PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Retention in care prior to antiretroviral treatment eligibility in sub-Saharan Africa: Systematic review of the literature
AUTHORS	Plazy, Melanie; Orne-Gliemann, Joanna; Dabis, François; Dray-Spira, Rosemary

VERSION 1 - REVIEW

REVIEWER	Tom Decroo Médecins Sans Frontières - OCB
REVIEW RETURNED	27-Nov-2014

GENERAL COMMENTS	Minor revision: 1) I had a few difficulties to understand well the research question. In the introduction you describe the three periods in the pre ART care continuum : 1) from HIV diagnosis to linkage to HIV care; 2) from linkage to HIV care to ART eligibility; 3) from ART eligibility to ART initiation. I recommend that you explain the reader that you will study retention for the second period, straight after the description of the 3 periods. Also I recommend that you describe with the same wording "retention in care prior to ART eligibility" across the paper, to facilitate the introduction of this indicator. Now you use different descriptions: "retention in care prior to ART eligibility" in the title "retention from linkage to HIV care to ART eligibility" "retention in HIV care before ART eligibility" "retention in pré-ART care among adults not yet eligible for ART" "retention in pré-ART care for people not-yet eligible to ART" 2) in Figure 2 "linkage to HIV or ART care only (n=16)" is not that easy to understand, please rephrase (for example: doesn't present data on retention in care prior to ART eligibility) 3) limitations: the limitation of the method is highlighted. Please also mention the diversity of the study designs across the studies retrieved. This diversity limits the interpretation of the proportion retained across the different studies.

REVIEWER	Alison Wringe LSHTM, London, UK
REVIEW RETURNED	08-Jan-2015

GENERAL COMMENTS	This is a well-conducted systematic review that has the potential to make a useful contribution to the literature on retention rates and factors associated with retention among individuals enrolled in pre-ART care and not yet eligible for treatment. Although three previous systematic reviews have been published on this topic, including a recent meta-analysis, this review includes factors associated with retention as well as retention rates, thus giving more information on one specific stage in the cascade. The manuscript contains several grammatical errors and needs to be edited by a native English speaker. SPECIFIC COMMENTS Article summary - I would think that a more important limitation would be some of the inevitable biases (including publication bias) or the difficulties in interpreting the large range of retention rates due to the different definitions and criteria used in the included studies. Abstract - The overall objective could be more precise. "..summarising the scientific knowledge.." could be understood as covering a broader range of studies including qualitative research, which this paper does not include. The authors are actually summarising rates and risk factors associated with retention among patients in pre-ART care prior to treatment eligibility. This should be corrected. Idem for the "article summary". Results: Also report the median retention rate as well as the range. Conclusion: Not entirely clear what is meant by "...sociodemographic, epidemiologic, programmatic and logistic determinants"? Could be better expressed as " ..sociodemographic, clinical and programmatic.." factors associated with retention". Although it seems that there are already data available on the sociodemographic factors –eg/ age, sex so its not clear why the conclusion is that more are needed? ********** Introduction - Overall, the introduction is concise and clear. - 2nd paragraph – remove the word "the" before "African countries". - Last paragraph – when detailing the difference between this paper and the previously published systematic reviews, I would focus on the fact that two of the three did not provide information on risk factors for retention (or loss to follow up) between enrolment in a HIV care programme and ART initiation (I believe). - The use of the word "barriers" again implies that you have reviewed the qualitative literature on retention in ART care, but this doesn't seem to be the case. It would be clearer to use the term "risk factors" if the paper is restricted to reviewing only quantitative analyses. Methods The methods used are clear. Could the authors justify the decision not to undertake a meta-analysis?

