Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in sub-Saharan African countries: a systematic review protocol

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Review question/objective
The objective of this review is to determine the effect of point of care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation.

Background
The Human Immuno-deficiency Virus (HIV) pandemic continues to affect sub-Saharan Africa more than any other region in the world. One major barrier to tackling this pandemic is diagnosing the 90% of individuals in these countries who have not been tested for HIV infection. Rapid point-of-care (or near-patient) testing is increasingly being used in developing world settings to improve diagnosis of HIV infections.\textsuperscript{1,2,3,4,5}

Effective care and treatment for HIV and Acquired Immuno-Deficiency Syndrome (AIDS) requires the integration of all stages of disease management, which includes: (1) HIV testing; (2) referral of those who test HIV-positive to a clinic for assessment; (3) assessment of those patients with CD4 test to determine eligibility for antiretroviral therapy (ART) or pre-ART care; (4) patient enrolment and retention in pre-ART care if not immediately eligible for ART; (5) patient initiation of ART as soon as eligible; and (6) maintenance of long-term ART adherence.\textsuperscript{6}

Antiretroviral therapy is the recommended treatment for HIV infection. ART involves taking a combination of antiretroviral (ARV) HIV drugs (a regimen) daily. A regimen contains three or more ARV drugs from at least two different drug classes. ARV drugs prevent HIV from multiplying. ARV drugs keep people with HIV healthy, but they cannot cure HIV infection or prevent HIV transmission. In most
developing countries, CD4 count is used as a criterion to determine eligibility for ART. In addition, it has been demonstrated that the use of the CD4 cell count criterion is superior to clinical staging in identifying clients eligible for ART. CD4 count is a laboratory test that measures the number of CD4 T lymphocytes (CD4 cells) in a sample of blood. In people with HIV, the CD4 count is the most important laboratory indicator of immune function and the strongest predictor of HIV progression. The World Health Organization (WHO) updated guideline on antiretroviral therapy for adults and adolescents, including pregnant women, now recommends that ART be initiated when CD4 cell counts reach or drop below 350 cells/mm3, regardless of whether or not patients have clinical symptoms. The CD4 count is also used to monitor response to ART.

Despite advances in the expansion of access to ART for HIV-positive patients in resource-limited settings, two-thirds of patients in need of treatment currently do not receive it.

Although worldwide funding for treatment in these settings has increased and the cost of delivery of ART has decreased, the financial sustainability of current coverage and the expansion of treatment to new patients are still concerns.

Accordingly, efforts to improve the efficiency and sustainability of ART are increasing. Low retention of patients undermines efforts to scale up ART. The existing limited evidence suggests that many patients fail to enroll in HIV care after referral from testing.

One solution proposed for the failure of many HIV Counseling and Testing (HCT) of clients to return for their CD4 test results is to integrate rapid, point of care testing (POCT) technologies, including point of care CD4 counting into HCT service sites. A point of care CD4 test is a CD4 test performed in the immediate vicinity of a patient to provide a rapid same-day result outside the conventional laboratory environment, in order to facilitate immediate clinical decision-making, including initiation and adjustment of anti-retroviral therapy. These technologies allow blood samples to be processed immediately, at the location where the HIV test is performed, so that a HCT client can receive CD4 count results on the same visit as the HIV test. In addition, they are characterized by being easy to use for non-laboratory personnel, highly automated with minimal manual steps, no requirement of precise sample measurement or manipulation, and results are easy to read. POC technologies do not require consistent electricity and refrigeration— the device can operate on battery power or an alternate power source. They utilize portable equipment that do not need manufacturer or specialized installation. Besides, they have a long shelf life for consumables (at least six months once consumables reach the facility, meaning they can be utilized at least for six months once they are delivered to health facilities). Furthermore, material wastes can be disposed off safely.

Rapid testing for HIV through various methodologies, using either blood or oral fluid samples, can give a result within 20 minutes with 97% to 100% sensitivity and specificity. Rapid point of care testing has the potential to allow post test counseling of those testing positive immediately after undergoing a test, which may increase the probability of patients returning for HIV specialist care, thus improving their health and reducing transmission.

The effect of point-of-care CD4 cell count tests on retention of patients and rates of ART initiation have been studied in some sub-Saharan African countries. For example, an observational study conducted in Mozambique indicated that point of care CD4 testing enabled clinics to stage patients rapidly on-site after enrolment. In addition, a South African pilot study indicated that patients offered
point of care CD4 testing as part of the HCT services were more likely to visit a referral clinic after testing.\textsuperscript{17} Another South African randomized controlled trial indicated that the receipt of a CD4 count at the time of HIV testing increases ART initiation rates. The study concluded that point-of-care diagnostics can be used to improve retention.\textsuperscript{29} However, the findings of these studies, have not yet been synthesized in the form of a systematic review. Therefore, in this review, we will attempt to pool evidence regarding effect of point-of-care CD4 cell count tests on retention of patients and rates of ART initiation in sub-Saharan African countries.

Keywords

Point of care CD4 test; ART retention; ART initiation

Inclusion criteria

Types of participants:

Adults and adolescents (aged more than or equal to 15 years) living with HIV who are aware of their HIV sero-status. Patients whose records suggest that they have been transferred to another facility will be excluded.

