Author’s response to reviews

Title: Is Treated HIV Infection Associated with Knee Cartilage Degeneration and Structural Changes? A Longitudinal Study using Data from the Osteoarthritis Initiative

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Version: 1 Date: 02 Apr 2019

Author’s response to reviews:

We would like to thank the reviewers for their review and comments. We have worked rigorously on responding to all comments and have modified and revised the resubmitted manuscript. Please find our point-by-point responses below. In the attached document comments are in italics and answers in standard font, changes made in the manuscript are highlighted in yellow both in the response letter (please see attached response letter) and the annotated manuscript.

Response to reviewers

Reviewer 1:

R 1.1: The manuscript reports a longitudinal study on the association between the metabolic disorders, which might affect PLWH on ART, and eventual knee cartilage structural changes.
The authors demonstrated that PLWH on ART have a higher tendency to present disordered cartilage matrix composition, increased joint inflammation and abnormalities of the IPFP and the SPFP, which altogether lead to a higher chance to develop osteoarthritis. Even though the sample size is relatively small, this analysis is the first of its kind, and definitely contribute to increase the knowledge and awareness of the side effects of ART on HIV patients. Therefore, I strongly believe that the study has good potential to positively contributes to increase the quality of life of PLWH. The authors show awareness and are critic to their work citing the major limitations of the study, like: small sample size, and the limited resolution of the WORMS scoring system to pick up cartilage composition changes. The imaging techniques are well described and results clearly stated, yet there are few issues which should be further discussed in introduction and discussion. In summary the manuscript is suitable for publication after some revision in the text, which I am suggesting below.

Author response 1.1: Thank you for the detailed review of our manuscript. We appreciate the input concerning our manuscript and hope to have satisfactorily addressed and answered all your comments in our revision.

R 1.2: The authors extensively introduce and discuss the topic of HIV, ART, Metabolic disorders and related cartilage structural changes/osteoarthritis. However, there is no reference on the available literature of HIV and hand osteoarthritis which in my opinion is worth to mention (some suggested publications: Larcher et al., Joint Bone Spine Oct;82(5):365-7; Tomi et al., Ann Rheum Dis 2016 Dec 75(12):2101-2107; Adizie et al., BMC Infectious Diseases (2016) 16:100).

Author response 1.2: Thank you for providing these valuable papers. We cited 2 of them in the BACKGROUND section. We did not use Adizie’s paper because osteoarthritis was not mentioned in this article.

Author action 1.2:

The following sentences were moved/added:

- BACKGROUND section, page 5 / line 92-95: MetS also affects up to half of HIV-infected patients receiving ART [9]. While studies have reported an increased prevalence and severity of radiographic hand osteoarthritis in patients with HIV-1 infection, in particular associated with MetS, the exact pathophysiology of OA in PLWH is not well understood [10,11].

The following citations/references were added:

- BACKGROUND section, page 5 / line 95: While studies have reported an increased prevalence and severity of radiographic hand osteoarthritis in patients with HIV-1 infection, in particular associated with MetS, the exact pathophysiology of OA in PLWH is not well understood [10, 11].
REFERENCES section, page 23 / line 486-492:


R 1.3: Authors states that, the PLWH included in the study are on ART regime since at least one year. Since it is still unclear how HIV comorbidities, ART treatments and metabolic disorders contributes to the onset of osteoarthritis, I think would be informative to at least mention or take in consideration this factor and the impact on the cartilage degeneration outcome.

Author response 1.3: Thank you for this helpful comment. Whether HIV per se or ART drugs can directly and independently affect the articular cartilage is indeed worth further investigation.

Author action 1.3:

The following sentences/citation were added:

- DISCUSSION section, page 15 / line 326-329: To date, little is known about whether HIV/ART can directly affect chondrocytes and cartilage matrix. However, considering that HIV was reported to be able to infect chondrocytes [32], the more direct association between HIV/ART and the cartilage matrix needs to be further explored.

The following reference was added:

- REFERENCES section, page 26 / line 560-561:


R 1.4: Results are corrected for ages, sex, race ecc… Still, (as recommended in point 2) would be nice a comment on the sex and past or actual activities of the patients (i.e.: job or practiced sports).

Author response 1.4: Thank you for this comment. In this study, both of the two groups consisted of 30% women and 70% men, which was described in the RESULTS section (please see page 12 / line 257). Gender differences in knee OA and HIV infection have always been a focus of previous research [1-3]. However, due to the small sample size, we did not investigate the
differences between HIV-infected men and women on cartilage degeneration and knee structural changes. Additionally, in the absence of more detailed data, the association between past or actual activities of the subjects and knee OA was not investigated in the present study.

Author action 1.4: The following sentences/citations were added:

- DISCUSSION section, page 17 / line 367-370: Studies have reported gender differences in knee OA and HIV infection [41-43]. However, due to the small sample size, we did not analyze the gender differences on cartilage degeneration and knee structural changes in HIV-infected subjects, which needs to be explored in future studies with larger sample sizes.

The following references were added:

- REFERENCES section, page 27-28 / line 589-598:


R 1.5: Minor points: 1. Line 158, 160, 218: Name of radiologists should be stated.