	Why was the search strategy not expanded beyond “retention” to include “attrition”, “loss to follow up” etc? Results - In relation to risk factors associated with retention, it would be useful to know which factors were assessed in each study, as well as which were actually statistically significantly associated with the outcome. In other words, it’s interesting to understand which factors were not investigated versus were not associated with the outcome. An additional column could be added to table 2 to address this. - It would have been useful if the authors undertook some assessment of the quality of the included studies (and possibly reported the results in a table?). - It would be useful to report the results in relation to the time period of the study as it may be expected that the retention rate would change as ART initiation criteria have evolved. Discussion - The findings in relation to low CD4 count being associated with retention seem contradictory to those found in a recent systematic review and meta-analysis on the same topic conducted by Mugglin et al. This should be discussed by the authors. - How do the other findings from this review relate to those reported in the 3 previously published systematic reviews on this topic? Eg/ in relation to the median retention rate reported. - Comment on the likely generalisability of their findings given the potential role of publication bias – eg/ if it is the better resourced programmes with better retention rates that analyse and publish their data. Limitations – mention the reasons for not conducting a meta-analysis? ********** FIGURES AND TABLES Table 1 should include the design of each of the included studies because study design is likely to influence retention rates. For example, retention rates may be higher if patients were enrolled in a randomised control trial, particularly if they received any intervention to improve attendance or retention. Conversely, retention rates may be relatively lower in cohort studies. Similarly it would be interesting to provide more information about the programme context of each included study (where mentioned in the publications), as there several programmatic factors that would influence retention – eg/ was the programme supported by an NGO such as MSF who often bring substantial additional resources to the clinics which could influence retention, or were they government-run and government-funded without any external support? This information could probably be incorporated into an extra column in table 1. Figure 1 is a useful addition to the paper. However, although it indicates why published papers were excluded from the final review, it does not specify why 3 conference abstracts were excluded (5 originally identified, 2 included in the review). It should be modified

	to include this information. Furthermore it states that “All” CROI, IAS and ICASA abstracts were screened which is somewhat of a greater claim than is made in the methods section of the paper which reports that the screening was restricted to a subset of conference tracks. This should be corrected in figure 1. Typos/poor english in figure 1: “Full-text” should read “full-texts”. “472 paper” should read “472 papers”. “HIV no major topic” should read “Study population non-HIV patients”(?), “not original studies, modelisation or methodological papers” should read “modelling or methodological papers not reporting previously unpublished patient data”. Out of the 8 papers excluded after the full text was read, distinguish between the number that were excluded due to “definition of retention unclear” and “study not specifically on retention in HIV care for non-ART eligible patients” - In fact, I would have thought that this latter criteria should not exclude studies unless it was also impossible to separately consider a sub-population of non-ART eligible patients in which retention could be described. Figure 3 is a nice way of reporting these findings, and the results are usefully stratified by the period during which retention was measured in each study. Would it also be possible to indicate along the x axis the average duration in each study (eg/ between the first and second CD4 measurements or from enrolment to study end) as that would presumably be directly associated with retention rates?

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Tom Decroo
Institution and Country Médecins Sans Frontières – OCB
Please state any competing interests or state ‘None declared’: None declared

Dear Editor
Dear authors

First of all, congratulations with the nice piece of work, relevant, well written, and well structured.
--> Thank you very much for your interest.

Minor revision:

1) I had a few difficulties to understand well the research question.
In the introduction you describe the three periods in the pre ART care continuum : 1) from HIV diagnosis to linkage to HIV care; 2) from linkage to HIV care to ART eligibility; 3) from ART eligibility to ART initiation.
I recommend that you explain the reader that you will study retention for the second period, straight after the description of the 3 periods.
--> Thank you for this comment. As the first and the second paragraphs of this introduction cover all the steps of the HIV cascade (that we have now defined in the first paragraph), we have added a sentence in the last paragraph of the introduction clarifying the research question (l.47-48): “In this paper, we have thus focused on the second step of the HIV cascade”.

Also I recommend that you describe with the same wording "retention in care prior to ART eligibility" across the paper, to facilitate the introduction of this indicator.

Now you use different descriptions:
"retention in care prior to ART eligibility" in the title
"retention from linkage to HIV care to ART eligibility"
"retention in HIV care before ART eligibility"
"retention in pré-ART care among adults not yet eligible for ART"
"retention in pré-ART care for people not-yet eligible to ART"
--> Thank you for your comment. We have done all the changes according to your suggestion, systematically using the expression "retention in care prior to ART eligibility".

2) in Figure 2 "linkage to HIV or ART care only (n=16)" is not that easy to understand, please rephrase (for example: doesn't present data on retention in care prior to ART eligibility)
--> Thank you. We have rephrased as follows: "Data on entry into HIV or ART care without data on retention in care".

