compared to 1:3 matched PWoH controls, controlling for previously diagnosed prevalent medical conditions.

Statistical interaction between HIV and COVID vaccination status was investigated.

Vaccination status was negatively associated with risk for persistent but not post-acute PCC.

HIV status did not impact risk for persistent nor post-acute PCC.

My main criticism concerns the lack of HIV-specific data in the manuscript. The KPMAS cohort also has data available on HIV-related parameters like use of ART, viral suppression, and CD4 counts in the KPMAS HIV Registry database. I recommend adding some descriptive HIV-related data to better characterize the PWH, and also to look into possible associations between HIV-related parameters and the risk of developing PCC.

Other comments

In post-acute PCC the defining health condition is diagnosed more than 30 days after diagnosis of COVID-19. I wonder if it is possible that the diagnosis date is actually substantially later than the date the symptoms first appeared? Does your claims database allow you to state with certainty that the post-acute symptoms really only developed many months after the COVID-19 diagnosis?

I wonder if there were differences in the duration and/or severity of the PCC between PWH and PWoH.

Line 92: In the paragraph "Matched Analysis: PWH vs PWoH" no absolute percentages who developed PCC after acquiring COVID-19 are given.

Line 99: "Among the individual PCC conditions, only gastrointestinal disorders, such as constipation and diarrhea (see Supplementary Table 1) had a significantly elevated 101 incidence in the incident time interval among PWH compared to PWoH (RR=1.70; 95% CI [1.13-2.55]; p=.01) (Figure 1)."

Gastrointestinal symptoms were the sole driver of the modestly increased risk for PCC in PWH. In general, gastrointestinal symptoms are particularly common in the population of PWH (on ART). I wonder how many of the gastrointestinal PCC were actually worsenings of pre-existing conditions? I assume here that minor pre-existing gastrointestinal symptoms might have gone unregistered in the KPMAS administrative databases.

Line 122: "Among the vaccinated patients who developed COVID, 20% developed PCC, while 20% among those who were unvaccinated at time of COVID diagnosis developed PCC (Table 1)."

Although the risk for PCC was the same in vaccinated and unvaccinated who developed COVID-19, I assume that the risk of developing COVID-19 was lower in the vaccinated, so for the vaccinated population as a whole the risk for PCC was probably lower. I recommend adding a statement to that effect to avoid giving the impression vaccination does not protect at all against PCC.

Line 124: "The interaction effect between HIV and vaccination on PCC incidence overall was not significant." Perhaps include the actual statistical results of testing for interaction effect.

Line 134: "The overall risk of PCC in the persistent time interval was significantly higher (85%) in those unvaccinated prior to COVID infection". Please provide the absolute risks (percentages) in both groups.

Do you have data on COVID-19 severity, and was severity associated with risk of developing PCC?

In lines 312-335 the criteria for considering a person as HIV positive are described but I have some difficulty fully understanding them. I am unsure if people on PrEP using either Truvada or Descovy, or those who used another triple regimen for PEP, could have been accidentally considered to be HIV positive. Please clarify.

In Table 2 only the overall PCC incidence is reported, not the incidences of persistent and post-acute PCC.

In Table 3 (unlike in Table 5) 'Asian' is not included as a racial category, while it was mentioned as a separate category in the Methods at line 366.

In Figures 1, 2 and 3 I would recommend adding a solid vertical reference line at value 1 to more easily assess statistical significance. Please also add the 95% CIs.

No adjustment for multiple testing is done. Some of the findings like for instance in the matched analysis you observed a lower risk for dizziness or vertigo symptoms in PWH with PCC, this might simply be a type 1 error (also because the opposite effect is seen in the unmatched analysis). Please discuss the issue of multiple testing in the limitations section of the Discussion.

Would it be possible to combine figures 1,2 and 3 into a single figure (with 3 lines per PCC symptom), so we can more easily assess if (the direction of) the observed relationships are consistent in these 3 analyses? Perhaps even use a logarithmic scale for the x-axis?

