Models for Accelerating Treatment Initiation: Workshop to Identify the Research Agenda

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Workshop Report

Submitted to:

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I. Background

In its 2015 revision of the global guidelines for HIV care and treatment, the World Health Organization has called for initiating lifelong antiretroviral treatment (ART) for all patients testing positive for HIV, regardless of CD4 cell count[1]. This revision follows a series of increases in the global guidelines in the threshold for initiating ART, from a CD4 count of ≤200 cells/mm^3 prior to 2010, to 350 until 2013, to 500 until September 2015. The evidence for this approach, often called "test and treat" (alternatively, "test and start" or "test and offer") comes from clinical trials, modeling exercises, and population-level data analyses. In its recommendation, the WHO cites three anticipated benefits from the change: reduced morbidity among HIV-infected patients; reduced risk of transmission from HIV-infected individuals to their partners; and "*increases in ART uptake and linkage to care, reduction in the time between HIV diagnosis and ART initiation regardless of baseline CD4 cell count and an increase in the median CD4 value at ART initiation*."

Although many low- and middle-income countries continue for budgetary and other practical reasons to apply a CD4 cell threshold of 350 or 500 for non-pregnant adults without Stage 3 or 4 conditions, it is clear that the trend in the coming years will be toward immediate eligibility for and offer of ART to all those diagnosed with HIV. As this happens, the number of patients in and the duration of "pre-ART care," defined as the interval between HIV diagnosis and ART initiation, will diminish rapidly, and the well-documented challenge of retaining patients in pre-ART monitoring for treatment eligibility will lose its importance. The challenge that will replace it is that of initiating individuals newly diagnosed as HIV-infected on ART as efficiently as possible, while ensuring that potential clinical harms are avoided and retention on ART is not jeopardized by the initiation process. Studies from throughout sub-Saharan African continue to document high losses of treatment-eligible patients from care before they receive their first dose of ARVs, due to a wide range of facility- and patient-level barriers to initiation. Under a test-and-start policy, large numbers of asymptomatic patients will be asked to commit to a lifelong therapy, potentially making loss to care both before and soon after initiation even more common.

Although obtaining a CD4 count will no longer impede ART initiation under a test-and-start policy, many patient and provider barriers will likely remain. Unlike the first two benefits mentioned in the WHO's guidelines, the last one depends on effectiveness of service delivery, rather than on the efficacy of the drugs themselves. Test-and-start will not solve the problem of linking patients to care or initiating them on ART efficiently without new approaches to service delivery. Patients tested in the community or in health facilities that do not provide ART will continue to require referral to a clinical facility providing ART services. The need to screen for tuberculosis symptoms and cryptococcal antigen and diagnose and begin treatment for these conditions, prior to initiating ART, will also remain. At treatment facilities, multiple required visits, long waiting times, stock outs of supplies, staff absences, and poor communication between staff and patients will continue to deter treatment initiation. Retention of patients on ART in the months after starting, moreover, may depend in part on the manner of treatment initiation. A simpler, more efficient, accelerated algorithm for ART initiation will be needed if test, start (and retain) is to realize the benefits expected.

To begin to develop such an algorithm—or multiple algorithms, differentiated to reflect differences in populations and settings—the Models of Accelerating Treatment Initiation (MATI) technical consultation was held in October 2015. It was premised on the observation that, while many studies have evaluated what to start (regimens) and when to start (eligibility), few have addressed the operational question of how to start ART, with "how" encompassing considerations of timing and speed; required laboratory tests and technologies for performing them; where to initiate; quantity and content of counseling and

education needed; and roles of different cadres of service providers, including facility- and community-based healthcare workers. The meeting took advantage of the fact that a number of operational studies are being completed in 2015 that address the "how" question. The MATI meeting reviewed and discussed data from new and recent research to develop a prioritized research agenda on how to optimize algorithms for treatment initiation in sub-Saharan Africa, with the goal of maximizing the number of patients who can be initiated and retained on ART with available financial, infrastructural, and human resources.

II. Existing Evidence

In preparation for the MATI meeting, a systematic review of the literature was conducted to identify and synthesize existing evidence on ART treatment initiation in sub-Saharan Africa. This review drew upon a larger review of interventions to improve linkage to care that was conducted for the World Health Organization earlier in 2015. The systematic review report is included as Appendix IV.

Previous research on the cascade of care between HIV testing and treatment initiation generally pertained to a three-stage process, as illustrated in Figure 1.

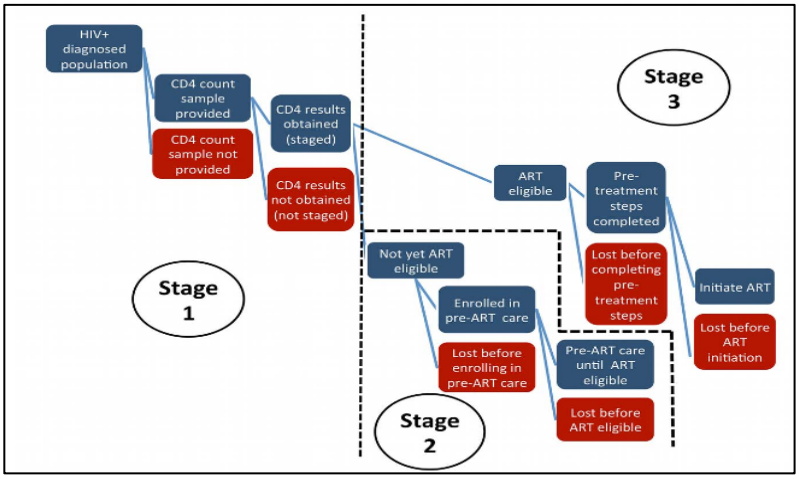


Figure 1. Stages of pre-ART care under previous guidelines. Source: Rosen and Fox (2011).[3]

One of the key points made in presenting the systematic review at the MATI meeting was that much of what is known about linkage to care, retention in pre-ART care, and ART initiation under previous CD4 count thresholds will lose its relevance when a threshold no longer exists—i.e., past data will not be a good predictor of future behavior. In particular:

- Data on testing to linkage to care (Stage 1 in Figure 1) will still be relevant, but the definition of "linkage to care" may change, as returning to the clinic solely to obtain a CD4 count result and learn one's eligibility for ART will no longer be required. Knowing in advance that ART is likely to be offered upon presentation at a clinic, rather than being merely one of two possibilities, may also change patient behavior after testing HIV positive.
- Data on pre-ART retention between linkage and treatment (Stage 2) eligibility will become largely irrelevant, as Stage 2 will effectively disappear from the cascade for most patients (and many of those who cannot or choose not to start ART immediately will need special services, such as TB treatment or social support)

- Data on eligibility to initiation (Stage 3) may remain relevant depending on whether the patients who link to care are similar to or different from previous populations and what steps are required to start treatment (CD4 count, adherence classes, etc.).

Based on these considerations, a new cascade was proposed at the meeting that better captures how service delivery is expected to work under the new guidelines. It is illustrated in Figure 2.

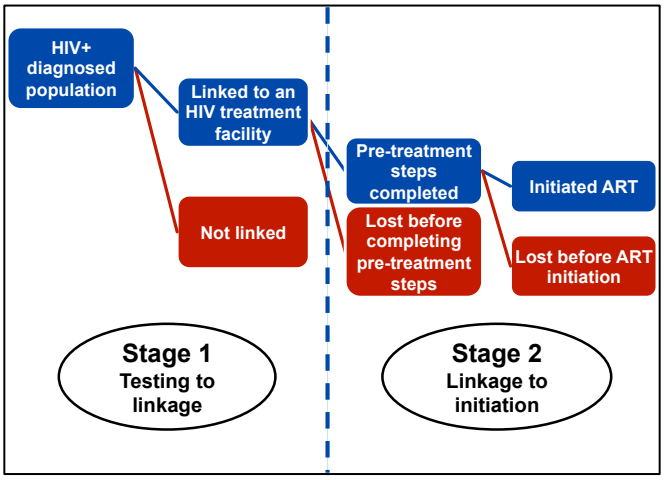


Figure 2. Proposed stages of pre-ART care under new guidelines.

Under the new cascade illustrated in Figure 2, the opportunities for patients to become lost to care before ART initiation have been cut in half (from six red boxes to three). The MATI meeting focused on opportunities to minimize attrition under this new cascade.

III. Objectives

The MATI technical meeting aimed to present and review what is known about the process of treatment initiation, identify gaps in the evidence base where additional research is needed, and recommend a research agenda for optimizing treatment initiation in the era of test and start. The objectives of the meeting were to:

- Present and assess new data from recent and ongoing studies that pertain to the "how" of treatment initiation.
- Identify and list key factors that will influence the success of treatment initiation models, taking into account differences in settings, populations, health systems, and considerations for patients who are eligible for ART but opt out of immediate treatment
- Inventory, describe, and report existing and promising models of treatment initiation
- Identify and list gaps in the evidence base where additional research would help to evaluate and prioritize the models.
- Agree upon and document research parameters, designs, and outcomes that will provide comparable information as efficiently as possible.
- Specify and produce a list of the highest priority research questions in which funding should be invested following the meeting.

The specific issues that the meeting intended to address included:

1. Timing and speed of treatment initiation: Once a patient has been diagnosed, how quickly can treatment be started, without risking starting "too fast" and jeopardizing patient welfare or post-initiation outcomes and retention?
    a. Number of clinic visits
    b. Time interval between visits and from start to finish

2. Minimum required steps to determine clinical eligibility: What do clinicians have to know before they prescribe ARVs, and what is the most efficient way to generate this information?
    a. Blood tests to determine regimen (e.g. creatinine, hemoglobin)
    b. Tuberculosis
    c. Cryptococcal meningitis
    d. Other IRIS risks
    e. Physical examination

3. Minimum required provision of counseling and education: What is the optimal number, duration, timing, staff cadre, and content of non-clinical interactions to ensure that patients are able and willing to adhere to ART?
    a. HIV/ART/adherence education
    b. Counseling and support
    c. Nurses/counselors/CHWs/lay persons in community
    d. Before or after initiating medications

4. Location of ART initiation: Can ART be initiated successfully in non-clinical locations?
    a. Same site HIV testing and initiation
    b. HIV testing and referral to a clinic for initiation
    c. HIV testing and initiation in non-clinic settings (e.g. home-based or other community locations)
    d. Role of home visits by community volunteers (e.g. community health workers) and clinic-based professional staff to support initiation in community and/or clinic settings
    e. Effect of location of initiation on early retention on ART

5. Patient behavior and decision-making: How can we convince patients to accept what we offer?
    a. Reducing known patient barriers to enrollment and initiation, including incentives
    b. Effect of model of ART initiation on patient retention on ART
    c. Targeting delivery models to different patient populations

6. The supply side: What do health systems need to have and do?
    a. Role of health system context in choosing models of service delivery
    b. Reducing known provider barriers to initiation
    c. Infrastructural requirements for accelerated initiation

7. The demand side: How many more patients will seek ART initiation?
    a. Pace of adoption of test-and-start at country level
    b. Proportion HIV-infected populations that will remain undiagnosed or decline treatment
    c. Capacity of existing models and/or need for new model(s)

8. Measuring success and data requirements: How should we evaluate different models of ART initiation?

a. Outcomes (ART initiation; retention on ART at 6 months after HIV testing)
b. Resource requirements (especially scarce human resources)
c. Provider costs and cost-effectiveness
d. Patient costs and benefits

The meeting focused on general adult populations in sub-Saharan Africa. To ensure that there would be sufficient time to address these issues in detail, the meeting explicitly excluded a number of topics. These were HIV testing (except as it relates to ART initiation); retention on and adherence to ART (except as these are affected by model of ART initiation); PMTCT (except to the extent that lessons can be drawn from Option B+); and pediatric populations and high-risk groups or key populations.

The MATI meeting was attended by 33 technical experts, program implementers, government officials, and donor agency staff. Areas of expertise represented included clinical medicine, epidemiology, health economics, public health, and program management. The meeting agenda, list of participants, and slides presented, excluding those for which presenters requested confidentiality, are appended to this report. The following sections of the report will focus on the research questions identified as priorities at the meeting, with the goal of creating a working research agenda.