3) limitations: the limitation of the method is highlighted. Please also mention the diversity of the study designs across the studies retrieved. This diversity limits the interpretation of the proportion retained across the different studies.
--> Thank you for this very important comment. We did not find many differences regarding the study designs; to highlight this, we have added the following sentence at the end of the study characteristics section: "All these studies used data collected in cohorts from either clinics with NGO supports or public HIV programmes". However, we agree that the interpretation of retention rates is very difficult but it primarily the case because of the diversity of retention's definition criteria; we have thus added this sentence in the discussion part: "Another limitation was that definition of retention in HIV care prior to ART eligibility substantially varied across the studies reviewed, making it challenging to compile and compare the retention rates reported in the various studies."

Reviewer Name Alison Wringe
Institution and Country LSHTM, London, UK
Please state any competing interests or state 'None declared': None declared

GENERAL COMMENTS

This is a well-conducted systematic review that has the potential to make a useful contribution to the literature on retention rates and factors associated with retention among individuals enrolled in pre-ART care and not yet eligible for treatment. Although three previous systematic reviews have been published on this topic, including a recent meta-analysis, this review includes factors associated with retention as well as retention rates, thus giving more information on one specific stage in the cascade. The manuscript contains several grammatical errors and needs to be edited by a native English speaker.
--> Thank you very much for your interest in our work. This manuscript has been re-read by a native English speaker and then edited for correcting the grammatical errors.

SPECIFIC COMMENTS

Article summary - I would think that a more important limitation would be some of the inevitable biases (including publication bias) or the difficulties in interpreting the large range of retention rates due to the different definitions and criteria used in the included studies.
--> Thank you for this comment. We have updated the article summary including these two bullets:
• "Few studies were included according to our selection criteria. Although we aimed to conduct an exhaustive review of the published literature, we cannot exclude that we missed some that did not correspond to our search equation.

• Also considering that the definitions of retention in HIV care prior to ART eligibility varied substantially, we decided not to conduct a meta-analysis.

Abstract - The overall objective could be more precise. "..summarising the scientific knowledge.." could be understood as covering a broader range of studies including qualitative research, which this paper does not include. The authors are actually summarising rates and risk factors associated with retention among patients in pre-ART care prior to treatment eligibility. This should be corrected. Idem for the "article summary".
--> Thank you for your comment. We have edited the objective, in both the abstract and the article summary.

Results: Also report the median retention rate as well as the range.
--> Since the criteria used for the definition of retention substantially differed across the various studies, we considered that it was inappropriate to compile the retention rates reported in the various studies in order to produce a median retention rate (see above, comment 3 of reviewer 1).

Conclusion: Not entirely clear what is meant by "...sociodemographic, epidemiologic, programmatic and logistic determinants"? Could be better expressed as " ..sociodemographic, clinical and programmatic.." factors associated with retention". Although it seems that there are already data available on the sociodemographic factors –eg/ age, sex so its not clear why the conclusion is that more are needed?
--> We agree that the association between retention in care prior to ART eligibility and age and sex are now well known. However, in "socio-demographic and economic factors" we additionally included employment, household composition, education level etc..
We have updated the sentence as follows: "Retention in pre-ART care in sub-Saharan Africa has been insufficiently described so far leaving major research gaps, especially regarding long-term retention rates and socio-demographic, economic, clinical and programmatic determinants"

****
Introduction

- Overall, the introduction is concise and clear.

- 2nd paragraph – remove the word "the" before "African countries".
--> Thank you. We have made the change.

- Last paragraph – when detailing the difference between this paper and the previously published systematic reviews, I would focus on the fact that two of the three did not provide information on risk factors for retention (or loss to follow up) between enrolment in a HIV care programme and ART initiation (I believe).
--> We have edited the sentence: "Three literature reviews have been conducted on HIV care prior to ART initiation in the recent years [2-4], but they mostly focused on linkage to care and provided very little information on retention in HIV care prior to ART eligibility as well as on risk factors for retention."

- The use of the word "barriers" again implies that you have reviewed the qualitative literature on retention in ART care, but this doesn't seem to be the case. It would be clearer to use the term "risk factors" if the paper is restricted to reviewing only quantitative analyses.
--> Ok. We have made the change.

