

The effect of exercise training on disease progression, fitness, quality of life, and mental health in people living with HIV on antiretroviral therapy: a systematic review

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The Effect of Exercise Training on Disease Progression, Fitness, Quality of Life, and Mental Health in People Living with HIV on ART: A Systematic Review
Journal of Clinical and Translational Research

Dear Dr. Lewis,

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a point-by-point response to every comment. An exemplary rebuttal letter can be found on at <http://www.jctres.com/en/author-guidelines/> under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Nov 16, 2015.

To submit a revision, go to <http://jctres.edmgr.com/> and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely

Rowan van Golen
Associate Editor
Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This the first systematic review, to my knowledge, of exercise interventions in people living with HIV. As such, it is potentially very useful for care providers and others hoping to understand the impact of exercise therapy in this setting, as well as the gaps in the knowledge base. Some revisions would be useful to make it more reader friendly and easier to digest for clinicians not as well versed in exercise interventions. Specific comments below:

Introduction:

1) The themes in the introduction focus primarily on various adverse impacts of antiretroviral therapy. However, many of these side effects, such as lipodystrophy, are much less common with newer regimens. Our more recent understanding of the increased cardiovascular risk conveyed by HIV infection itself, as demonstrated in many studies, provides another compelling reason for people living with HIV to engage in physical exercise programs.

Methods:

2) Is there a reason the authors chose to include only studies where >60% of patients were on ART? I can think of several but a presentation of the logic would be useful.
3) If there were disagreements between the two independent reviewers, how were they resolved?

Results

4) I would not recommend combining "Results and Discussion" as a single category, these are usually separate.
5) A flowchart of the studies screened in and then excluded for various reasons would be useful to allow readers to understand how the investigators got from 340 articles to 18 studies.
6) It is difficult to bounce back and forth between the tables and the results section, because they seem to follow different logic patterns. The results text seems to be outcomes based, discussing disease progression as an outcome and summarizing study findings there, then moving on to other exercise-related outcomes. The tables, however, are divided by type of intervention (aerobic v resistance v CARET). This is a bit confusing and either more signposts are needed within the text to guide the reader to the appropriate table, or a different alignment of tables should be considered.
7) Overall the tables are very text heavy and hard to read or interpret. More detail than is necessary is presented on the individual interventions - this information could go into a summary appendix. The incorporation of a figure or some other visual representation of the studies reviewed (perhaps color coding for the positive vs no difference vs negative outcomes rather than the descriptions, which can be found within the text) would be helpful.
8) The findings of the Tiozzo study are confusing as CD4 cell count should not be decreasing at all in a population where 100% are on treatment. The authors should discuss this odd

finding either in the results or in the discussion below.

Summary and practical applications

- 9) The authors state "no evidence was found to support the notion that structured exercise training worsens disease progression." Is there any reason that anyone would have that notion? It seems hard to imagine a physiologic pathway in which exercise would worsen HIV progression.
- 10) Could the authors speculate as to why exercise would improve the CD4+ T cell count? Also, knowing the magnitude of the CD4 count change would be useful as it may or may not be clinically significant.
- 11) How do these findings, particularly with regard to improvements in physical and psychological benefits compare to those seen with similar interventions in HIV-uninfected populations? I am left wondering whether these interventions have more of an impact for people living with HIV, or if they are just the same as in the general population.
- 12) The summary seems to imply that the Fillipas study showed an improvement in ART adherence, if so, I would put that into the table as this would be a significant clinical outcome. If other studies also showed ART adherence improvements, the authors may want to consider including those findings in the "Disease progression" section and expanding that to HIV-related outcomes (CD4, VL, adherence etc...)
- 13) It is unclear what evidence is being used to guide the "suggested weekly program" mentioned in this section- are these specifically based on findings from the studies reviewed? If so, please cite them or call them out.
- 14) The authors state: "However, caution must be taken with the "dose" of exercise prescribed for the immune deficient HIV patient. Even a single session of excessive volume and intensity may result in an "open window" period in which an increased vulnerability to viruses and bacteria infection occurs." References should be included to back this statement up and put it into context - this is unlikely to be the case in the majority of patients on ART, similar to the ones being studied here, who are not at high risk for infections.
- 15) The statement "Given the continued reliance on ART by the medical community" is subject to various interpretations and should perhaps be clarified or revised. The medical community is not actually relying on ART as opposed to other options. ART is the only effective treatment for HIV, which is needed by people living with HIV to prevent death from AIDS. The phrasing makes it sound like it would be best if the medical community did not use ART.
- 16) More guidance could be provided by the authors, who are clearly quite knowledgeable re. exercise interventions, as to which interventions would be most worth of further study, based on their review.
- 17) It would be helpful for clinicians to have guidance on the appropriate timing of these interventions- are there any data to indicate they should begin before ART start, or are these interventions only to be deployed only once a patient is on ART and has a suppressed viral load?