IV. Prioritized Research Agenda

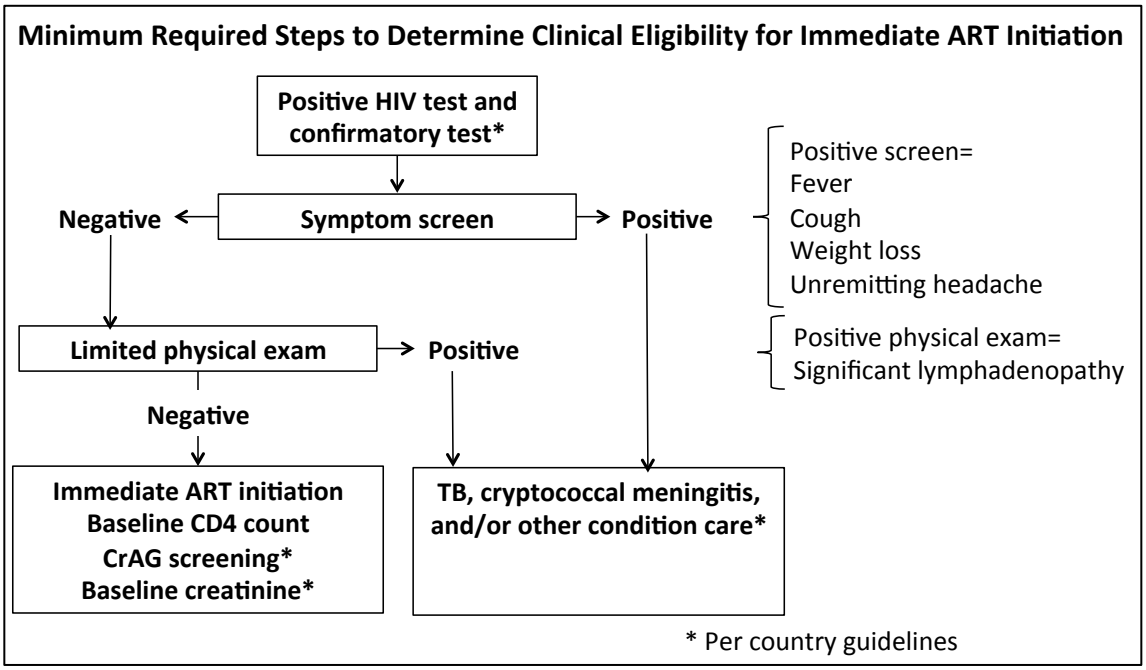
The meeting identified six research priority questions or issues from among the many ideas proposed. The priority questions vary widely in scale and scope, and thus in the time and resources that it will take to answer them. In this section, we first specify each question, then report issues and concerns that arose in the discussion of the question. We next discuss how it might be answered and options for study designs. We conclude with a short discussion of suggested next steps.

As explained above, the research agenda pertains to general adult populations. Many of the same questions will be relevant and important for other populations, including pregnant women, children, and high-risk groups, such as MSM and PWID. There may, however, be variations of the questions below, or other even higher priority issues, for these groups. Research on treatment initiation for each of these other populations is also needed.

Question 1

Is a simplified ART initiation clinical algorithm as illustrated in Figure 3 as safe as standard of care, as measured by the probability of serious adverse events (death, hospitalization, incidence of co-morbidities)?

Figure 3. Simplified clinical algorithm



Considerations

- What conditions are missed or mismanaged with this algorithm?
  - Cryptococcal antigen positive that develop cryptococcal meningitis or death
  - Tuberculosis unmasking leading to hospitalization or death
  - Unmeasured elevated creatinine that precipitates renal failure
  - Adherence risks (e.g. substance abuse or mental health conditions)
- Does the physical exam have added value to identify high risk patients?
- Would a medical history have added value to identify high risk patients?
- What proportion of patients are ineligible for immediate ART initiation due to a non-specific symptom screen?
- Are there patients or populations who would be excluded from this approach ex-ante? E.g. children, non-naïve re-initiators, patients with pre-existing co-morbidities?
- Question focuses on the clinical algorithm only; should non-clinical services (adherence education, counseling, etc.) and determination of patient acceptance of ART be tailored to the clinical algorithm as an inherent part of it, or can non-clinical services be dealt with separately?
- "One visit" or "same day" refer to the first visit to the initiating clinic for HIV care. This could be the day of diagnosis or a later date. Would the algorithm differ based on whether the patient is newly versus previously diagnosed?

Research design

- Full answer requires an individually randomized trial
  - Cluster randomization also possible
  - Ultimately need an evidence base representing multiple settings and populations
  - This design will take a minimum of 2-3 years to complete, depending on enrollment rates and duration of follow-up
- Observational data could be used to generate answers to some aspects of the overall question in 1-2 years
  - What proportion of patients are not eligible to start ART immediately based on criteria other than CD4 count? Could be answered with retrospective electronic medical record data with relatively good follow up and completeness of reporting.
  - How well is the algorithm likely to perform? Collect the data for the algorithm from a prospective cohort while retaining standard of care; estimate proportion who would be incorrectly tracked (initiation or delay) using the algorithm compared to what was actually done (essentially a simulation study). Could estimate Se and Sp (PPV and NPV) of such a screening approach.
  - What is the net change in patient outcomes (viral suppression) likely to be if the simplified algorithm is implemented? Develop a model to determine the extent to which negative outcomes after initiation can increase without wiping out the overall benefits of the algorithm.
  - What proportion of patients presenting at clinics were diagnosed prior to their "first visit for HIV care" and/or outside a clinic setting? Could be answered with a simple prospective cohort study or possibly with retrospective data if HIV testing history is well recorded.
  - In Option B+ programs, where patients are initiated on a standard first-line regimen without prior lab tests, what proportion have had regimen changes or adverse reactions? Could be answered with retrospective electronic medical record data with relatively good follow up and completeness of reporting. Pregnant women may be representative of patients with higher CD4 counts and thus not a perfect proxy but would provide some relevant information.

Discussion

This is a high priority research question and merits a randomized controlled trial in multiple settings with different patient characteristics. While a trial will take some time to develop, fund, and launch, if high volume study sites are chosen, then enrollment and follow up can be completed quickly, as outcomes can be assessed very soon after study enrollment. A collaborative protocol should be developed and submitted for funding. In the meantime, observational work should be done to help prepare for the trial and inform other efforts to accelerate treatment initiation. (Note: the MATI participants who developed Figure 3 are planning to meet at CROI in Boston in late February 2016 to discuss how to develop a trial.)

Question 2

What is the optimal timing/speed of initiation, as measured by early ART outcomes (initiation of ART, retention on ART, viral suppression) and cost-effectiveness?

Considerations

- Options are same-day opt-out; one or two visits within a specified time period (e.g. a week); "as soon as possible;" standard of care.

- There is little evidence on the importance of pre-initiation clinic visits overall, and no evidence to support more than two visits (or three, if the initial visit for an HIV test is separate); question is really whether it's better to make one visit or two visits the default.
- Are there models for delivering pre/post initiation treatment literacy sessions outside the clinic, e.g. as community programs, and is this as effective as providing services in the clinic?
- Is more than one education session required during initiation process to obtain good short-term outcomes?
- Does the effect on treatment outcomes of visit schedule or content after initiation vary by visit schedule or content before initiation?
- Likely best strategy is some combination of single visit for those who are able (have time, are emotionally and physically well, state their readiness) and individualized schedule for those who are not

Research design

- Full answer requires a cluster-randomized, prospective trial; programmatic innovations and guideline changes seem likely to overtake the results of such a trial
- Could consider a non-randomized, controlled evaluation design (three arm: standard of care (control); same-day opt-out; patient selection of same-day, two-visit, or individualized schedule)
- A cost-effectiveness model with parameters generated by the studies presented at the meeting (and others) could explore the impacts and costs of alternative strategies, consider how much same- day initiation has to increase uptake of ART to justify implementing it as national policy.

Discussion

The two-visit algorithm developed by MSF is included in South Africa's new Adherence Guidelines and will be evaluated in a cluster-randomized trial as part of the ENHANCE study (Boston University/HE^{2}RO). A three-arm evaluation as described above should be considered for implementation within a large treatment support program (e.g. PEPFAR partner) that has access to multiple sites and staff and high volumes of treatment initiators and is not in South Africa. In the short-term, development of a cost-effectiveness model that can capture differences in the treatment initiation algorithm would be a valuable contribution.

Question 3

What changes to clinic management, capacity, and resources are needed to support accelerated ART initiation, and particularly same-day initiation?

Considerations

- Focus is on human and infrastructural resources and management (staff training; staff responsibilities and schedules; on-site information for staff; staff/patient ratios; clinic space allocation; patient flow; data management and clinical records; etc.)
- Patient volume must be taken into account—can as many patients be initiated in a day using a single-visit algorithm as under standard care? Would decentralizing other services, such as pharmacy refills for stable patients, allow more new patients to be initiated?

- Approaches for improving clinic ability to implement same-day initiation could include systems engineering, continuous quality improvement, enhanced training with feedback, other.
- Should include data system for patient management, service delivery monitoring, performance/outcomes evaluation.
- Potential solutions will be constrained by existing policies, HR rules, infrastructural availability, etc.

Research design

- Unclear how best to answer this question, as optimal strategies are likely to differ widely by country and setting.
- A survey of existing capacity and procedures could provide a useful starting point. (E.g., how many staff initiate patients on ART? Every day or only some days? How much time does it take? What space do they use? Etc.)
- Would a best/worst performer design (positive/negative deviance), to identify differences between efficient and inefficient initiators, generate useful information? (See design ideas in Gimbel et al 2014[2].)

Discussion

This is an operational question that will likely be answered through an iterative, empirical approach as governments and treatment support programs adjust to new recommendations on accelerated treatment initiation and the larger numbers of eligible patients under the new WHO guidelines. To generate an initial set of information and ideas about clinic capacity and what changes will be needed to accelerate ART initiation, a survey of existing capacity and procedures should be undertaken from a sample of sites purposively selected to capture variation in ART outcomes (which may reflect variation in effectiveness of treatment initiation as well). For some aspects of the question, operational guidance documents could be developed and disseminated. The International AIDS Society may develop such guidance under its BMGF-funded project.

Question 4

Is initiation of ART outside the facility (community- or home-based) safe, effective, and cost-effective, as measured by the probability of serious adverse events (death, hospitalization, incidence of co-morbidities), ART outcomes (retention on ART, viral suppression), and cost per outcome achieved?

Considerations

- There are three discrete sets of patients who must be served, and the optimal location of ART initiation may be different for each:
  - Newly diagnosed (just tested);
  - Previously diagnosed but declined treatment or were lost from pre-ART care; and
  - Re-initiators. The number of re-initiators is expected to increase; reasons for stopping ART previously should be addressed during re-initiation.
- What benefits are expected from service delivery outside the clinic? (Increased access, higher rate of acceptance of ART, reduced patient costs, reduced crowding in clinics, resource reallocation to other clinical services?)

- Answer probably varies by population (asymptomatic patients, symptomatic patients, re-initiates, etc.): "For whom is initiation outside the facility safe and effective?"
- Cost effectiveness must be taken into account, as non-clinic service delivery could be more or less expensive than clinic service delivery, with wide variation by patient density, distances to facilities, healthworker cadre employed, etc.
- How long will community or home-based service delivery continue after initiation? If patients face barriers in accessing clinics, community-based initiation must be followed by community-based ART delivery.
- Medical records must be linked to a central database, so that facilities receiving patients who were initiated off site can manage them
- Is integration of community and home-based ART initiation with existing non-clinic services (e.g. CHWs in Zambia, WBOTS in South Africa) desirable? Essential?

Research design

- Full answer requires one or more cluster-randomized trials
  - Ultimately need an evidence base representing multiple settings, populations, and models of delivery
  - This design will take a minimum of 3+ years to complete, depending on enrollment rates and duration of follow-up
- Opportunities to collaborate on interventions already underway or being developed by governments and treatment support partners should be sought and rigorous evaluations conducted
- A cost-effectiveness model should be developed that would help define the minimum effectiveness and/or maximum cost for a model to offer a viable policy option for any particular country

Discussion

A number of trials of community-and home-based initiation are underway or have recently been completed, with varying results in terms of linkage to care and retention on ART. Of note is the DO-ART trial underway in South Africa and Uganda. More trials and evaluations of pilot projects in this area will be needed to build a sufficient evidence base. Scalability and affordability of models beyond pilot projects should also be addressed. A robust model that indicates the conditions under which community- or home-based service delivery is likely to generate net benefits should be developed as a first step, to help target and refine the future research.

Question 5

Why do some patients not start ART when advised and which interventions will be effective in changing behavior to increase and accelerate ART uptake?

Considerations

- This is the demand side of the equation—focuses on patients who decline to start treatment despite eligibility; likely to be of increasing importance as more patients become eligible
- Actual rates of refusal and duration of delays are unknown, because of the inability to trace patients between facilities (and in many settings, over time—a patient who fails to return on schedule may

be recorded as a new patient later on); as noted above, moreover, past behavior may not be a good predictor of future behavior, due to the change in eligibility guidelines.

