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Journal

Current HIV/AIDS Reports, 16(4)

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Publication Date

2019-08-01

DOI

10.1007/s11904-019-00451-8

Peer reviewed

HHS Public Access

Author manuscript

Curr HIV/AIDS Rep. Author manuscript; available in PMC 2023 November 17.

Published in final edited form as:

Curr HIV/AIDS Rep. 2019 August ; 16(4): 292–303. doi:10.1007/s11904-019-00451-8.

Interventions to Improve Linkage to HIV Care in the Era of "Treat All" in Sub-Saharan Africa: A Systematic Review

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Abstract

Purpose of the review: In 2015, antiretroviral therapy (ART) was recommended for all people living with HIV (PLHIV) regardless of CD4 count ("Treat All"). To better understand how to improve linkage to care under these new guidelines, we conducted a systematic review of studies evaluating linkage interventions in Sub-Saharan Africa under Treat All.

Recent findings: We identified fourteen eligible articles and qualitatively analyzed the effectiveness of the interventions. Increases in linkage were reported by supply-side and counseling interventions. Mobile testing and economic incentives did not increase linkage.

Summary: Given the lag time between adoption and implementation, only two of the studies were conducted in a Treat All setting. None of the interventions specifically focused on re-linking PLHIV who had disengaged from care. Future studies must design interventions that target not only newly diagnosed or treatment naïve PLHIV, but should explicitly focus on PLHIV who have disengaged from care.

Keywords

HIV; linkage to care; intervention; treat all; ART initiation; Sub-Saharan Africa; treatment as prevention

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Conflict of interest

The authors do not have any conflicts of interest to report.

Human and animal rights

The article does not contain any studies with human or animal subjects performed by any of the authors.

VII. Supplementary material

Search Strategy (attached)

I. Introduction

In 2015, the World Health Organization (WHO) released new guidelines recommending that all people living with HIV (PLHIV) receive antiretroviral therapy (ART) regardless of CD4 count or WHO clinical stage [1]. These recommendations eliminated ART eligibility criteria and delays between diagnosis and treatment initiation, and brought forth a new era in the epidemic response known as “Treat All.” The goal of these new procedures is for all PLHIV take ART to extend the length and quality of life and reduce the risk of transmission to others [1–4].

Yet even in this age of universal treatment, when record numbers of people are receiving ART [5], many PLHIV still face significant barriers to receiving HIV care, initiating ART, and achieving viral suppression. The Joint United Nations Programme on HIV/AIDS (UNAIDS) has specifically identified stigma, violence, marginalization, unfavorable policies, and poverty and inequality as major barriers to achieving positive health outcomes among PLHIV [5]. These barriers are particularly acute in Sub-Saharan Africa, a region that disproportionately carries the global burden of HIV [6,7]. UNAIDS estimates that only 66% of PLHIV in eastern and southern Africa and 40% of PLHIV in western and central Africa are on ART [5]. Although Treat All is expected to remove policy-related barriers, other obstacles remain, such as economic constraints. This underscores the ongoing need for programs to bolster pathways to HIV care and treatment via programs aimed to link PLHIV to care.

Although widely recognized as a welcome policy change, the current WHO guidelines have also created new challenges for linkage to HIV care in Sub-Saharan Africa [8]. The adoption of Treat All has generated a much larger, diverse group of PLHIV who are now ART eligible and may or may not have been previously ART eligible and/or in care (including pre-ART care) under the previous guidelines. In particular, three unique groups of PLHIV now qualify for ART: 1) those who receive a HIV positive diagnosis for the first time in the era of Treat All; 2) those who are already aware of their HIV-infected status but have never been on ART (i.e., were previously in pre-ART care or never linked to care); and 3) PLHIV who were previously on ART but have disengaged from care (i.e., lost to follow-Up (LTFU)). Despite their common need to be linked or re-linked to HIV care, there may be distinct differences in their willingness and motivation. For example, those who are newly diagnosed might be more highly motivated to seek care than those who have disengaged from care depending on their level of HIV/ART knowledge, beliefs surrounding ART, and level of self-efficacy [9]. Additionally, PLHIV who know their status but were previously treatment ineligible might be unaware that they now qualify for ART or might be less likely to link to care if they led productive lives in the absence of treatment [9]. Indeed, the population of PLHIV who are asymptomatic and eligible for treatment has likely dramatically increased under universal ART policy. Although the challenge of linking or re-linking asymptomatic PLHIV to care existed under previous treatment guidelines, this issue has become even more pertinent with the expansion of ART eligibility to all PLHIV regardless of immunologic status. Consequently, interventions for linkage to care must be cognizant of these differences in PLHIV and customized to best serve each of these target populations.