Methods

The methods used are clear.

Could the authors justify the decision not to undertake a meta-analysis?
--> A meta-analysis is useful when there are a sufficient number of studies included, and when the definitions of the studied outcome are not too different. This was not the case at the end of our literature review; this is why we have decided to not conduct a formal meta-analysis. We have completed the discussion on limitations by explaining our choice: “A limitation of this review is that we only found a few number of published studies exploring retention in HIV care prior to ART eligibility. Although we aimed to conduct an exhaustive review of the published literature, we cannot exclude that we missed some that did not correspond to our search equation; however, we have searched three different and large databases and enlarged our search to HIV conferences abstracts. Another limitation was that the definition of the retention in HIV care prior to ART eligibility substantially varied across the studies reviewed, making it challenging to compile and compare the retention rates reported in the various studies. Considering the small number of studies and the non-standardized definitions of retention in HIV care prior to ART eligibility, we could not conduct a meta-analysis.”

Why was the search strategy not expanded beyond “retention” to include “attrition”, “loss to follow up” etc?
--> We decided not to include “follow-up” as it is a too large term that cover many questions regarding quality of the health system services, whereas the term “retention” is more focalized on the concept of “visit diligences”. It is right that we could have included the word “attrition”: after doing this using the same time period of the previous search, about 60 additional papers have been identified through the search equation; however, none of them verified the inclusion criteria.

Results
- In relation to risk factors associated with retention, it would be useful to know which factors were assessed in each study, as well as which were actually statistically significantly associated with the outcome. In other words, it’s interesting to understand which factors were not investigated versus were not associated with the outcome. An additional column could be added to table 2 to address this.
--> Thank you for this comment. We totally agree and this had been done in the submitted manuscript. We recognize however that the titles of the columns were confusing. We have thus modified the name of the last column replacing “factors not associated with LTFU in pre-ART care” by “factors investigated not associated with retention in pre-ART care”.

- It would have been useful if the authors undertook some assessment of the quality of the included studies (and possibly reported the results in a table?).
--> Considering the limited number of identified then selected studies, we did not apply any specific quality criteria to their assessment beyond the strict reference selection criteria.

- It would be useful to report the results in relation to the time period of the study as it may be expected that the retention rate would change as ART initiation criteria have evolved.
--> Thank you for this comment. We agree about the importance of this point, however, many of the studies reported have been conducted over a relatively long time period (one from 2004 to 2011, another one from 2005 to 2012, two from 2004/2005 to 2009, one from 2008 to 2011 and one from 2009 to 2012) and it is thus difficult to interpret the temporal evolution of the retention rates.

Discussion

- The findings in relation to low CD4 count being associated with retention seem contradictory to those found in a recent systematic review and meta-analysis on the same topic conducted by Mugglin et al. This should be discussed by the authors.
--> In their paper, Mugglin et al. presented predictors of: i/ “loss to program between determination of

ART eligibility and start of ART" (Table S1 in their appendix) and ii/ "having CD4 cell count determined and starting ART" (Table S2). Whereas we reviewed factors associated with retention in care prior to ART eligibility. We can thus assume that the association between retention in HIV care and CD4 count vary according to whether individuals are eligible or not for ART.

- How do the other findings from this review relate to those reported in the 3 previously published systematic reviews on this topic? Eg/ in relation to the median retention rate reported.
--> We have found that retention rates varied between 23% and 88%, that is consistent with previous published systematic reviews on this topic.

- Comment on the likely generalisability of their findings given the potential role of publication bias – eg/ if it is the better resourced programmes with better retention rates that analyse and publish their data.
--> We have added a sentence in the limits part: "Finally, the generalisability of these findings need to be done with caution; indeed, it is possible that only HIV programmes with better resources have analysed and published their data".