- Unclear how demand for treatment is affected by service delivery models—would better models of treatment initiation overcome non-clinical barriers to uptake, or are these two different problems?
- It's also unclear whether rates of treatment refusal will increase or decrease under the new guidelines—could decrease if public perception is "everyone with HIV should be on treatment" or increase if asymptomatic patients simply don't want treatment (and absolute numbers of patients initiating ART could increase even with a higher refusal rate)
- Can existing structures such as adherence clubs or community groups be recruited to help overcome barriers to initiation?
- Is there a role for incentives in creating demand for ART initiation?
- There is certainly a need for more and more focused survey and qualitative research to understand refusal to start treatment, but demand will also evolve under new guidelines, making this a moving target
- Barriers are likely to be setting- and population-specific to some degree; will need data from multiple populations

Research design

- Could trace and interview patients who test positive for HIV but don't link to care or initiate ART, though some work like this has already been done (e.g. see Barnabas presentation)
- Less valuable to ask patients what they would do, hypothetically, under the new guidelines, than to observe what they actually do, once the guidelines are adopted
- Probably most efficient to add this as a secondary objective to other studies, rather than undertaking new stand-alone studies
- Can also analyze impact of previous guideline changes on demand for treatment (e.g. change from CD4 count < 200 to < 350 or from <350 to < 500; see Bor et al presentation at CROI 2016).

Discussion

Understanding why people decline to start treatment seems essential to achieving 90-90-90 goals but is somewhat separate from the "how" of treatment initiation, except to the extent that simplifying the initiation process may encourage higher uptake. Researchers with access to household data collection and/or patient tracing capacity should be encouraged to undertake studies of this issue to try to identify major reasons for declining treatment. It is premature to design or evaluate interventions—formative research is needed.

Question 6

How long does it take to start ART under current practices and how will this change when the new WHO guidelines (no CD4 count threshold for treatment eligibility) are adopted, as measured by number of clinic visits and duration from start to end?

Considerations

- This is a baseline question: we have to understand what is happening now in order to improve it, and there is very little information available about current practices

- Countries may or may not issue procedural guidelines that change current practices when they remove the CD4 count threshold for initiation

Research design

- Probably cannot answer this question retrospectively, as few data sets capture the details of clinic visits and service delivery during the initiation process
- A cross-sectional survey of clinic practices combined with small cohort studies to record actual durations (number of visits and time from start to end) would provide an answer
- Should be multi-country and capture variability between sites within countries

Discussion

A robust baseline data set describing current practices would provide a base for further research and guideline development. A common protocol applied by multiple research teams with existing capacity in different countries and settings should be considered.

V. Research Design Considerations

In addition to identifying priority research questions, MATI participants also discussed research design and methods and challenges we will face in implementing the research agenda.

Primary outcomes

One of the major obstacles to assessing and synthesizing existing studies is the heterogeneity in outcomes reported, which made it difficult to compare results across studies or draw general conclusions. There was thus broad agreement that evaluations of models of treatment initiation should report on a standard set of primary outcomes:

- **ART initiation rate** (=patients initiating ART / all treatment-eligible patients).
    - The timing of this outcome—how long an interval should be allowed for initiation—was not discussed. The studies presented used intervals ranging from 14 days (Geng et al) to 90 days (Rosen et al) after initial clinic presentation. The starting point of the interval also varied between date of HIV test (diagnosis) and date of treatment eligibility (CD4 count). Under the new WHO guidelines, diagnosis and eligibility will be simultaneous. In all studies presented, more than half of patients in the standard of care arms initiated treatment within one month (28 days) of initial clinic presentation, confirming that one month is sufficient time for all procedures to be completed. We recommend that "ART initiation within 28 days of first HIV-related clinic visit" be used as the standard outcome for studies aimed at accelerating or increasing uptake of ART initiation.
    - The denominator for this outcome is "all treatment-eligible patients." As noted above, in the future nearly all patients will be eligible, but currently most countries continue to apply an eligibility threshold. The denominator for this outcome should include all patients who are eligible whether or not their eligibility has been determined and conveyed to them. Thus a patient who has a CD4 count under the threshold but does not return to obtain the CD4 count result should be included in the denominator.

- **Viral suppression** (=patients virally suppressed / all treatment-eligible patients).

  - The timing of this outcome will depend on when routine viral loads are done under national guidelines. South Africa, one of the few countries that already performs viral loads under standard care, does it six months after treatment initiation, which is also the WHO's recommendation. In this case, viral suppression in months 5-7 after treatment initiation can be regarded as a positive outcome, allowing for flexibility in test timing. A window of one month before or after the scheduled date for a viral load may be a reasonable standard.
  - As above, the denominator for this outcome is "all treatment-eligible patients." A patient who is eligible for treatment but never initiates would thus be included in the denominator (presumably not suppressed, as a viral load is unlikely to be done for a patient who never initiated treatment).

- **Retention in care** (=patients retained on ART / all treatment-eligible patients).

  - Where viral loads are not available, or as an additional measure, retained in care and on ART is another reasonable outcome. Since the focus of MATI is on ensuring that the manner of ART initiation does not harm post-initiation outcomes, retention in care 6 months after ART initiation should be estimated. Definitions of retention in care will vary by national guidelines, data availability, and researcher norms.
  - Denominator as above.
  - For retention in care and viral suppression, there is no ART initiation date for patients who are lost before initiation. For these patients, the outcome could be assessed one month (28 days) plus the specified interval (e.g. 6 months) after first HIV-related clinic visit. This allows the patient the same 28 days to start ART as suggested for the ART initiation outcome, plus the same duration of potential follow up as the patients who did start ART.

- **Cost-effectiveness** (=cost/outcome achieved).

  - Most models for accelerating ART initiation will have different costs of service delivery than standard care, and cost is thus a critical outcome to include in an evaluation. Cost can be measured for any of the three outcomes listed above, with costs incurred over a specified time period consistent with the outcome measure.
  - Provided that the primary patient outcomes are measured consistently, there is no immediate programmatic need to estimate utility outcomes such as cost/QALY or cost/DALY. These outcomes can be modeled secondarily when needed.
  - Whenever possible, benefits and costs to patients should also be estimated and presented as part of the economic evaluation.

Other outcomes that should be evaluated

- **Acceptability**

  - Is the model of initiation acceptable to individual patients and to communities? Standard methodology and outcome definitions required for evaluating this.
  - Uptake of intervention (=1 – refusal rate) could be considered a proxy for acceptability but does not explain reasons for patient or community choices or allow ranking of preferences.

- **Scalability**

  - Many papers assert that an intervention is scalable without defining the term or providing evidence—often just mean that it was feasible to implement it in their study.
  - Standard methodology and definitions required for evaluating this.
  - Could estimate incremental resource requirements per thousand patients initiated, compared to standard of care, for critical resources (staff, laboratory infrastructure, clinic space, etc.)

Other research design considerations and challenges

- Studies should start with treatment eligibility and end with viral suppression/retention whenever possible (or with treatment initiation if longer follow-up is not possible). Intermediate endpoints (e.g. linkage to care) are useful but not sufficient. (For example, an evaluation of an intervention aimed at improving linkage to care should report ART uptake among those eligible, as well as the linkage outcome.)

- Many interventions to accelerate treatment initiation will be multi-faceted—essentially a package of changes to standard care. The individual components may vary widely—some entail major changes or new services, others small improvements to the status quo. In most cases, the effect of individual components of the intervention cannot be distinguished. For multi-faceted interventions that are found to be effective, follow-on research to test individual components may be warranted, particularly for components that are resource-intensive or difficult to scale up.

VI. Inventory of Studies Underway

This inventory of studies currently underway or very recently completed in sub-Saharan Africa was compiled from searching clinicaltrials.gov and through personal contacts. We note that of the 14 studies listed, 7 are being conducted solely in South Africa, and only 5 African countries are represented overall. (One study is located in Haiti but is included due to its relevance to the MATI topic and similarity of setting.)

Study Title	Principal investigator	Country	Design	Intervention	Comparison	Relevant Outcomes	Timeline	Further information
Start TB Patients on ART and Retain on Treatment: Combination Intervention Package to Enhance Antiretroviral Therapy Uptake and Retention during TB Treatment in Lesotho (START)	Howard, Andrea (Columbia University)	Lesotho	Cluster randomized	Nurse training; transport reimbursement; health education; SMS adherence support	Standard care	ART initiation < 9 months; ART retention < 6 months; time to initiation (limited to TB co-infected)	Estimated March 2016	https://clinicaltrials.gov/ct2/show/NCT01872390
ENGAGE4HEALTH: A Combination Intervention Strategy for Linkage and Retention in Mozambique	Elul, Batya (Columbia University)	Mozambique	Individually randomized	POC CD4 count, accelerated ART initiation, and SMS appointment reminders (with or without financial incentives)	Standard care	ART initiation?	Estimated June 2016	https://clinicaltrials.gov/ct2/show/NCT01930084
Rapid Initiation of Treatment (RapIT)	Rosen, Sydney (Boston University)	South Africa	Individually randomized	Single-visit ART initiation using accelerated procedures and POC tests	Standard care	Viral suppression < 10 mos of study enrollment; ART initiation < 90 days of study enrollment; retention < 10 mos; time to initiation	Completed; results at CROI 2016	https://clinicaltrials.gov/ct2/show/NCT01710397
Feasibility of Multidisciplinary Point of Care Testing in Active HIV Treatment Clinics and Impact on Patient Outcomes	Stevens, Wendy (NHLS/Wits University)	South Africa	Individually randomized	POC laboratory tests	Standard care	Retention in care at 12 months; Initiation of ART	Completed; results available?	wendy.stevens@nhls.ac.za
Fast Track ART/TB Initiation & Aligned Counselling Model	Wilkinson, Lynne (MSF)	South Africa	Single-arm evaluation	Two-visit ART initiation with adapted counseling	None	ART initiation; retention at 1 and 6 months; viral suppression at 6 months	Completed; results available?	https://www.msf.org.za/download/file/fid/7532
Thol'Impilo: Bringing People Into Care	Charalambous, Salome (Aurum Institute)	South Africa	Individually randomized	POC CD4 count or POC CD4 count and counseling or POC CD4 count and transport reimbursement	Standard care	ART initiation < 90 days	Estimated June 2015	https://clinicaltrials.gov/ct2/show/NCT02271074
iLink (Incentives for Linkage to ART) Study: A Mixed-methods Study to Improve Linkage to HIV Care	Maughan-Brown, Brendon (University of Cape Town)	South Africa	Individually randomized	Financial incentive to start ART following mobile testing	Standard care	ART initiation < 3 months; time to ART initiation; retention at 12 months	Estimated Nov 2016	https://clinicaltrials.gov/ct2/show/NCT02440386
Engagement to Care South Africa (ICARE)	Lippman, Sheri (UCSF)	South Africa	Individually randomized	Mobile phone airtime and text messages with or without peer navigators	Mobile phone airtime	Time to ART initiation; retention on ART at 12 months	Estimated March 2016	https://clinicaltrials.gov/ct2/show/NCT02417233

Study Title	Principal investigator	Country	Design	Intervention	Comparison	Relevant Outcomes	Timeline	Further information
						months of eligibility determination		
Assessing HIV testing and linkages to care in primary health care clinics in South Africa	Ahmed, Shahira (Boston University)	South Africa	Observational	No intervention; evaluation of standard care	n/a	ART initiation < 3 months; retention in care at 12 months	Starting Feb 2016	shahira@bu.edu
Early Enrollment and Retention in HIV Care and Treatment among Clients Diagnosed in Two HIV Testing Settings in Swaziland: An Evaluation of a Pilot Program of New Linkage and Retention Procedures (RetroLink)	Duncan Mackellar (CDC)	Swaziland	Observational	No intervention; evaluation of standard care	n/a	ART initiation; time to initiation	Completed; results available in report format	dym4@cdc.gov
Link4Health: A Combination Strategy for Linkage and Retention, Swaziland (L4H)	El Sadr, Wafaa (Columbia University	Swaziland	Cluster randomized	POC CD4 count, accelerated ART initiation, care and prevention package, financial incentives	Standard care	ART initiation?	Estimated Dec 2015	https://clinicaltrials.gov/ct2/show/NCT01904994
Streamlined Initiation of Antiretroviral Therapy in the Public Health Setting (START-ART)	Geng, Elvin (UCSF)	Uganda	Stepped wedge cluster randomized	POC CD4 count; provider training; clinic performance feedback	Standard care	ART initiation < 2 weeks; ART initiation < 90 days.	Estimated May 2016	https://clinicaltrials.gov/ct2/show/study/NCT01810289
Linkages Study	Celum, Connie (University of Washington)	Uganda, South Africa	Individually randomized	Lay counselor clinic visit facilitation or home visits following home-based CD4 count	Referral to clinic following home-based CD4 count	ART initiation < 9 months	Completed; results at IAS 2015	https://clinicaltrials.gov/ct2/show/NCT02038582
The DO ART Study Delivery Optimization for Antiretroviral Therapy: A prospective, interventional, randomized study of community-based ART initiation, delivery, and monitoring in South Africa and Uganda	Ruanne Barnabas (University of Washington)	Uganda, South Africa	Individually randomized	Home ART initiation and decentralized monitoring and ART resupply	Standard of care	Viral suppression at 12 months; cost	Enrollment to begin March 2016	rbarnaba@uw.edu
Same-Day HIV Testing and Treatment Initiation to Improve Retention in Care	Koenig, Serena (Brigham Hospital)	Haiti	Individually randomized	Same-day ART initiation	Standard care	Retention in care at 12 months; initiation?	Estimated Jan 2016	https://clinicaltrials.gov/ct2/show/NCT01900080