Randomized controlled trials and quasi-experimental studies have evaluated a wide range of interventions aimed at linking PLHIV to care [10–23]. Prior to Treat All, most linkage intervention studies focused on programs to connect those with a new diagnosis to pre-ART care or to ART, if eligible [8,24,25]. Systematic reviews [24–27] have previously assessed such interventions, but there is a gap in the literature on the effectiveness of linkage strategies in the era of Treat All, which dramatically changes the context of linkage as the pool of PLHIV is more heterogenous. Specifically, treatment-eligible PLHIV (i.e., all PLHIV) now will have more diverse experiences with HIV care, many if not most will be asymptomatic, and all PLHIV can and should begin ART immediately. Thus, it is essential to understand the effectiveness of such interventions in the age of universal ART to identify any gaps in knowledge and whether specific interventions are more effective for certain groups of PLHIV than others.

At the same time, a growing interest in implementation science, the study of "methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice" [28], has sharpened the focus on accelerating the research-to-use pipeline [28–30]. As part of this effort, understanding implementation (i.e., design, processes, and impact) can inform program improvement and facilitate the comparison of evidence across different contexts [28,30]. Towards that end, we sought to understand whether there were common pathways of impact for effective linkage interventions, as well as characteristics of ineffective programs that should be eliminated or improved in future programs. Thus, the objective of this systematic review was to assess the effectiveness of interventions linking PLHIV to care in Sub-Saharan Africa in the era of Treat All.

II. Methods

Search strategy and inclusion criteria

In August 2018, we searched PubMed/MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science to identify relevant articles describing evaluations of interventions for linkage to HIV care in the era of Treat All in Sub-Saharan Africa. All titles and abstracts were screened by one author (NK), and relevant full-text papers were independently reviewed by at least two authors (NK, WM, or OM). A fourth author (SM) reviewed any disagreements, and final inclusion decisions were determined by group consensus. We also reviewed the reference lists of included articles to identify additional papers of interest. Any conference abstracts identified in the search were reviewed to determine if the authors later published a full-text manuscript. The protocol was pre-registered with PROSPERO Register of Systematic Reviews (#CRD42018110036).

The primary inclusion criteria were articles describing the evaluation of interventions targeting linkage to care in the era of Treat All (≥2014) in Sub-Saharan Africa (as defined by the World Bank) [31]. The primary search was conducted without language restrictions but was restricted to a publication date of 2014 or later, given the objective to review the evidence in the era of Treat All. Studies had to describe experimental or quasi-experimental evaluations; uncontrolled pre-post evaluations, cross-sectional studies, retrospective studies, and qualitative studies were not eligible. Given the heterogeneity of the definition of "linkage to care," the authors assessed the presentation of at least one linkage outcome on a

case-by-case basis. Commonly used linkage outcomes included measurement of attendance at an initial HIV care visit, initiation of ART, or the time to either event. Eligible studies had to include a measure of association (e.g., risk ratio) or provide enough information for the authors to calculate such a measure.

We created a unique search strategy for each database by employing its controlled vocabulary, index, and/or free text terms (see supplementary material). All search strategies combined terms for (1) HIV, (2) linkage, (3) Sub-Saharan Africa, and (4) study design restrictions. We searched for clinical trials in PubMed/MEDLINE using a version of Cochrane's "Highly Sensitive Search Strategy" for identifying randomized controlled trials [32].

We later amended the protocol to exclude studies that collected data prior to 2014, as this review specifically aimed to evaluate interventions in the era of Treat All. Although not specified in the protocol, after the search we excluded studies focusing exclusively on pregnant women because antenatal care (ANC) and HIV care are integrated in many parts of Sub-Saharan Africa, making it difficult to differentiate motivation for ANC and prevention of mother-to-child HIV transmission from HIV care for one's health. Additionally, pregnant women possess different motivations to seek HIV care, such as protecting their infant from HIV. Additionally, pregnant women have been eligible for ART without restriction under the WHO's recommendation for "Option B+" since 2012 [33]. Thus, studies focusing exclusively on pregnant women were excluded.

Data abstraction & analysis

Two authors (WM & NK) independently abstracted data into a predetermined data abstraction sheet. The primary outcome of interest was linkage to care. In addition to detailed information about each study, we abstracted the most adjusted relative measure of linkage to care (e.g., risk ratio (RR), odds ratio (OR)) for all intervention arms to account for potential confounding.