Limitations – mention the reasons for not conducting a meta-analysis?
--> See above our response to reviewer's first comment on the methods

****
FIGURES AND TABLES

Table 1 should include the design of each of the included studies because study design is likely to influence retention rates. For example, retention rates may be higher if patients were enrolled in a randomised control trial, particularly if they received any intervention to improve attendance or retention. Conversely, retention rates may be relatively lower in cohort studies. Similarly it would be interesting to provide more information about the programme context of each included study (where mentioned in the publications), as there several programmatic factors that would influence retention – eg/ was the programme supported by an NGO such as MSF who often bring substantial additional resources to the clinics which could influence retention, or were they government-run and government-funded without any external support? This information could probably be incorporated into an extra column in table 1.
--> Thank you for this comment. We have completed Table 1 as suggested and added a sentence in the results part: "All these studies used data collected in cohorts from either clinics with NGO supports or public HIV programmes".

Figure 1 is a useful addition to the paper. However, although it indicates why published papers were excluded from the final review, it does not specify why 3 conference abstracts were excluded (5 originally identified, 2 included in the review). It should be modified to include this information. Furthermore it states that "All" CROI, IAS and ICASA abstracts were screened which is somewhat of a greater claim than is made in the methods section of the paper which reports that the screening was restricted to a subset of conference tracks. This should be corrected in figure 1.
--> Thank you for this comment. We have updated Figure 1 according to reviewer's suggestion and added the following sentence at the beginning of the Results part: "In addition, we also identified five studies from the conference proceedings search; three of them were excluded because duplicated with included papers".

Typos/poor english in figure 1: "Full-text" should read "full-texts". "472 paper" should read "472 papers". "HIV no major topic" should read "Study population non-HIV patients"(?), "not original studies, modelisation or methodological papers" should read "modelling or methodological papers not

reporting previously unpublished patient data".
--> Thank you. The corrections have been done in Figure 1.

Out of the 8 papers excluded after the full text was read, distinguish between the number that were excluded due to "definition of retention unclear" and "study not specifically on retention in HIV care for non-ART eligible patients" - In fact, I would have thought that this latter criteria should not exclude studies unless it was also impossible to separately consider a sub-population of non-ART eligible patients in which retention could be described.
--> The eight studies were indeed studies investigating the whole pre-ART care cascade, but for which there was no indication of retention specifically among individuals who were not eligible for ART, or with no distinction between ART-eligible and not-yet ART eligible individuals. We have thus removed the mention "definition of retention unclear".

Figure 3 is a nice way of reporting these findings, and the results are usefully stratified by the period during which retention was measured in each study. Would it also be possible to indicate along the x axis the average duration in each study (eg/ between the first and second CD4 measurements or from enrolment to study end) as that would presumably be directly associated with retention rates?
--> Thank you. We agree that follow-up duration is an important point to consider. This is the reason why it was indicated in the 4th column of Table 2. We did not include it in Figure 2 in order to avoid redundancy.

VERSION 2 – REVIEW

REVIEWER	Tom Decroo MSF OCB
REVIEW RETURNED	23-Mar-2015

GENERAL COMMENTS	major revision: During a first review I recommended to use consistently proposed definitions across the paper. The three steps proposed for pré-ART retention are interesting. However they are not consistently applied in the intro, methods, results and discussion. I see 2 options Or aim at reviewing overall pré ART retention, and discuss the proposed classification Or apply consistently the definitions proposed

REVIEWER	Alison Wringe LSHTM, UK
REVIEW RETURNED	20-Mar-2015

GENERAL COMMENTS	I think that the last round of edits have strengthened the paper - I look forward to seeing it published! Congratulations on an interesting paper.

VERSION 2 – AUTHOR RESPONSE

Reviewer Name Alison Wringe
I think that the last round of edits have strengthened the paper - I look forward to seeing it published!

Congratulations on an interesting paper.
Thank you very much for this comment.

Reviewer Name Tom Decroo
Dear Authors
major revision:
During a first review I recommended to use consistently proposed definitions across the paper. The three steps proposed for pré-ART retention are interesting. However they are not consistently applied in the intro, methods, results and discussion.
I see 2 options
Or aim at reviewing overall pré ART retention, and discuss the proposed classification
Or apply consistently the definitions proposed
Kind regards
Thank you for this comment. In order to be as consistent as possible, we have completed the previous changes that considered your previous comment, and replaced “retention in pre-ART care” by “retention in HIV care prior to ART eligibility”, at each time we specifically considered the period before ART eligibility.