Models for Accelerating Treatment Initiation
Technical Consultation Agenda

Day 1 (October 21, 2015)—Get the Information on the Table

Time	Session	Speakers
8:30-9:00	Registration	
9:00-9:30	Introduction/Objectives/Agenda	Papa Salif Sow, Sydney Rosen
Session 1: Data (Session Chair: Papa Salif Sow)		
09:30-9:50	*Existing Data*	
	Review of Published Studies on Models of ART Initiation	Matthew Fox
9:50-10:45	*New Data (10 minute presentations)*	
	RapIT: Initiating ART on the First Visit	Sydney Rosen
	Point of Care Laboratory for ART Initiation	Lesley Scott
	START: Streamlined ART Start Strategy	Charles Holmes on behalf of Elvin Geng
	Fast-Track ART Initiation	Lynne Wilkinson
	Home-Based Linkage and ART Initiation	Ruanne Barnabas
10:45-11:00	Break	
11:00-11:45	Questions and Discussion of Data Presented	Panel: All Presenters from Session 1; Nathan Ford (Facilitator)
11:45-12:15	General discussion	All Participants
12:15-01:15	Lunch	
Time	**Session**	**Speakers**
Session 2: Issues to Consider (Session Chair: Sydney Rosen)		
1:15-2:15	*Clinical Issues (10 minute presentations)*	
	Tuberculosis Diagnosis and Treatment and ART Initiation	Yuka Manabe
	Cryptococcal Meningitis Screening and Treatment and ART Initiation	Bruce Larson
	Clinic Capacity and Constraints for ART Initiation	Francois Venter
	Community Capacity and Constraints for ART Initiation	Morten Skovdal
	Care for Eligible Patients Who Decline ART	Ribakare Muhayimpundu
2:15-2:45	Questions and Discussion of Topics Presented	Panel: All Presenters on Clinical Issues
2:45-3:00	Break	
3:00-3:30	*Technical Issues (10 minute presentations)*	
	Cost and Cost-Effectiveness Considerations	Paul Revill
	Data Systems for Accelerating ART Initiation	Meg Osler
	Role of Laboratories in ART Initiation	John Nkengasong
3:30-4:00	Questions and Discussion of Topics Presented	Panel: All Presenters on Technical Issues
4:00-4:15	What Information Do National Governments Need?	Yogan Pillay
4:15-4:45	International Technical Agency Approaches (WHO and IAS)	Nathan Ford, Anna Grimsrud

4:45-5:00	General Discussion and Wrap-Up of Day	All Participants
6:00 onwards	Gathering at Dopio Zero, Corner Church St and St. George's Mall	All Welcome

Day 2 (October 22, 2015)—Discuss What to Do About It

Time	Session	Speakers
09:00-09:15	Introduction/Objectives/Agenda	Sydney Rosen
Session 1: International Agency and Government Perspectives (Session Chair: Matt Fox)		
9:15-10:15	Panel Discussion of Donor Priorities and Plans: PEPFAR (CDC, USAID), Global Fund, Bill & Melinda Gates Foundation	Jon Kaplan, Annette Reinisch, Peter Ehrenkranz, Carol Langley
10:15-10:30	Break	
Session 2: Review of the Evidence Base (Session Chair: Peter Ehrenkranz)		
10:30-11:30	What Do We Know? Inventory of Delivery Models and Data	Tendani Gaolathe, Charles Holmes (Facilitators)
11:30-1:00	Breakout Group Discussions: What Do We Need to Know? Gaps in the Evidence Base and Opportunities to Fill Them	Breakout Groups, Topics TBD
1:00-2:00	Lunch	
2:00-2:40	Report Back and Full Group Discussion: What Do We Need to Know? Gaps in the Evidence Base and Opportunities to Fill Them	Francois Venter (Facilitator)
Session 3: Research Agenda (Session Chair: Papa Salif Sow)		
2:40-3:30	Data Quality, Designs, and Key Outcomes for Evaluation	Matt Fox (Facilitator)
3:30-3:45	Break	
3:45-4:15	Prioritization of Research Questions	Ruanne Barnabas (Facilitator)
4:15-4:30	Wrap-Up and Next Steps	Papa Salif Sow, Sydney Rosen

Models for Accelerating Treatment Initiation
Technical Consultation Participants
October 21 & 22, 2015
Cape Town, South Africa

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Presentations/report back from breakout groups at MATI meeting

GROUP 1

Topic:

Timing and speed of treatment initiation*: Once a patient has been diagnosed, how quickly can treatment be started, without risking starting "too fast" and jeopardizing patient welfare or post-initiation outcomes and retention?*

Minimum required provision of counseling and education*: What is the optimal number, duration, timing, staff cadre, and content of non-clinical interactions to ensure that patients are able and willing to adhere to ART?*

1. What % of Option B+ women have treatment changes after initiation? (Retrospective data analysis)

2. Which approach to offering ART has the best outcomes? (Prospective cluster randomized trial)

- Opt out—encourage same day unless you request not
- Offer—encourage same day or within week, unless you request out
- Standard care—whatever the clinic is doing

3. How should clinics be managed for same-day initiation? (Operational study)

4. Are there models for delivering pre/post initiation treatment literacy sessions outside the clinic? (Implementation evaluation)

5. Is more than one education session required during initiation process to obtain good short term outcomes? (Individually randomized trial)

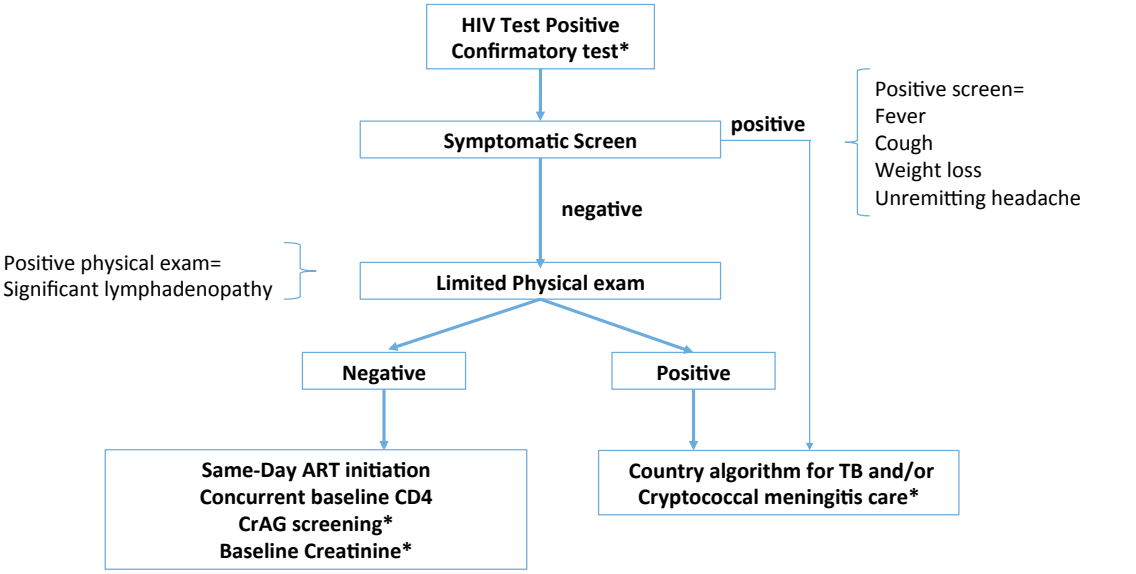
GROUP 2

Topic:

***Minimum required steps to determine clinical eligibility**: What do clinicians have to know before they prescribe ARVs, and what is the most efficient way to generate this information?*

a. Blood tests to determine regimen
b. Tuberculosis
c. Cryptococcal meningitis
d. Baseline viral load?
e. Physical examination

Minimum Required Steps to Determine Clinical Eligibility for Same-Day ART Initiation



* Per country recommendations

1. What do you miss with this algorithm?
    a. Cryptococcal antigen positive that develop CM or death
    b. Tuberculosis unmasking leading to hospitalization or death
    c. Unmeasured elevated creatinine that precipitates renal failure

2. Does the physical exam have added value to identify high risk patients?

GROUP 3

Topic:

***Location of ART initiation**: Can ART be initiated successfully in non-clinical locations?*

a. *Same site HIV testing and initiation*
b. *HIV testing and referral to a clinic for initiation*
c. *HIV testing and initiation in non-clinic settings (e.g. home-based or other community locations)*
d. *Role of home visits by community volunteers (e.g. community health workers) and clinic-based professional staff to support initiation in community and/or clinic settings*
e. *Effect of location of initiation on early retention on ART*

Patient Population	**Location of Initiation**
Newly diagnosed (the entry is testing)	1) Home initiation 2) Community venue based initiation 3) Facility-based SOC
Outreach to persons re-initiating ART (Underserved)	
Persons who refused treatment in the facility (Underserved)	

Outcomes: Rate and proportion of treatment initation, cost, suppression, choice and acceptability

Important question – what is their follow-up strategy

GROUP 4

Topic:

***The demand side: patient behavior and decision making**: What can be done to affect patient behaviors in ways which may lead to successful initiation on ART?*

a. Reducing known patient barriers to enrollment and initiation, including incentives
b. Effect of model of ART initiation on patient retention on ART
c. Targeting delivery models to different patient populations

1. How do we identify individual patient-level barriers and approaches to address these barriers, incorporating patient centered approaches to optimize ART initiation and retention/adherence along the cascade?

2. How can we use existing or innovative approaches, e.g. community groups/CBOs, to address supply and demand barriers to initiation and retention/adherence along the cascade?

3. Are incentives useful in changing patient behaviors, specifically encouraging ART initiation and retention/adherence along cascade – what kind, at what levels, what are adverse consequences?

4. What are community perceptions and acceptability of standard vs rapid vs same-day ART initiation and how do perceptions affect uptake re initiation, retention and adherence?

5. Are there differentiated ICT approaches to messaging (e.g. SMS messaging) to encourage initiation/retention/adherence for different populations, settings, and stage along the cascade?

6. How can these approaches be integrated into bundles of services, e.g. integrating into population health approaches/integrated care?

7. Which behavior change approaches are acceptable, feasible, cost-effective and can be taken to scale? For each approach/intervention, is this approach effective for specific populations, including KPs, or can this be adapted for different populations? Can we use modeling to estimate increase in demand for ART initiation associated with each of the above approaches, and associated costs and necessary resources (ARVs, HR/staffing, etc)?

GR0UP 5

Topic:

The supply side: what do health systems need to have and do?

a. Role of health system context in choosing models of service delivery
b. Reducing known provider barriers to initiation
c. Infrastructural requirements for accelerated initiation
d. Other resource requirements and bottlenecks

1. Skilled human resources:
   a. Which HRH strategies (team size & mix, skills/task sharing) increase the rate of ART initiation?
   b. How to train, mentor and motivate providers to increase the rate of ART initiation?

2. Service decongestion: What novel service delivery strategies increase the rate of ART integration?
   a. Service integration
   b. Visit frequency/schedule
   c. ART distribution approach (pharmacy vs. point of service vs. community)

3. Governance: What are effective, scalable models to improve governance to enable rapid ART initiation?
   a. Systems engineering, quality improvement, audit with feedback
   b. Facility + higher-level administrative units

4. Commodities and supply chain: How to continuously provide essential, quality laboratory and medical supplies (including ARVs) to enable rapid ART initiation?

5. IT/Communication: How can IT better service rapid ART initiation?

Interventions to improve the rate or timing of initiation of antiretroviral therapy for HIV in sub-Saharan Africa: Meta-analyses of effectiveness

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Authors' contributions: MPF and SR designed the study, conducted the literature searches, analyzed the data, and drafted the manuscript. TB, PG, RB and EN provided input into the design and analysis and edited the manuscript.

Abstract

Introduction As global policy evolves toward initiating lifelong antiretroviral therapy (ART) regardless of CD4 count, initiating individuals newly diagnosed with HIV on ART as efficiently as possible will become increasingly important. To inform progress, we conducted a systematic review of pre-ART interventions aiming to increase ART initiation in sub-Saharan Africa.

Methods We searched PubMed, Embase, and the ISI Web of Knowledge from January 1, 2008, to March 1, 2015, extended in PubMed to August 10, 2015, for English language publications pertaining to any country in sub-Saharan Africa and reporting on general adult populations. We included studies describing interventions aimed at increasing linkage to HIV care, retention in pre-ART or uptake of ART, which reported ART initiation as an outcome. We synthesized the evidence on causal intervention effects in meta-analysis of studies belonging to distinct intervention categories.