Due to variability in study design, we noted the quality of each eligible study to allow for comparability of results across trials [32]. We also examined which group(s) of PLHIV each study aimed to link to care in the era of Treat All: 1) those who receive a new HIV positive diagnosis in the era of Treat All (group 1); 2) PLHIV aware of their status but ART naive (i.e., were previously in pre-ART care or never linked to care, group 2); and 3) PLHIV previously on ART but disengaged from care (i.e., LTFU, group 3). Eligible studies were categorized into at least one of these groups if it was explicitly mentioned in the paper, or we inferred upon our assessment. All data analysis was conducted using Excel, Stata v15.1, and R v3.4.1.

We qualitatively evaluated the effectiveness of interventions by grouping studies with similar intervention strategies and potential impact pathways and then examined trends or similarities between studies. We identified four main categories based on the review results: mobile/home testing and counseling, combination intervention strategies and financial incentives, home-based counseling and/or clinic escort, and supply-side interventions. In addition to intervention type, we considered the mechanisms employed by each intervention

to improve linkage to HIV care, such as mitigating individual and structural barriers to HIV or CD4 testing, reducing the individual burden associated with visiting an HIV care facility, appealing to an individual's innate desire to remain healthy through behavior change, and reducing structural barriers to HIV care.

Because the eligible studies covered a wide range of interventions and populations, we did not pool measures of association. Instead, we grouped studies by the type of intervention and created a forest plot to visualize the effect of the interventions.

III. Results

Search results

In August 2018, the search strategy identified 5198 records of interest (Figure 1). After removing 891 duplicates, 4307 records remained. Of these, 3480 were eliminated after a review of titles, and of the 827 records remaining, 750 were ineligible after abstract review. Seventy-seven full text papers were independently reviewed by at least two authors, and fourteen papers met the final inclusion criteria. No additional studies were identified from reviewing reference lists.

Description of the studies

The eligible studies only occurred in eastern and southern Africa (Table 1) and varied in terms of study design (cluster randomized trial, individual randomized trial, and prospective cohort). All but one study targeted the general adult population; one study included both children and adults [22]. None of the studies exclusively focused on high-risk groups such as female sex workers or men who have sex with men.

Although all studies were partially conducted in the era of universal ART (2014 and later), only two studies actually occurred in a setting where Treat All had been adopted and presumably implemented [12,13] (Table 2). The other twelve studies, despite being conducted in 2014 or later, occurred when ART eligibility was based on CD4 and/or WHO staging. However, many papers framed their studies within a Treat All context and highlighted the importance of universal ART moving forward [10,15,17, 22].

The included studies were evenly split in terms of the three PLHIV groups they primarily targeted. Four studies [10,14,15,18] only recruited PLHIV who were newly diagnosed (group 1), four studies [11,13,16,23] included any PLHIV who had never been on ART (groups 1 and 2), and four studies [12,19,21,22] included any PLHIV, including those newly or previously diagnosed and/or previously on ART or treatment naive (groups 1, 2, and 3) (Table 1). The remaining two studies did not provide enough information to receive a classification, but likely focused on PLHIV who were newly diagnosed (group 1) [17,20]. None of the studies focused exclusively on group 3: re-linking PLHIV who had previously accessed HIV care and/or ART.

The linkage interventions varied in terms of design and were subsequently grouped according to intervention type: mobile/home testing and counseling [17,18,22], combination intervention strategies and financial incentives [10,11,14,19], home-based counseling and/or

clinic escort [12,16,20,21], and supply-side interventions [13,15,23] (Table 2). Most studies occurred outside of a clinical setting but differed widely in terms of intervention content (e.g., reminder phone calls, partner referral services, conditional economic incentives).

The methodological quality of each study was assessed, and most had a low overall risk of bias. In particular, all but one study [20] attempted to reduce reporting bias by pre-registering a protocol with specified outcomes. Some performance and detection bias was likely introduced since blinding was not possible for the majority of interventions (e.g., point-of-care (POC) CD4 testing or counseling). Other potential sources of bias could be due to spillover effects in cluster-randomized trials [10,14–16,22,23] or small sample sizes [11–13,16]. Since the Cochrane risk of bias tool is designed to evaluate experimental studies, two prospective cohort studies [17,18] were not included; however, these studies may have threats to validity as a consequence of their observational nature, as randomization was not used to minimize confounding.

Linkage results by intervention type

Six of the fourteen interventions significantly increased linkage to HIV care as defined in the individual studies [12,13,15,16,22,23]. Because of the diversity of the interventions (Table 2), we did not pool linkage outcomes or conduct a meta-analysis; however, the relative measures of association for each study are presented in a forest plot (Figure 2), and the detailed results of each intervention category are presented below.