In Figure 1 anosmia is not shown, why?

In Figure 3 the line for anosmia appears to be (right) truncated. I guess the upper bound is actually extremely high.

Version 1:

Reviewer comments:

Reviewer #2

(Remarks to the Author)

The authors have responded adequately to all issues I raised in my review. I have no further comments or questions.

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Point-by-Point Responses

Dear Editors and Reviewers,

We appreciate the opportunity to submit our revisions as requested by you. Here, we give point-by-point responses to your suggestions and criticisms. Additionally, we corrected various typographic or grammatical errors throughout.

Thank you,

The Authors.

Reviewer #1 (Remarks to the Author):

Brief summary of the manuscript

The study explores the incidence of long COVID in people living with HIV compared to people living without HIV using a matched population, controlling for previously diagnosed conditions.

Overall impression of the work

The time interval definitions do not meet the latest long COVID definitions, that set the cut-off score to experiencing symptoms for more than 120 days post infection. The authors chose 2 different time intervals, 0-29 days post infection and 30-180 days post infection and they do not report following any guideline or definition for this cut-off. However, the author used a large database, there is good representation of both sexes, the author included a wide demographic with regards to race, and reported a number of relevant factors such as the type of COVID-19 variant, the vaccination status and a number of comorbidities. The long COVID definition with regards to the symptoms was well developed and the analysis controlled for pre-existing conditions, which allows to assess the true prevalence of the disease, something that is currently missing from the literature. The authors also report the incidence of each individual symptom on top of the incidence of long COVID, which provides a more wide picture and helps better understanding the disease. If the cut-off is adjusted according to the latest National Academies of Sciences, Engineering, and Medicine (NASEM) definition (<https://nap.nationalacademies.org/catalog/27768/a-long-covid-definition-a-chronic-systemic-disease-state-with>), this paper could offer a lot of valuable data and help better understand the risk of long COVID in people with HIV. It is suggested that the authors re-run the analysis using the 120 days cut-off and re-submit the manuscript.

Response: We thank the reviewer for their interest in the work. We have explained now how we have derived the long COVID definitions and comparisons we employed, and make a note that while many feel there is a broad definition of long COVID, there is not full appreciation of how this can be employed and used within a large health care system in the United States (throughout the manuscript).

We also have rerun the definition using the 120 day definition within our methodology (see lines 89-93 in the clean version and Figure 1).

Specific comments, with recommendations for addressing each comment

1. It is suggested that the authors use person-based language throughout the manuscript. For instance, use people living with HIV vs PWH.

Response: We updated “people with HIV (PWH)” to people living with HIV (PLWH) throughout the manuscript.

2. It is also suggested that the authors use the term long COVID, which is the patient advocated term.

Response: We included the term long COVID throughout the manuscript.

3. The Introduction is too long and needs to be shortened. It is unclear why the authors spend such an extended part of the text describing a previous study and even referring to a Table within that study in this paper.

Response: The introduction is to set the stage as we’re building on a previous study. However, we deleted one sentence.

4. It is suggested that the Methods are moved before the Results to improve the flow of the manuscript.

Response: Previously, we were directed to move to after the discussion section. However, to accommodate this direction, we moved the Methods section before the Results.

5. (Lines 59-61): “However, the incidence of PCC among PWH compared to people without HIV (PWoH), or those who have not tested positive for HIV, has not been examined.” The following article investigated whether adults living with HIV were associated with increased chance of developing Long COVID compared to adults living without HIV and found the current evidence limited and inconclusive. Please cite: 10.1016/j.eclinm.2024.102993

Response: Lines 54-56: We added the article to the references section.

6. It would be interesting to also report the incidence in the unmatched populations, and conduct an adjusted analysis, as the large sample size would allow for a large number of factors to be included in the model, including CD4 count and viral load.