Results and Discussion We identified 22 studies, which evaluated 24 interventions and included data on 44,048 individual patients. 12 of 22 studies were observational. Rapid/point-of-care CD4 count technology (6 interventions) (RR: 1.30; 95%CI: 1.02-1.67), interventions within home based testing (2 interventions) (RR: 2.00; 95%CI: 1.36-2.92), improved clinic operations (3 interventions) (RR: 1.36; 95%CI: 1.25-1.48) and a package of patient-directed services (3 interventions) (RR: 1.54; 95%CI: 1.20-1.97) were all associated with increased ART initiation as was HIV/TB service integration (3 interventions) (RR: 2.04; 95%CI: 0.59-7.01) but with high imprecision. Provider initiated testing (3 interventions) was associated with reduced ART initiation (RR: 0.91; 95%CI: 0.86-0.97). Counseling and support interventions (2 interventions) (RR 1.07; 95%CI: 0.93-1.24) had no impact on ART initiation. Overall the evidence of outcomes was graded as low or moderate quality using the GRADE criteria.

Conclusions The literature on interventions to increase uptake of ART is limited and of mixed quality. Point-of-care CD4 count and improving clinic operations show promise. More implementation research and evaluation is needed to identify how best to offer treatment initiation in a manner that is both efficient for service providers and effective for patients.

Introduction

A persistent challenge confronting national HIV care and treatment programs in low- and middle-income countries is late initiation of antiretroviral therapy (ART) and high patient attrition between HIV testing and treatment initiation. A recent systematic review found no significant change in CD4 cell counts at ART initiation in sub-Saharan Africa between 2002 and 2013, with the median remaining well below 200 cells/mm^{3}the original (and lowest) threshold for treatment eligbility[1]. The first published systematic review of retention in pre-ART care in sub-Saharan Africa estimated that 40% of patients testing positive for HIV were not linked to care to learn if they were eligible for treatment, and 30% who were eligible never started treatment.[2] Later systematic reviews have confirmed these findings of high rates of patient attrition before starting treatment despite eligibility under the prevailing threshold[3–5].

As global and national guidelines evolve toward initiating lifelong ART for all patients testing positive for HIV, regardless of CD4 cell count[6], the number of diagnosed patients who are not eligible for ART will diminish rapidly. The challenge of retaining patients in pre-ART care will lose its importance, to be replaced by the challenge of initiating on ART individuals newly diagnosed with HIV as efficiently as possible—in other words, maximizing the proportion of patients who do start treatment promptly, while minimizing the costs to both patients and the healthcare system. In recent years, a number of interventions have been developed and implemented that aim to increase uptake of ART for patients known or found to be eligible. To help inform continued progress in this area, we conducted a systematic review of the literature from 2008 to 2015 of pre-treatment interventions that reported the effect of the intervention on ART initiation in sub-Saharan Africa.

Methods

This review is drawn from a larger systematic review of interventions to facilitate linkage to care and ART initiation conducted to support development of the World Health Organization's 2015 Consolidated Guidelines for the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection and completed in June 2015. We include here the subset of articles in that review that were conducted in sub-Saharan Africa and reported rates and/or timing of ART initiation as an outcome.

Search strategy and inclusion criteria

We included in the review randomized controlled trials, quasi-experimental trials, observational cohort studies, and program evaluations describing interventions to improve linkage to or retention in pre-ART care or to improve uptake of ART for those eligible. We searched for studies published or presented in English in 2008 or later pertaining to any country in sub-Saharan Africa and reported on general adult populations. Studies explicitly enrolling high risk populations (e.g. sex workers) were excluded, as were those of interventions to improve initiation of ART for pregnant women in prevention of mother-to-child transmission (PMTCT) programs, as these comprise a different programmatic area than general HIV care. We limited the review to studies that included a comparison with standard-of-care (acknowledging that standard of care varies across settings), so that the effect size could be estimated and would be relevant to routine practice. We required that each study report an effect estimate for the intervention or risk/rates of outcomes between the two groups compared. Finally, as noted above, we required that each study report an outcome of an effect on the rate or timing of ART initiation. We accepted each article's own definition of "initiation" but presume that in nearly every case it referred to a patient being prescribed or dispensed an initial supply of ARVs.

To identify studies, we searched PubMed, Embase, and the ISI Web of Knowledge from January 1, 2008, to March 1, 2015, for English language publications. Within each index, we combined "HIV" or "antiretroviral therapy" with any of "linkage," "pre-ART," "initiation," "retention," "attrition," "adherence," "loss to follow up," or "patient compliance" and any of "efficacy," "evaluation," "intervention," or "trial" (Additional file 1). To find relevant abstracts, we manually searched conference sessions on linkage to care and retention in care at AIDS and IAS conferences from 2008 to 2014 and CROI 2014 and 2015 (CROI abstracts from earlier years are not available). To identify sources missed by these methods, we searched reference lists of review articles identified through electronic database searches. PubMed was also searched to determine if conference abstracts have been published as full articles.

We then screened the articles that met the criteria for inclusion in the larger review for results pertaining to ART initiation, sub-Saharan Africa, and adults. Finally, we updated the search for publications between March 1 and August 10, 2015 using a targeted search strategy focusing on initiation, using the search syntax [(HIV OR "antiretroviral therapy") AND (initiation) AND (efficacy OR evaluation OR intervention OR trial) AND (Africa)] in PubMed and manually searched abstracts presented at IAS 2015.

M.P.F. conducted the primary search and S.R. conducted the targeted search. After excluding those whose titles were not relevant, abstracts were read to determine eligibility. Full-text articles were reviewed by both authors to confirm eligibility. Uncertainties were resolved through consensus of both authors. We did not contact the authors of studies for primary data.

Analysis

After extracting a standard set of indicators from each article, we first described the interventions included as to country, population, intervention, dates, and outcomes. We then grouped the interventions by major approach into seven categories: counseling and support, HIV/TB integration, interventions within provider initiated HIV testing, home-based HIV self-testing, use of a rapid/point-of-care CD4 count, improved clinic operations, and implementing a package of patient-centered services. Where an intervention could arguably be assigned to more than one category, we chose the one that captured the aspect of the intervention most emphasized by the authors. By category, we estimated the measure of effect for each study, with corresponding 95% confidence intervals as reported, or when not reported, as calculated from the data.

We assessed the quality of the body of studies in each category of interventions using the GRADE methodology[7]. We note that because many of the studies reviewed were observational in nature, few were expected to be considered high quality using the GRADE methodology. We then conducted a random-effects meta-analysis for each category to estimate a summary relative risk and 95% confidence interval for each category of interventions. For each we present the results, relative weights and the corresponding I^2 values.

Results

Our primary search, illustrated in Figure 1, identified a total of 8044 full text articles and abstracts. After an initial screen of the titles and abstracts, 409 citations met our initial screening criteria. Upon further review, 136 were deemed relevant for full text review. Of these, 22 met all the inclusion criteria and were included in the final review.

The 22 included studies, which evaluated 24 interventions, are described in Table 1. They included data on 44,048 individual patients. Nine countries were represented, all in eastern or southern

Africa. Three studies enrolled both adult and pediatric patients as defined by the studies, while the rest enrolled only adults. All of the studies were published in 2010 or later, with a large proportion (55%, 12/22) published in 2014 or 2015, signaling a recent rise in attention to this issue. About 55% (12/22) of the studies included were observational in nature with either pre-post (36%, 8/22) or parallel (18%, 4/22) designs. The remaining 45% (10/22) were randomized trials, primarily individually randomized trials (32%, 7/22).

The interventions evaluated in each study, the outcomes assessed, and the results as grouped by the authors are presented in Table 2. Table 3 presents our assessment of the quality of the evidence and meta-analysis results by category of intervention. Below we summarize results for each category of interventions and the evidence for each as shown in Tables 1-3. Effects of all the interventions are synthesized using a random effects meta-analysis in Figure 2. Forest plots for each set of interventions with corresponding weights and I^2 values (Additional file 2).

Counseling and support interventions

We identified five counseling and support interventions evaluated in four studies, all conducted in South Africa and/or Uganda. In total, the studies included 2912 individuals. All were individually randomized trials. The interventions were lay counselor home visits after a home-based CD4 count[8]; lay counselor clinic visit facilitation[8]; home visits, calls, and text messages by patient navigators[9]; home visits by peer supporters[10]; and provision of an informational brochure to patients explaining how to obtain further care[11]. Rates of ART initiation among control-arm patients eligible for treatment were low, at only 32% when pooled across the four studies. Only one of the four interventions, lay counselor home visits, had a significant positive effect, with a risk difference of 7% (relative risk [95% CI] 1.23 [1.03-1.46])[8]. The meta-analysis estimated that the counseling and support interventions included in the review had little to no impact on ART initiation (RR 1.07; 95%CI: 0.93-1.24). Because all four studies were randomized trials, this was the intervention category with the overall best quality and was graded as moderate quality, as shown in Table 3.

HIV/TB integration

We found three studies that reported on interventions to integrate HIV and TB services. One was a cohort study in South Africa that examined co-locating HIV and TB services (referred to as "semi-integrated")[12], while two were pre-post studies of fully integrated HIV and TB services, one in Uganda[13] and one in the Democratic Republic of Congo[14]. In total, the three studies included 1695 subjects. Two of the three studies showed a large benefit. When pooled across the three studies, rates of ART initiation were moderate in the control arm (39%). When combined in a meta-analysis, HIV/TB service integration was associated with 2-fold increase in ART initiation compared to non-integrated care (RR: 2.04; 95%CI: 0.59-7.01) but with very poor precision. With only three studies, all of which were observational, the overall quality of evidence was very low.

Provider initiated HIV testing

Two studies reported the impact of provider initiated HIV testing (PITC) on ART initiation, one in South Africa[15] and one in Zambia[16]. One was a pre-post studies and one was a cohort study. They included a total of 9636 subjects. One of the interventions showed a very small increase and the other a decrease in ART initiation associated with PITC. Overall ART initiation in the control group was 69%. When the data were combined through meta-analysis, PITC was the only category of interventions that was associated with reduced ART initiation (RR: 0.91; 95%CI: 0.86-0.97). This should be interpreted with caution as the absolute reduction in ART initiation was only 1%. In addition it is important to note here that patients in PITC and those identified through VCT are likely

different with respect to their disease stage, making it difficult to draw strong conclusions. As there were only two studies and all were observational, the overall quality of the evidence was very low.

Interventions combined with home-based HIV testing

Two cluster-randomized trials examined the effect on ART initiation of interventions combined with home-based HIV testing, one in Kenya and one in Malawi. The study in Kenya compared home-based testing with point of care (POC) CD4 counts to home-based testing with standard referral[17]. The study in Malawi compared home-based testing with optional home ART initiation to home-based testing with facility-based care[18]. Both showed a benefit in term of ART initiation. In our meta-analysis, home based testing was associated with an increase in ART initiation (RR: 2.00; 95%CI: 1.36-2.92). The studies included a total of 17,352 subjects, but it is important to note that the denominator in the Malawi study[18] included all persons tested, not just those testing HIV-positive or eligible for ART, making overall rates of ART initiation appear very low. This has a strong influence on the overall results, as the pooled rate of ART initiation in the control group was just 0.7%, leading the meta-analysis relative estimate of a 100% increase in ART initiation to translate into only a 1.7% absolute increase. While both of the studies included were RCTs, as there were only two studies, the overall quality of the evidence was graded as low.

Rapid point-of-care CD4 count technology

Five observational studies and one randomized trial evaluated the effect of rapid/point-of-care CD4 count technology on ART initiation in South Africa (3), Botswana, Malawi, and Mozambique. Three tested the effect of point of care testing using Alere Pima machines[19–21] and two used same day BD FACSCount results[11,22]. One study did not report the sample size or a confidence interval for its reported relative risk so could not be included in the meta-analysis. The remaining four studies enrolled 1819 subjects. The pooled rate of ART initiation in the control group was 47%. Three of the interventions showed a benefit, while two showed little or no effect. In our meta-analysis, rapid/point-of-care CD4 count technology was associated with an increase in ART initiation (RR: 1.30; 95%CI: 1.02-1.67). While this category had the largest number of studies, all but one were observational, and the overall quality of the evidence was thus considered low.

Improved clinic operations

Two studies conducted in South Africa[23,24] and one in Mozambique[7] evaluated multi-faceted changes to clinic operations. The interventions, which were very diverse, are described in detail in Tables 1 and 2. Each included two or more of a range of activities: enhanced counseling and support, task shifting, provider training, point-of-care technology, HIV service integration, improved clinic management, and others. Two were RCTs (1 individually randomized, 1 cluster randomized) and one was an observational study. One study did not report the sample size[25], but for the two remaining, the total number of subjects was 9,626. The pooled rate of ART initiation in the control group was 63%. All three of the interventions increased ART initiation (though one had a very wide confidence interval)[23]. In our meta-analysis, improved clinic operations showed a benefit in terms of increased ART initiation (RR: 1.36; 95%CI: 1.25-1.48). This result should be interpreted with caution, however, given the heterogeneity of the interventions. The specific mix of activities included in each intervention may determine its effect, such that different combinations would produce different results from those reported here. Overall the quality of the evidence was low, as there were only three studies and one was a pre-post design.