Reviewer #2: General comments

The survey has a great clinical relevance both for patients with HIV and for the physical education teachers, as the importance of exercise training in combating the adverse effects of antiretroviral therapy. For a better understanding of the survey, it is necessary that even in the introduction a few points are described.

Ideally, recent data describing the amount of people living with HIV. Before describing the effects of ART should explain what the disease (especially destruction of CD4 + lymphocytes), description of the acute phase, asymptomatic, early symptomatic, AIDS and clinical symptoms. Then continuing the description of antiretroviral therapy as target audience, general care, adverse effects. This understanding is necessary to design therapy.

Comments off

In Topic 3.1 author described the benefits of physical activity, but does not describe whether these effects were seen only in people who used Antiretroviral therapy;

In Topic 3.2 is necessary that the author describes its conclusion after all discussion;

Limitations of the study should be described in the working method;

The standards of journals should be carefully checked and revised, attention for references;

Attention to writing and agreement, it is necessary to change some unusual terms for writing scientific articles.

Author's Rebuttal:

November 16th, 2015

Michal Heger

Journal of Clinical and Translational Research
Amsterdam, Netherlands

Dear Editor:

We are submitting the revised version of the manuscript "**The Effect of Exercise 24 Training on Disease Progression, Fitness, Quality of Life, and Mental Health in People Living with HIV on ART: A Systematic Review**" for publication in the Journal of Clinical and Translational Research as a systematic review paper.

We would like to thank you for this review process. We did our best for trying to reach 29 the level of quality necessary to be accepted in this respectable Journal. Below you will find the responses to the comments pointed by the referees. We have made the necessary changes in the manuscript so all the reviewers' suggestions were addressed.

This review has not been previously published in whole or in part, is not presently under consideration by another journal, and will not be submitted to another journal before a final editorial decision from the Journal of Clinical and Translational Research is rendered. All authors have made sufficient contributions and have approved the submitted manuscript. We have no relationship with industry or financial or other conflicts of interest to disclose.

Please find below reviewers' comments followed by our responses.

Sincerely,



John E. Lewis, Ph.D.

RESPONSES TO REVIEWERS

Reviewer #1:

This the first systematic review, to my knowledge, of exercise interventions in people living with HIV. As such, it is potentially very useful for care providers and others hoping to understand the impact of exercise therapy in this setting, as well as the gaps in the knowledge base. Some revisions would be useful to make it more reader friendly and easier to digest for clinicians not as well versed in exercise interventions. Specific comments

below:

Introduction:

1) The themes in the introduction focus primarily on various adverse impacts of antiretroviral therapy. However, many of these side effects, such as lipodystrophy, are much less common with newer regimens. Our more recent understanding of the increased cardiovascular risk conveyed by HIV infection itself, as demonstrated in many studies, provides another compelling reason for people living with HIV to engage in physical exercise programs.