Response: Thank you for pointing this out. The number of HIV patients were actually smaller in the unmatched population because it only included Delta and Omicron periods. Our matched results (for HIV) are robust, and although we did not include CD4 count and viral load in the model, we showed only 4% of HIV patients had CD4 < 200 and only 2% had a moderate viral load & <1% had a high viral load. These counts would not likely be meaningful in our analysis.

Reviewer #2 (Remarks to the Author):

Summary

Investigation of risk of PCC in KPMAS cohort, stratified by HIV and COVID vaccination status. KPMAS is an integrated closed healthcare system, and is well-suited for this investigation as KPMAS has high ascertainment of COVID-19 vaccination, testing and PCC-related diagnoses among both PWH and PWoH. PCC are subdivided in those that developed within 30 days of PCR-proven COVID-19 diagnosis ('persistent conditions'), and those that developed later ('post-acute incident conditions'). PWH were compared to 1:3 matched PWoH controls, controlling for

previously diagnosed prevalent medical conditions. Statistical interaction between HIV and COVID vaccination status was investigated. Vaccination status was negatively associated with risk for persistent but not post-acute PCC. HIV status did not impact risk for persistent nor post-acute PCC.

My main criticism concerns the lack of HIV-specific data in the manuscript. The KPMAS cohort also has data available on HIV-related parameters like use of ART, viral suppression, and CD4 counts in the KPMAS HIV Registry database. I recommend adding some descriptive HIV-related data to better characterize the PWH, and also to look into possible associations between HIV-related parameters and the risk of developing PCC.

Response: Thank you for your review and suggestions. We have now looked at these specifically. Please see in the Results lines 211-213: Among PLWH, 5% had CD4 <200 cells/mm³, and 88% had undetectable viral load as measured closest to date of initial COVID diagnosis. Within the PLWH cohort, there were no statistically significant associations between sex, race, BMI and the incidence of PCC.

Other comments

In post-acute PCC the defining health condition is diagnosed more than 30 days after diagnosis of COVID-19. I wonder if it is possible that the diagnosis date is actually substantially later than the date the symptoms first appeared? Does your claims database allow you to state with certainty that the post-acute symptoms really only developed many months after the COVID-19 diagnosis?

Response: As we utilized our electronic health record data, we acknowledge this is a possible limitation, but as we noted in our strengths and limitations as a closed healthcare system, our patients would only seek us for healthcare, and captured via electronic health record or claims (which we incorporated into our electronic health record; see lines 358-364).

I wonder if there were differences in the duration and/or severity of the PCC between PWH and PWoH.

Response: Thank you for this comment. We wonder the same, but our data is limited in this, as we do not have definite dates of resolution of the long COVID condition. We addressed this comment in the Discussion section. Please refer to lines 370-371.

Line 92: In the paragraph "Matched Analysis: PWH vs PWoH" no absolute percentages who developed PCC after acquiring COVID-19 are given.

Response: Please see lines 207-219, where we have provided percentages.

Line 99: "Among the individual PCC conditions, only gastrointestinal disorders, such as constipation and diarrhea (see Supplementary Table 1) had a significantly elevated 101 incidence in the incident time interval among PWH compared to PWoH (RR=1.70; 95% CI [1.13-2.55]; p=.01) (Figure 1). Gastrointestinal symptoms were the sole driver of the modestly increased risk for PCC in PWH. In general, gastrointestinal symptoms are particularly common in the population of PWH (on ART). I wonder how many of the gastrointestinal PCC were actually worsening of pre-existing conditions? I assume here that minor pre-existing

gastrointestinal symptoms might have gone unregistered in the KPMAS administrative databases.

Response: We listed in limitations that patients would likely only seek care if they were symptomatic with COVID, so asymptomatic or mildly symptomatic cases of acute COVID may be unrecorded. Same could be said for GI issues (see lines 358-384).

Line 122: "Among the vaccinated patients who developed COVID, 20% developed PCC, while 20% among those who were unvaccinated at time of COVID diagnosis developed PCC (Table 1)." Although the risk for PCC was the same in vaccinated and unvaccinated who developed COVID-19, I assume that the risk of developing COVID-19 was lower in the vaccinated, so for the vaccinated population as a whole the risk for PCC was probably lower. I recommend adding a statement to that effect to avoid giving the impression vaccination does not protect at all against PCC.