Package of patient services

We identified three studies that explored the impact of a package of patient-directed services. As with the previous category, each package included two or more services, described in detail in Tables 1 and 2. One was a pre-post study in Swaziland[26] that tested the effect of a package of pre-ART services; one a pre-post study in Uganda testing the effect of SMS notification of CD4 results combined with transport reimbursement[27]; and the third a randomized trial in Uganda[28] that tested a package of enhanced linkage with case-management referral. All three showed a benefit in terms of treatment initiation. The rate of ART initiation in the control group was 63%. In our meta-analysis, the interventions were associated with an increase in initiation (RR: 1.54; 95%CI: 1.20-1.97). As there were only three studies and two were observational, the evidence was considered low quality.

Discussion

Over the decade of large scale public sector access to HIV treatment in sub-Saharan Africa, numerous reviews have documented losses from the HIV care and treatment cascade[29], documenting particularly high attrition between HIV testing and ART initiation[2]. In light of the World Health Organization's recent recommendation that treatment be offered to all people living with HIV with HIV at any CD4 count[30], the steps needed for patients to access care will change dramatically, effectively eliminating the interval of "pre-ART care" during which ineligible patients were monitored for disease progression. In the new cascade of care that the WHO recommendations suggest, the most likely points at which patients who test positive for HIV will become lost to care are between linkage from an HIV testing site to an HIV treatment site and between an initial visit to an HIV treatment site and ART initiation. To inform this new paradigm, we systematically reviewed the literature on interventions aimed at pre-ART care but which specifically focused on, or presented data on, changes in the rate or timing of ART initiation, the outcome most relevant to this new, simplified cascade of care. We focused on sub-Saharan Africa as most of the studies we identified overall were from this region, making it difficult to generalize to other areas.

Because interventions to improve pre-ART care outcomes are diverse and heterogeneous, we grouped the interventions into categories representing similar approaches to improving care. While the overall body of evidence was mixed, we found several approaches that were promising in terms of ART initiation. Integrating HIV and TB services, whether through simply co-locating the services, or fully integrating them, was associated with a roughly 40% increase in rates of ART initiation among individuals with active TB and living with HIV. This finding expands upon the conclusions of a previous 2011 review[31] which found benefits from co-locating services for adherence and retention on ART but provided little evidence on whether co-location improved ART uptake. As our results are based on only three studies and low quality evidence, and one of the three studies did not find a benefit for ART initiation, more research on TB/HIV integration interventions is needed before strong conclusions can be drawn.

Another area that showed promise was the use of rapid and/or point of care CD4 count technology. Use of machines such as the Alere Pima for rapid CD4 results increases the proportion of patients who learn that they are eligible for treatment and reduces the number of visits required to initiate treatment[32]. As the most recent WHO recommendation to initiate ART regardless of CD4 count is adopted into national policies, the CD4 count will lose its primary role in establishing treatment eligibility. Nonetheless, CD4 counts may be retained as a valuable clinical component of the initiation algorithm in many countries for years to come, in identification of the sickest. In the studies reviewed here, use of rapid and/or point of care CD4 count technology was associated with about a 40% increase in ART initiation (random effects RR 1.37; 95% CI: 1.26-1.48) compared to standard of care referral for CD4 testing. Offering a point of care CD4 count has previously been

shown to be effective at increasing the proportion of patients who receive their CD4 test results[32–34]. Our findings with regard to ART initiation are in the same direction as, but smaller than, those of a previous meta-analysis on point of care CD4 testing, which reported a relative risk of 1.8 (95% CI: 1.1-2.9)[33].

Finally, multi-faceted interventions that improved clinic operations or offered a package of patient services also showed promise and perhaps have the most relevance to future treatment guidelines. Such approaches target more than one step in the cascade, strengthening both linkage to care after HIV testing and treatment initiation after linkage. In these two categories we found only five studies in total, but all reported a benefit, with a combined risk ratio of 1.36 (95% CI: 1.25-1.48) for improved clinic operations and 1.54 (95% CI: 1.20-2.00) for improvements in the package of patient services. Although these results agree with data from other parts of the world and in other patient populations, the approaches remain diverse and the quality of the evidence is low. More high quality studies will be needed before we can draw strong conclusions and discern which specific components of the interventions might be most important for achieving results.

Other interventions, including peer and lay counselor support and provider-initiated HIV testing showed little impact on ART initiation. This is particularly disappointing for peer and lay counselor support, which had previously been found to be effective at increasing linkage to care[32] but here had no benefit for ART initiation. PITC, moreover, appears to be associated with a slight reduction in ART initiation, though in light of the low quality of evidence, at best we can say there appears to be no benefit. PITC may be identifying patients who do not wish to volunteer for care, and thus increase the denominator (patients who could start ART) without changing the numerator (patients who do start ART). In contrast, the studies reviewed suggest that interventions within a platform of home-based HIV testing interventions have promise for increasing ART uptake.

Beyond the small number of studies found that estimated the effect of interventions in increasing ART uptake, the overall quality of the studies was quite poor. To some extent, the apparent low quality of the literature reviewed here stems from the fact that interventions to improve pre-ART care and increase uptake of ART are largely structural or behavioral. Unlike for drug trials, results depend heavily on the details of how the intervention was designed, to whom it was delivered (in terms of population age, gender, socioeconomic status) where it was delivered (community, facility level, etc.), which outcomes were assessed, and to what they were compared (standard of care, another intervention, etc.). In this review, we found very few reports of studies that evaluated the effect of the same intervention on the same outcome or population. For example, a point-of-care CD4 count using the same technology may have sharply different results in urban and rural settings, or when used at community-based or facility-based HIV testing sites. For this reason, trying to generalize from just a few studies—even those of moderate or high quality—is potentially misleading. For every intervention considered, context—location, population, outcome, etc.—is an essential component of understanding effectiveness.

In addition to the need for more, and more rigorous, evaluations of interventions, a consideration that was omitted from nearly all the studies reviewed here is retention of patients on ART in the immediate aftermath of initiation. For most researchers examining the pre-ART care period, ART initiation has been an endpoint, with no follow-up to investigate whether the mode or timing of initiation is associated with outcomes once treatment has been started. As the global paradigm for "pre-ART care" evolves, and more effective ways to move patients from HIV testing to ART initiation are sought and implemented, studies that assess not just uptake of ART, but uptake with early retention on ART, would strengthen the evidence base.

In conclusion, in a systematic review of the literature from 2008 to mid-2015 reporting on interventions to increase rates of ART initiation in sub Saharan Africa, we found only 22 studies. They were diverse in nature, ranging from counseling or technology interventions focused on one step in the pre-ART cascade to multi-faceted rearrangements of how care is provided. Some promising approaches were identified and merit further research on their effect and cost-effectiveness in a range of settings and populations. For all the approaches identified, however, the number of studies was small and quality mixed. In view of the new global recommendation of starting all HIV-positive individuals on ART, rather than attempting to retain those with high CD4 counts in pre-ART care, researchers must invest far more effort in identifying and evaluating how best to offer treatment initiation in a manner that is both efficient for service providers and effective for patients, without jeopardizing treatment outcomes.

References

1. Siedner MJ, Ng CK, Bassett I V, Katz IT, Bangsberg DR, Tsai AC. Trends in CD4 count at presentation to care and treatment initiation in sub-Saharan Africa, 2002-2013: a meta-analysis. Clin Infect Dis 2014; 60: 1120–7.
2. Rosen S, Fox MP. Retention in HIV care between testing and treatment in Sub-Saharan Africa: a systematic review. PLoS Med 2011; 8: e1001056.
3. Mugglin C, Estill J, Wandeler G, et al. Loss to programme between HIV diagnosis and initiation of antiretroviral therapy in sub-Saharan Africa: systematic review and meta-analysis. Trop Med Int Heal 2012; 17: 1509–20.
4. Kranzer K, Govindasamy D, Ford N, Johnston V, Lawn SD. Quantifying and addressing losses along the continuum of care for people living with HIV infection in sub-Saharan Africa: a systematic review. J Int AIDS Soc 2012; 15: 17383.
5. Govindasamy D, Ford N, Kranzer K. Risk factors, barriers and facilitators for linkage to antiretroviral therapy care. AIDS 2012; 26: 2059–67.
6. Doherty M. New Directions in the 2015 Consolidated ARV Guidelines Update. Geneva: World Health Organization, 2015.
7. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Br Med J 2008; 336: 924–6.
8. Barnabas R V, Van Rooyen H. Community-based HIV testing and linkage effectively delivers combination HIV prevention: results from a multisite randomized trial. IAS 2015 Conf 2015; AbstractMO.
9. Bassett I V, Coleman S, Giddy J, et al. Linkage to HIV/TB care in South Africa: a randomized trial of health navigators. Conference on Retroviruses and Opportunistic Infections 2015, Seattle, February 23-26, 2015 (Abstract 93).
10. Chang L, Nakigozi G, Billioux VG, et al. Peer support and engagement, HIV care, and sexual behaviors among PLHIV not on ART: a randomized trial. Conference on Retroviruses and Opportunistic Infections 2014, Boston (Abstract 1057).
11. Faal M, Naidoo N, Glencross DK, Venter WD, Osih R. Providing immediate CD4 count results at HIV testing improves ART initiation. J Acquir Immune Defic Syndr 2011; 58: e54–9.
12. Louwagie G, Girdler-Brown B, Odendaal R, Rossouw T, Johnson S, Van der Walt M. Missed opportunities for accessing HIV care among Tshwane tuberculosis patients under different models of care. Int J Tuberc Lung Dis 2012; 16: 1052–8.
13. Hermans SM, Castelnuovo B, Katabira C, et al. Integration of HIV and TB services results in improved TB treatment outcomes and earlier prioritized ART Initiation in a large urban HIV Clinic in Uganda. J Acquir Immune Defic Syndr 2012; 60: e29–35.
14. Van Rie A, Patel MR, Nana M, et al. Integration and task shifting for TB/HIV care and treatment in highly resource-scarce settings: one size may not fit all. J Acquir Immune Defic Syndr 2014; 65: e110–7.

15. Clouse K, Hanrahan CF, Bassett J, Fox MP, Sanne I, Van Rie A. Impact of systematic HIV testing on case finding and retention in care at a primary care clinic in South Africa. Trop Med Int Heal 2014; 19: 1411–9.
16. Topp SM, Li MS, Chipukuma JM, et al. Does provider-initiated counselling and testing (PITC) strengthen early diagnosis and treatment initiation? Results from an analysis of an urban cohort of HIV-positive patients in Lusaka, Zambia. J Int AIDS Soc 2012; 15: 1–9.
17. Desai MA, Okal D, Rose C, et al. Point-of-Care CD4 (Pima) Impact on linkage to care with home-based HIV testing, Kenya. Conference on Retroviruses and Opportunistic Infections 205, Seattle, February 23-26, 2015 (Abstract 30329).
18. MacPherson P, Lalloo DG, Webb EL, et al. Effect of optional home initiation of HIV care following HIV self-testing on antiretroviral therapy initiation among adults in Malawi: a randomized clinical trial. JAMA 2014; 312: 372–9.
19. Jani I V, Sitoe NE, Alfai ER, et al. Effect of point-of-care CD4 cell count tests on retention of patients and rates of antiretroviral therapy initiation in primary health clinics: An observational cohort study. Lancet 2011; 378: 1572–9.
20. Nicholas S, Schramm B, et al. Effect of point-of-care cD4 testing on time to aRT-initiation and Pre-aRT attrition in rural decentralized health centers in Chiradzulu District, Malawi. IAS 2015.
21. Moyo M, et al. Effect of PIMa point of care instruments for CD4 counting on time to ART initiation in rural Botswana. IAS 2015.
22. Larson B a., Schnippel K, Brennan A, et al. Same-day CD4 testing to improve uptake of HIV care and treatment in South Africa: Point-of-care is not enough. AIDS Res Treat 2013; 6–10.
23. Fairall L, Bachmann MO, Lombard C, et al. Task shifting of antiretroviral treatment from doctors to primary-care nurses in South Africa (STRETCH): A pragmatic, parallel, cluster-randomised trial. Lancet 2012; 380: 889–98.
24. Rosen S, Maskew M, Fox MP, et al. Rapid ART initiation reduces loss between HIV testing and treatment: the RapIT trial. Conference on Retroviruses and Opportunistic Infections 2015, Seattle, February 23-26, 2015 (Abstract 1091).
25. Pfeiffer J, Montoya P, Baptista AJ, et al. Integration of HIV/AIDS services into African primary health care: Lessons learned for health system strengthening in Mozambique - A case study. J Int AIDS Soc 2010; 13: 3.
26. Burtle D, Welfare W, Elden S, et al. Introduction and evaluation of a 'pre-ART care' service in Swaziland: an operational research study. BMJ Open 2012; 2: e000195–e000195.
27. Siedner MJ, Santorino D, Lankowski AJ, et al. A combination SMS and transportation reimbursement intervention to improve HIV care following abnormal CD4 test results in rural Uganda: a prospective observational cohort study. BMC Med 2015; 13: 160.
28. Wanyenze RK, Kamya MR, Fatch R, et al. Abbreviated HIV counselling and testing and enhanced referral to care in Uganda: A factorial randomised controlled trial. Lancet Glob Heal 2013; 1: e137–45.
29. Fox MP, Rosen S. Retention of adult patients on antiretroviral therapy in low- -and middle--income countries: systematic review 2008. J Acquir Immune Defic Syndr 2015; 69: 98–108.
30. World Health Organization. Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV. Geneva: WHO, 2015.
31. Uyei J, Coetzee D, Macinko J, Guttmacher S. Integrated delivery of HIV and tuberculosis services in sub-Saharan Africa: a systematic review. Lancet Infect Dis 2011; 11: 855–67.
32. Govindasamy D, Meghij J, Kebede Negussi E, Clare Baggaley R, Ford N, Kranzer K. Interventions to improve or facilitate linkage to or retention in pre-ART (HIV) care and initiation of ART in low- and middle-income settings - a systematic review. J Int AIDS Soc 2014; 17: 19032.
33. Wynberg E, Cooke G, Shroufi A, Reid SD, Ford N. Impact of point-of-care CD4 testing on linkage to HIV care : a systematic review. J Int AIDS Soc 2014; 17: 18809.
34. Okeke NL, Ostermann J, Thielman NM. Enhancing linkage and retention in HIV care: a review of interventions for highly resourced and resource-poor settings. Curr HIV/AIDS Rep 2014; 11: 376–

92.
35. Matambo T, Hildebrand K, Mwongera C, et al. Impact of a mobile HIV/TB service on pre-ART retention among migrant farm-workers in Musina, South Africa. AIDS 2012, Washington DC (Abstract TUPE719).