Mobile or home-based testing & counseling

Two similar prospective cohort studies (Sanga et al. 2017 & Asiimwe et al. 2017) evaluated linkage to care following mobile or home-based versus facility-based HIV testing in Tanzania and Uganda, respectively [17,18]. Both studies observed lower levels of linkage to care in the community-based (i.e. intervention) arm versus the facility-based (i.e. comparison) arm (Sanga RR: 0.82, 95% CI: 0.76–0.89; Asiimwe RR: 0.84, 95% CI: 0.79–0.89) (Table 2). In a cluster randomized trial in Kenya, Desai et al. 2017 [22] compared the effectiveness of home CD4 testing and counseling. Both study groups received home-based HIV testing, but the intervention group was also offered home-based POC CD4 testing and counseling, which significantly increased linkage to care at six months (58% vs. 34%; Hazard ratio (HR): 2.14, 95% CI: 1.67–2.74; RR: 1.72, 95% CI: 1.44–2.05).

Combination intervention strategies & financial incentives

Several studies targeted multiple barriers to care by examining the effectiveness of combination intervention strategies [10,14,19] (Table 2). Elul et al. 2017 and McNairy et al. 2017 tested similar interventions in Mozambique and Swaziland, respectively, that both included POC CD4 testing at the time of HIV testing, accelerated ART initiation if CD4 ≤350, text messages, and conditional financial incentives [10,14]. McNairy et al. 2017 also incorporated a health education component into their intervention [10]. The interventions did not significantly improve linkage to care at one month in either study (Elul et al. 2017 RR: 1.48, 0.93–2.35; McNairy et al. 2017 RR: 1.08, 95% CI: 0.97–1.21), although retention at twelve months did increase in both studies (RR: 1.32, 95% CI: 1.12–1.54; RR 1.48, 95% CI:1.18–1.86). Additionally, both interventions increased the same primary

combined outcome of linkage at one month and retention at twelve months (RR: 1.55, 95% CI: 1.07–2.25; RR: 1.50, 95% CI: 1.12–1.99). Hoffmann et al. 2017 [19] implemented a combination intervention utilizing POC CD4 testing, care facilitation, and a financial incentive for linkage to care in South Africa. Of the three combination intervention strategies employed, only the Hoffmann study reported an increase in clinic-verified linkage to care in the care facilitation arm (HR: 1.4, 95% CI: 1.1–1.7).

Several studies of combination interventions were also designed to specifically examine the *additional* effect of financial incentives. Both Hoffmann and Elul included a third study arm to examine the added effect of a financial incentive; neither observed an increase in linkage (Hoffmann et al. 2017 HR: 1.1, 95% CI: 0.88, 1.30; Elul et al. 2017 RR=0.94, 95% CI: 0.76–1.18). Maughan-Brown et al. 2018 [11] conducted a randomized controlled trial in South Africa where participants in the intervention arm qualified to redeem a voucher (valued at ~23 USD) conditional upon ART initiation; the investigators found that linkage to care and ART initiation at three months did not increase over the standard of care (OR: 0.70, 95% CI: 0.26–1.91; OR: 0.67, 95% CI: 0.26–1.78, respectively).

Home-based counseling and/or clinic escort

Hewett et al. 2016 and Barnabas et al. 2016 described linkage interventions utilizing home-based testing, counseling, and referral, and/or escort to the clinic by a community health worker [20,21]. Specifically, Hewett et al. 2016 conducted a randomized controlled trial in Zambia with one intervention arm receiving enhanced counseling, referral, and follow-up and a second intervention arm adding an escort to the clinic [20]. Similarly, Barnabas et al. conducted a randomized controlled trial in South Africa and Uganda where the intervention group received POC CD4 testing and either home counseling or escort to the clinic [21]. None of the intervention versions in these trials increased linkage to care over and above standard services except for one study: Barnabas et al. 2016 observed a small increased proportion of PLHIV linked to care at nine months when comparing escort to the clinic by a counselor to the standard, passive referral process (98% vs. 89%, RR: 1.09, 95% CI: 1.05–1.13). Despite the limited effectiveness of the interventions, Barnabas et al. 2016 noted high overall levels of linkage across all study arms (>90%) (Table 2).

Two other studies evaluated the effect of counseling interventions outside of a clinical setting and reported increases in linkage to care [12,16]. Ruzagira et al. 2017 [16] conducted a cluster randomized trial in Uganda where PLHIV were offered home-based counseling at one and two months post-test; increased levels of linkage at six months were observed in the intervention group (51% vs. 33%, OR: 2.14, 95% CI: 1.24–3.7). Ayieko et al. 2018 [12] had clinic officers call participants within one hour of post-test counseling to offer patient-centered counseling; they found an increase in linkage to care in the intervention group (41%) compared to the control group (24%) at 30 days (RR: 1.70, 95% CI: 1.01–2.87).