Response: thank you for pointing this out. We added the following statement to the Discussion section (lines 319-323); "Additionally, this analysis only looked at those who developed COVID-19 after being vaccinated. It is likely that the risk of developing COVID is lower for the vaccinated cohort and therefore, the risk of developing long COVID in the vaccinated population as a whole is likely lower than the results of this analysis."

Line 124: "The interaction effect between HIV and vaccination on PCC incidence overall was not significant." Perhaps include the actual statistical results of testing for interaction effect.

Response: Please see lines 239-240: We added the statistical results of testing for interaction effect "The interaction effect between HIV and vaccination on PCC incidence overall was not significant ($p=.97$)."

Line 134: "The overall risk of PCC in the persistent time interval was significantly higher (85%) in those unvaccinated prior to COVID infection". Please provide the absolute risks (percentages) in both groups.

Response: We added absolute risks (percentages) in both groups (see lines 206-208).

Do you have data on COVID-19 severity, and was severity associated with risk of developing PCC?

Response: Unfortunately, we do not have severity of acute COVID in this analysis. However, we hope to consider this for future manuscripts. We noted this in our limitations (line 370-371).

In lines 312-335 the criteria for considering a person as HIV positive are described but I have some difficulty fully understanding them. I am unsure if people on PrEP using either Truvada or Descovy, or those who used another triple regimen for PrEP, could have been accidentally considered to be HIV positive. Please clarify.

Response: We appreciate the reviewer pointing this out. We have added to lines 107-108: The following note was added for clarification "Note that patients taking HIV PrEP (as noted in the

electronic health record and no history of quantifiable HIV RNA or nor a positive HIV antibody test) are excluded.”

8In Table 2 only the overall PCC incidence is reported, not the incidences of persistent and post-acute PCC.

Response: Thank you for this suggestion. We added the incidences of persistent and post-acute PCC (see Table 2).

In Table 3 (unlike in Table 5) 'Asian' is not included as a racial category, while it was mentioned as a separate category in the Methods at line 366.

Response: We included 'Asian' to the Table 2 to align with our previous Table 5, which has been combined into our Table 2.

In Figures 1, 2 and 3 I would recommend adding a solid vertical reference line at value 1 to more easily assess statistical significance. Please also add the 95% CIs.

Response: We thank you for that great suggestion. All three figures now have vertical reference line at OR=1.00.

No adjustment for multiple testing is done. Some of the findings like for instance in the matched analysis you observed a lower risk for dizziness or vertigo symptoms in PWH with PCC, this might simply be a type 1 error (also because the opposite effect is seen in the unmatched analysis). Please discuss the issue of multiple testing in the limitations section or the Discussion.

Response: We added the following statement to the Discussion section (lines 373-374) “Lastly, no adjustments for multiple testing were performed, which may have led to less likely positive significance for some of our individual PCC conditions.”

Would it be possible to combine figures 1,2 and 3 into a single figure (with 3 lines per PCC symptom), so we can more easily assess if (the direction of) the observed relationships are consistent in these 3 analyses? Perhaps even use a logarithmic scale for the x-axis?

Response: Thank you for posing these questions. We added a reference line at value 1.00 for the three figures (now Figures 2, 3, 4). We did not modify the x axis but did add the reference line. The figures are independent analyses; thus, we are keeping them as independent figures.

In Figure 1 anosmia is not shown, why?

Response: Thank you for noticing this, and we discussed how best to convey this. We have added the following note under the figure, “Insufficient observations to calculate risk and confident intervals for Anosmia.” (See Figure 1.)

In Figure 3 the line for anosmia appears to be (right) truncated. I guess the upper bound is actually extremely high.

Response: Thank you for pointing this out. We fixed the line, so it no longer appears to be (right) truncated (see revised Figure 4).