Table 1. Characteristics of studies included in the review

Publication			Location		Study				
Study ID	**Type**	**Year**	**Country**	**Sites**	**Design**	**Population**	**Data collection**	**Starting point**	**Ending point**
Counseling/support									
Barnabas 1[8]	Abstract	2015	South Africa and Uganda	KwaZulu Natal and Sheema Districts	Individually randomized trial	HIV positive patients at home based testing	June 2013 - Feb 2015	HIV testing	ART initiation
Barnabas 2[8]	Abstract	2015	South Africa and Uganda	KwaZulu Natal and Sheema Districts	Individually randomized trial	HIV positive patients at home based testing	June 2013 - Feb 2015	HIV testing	ART initiation
Bassett[9]	Abstract	2015	South Africa	2 hospital outpatient departments and 2 primary health clinics	Individually randomized trial	Adults newly testing HIV positive and ART eligible		HIV testing	On ART 3 months
Chang[10]	Article	2015	Uganda	Rakai District	Individually randomized trial	Adults HIV positive not on ART	June 2011 to July 2013	HIV testing	ART initiation
Faal 1[11]	Article	2011	South Africa	One urban primary health care clinic (Esselen clinic) in the inner city of Johannesburg	Individually randomized trial	Adults newly testing HIV positive and ART eligible	Aug to Dec 2009	HIV testing	ART initiation
HIV/TB integration									
Hermans[13]	Article	2012	Uganda	The Infectious Diseases Institute at Makerere, University College of Health Sciences in Kampala, Uganda	Pre/post cohort study	Adults HIV positive with TB	2007 and 2009	TB treatment initiation	ART initiation
Louwagie [12]	Article	2012	South Africa	46 TB treatment points in Tshwane, South Africa	Cohort study	Adults HIV positive with TB who were ART eligible	Oct 2008 to March 2009 (enrollment)	HIV testing	ART initiation
Van Rie [14]	Article	2014	Democratic Republic of Congo (DRC)	5 clinics in Kinshasa, DRC	Pre/post cohort study	Adults HIV positive with TB	January 2006 - November 2009	HIV testing	ART initiation
Provider initiated counseling and testing									
Clouse[15]	Article	2014	South Africa	Witkoppen Health and Wellness Centre	Pre/post cohort study	Adults newly testing HIV positive and ART	Jan 2010 - July 2012 (enrollment)	HIV testing	ART initiation

Publication			Location		Study				
Study ID	**Type**	**Year**	**Country**	**Sites**	**Design**	**Population**	**Data collection**	**Starting point**	**Ending point**
Topp[16]	Article	2012	Zambia	Seven urban-integrated primary care clinics	Cohort study	Adults and children newly testing HIV positive and ART eligible	July 2008 to June 2011	HIV testing	ART initiation
Interventions within home based HIV testing									
Desai[17]	Abstract	2015	Kenya	2 rural districts of Western Kenya	Cluster randomized trial	Adults newly testing HIV positive	July 2013-February 2014 (enrollment)	HIV testing	ART initiation
MacPherson[18]	Article	2014	Malawi	Multiple sites in Blantyre, Malawi	Cluster randomized trial	Adults (all) in the study clusters	Jan 30 to Nov 5, 2012	HIV testing	ART initiation
Rapid/point-of-care CD4 count technology									
Faal 2[11]	Article	2011	South Africa	One urban primary health care clinic (Esselen clinic) in the inner city of Johannesburg	Individually randomized trial	Adults newly testing HIV positive and ART eligible	Aug to Dec 2009	HIV testing	ART initiation
Jani[19]	Article	2011	Mozambique	Four public primary health clinics in the Maputo and Sofala provinces	Cohort study	Enrolled adults and children getting a blood draw for CD4 staging	2009	CD4 staging completion	ART initiation
Larson[22]	Article	2013	South Africa	Themba Lethu Clinic, Johannesburg	Pre/post cohort study	Adults newly testing HIV positive	January 2008–July 2010	HIV testing	ART initiation
Matambo [35]	Abstract	2012	South Africa	Musina Sub-District	Pre/post cohort study	Adults newly testing HIV positive	July 2009 to December 2011	HIV testing	ART initiation
Moyo [21]	Abstract	2015	Botswana	6 rural clinics in Tutume	Pre/post cohort study		Jan 2013 to Feb 2014		ART initiation
Nicholas [20]	Abstract	2015	Malawi	Rural decentralized health centers in Chiradzulu District, Malawi	Cohort study	Adults and children	July 2013 to October 2014	CD4 blood draw	ART initiation
Improved clinic operations									
Fairall[23]	Article	2012	South Africa	31 primary care clinics in the Free State Province	Cluster randomized trial	Adults HIV positive not on ART but eligible or approaching eligibility	Jan 28, 2008 to June 30, 2010	CD4 staging completion	ART initiation
Pfeiffer[25]	Article	2010	Mozambique	12 clinics in Sofala and Manica Provinces	Pre/post cohort study	Adults eligible for ART	2004 to 2007	ART eligibility	ART initiation

Publication			Location		Study				
Study ID	**Type**	**Year**	**Country**	**Sites**	**Design**	**Population**	**Data collection**	**Starting point**	**Ending point**
Rosen[24]	Abstract	2015	South Africa	Two public sector outpatient clinics in Johannesburg	Individually randomized trial	Adults newly testing HIV positive	April 2013-Aug 2014 (enrollment)	HIV testing	ART initiation
Package of patient services									
Burtle[26]	Article	2012	Swaziland	Good Shepherd Hospital, the district referral hospital for the Lubombo region	Pre/post cohort study	Adults eligible for ART	February 2009-Feb 2010 (enrollment)	ART eligibility	ART initiation
Siedner [27]	Article	2015	Uganda	Mbarara, Uganda	Pre/post cohort study	Adults HIV positive	Jan 2012-Nov 2013	CD4 blood draw	ART initiation
Wanyenze[28]	Article	2013	Uganda	Mulago Hospital, Uganda	Individually randomized trial	Adults newly testing HIV positive and ART eligible	May 2008 to June 2011 (enrollment)	ART eligibility	ART initiation

- *ART initiation* indicates that at least the first dose of ARV medications has been prescribed or dispensed.

Table 2. Reported results of included studies

Study ID	Intervention	Comparison	Outcome	Timing of outcome	N intervention (control)	Risk/rate intervention (control)	Effect size	95% confidence interval	p value	Interpretation
Counseling and support										
Barnabas 1	Clinic visit facilitation	Standard of care referral	ART initiation		431 (423)	0.37 (0.34)	RR 1.11		0.26	Clinic visit facilitation was not associated with any difference in ART initiation
Barnabas 2	Lay counselor follow-up	Standard of care referral	ART initiation		449 (423)	0.41 (0.34)	RR 1.23		0.028	Lay counselor follow up was associated with an increase in ART initiation
Bassett	Patient navigators using a strengths-based case management approach and scheduled phone calls and text messages over 4 months	Standard of care	On ART for those ART eligible	3 months on ART	618 (528)	0.34 (0.37)	RR 0.92*	0.79 - 1.07*	0.6	This approach to patient navigation was not associated with an increase in linkage to care
Chang	Peer supporters with monthly visits to provide support and counseling	Standard of care	Currently on ART (self-reported)	One year	194 (199)	0.37 (0.36)	PR 1.03	0.78 - 1.34		This approach to peer support was not associated with an increase in treatment initiation
Faal 1	Immediate receipt of CD4 count results (FACSCount)	Standard collection of CD4 result only	ART initiation	1 month	35 (36)	0.37 (0.25)	RR 1.49*	0.37 - 3.03*		Leaflets were not associated with a significant increase in ART initiation among those ART eligible.
HIV/TB integration										
Hermans	Integrated TB/HIV care and treatment	Standard of care	ART initiation		243 (228)	0.57 (0.66)	RR 0.86	0.75 – 1.0*	0.034	ART and TB treatment integration did not lead to an increase in ART initiation
Louwagie	ART and TB care at same site ('semi-integrated')	Geographically separately rendered HIV and TB care	ART initiation		105 (233)	0.71 (0.45)	sHR 2.49	1.06 - 5.88		ART and TB treatment under one roof was associated with an increase in ART initiation for HIV-positive TB patients
Van Rie	Integrated TB/HIV care and treatment	Standard of care referral to centralized ART facility after diagnosis	ART initiation		513 (373)	0.69 (0.17)	RR 4.06*	3.21 - 5.13*		Integrated services was associated with an increase in ART initiation
Provider initiated HIV testing										

Study ID	Intervention	Comparison	Outcome	Timing of outcome	N intervention (control)	Risk/rate intervention (control)	Effect size	95% confidence interval	p value	Interpretation
Clouse	Systematic opt-out HCT for all adult clients	Targeted PICT and voluntary counseling and testing	ART initiation	12 months after diagnosis	717 (744)	0.64 (0.59)	RR 1.08*	1.00-1.18*	0.05	Systematic opt-out HCT was associated with a small increase in ART initiation among those ART eligible
Topp	Provider initiated testing and counseling for adults and children	Voluntary counseling and testing	ART initiation		1655 (6520)	0.72 (0.69)	aOR 0.9	0.82 - 0.97	0.01	Integrated care was associated with a small decrease in the odds of being initiated on ART if eligible
Interventions combined with home based HIV testing										
Desai	POC CD4 count at home based HIV testing with referral	Standard of care home based HIV testing and referral	ART initiation		371 (321)	0.17 (0.10)	RR 1.65*	1.11 - 2.54*	0.01	POC CD4 during home-based HCT was associated with an increase in ART initiation
MacPherson	HIV self-testing followed by optional home initiation of HIV care	HIV self-testing accompanied by facility- based HIV care	ART initiation	6 months	8194 (8466)	0.022 (0.007)	aRR 2.44	1.61 - 3.68	<0.001	HIV self-testing followed by optional home initiation was associated with a significant increase in ART initiation over 6 months among all testers
Rapid/Point-of-care CD4 count										
Faal 2	Same day CD4 count results (FACSCount)	Standard collection of CD4 result only	ART initiation	1 month	43 (36)	0.65 (0.25)	RR 2.1	1.39 - 3.17		Same day receipt of CD4 counts was associated with a significant increase in ART initiation among those ART eligible.
Jani	POC CD4 count (Pima)	Standard of care lab referral of blood for CD4 staging	ART initiation		437 (492)	0.65 (0.61)	OR 1.07*	0.87 - 1.30*		POC CD4 count staging was not associated with a significant increase in ART initiation among those eligible
Larson	Same day CD4 count results (FACSCount)	Standard of care	ART initiation	≤ 16 weeks	273 (223)	0.49 (0.46)	aRR 1.2	0.99 - 1.46	0.06	Rapid POC CD4 results were associated with a small non-significant increase in ART initiation among eligible
Matambo	Integrated mobile HIV/TB primary health care with POC CD4 testing (Pima)	Standard of care	ART initiation		226 (380)	0.83 (0.51)	RR 1.63*	1.45 - 1.83*	<0.0001	Integrated services was associated with an increase in linkage to care
Moyo	Point of care CD4 count (PIMA)	Standard of care	ART initiation				RR 1.33		0.01	POC led to an increase in ART initiation