Author response 1.5: Thank you for pointing that out. Name of the radiologists were added in the revised manuscript.

Author action 1.5: The following words were added/deleted:

- METHODS section, page 8 / line 161,163: the numbers of participants with available images at each time point are summarized in Additional File 3) of HIV subjects and controls were assessed by one radiologist (X.X. Y.L. 4 years of experience) blinded to subject characteristics and under supervision of a board certified musculoskeletal radiologist (X.X.X. T.M.L. 24 years of experience).

- METHODS section, page 10 / line 201: Using sagittal 2D IW fat-suppressed TSE sequences, two radiologists (X.X.X. T.M.L. and X.X. Y.L.) assessed the size and highest signal intensity of IPFP signal abnormalities and the highest signal intensity of SPFP signal abnormalities (due to the small volume of the SPFP, the size of signal abnormalities was not assessed).
- METHODS section, page 10 / line 220: Each score of the gradings was graded twice by two radiologists (X.X.X. T.M.L. and X.X. Y.L.) on two separate occasions with a separation of 4 weeks in between those two readings.

R 1.6: Minor points:

2. Line 336: 'presented with a diffuse': 'with' can be deleted.

3. Line 342: 'Studies have reported' can be change to 'studies have been reported'.

4. Line 464: Reference (V LV, P M, M R, G M) should be formatted to the journal's style.

Author response 1.6: Thank you for pointing these mistakes out. We have corrected them in the revised manuscript.

Author action 1.6: The following words were added/deleted:

- RESULTS section, page 16 / line 342: In our study, two out of ten HIV-infected subjects presented with a diffuse and homogeneous increased signal intensity throughout the whole IPFP, which was different from the imaging features of OA-associated Hoffa-synovitis and was not observed in the 20 HIV negative subjects.

- RESULTS section, page 16 / line 348: However, in previous knee OA studies have been reported that SPFP signal changes may be similar to that observed in the IPFP which is characterized by inflammation, swelling, hypertrophy and fibrosis.

- REFERENCES section, page 22 / line 471-472:


Reviewer 2

R 2.1: The manuscript describes the relationship between osteoarthritis and HIV patients using a variety of scores and checking for knee abnormalities using MRI scans. The results of the study show that there is a relationship between patients using antiretroviral therapy and osteoarthritis indications. Though the results show a clear relationship, the following questions need to be answered prior to publication,

Author response 2.1: Thank you for the detailed review and the input to our manuscript. We hope to have satisfactorily addressed and answered to all your comments in our revision.
R 2.2: The data proves clinical indications of osteoarthritis. Do you have any synovial fluid and assessed the proteins in both control and antiretroviral therapy patients to understand what are the biological markers in fluid causing osteoarthritis in the latter patients?

Author response 2.2: Thank you for this question. Osteoarthritis-related biomarkers in synovial fluid and the association between these biomarkers and cartilage degeneration were widely studied [4]. Regrettably, since synovial fluid was not in the biospecimen collection list of the OAI (Osteoarthritis Initiative), the analysis of synovial fluid biomarkers was not possible. However, the OAI collected serum, plasma, and urine biospecimens for all participants, which made it possible to investigate the association between molecular biomarkers and cartilage matrix and knee joint morphology by using the OAI datasets. In our previous study, we have reported weak but significant associations between serum biochemical markers of OA (serum hyaluronic, serum MMP 3, serum cartilage oligomeric matrix protein) and MRI T2 biochemical degeneration of the cartilage matrix [5]. However, because of the small number of subjects and the limited correlations in the previous study we did not analyze these data in the current study. Clearly larger scale studies are required to investigate these biomarkers in subjects with HIV and their relation to OA.

Author action 2.2: The following sentences/citation were added in the limitations section of the discussion to address this issue:

- DISCUSSION section, page 18 / line 376-382: Moreover, in this study we did not investigate the relationship between serum and synovial fluid biomarkers and their relation to HIV and OA. Synovial fluid biospecimens were not available in the OAI database. We previously investigated the relationship between serum and imaging biomarkers in a larger cohort and only found weak relationships [44]. Because of the small number of subjects we did not analyze these relationships in this study. Larger scale studies are required to investigate these biomarkers in subjects with HIV and their relation to OA in the future.

The following reference was added:

- REFERENCES section, page 28 / line 599-602:


R 2.3: Similar to question 1, do the authors have any indications on the cellular activity of chondrocytes under the conditions described and can a short in vitro experiment be performed to observe the changes in chondrocytes activity in the presence of antiretroviral drugs?
Author response 2.3: Thank you for this question. The main functions of chondrocytes are to synthesize and maintain cartilage matrix [6]. We agree, that if the cellular activity of chondrocytes could be observed and evaluated this would have been of great value to further explore the pathophysiology of cartilage matrix changes in HIV-infected subjects on ART. However, unfortunately the OAI does not provide any such data. In this study, T2-based measurements were used to characterize the change of cartilage matrix composition especially the change of collagen and water content and may thus to some extent reveal the cellular activity of chondrocytes indirectly. However, since cartilage matrix degeneration is a multifactorial process, the value of T2 based measurements in reflecting chondrocyte activity is limited.

References