à Thank you for this comment. We agree with the reviewer that many of these side effects are much less common with new regimens. We understand that the risk of cardiovascular disease increases with age, regardless of HIV status, and thanks to antiretroviral therapy, HIV patients are living longer and this, together with the side effects of ART (that still exists), predispose them to cardiovascular risks that can affect quality of life and mental health. This information was included on introduction.

Our systematic review included only studies in which most of the participants were taking antiretroviral medications to focus on the impact exercise can have specifically on the side effects of ART. As stated in our introduction: Today's standard of care has shifted from treating HIV as an acute, fatal diagnosis to focusing more on the management of long-term adverse effects related to *both* HIV infection and pharmacological treatment of the disease. In addition to pharmacological treatments, effective, safe, and feasible interventions are needed to manage and prevent the anatomical/physical, metabolic, and psychological abnormalities and problems associated with HIV and ART Furthermore, this systematic

review has a second part in which we look at the effect of exercise on metabolic syndrome secondary to ART. The idea of the review is to inform clinicians about the benefits of exercise on symptom management that could potentially help to maintain compliance.

The systematic review included Methods:

2) Is there a reason the authors chose to include only studies where >60% of patients were on ART? I can think of several but a presentation of the logic would be useful.

Our original idea was to include studies that ONLY included patients on ART; however, that inclusion reduced the number of studies to be included to about half, missing out on valuable information. We only wanted to focus on the effect of exercise on side effects secondary to ART as a benefit for symptom management. Thus, the reviewers agreed to include only studies where >60% of patients were on ART.

2) If there were disagreements between the two independent reviewers, how were they resolved?

A third reviewer was approached to resolve disagreements. This is now stated in methods section.

Results

3) I would not recommend combining "Results and Discussion" as a single category, these are usually separate.

- addressed

4) A flowchart of the studies screened in and then excluded for various reasons would be useful to allow readers to understand how the investigators got from 340 articles to 18 studies.

- included

6) It is difficult to bounce back and forth between the tables and the results section, because they seem to follow different logic patterns. The results text seems to be outcomes based, discussing disease progression as an outcome and summarizing study findings there, then moving on to other exercise-related outcomes. The tables, however, are divided by type of intervention (aerobic v resistance v CARET). This is a bit confusing and either more signposts are needed within the text to guide the reader to the appropriate table, or a different alignment of tables should be considered.

- the tables were rearranged

7) Overall the tables are very text heavy and hard to read or interpret. More detail than is necessary is presented on the individual interventions - this information could go into a summary appendix. The incorporation of a figure or some other visual representation of the

studies reviewed (perhaps color coding for 22 the positive vs no difference vs negative outcomes rather than the descriptions, which can be found within the text) would be helpful.

The text was reduced and the positive outcomes are italicized.

8) The findings of the Tiozzo study are confusing as CD4 cell count should not be decreasing at all in a population where 100% are on treatment. The authors should discuss this odd finding either in the results or in the discussion below.

à **Discussed**

Summary and practical applications

9) The authors state "no evidence was found to support the notion that structured exercise training worsens disease progression." Is there any reason that anyone would have that notion? It seems hard to imagine a physiologic pathway in which exercise would worsen HIV progression.

à **Reworded**

10) Could the authors speculate as to why exercise would improve the CD4+ T cell count? Also, knowing the magnitude of the CD4 count change would be useful as it may or may not be clinically significant.

à **Discussed**

11) How do these findings, particularly with regard to improvements in physical and psychological benefits compare to those seen with similar interventions in HIV-uninfected populations? I am left wondering whether these interventions have more of an impact for people living with HIV, or if they are just the same as in the general population.

-- **discussed**

12) The summary seems to imply that the Fillipas study showed an improvement in ART adherence, if so, I would put that into the table as this would be a significant clinical outcome. If other studies also showed ART adherence improvements, the authors may want to consider including those findings in the "Disease progression" section and expanding that to HIV-related outcomes (CD4, VL, adherence etc...)