Study ID	Intervention	Comparison	Outcome	Timing of outcome	N intervention (control)	Risk/rate intervention (control)	Effect size	95% confidence interval	p value	Interpretation
Nicholas	Point of care CD4 count (PIMA)	Standard of care	ART initiation	Any time	253 (259)		RR 0.96	0.91 - 1.01		POC led to no overall increase in ART initiation among those eligible
Improved clinic operations										
Fairall	Prescribing nurses given educational outreach training sessions about ART prescribing and task shifting to nurses	Standard of care	ART initiation	At least 12 months	5390 (3862)	0.69 (0.63)	RR 1.24[#]	0.88 - 1.73	0.218	Training and task-shifting to nurses was associated with a small non-significant increase in ART initiation
Pfeiffer	HIV service integration including co-location of services; training personnel to provide multiple services; training to link separate services; strengthening linkages between facility levels; and harmonization of data collection	Standard of care	ART initiation	≤ 90 days of eligibility			RR 1.58	1.17 - 2.14		HIV service integration was associated with an increase in ART initiation
Rosen	Immediate (rapid) ART initiation including POC technology and service delivery acceleration	Standard of care	ART initiation	≤ 90 days after testing HIV positive and ART eligible	185 (189)	0.98 (0.72)	RR 1.35	1.23 - 1.48		Immediate ART initiation was associated with an increase in uptake of ART within 90 days
Package of patient services										
Burtle	Introduction of pre-ART interventions, including task shifting, counseling, clinical staging, timely ART initiation, social and psychological support	Standard of care	ART initiation		419 (68)	0.81 (0.53)	RR 1.53*	1.22 - 1.92*		The intervention was associated with a 50% increase in ART initiation among those ART eligible
Siedner	SMS notifying patients of CD4 results; if early return to clinic required, 1 of 3 messages and transport reimbursement	Standard of care	ART initiation		110 (26)	0.96 (0.81)	aHR 2.26	1.38 - 3.73	0.001	SMS notification was associated with a significant increase in ART initiation

Study ID	Intervention	Comparison	Outcome	Timing of outcome	N intervention (control)	Risk/rate intervention (control)	Effect size	95% confidence interval	p value	Interpretation
Wanyenze	Enhanced linkage with case-management referral (counseling, assisted disclosure of HIV status, staff introduction and scheduling, reminder via telephone or home visit 1 week before the scheduled appointment) and tracing of lost patients	Standard linkage to care (explanation of services, hours, and locations of the clinics nearby)	ART initiation among those eligible	1 year	202 (183)	0.78 (0.71)	aHR 1.29[@]	1.03 - 1.67[@]	0.03	Enhanced linkage was associated with a significant increase in ART initiation among those eligible

RR, relative risk; aRR, adjusted relative risk; aIRR, adjusted incidence rate ratio; OR, odds ratio; aOR, adjusted odds ratio; aHR, adjusted hazard ratio; PR, prevalence ratio
*Relative risk and 95% CI not reported but approximated from the data
Adjusted for clustering
@ Presenting the invers of the results (i.e. 1/(results presented)) as the comparison provided was the effect of standard of care vs. intervention.

Table 3. GRADE quality assessment and random effects meta-analysis of categories of interventions to improve ART initiation

# (type) studies	Risk of:				N intervention (control)	Risk intervention (control)	Random effects meta-analysis relative risk (95% CI)	Quality
	Bias	Inconsistency	Indirectness	Imprecision				
Counseling and support								
5 (5 iRCT)**	Not Serious	Not Serious	Not Serious	Not Serious	1727 (1185)	0.34 (0.32)	1.07 (0.93-1.24)	Moderate[1]
HIV/TB integration								
3 (2 pre/post, 1 cohort)	Serious	Not Serious	Serious	Not Serious	846 (849)	0.66 (0.39)	2.04 (0.59-7.01)	Very Low[2]
Provider initiated HIV testing								
2 (1 cohort, 1 pre/post)	Serious	Serious	Serious	Not Serious	2399 (7237)	0.68 (0.69)	0.91 (0.86-0.97)	Very low[2]
Interventions combined with home based HIV testing								
2 (2 cRCT)	Not Serious	Not Serious	Not Serious	Serious	8565 (8787)	0.03 (0.01)	2.00 (1.36-2.92)	Low[2]
Rapid/point-of-care CD4 count technology								
6 (3 pre/post, 2 cohort, 1 iRCT)^	Serious	Serious	Serious	Not Serious	897 (922)	0.58 (0.47)	1.30 (1.02-1.67)	Low
Improved clinic operations								
3 (1 iRCT, 1 cRCT, 1 pre/post)	Serious	Not Serious	Not Serious	Not Serious	5575 (4051)	0.70 (0.63)	1.36 (1.25-1.48)	Low[1]
Package of patient services								
3 (1 iRCT, 2 pre/post)	Serious	Not Serious	Serious	Not Serious	731 (277)	0.80 (0.63)	1.54 (1.20-1.97)	Low[1]

[1]Graded down one level as few studies
[2]Graded down two levels as few studies and risk of bias
^ One study (Moyo) not included in meta-analysis as no Ns provided and no variance provided
cRCT, cluster randomized trial; iRCT, individually randomized trial
** 4 interventions from 3 studies. As the same control was used for comparison to both interventions in Barnabas 2015, we did not double count the control group in the total control subjects

Figure 1. Flow chart of included and excluded studies (as per PRISMA)

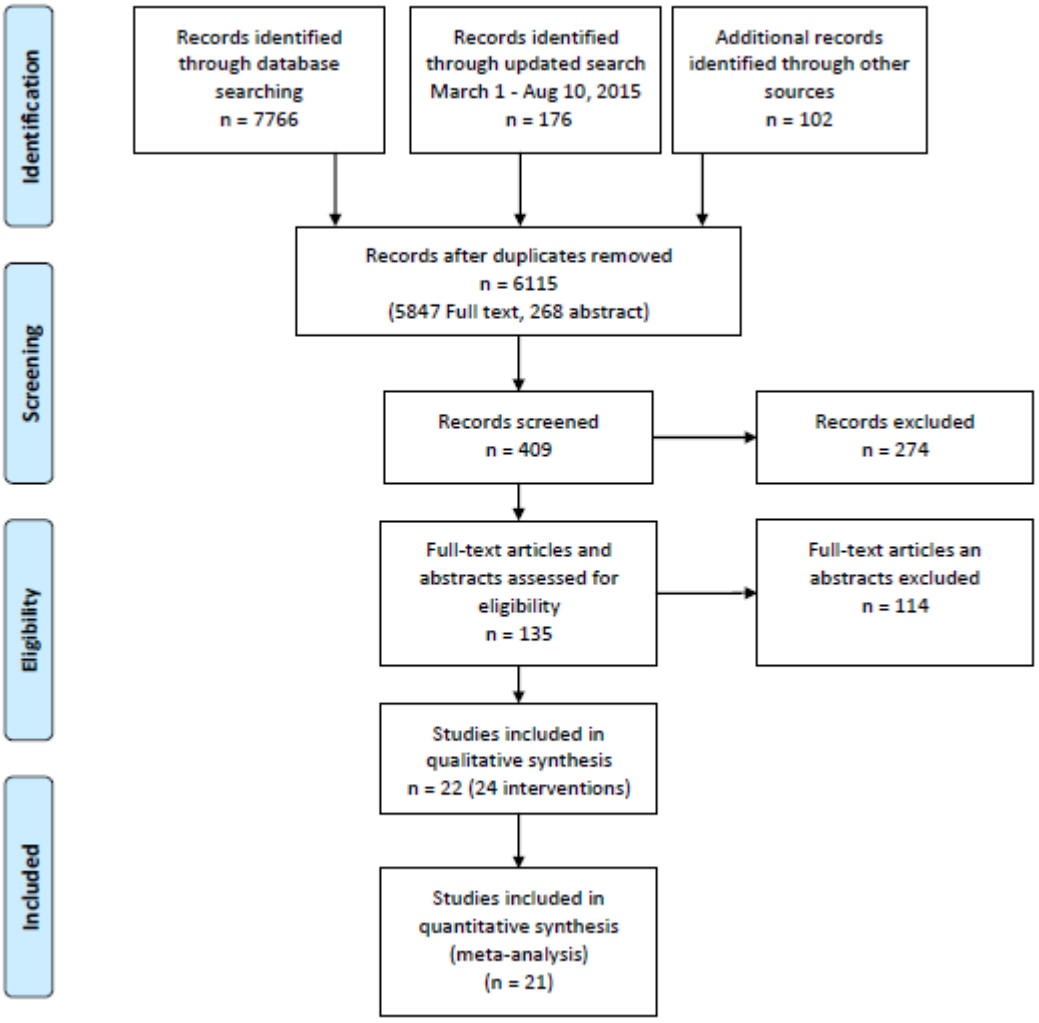
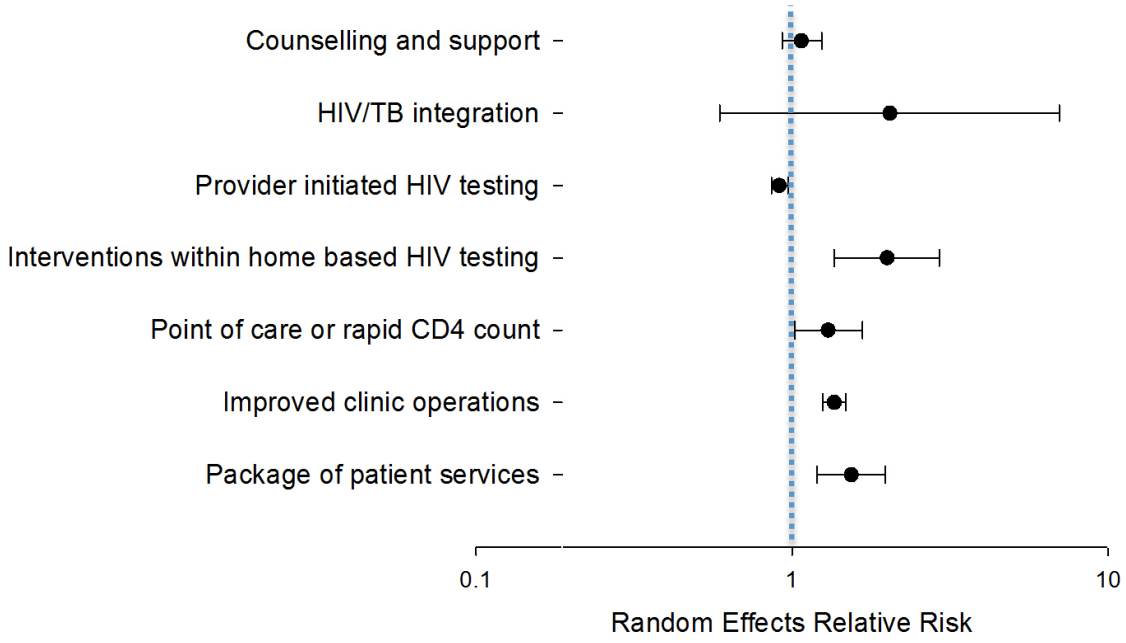


Figure 2. Summary relative risks from a random effects meta-analysis of data from each category of intervention



Additional file 1. Search Strategy for Each Bibliographic Database

Database	Search
PubMed	((linkage OR pre-ART OR initiation OR retention OR attrition OR "loss to follow up") AND ((HIV OR "antiretroviral therapy")) AND ((efficacy OR evaluation OR intervention OR trial))) AND (("2008/01/01"[PDat] : "3000/12/31"[PDat]) AND Humans[Mesh] AND English[lang])
ISI Web of Knowledge	(TS=((HIV OR "antiretroviral therapy")) AND TS=((linkage OR pre-ART OR initiation OR retention OR attrition OR "loss to follow up")) AND TS=((efficacy OR evaluation OR intervention OR trial))) *AND* LANGUAGE: (English) *AND* DOCUMENT TYPES: (Article OR Proceedings Paper) Indexes=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH Timespan=2008-2015
EMBASE	'hiv'/exp or hiv or 'antiretroviral therapy' and (linkage or 'pre art' or initiation or retention or attrition or 'loss to follow up') and (efficacy or 'evaluation'/exp or evaluation or intervention or trial) and [english]/lim and [abstracts]/lim and [2008-2015]/py and [embase]/lim and [humans]/lim
LILACS Portal	(HIV OR antiretroviral) AND (linkage OR pre-ART OR initiation OR retention OR attrition OR adherence OR compliance) AND (efficacy OR evaluation OR intervention OR trial) AND (db:("LILACS"))
Global Index Medicus	(HIV) AND (linkage OR retention)
African Index Medicus	(HIV) AND (linkage OR retention)

Additional file 2. Forest plots of each intervention, relative weights and corresponding I^2 values