Types of intervention(s)/phenomena of interest:

Point of care CD4 testing

Comparator:

Baseline results (results before the introduction of point of care CD4 testing) or clients who were not provided with rapid point of care CD4 tests.

Types of outcomes

The primary outcomes will be: CD4 staging, and initiation of antiretroviral treatment of enrolled patients.

Successful CD4 staging is defined as a staging visit to give the patients their CD4 results and assess eligibility for treatment within 90 days of enrolment (enrolment is an active [intentional] visit by the patient for pre-ART care [before or after staging]).\textsuperscript{14}

Successful treatment (ART) initiation is defined as documentation of dispensed antiretroviral drugs within 60 days of a staging visit and patients will be considered lost to follow-up if they do not start treatment during this period.\textsuperscript{14,18}

In addition, timeframes will be included for the following pretreatment stages: from enrolment to CD4 staging visit, from staging to treatment initiation for eligible patients, and from enrolment to initiation of antiretroviral treatment.\textsuperscript{14}

Types of studies

This review will consider both experimental and epidemiological study designs including randomized controlled trials, non-randomized controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies for inclusion.
Search strategy

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilized in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by an analysis of the text words contained in the title and abstract, and of the index terms used to describe article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies reported in English from 2004 to 2013 will be considered for inclusion in this review. This is because significant improvements have been made in the access to ART in low-income and middle-income countries after 2004. The search for unpublished studies will include: Mednar, Google Scholar, and proQuest. The initial search terms to be combined and used are: people living with HIV (for population); point of care CD4 testing, rapid CD4 testing (for intervention); patient retention, treatment initiation, ART initiation, CD4 staging (for outcome).

Assessment of methodological quality

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardized critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix I). Any disagreements that arise between the reviewers will be resolved through discussion.

Data collection

Data will be extracted independently by the two reviewers from papers included in the review using the standardized data extraction tool from JBI-MAStARI (Appendix II). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. The authors of primary studies will be contacted by email in case there is incomplete information.

Data synthesis

Quantitative data will, where possible, be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Before conducting meta-analyses, heterogeneity will be assessed statistically using the standard Chi-square and visual inspection of the meta-analysis output on a forest plot. Because of the possibility of low power if there are few studies, we will use a significance level of $P < 0.1$ in order to protect against the possibility of falsely stating that there is no heterogeneity present. Data will also be explored using subgroup analyses based on the different study designs included in this review.

The data syntheses will be based on the random effects model. Effect sizes expressed as Odds Ratio (OR) and Risk Ratio (RR) (for categorical data) and standardized mean differences (SMD) (for continuous data) and their 95% confidence intervals will be calculated using the DerSimonian and Laird method.
Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.

**Conflicts of interest**

We declare neither financial nor intellectual conflict of interest in this work.

**Acknowledgements**

We would like to acknowledge the Joanna Briggs Institute (JBI) and Jimma University (Ethiopian Malaria Alert Centre: a Collaborating Centre of the Joanna Briggs Institute) for their support.
References


Appendix I: Appraisal instruments

MAStARI Appraisal instrument

**JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial**

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
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<tbody>
<tr>
<td>1. Was the assignment to treatment groups truly random?</td>
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<td>2. Were participants blinded to treatment allocation?</td>
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<td>3. Was allocation to treatment groups concealed from the allocator?</td>
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<td>4. Were the outcomes of people who withdrew described and included in the analysis?</td>
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<td>5. Were those assessing outcomes blind to the treatment allocation?</td>
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<td>6. Were the control and treatment groups comparable at entry?</td>
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<td>7. Were groups treated identically other than for the named interventions</td>
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<td>8. Were outcomes measured in the same way for all groups?</td>
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<td>9. Were outcomes measured in a reliable way?</td>
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<td>10. Was appropriate statistical analysis used?</td>
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Overall appraisal: Include [ ] Exclude [ ] Seek further info. [ ]

Comments (Including reason for exclusion)


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JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer __________________________  Date __________________________
Author __________________________  Year _______  Record Number _______

1. Was study based on a random or pseudo-random sample? □ □ □ □
2. Were the criteria for inclusion in the sample clearly defined? □ □ □ □
3. Were confounding factors identified and strategies to deal with them stated? □ □ □ □
4. Were outcomes assessed using objective criteria? □ □ □ □
5. If comparisons are being made, was there sufficient descriptions of the groups? □ □ □ □
6. Was follow up carried out over a sufficient time period? □ □ □ □
7. Were the outcomes of people who withdrew described and included in the analysis? □ □ □ □
8. Were outcomes measured in a reliable way? □ □ □ □
9. Was appropriate statistical analysis used? □ □ □ □

Overall appraisal: Include □  Exclude □  Seek further info □

Comments (Including reason for exclusion)
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Appendix II: Data extraction instruments

MAStARI data extraction instrument

### JBI Data Extraction Form for Experimental / Observational Studies

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<tr>
<td>Author</td>
<td>Year</td>
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<td>Journal</td>
<td>Record Number</td>
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#### Study Method

- RCT □
- Quasi-RCT □
- Longitudinal □
- Retrospective □
- Observational □
- Other □

#### Participants

- Setting
- Population

#### Sample size

Group A □
Group B □

#### Interventions

- Intervention A
- Intervention B

Authors Conclusions:

Reviewers Conclusions:
### Study results

#### Dichotomous data

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<th>Outcome</th>
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#### Continuous data

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