– **The summary does not imply Fillipas or any study reviewed found an improvement in adherence since adherence was not assessed in any of the studies during the course of the intervention.**

13) It is unclear what evidence is being used to guide the "suggested weekly program" mentioned in this section- are these specifically based on findings from the studies reviewed? If so, please cite them or call them out.

– ACSM guidelines. References were added

14) The authors state: "However, caution must be taken with the "dose" of exercise prescribed for the immune deficient HIV patient. Even a single session of excessive volume and intensity may result in an "open window" period in which an increased vulnerability to viruses and bacteria infection occurs." References should be included to back this statement up and put it into context - this is unlikely to be the case in the majority of patients on ART, similar to the ones being studied here, who are not at high risk for infections.

- addressed

15) The statement "Given the continued reliance on ART by the medical community" is subject to various interpretations and should perhaps be clarified or revised. The medical community is not actually relying on ART as opposed to other options. ART is the only effective treatment for HIV, which is needed by people living with HIV to prevent death from AIDS. The phrasing makes it sound like it would be best of the medical community did not use ART.

– reworded.

16) More guidance could be provided by the authors, who are clearly quite knowledgeable re. exercise interventions, as to which interventions would be most worth of further study, based on their review.

- Noted

17) It would be helpful for clinicians to have guidance on the appropriate timing of these interventions- are there any data to indicate they should begin before ART start, or are these interventions only to be deployed only once a patients is on ART and has a suppressed viral load?

– there are no studies that suggest the timing of exercise interventions in this population. This is very hard to assess since a clinical trial in which a person with HIV is denied ART for x amount of time to assess if exercise interventions would be better before starting ART regimen would be considered unethical since the participant is being denied the standard of care. In

Reviewer #2:

General comments

The survey has a great clinical relevance both for patients with HIV and for the physical education teachers, as the importance of exercise training in combating the adverse effects of antiretroviral therapy. For a better

understanding of the survey, it is necessary that even in the introduction a few points are described. Ideally, recent data describing the amount of people living with HIV. Before describing the effects of ART should explain what the disease (especially destruction of CD4 + lymphocytes), description of the acute phase, asymptomatic, early symptomatic, AIDS and clinical symptoms. Then continuing the description of antiretroviral therapy as target audience, general care, adverse effects. This understanding is necessary to design therapy.

– We believe that the discussion of HIV and how it affects the body has been extensively described in the literature; thus, we did not feel the need of discussing HIV symptomology as it is not the focus of the review.

The target audience of this review is the clinician who treats HIV patients and is well aware of the symptoms of the disease and its therapy per se. Thus the focus of this review is to give insights to clinicians on the benefit of exercise on symptom management related to ART side effects in order to improve compliance to regimen.

Comments off

In Topic 3.1 author described the benefits of physical activity, but does not describe whether these effects were seen only in people who used Antiretroviral therapy

– This systematic review is on the Effect of Exercise Training on Disease Progression, Fitness, Quality of Life, and Mental Health in People Living with HIV on ART, thus these effects discussed were only in those on ART.

In Topic 3.2 is necessary that the author describes its conclusion after all discussion; - the paper has a conclusion after the discussion. Limitations of the study should be described in the working method- limitations of the review are discussed in the discussion. Limitations of the studies included in the review are discussed in the results. The standards of journals should be carefully checked and revised, attention for references: References were revised. Attention to writing and agreement, it is necessary to change some unusual terms for writing scientific articles. - noted

2nd Editorial Decision

Ref.: Ms. No. JCTRes-D-15-00008R1

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Journal of Clinical and Translational Research

Dear Dr. Lewis,

I am pleased to inform you that your revised manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

Thank you for submitting your work to JCTR.

Kindest regards,

Journal of Clinical and Translational Research
Peer review process file 201503.001



Rowan van Golen
Associate Editor
Journal of Clinical and Translational Research