Supply-side interventions

Three studies tested interventions to reduce supply-side barriers to HIV care, and all three observed increases in linkage to care [13,15,23]. Cherutich et al. 2017 [15] implemented

immediate partner tracing of PLHIV to link HIV-positive partners to care in Kenya. Compared to delayed tracing, partners in the intervention arm had a significantly higher rate of linkage to care at six weeks (IRR: 4.4, 95% CI: 2.6–7.4). In Lesotho, Labhardt et al. 2018 [13] offered same-day ART initiation, counseling, and a modified appointment schedule compared to standard referral and ART initiation procedures, and the intervention arm had significantly higher linkage at 90 days (68.6% vs. 43.1%, RR: 1.59, 95% CI: 1.27–1.99). Amanyire et al. 2016 [23] presented a clinic-based intervention for staff to improve linkage to care through staff training, rapid POC CD4 testing, and feedback on ART initiation relative to other clinics. The intervention increased ART initiation among PLHIV who were ART naive (14-day RR: 1.86, 95% CI: 1.72–2.02).

IV. Discussion

Although Treat All is a relatively new strategy in the global HIV epidemic response, this review underscores that significant gaps exist in the evidence on how to increase linkage to HIV care across Sub-Saharan Africa. On average, one of every three PLHIV in eastern and southern Africa and almost two out of every three PLHIV in western and central Africa are not currently accessing ART even though all are now eligible [5]. In response to these significant gaps, an international group of HIV experts recently noted that strategies to promote timely linkage to HIV care are a critical research priority for Sub- Saharan Africa in the era of Treat All [34]. We conducted a systematic review to understand the state of the evidence for linkage interventions in the age of universal ART, given that different strategies may be necessary now that ART eligibility criteria have been lifted and the pool of PLHIV requiring ART is much larger and varied, including more asymptomatic PLHIV. Less than half of the interventions evaluated were found to significantly increase linkage to care. Successful interventions employed strategies such as accelerated partner tracing [15], same-day ART initiation [13], clinic training and capacity building [23], post-test counseling phone calls [12], and home-based POC testing [22] and counseling [16,22]; however, not every study using these approaches in this review was effective. Furthermore, although the WHO released new guidelines in 2015, many countries did not have the capacity or resources to immediately begin offering Treat All services nationwide [35]. Consequently, only two studies included in this review occurred in places where Treat All had actually been implemented, highlighting a gap in global knowledge about how best to link PLHIV to care now that virtually all of Sub-Saharan Africa has eliminated ART eligibility criteria [35]. Given the relatively recent adoption of these procedures, further research is urgently needed to fully evaluate linkage interventions under Treat All.

Even though Treat All expanded the number of PLHIV who are now eligible for ART, none of the fourteen eligible studies conducted since 2014 specifically focused on re-linking PLHIV who had fallen out of HIV care and/or who were previously on ART. This high-priority group with demonstrated barriers to care – whether individual, household, or community [9] – will continue to grow as Treat All expands, more PLHIV initiate ART, and some disengage from care, thereby creating an essential group to reach if the epidemic is to end by 2030 [5]. In particular, a previous review and meta-analysis estimated that ART retention at 36 months in Africa was only 65% [41], which corresponds to a substantial pool of PLHIV who will require re-linkage in the coming years. The UNAIDS goal to eliminate

HIV as a public health threat by 2030 largely relies upon treatment as prevention through the high uptake of ART and high levels of adherence [5]; thus, timely research is needed to implement and evaluate linkage interventions specifically targeted at this critically important group of PLHIV.

Despite the variety of eligible studies in this review, examining the interventions by category revealed several notable findings. Specifically, mobile HIV testing was associated with lower levels of linkage to care than traditional, facility-based testing in some studies [17,18]. These results are somewhat unsurprising because many facility-based HIV testing and counseling programs are often co-located with HIV care, facilitating timely access to care. However, home-based POC CD4 testing and counseling following mobile HIV testing actually increased linkage to care when compared to standard (facility-based) procedures in another study [22]. Although mobile HIV testing did not consistently improve linkage over facility-based testing, it remains an essential tool that can be used to identify harder to reach PLHIV who otherwise would not be able to or do not want to access clinic-based testing. Notably, the majority of studies in this review evaluated interventions in a community or home-based environment, and many occurred following mobile HIV testing [11–13,15,16,20–22].

Furthermore, studies of combination strategies targeting multiple barriers to HIV care did not increase linkage compared to standard referral procedures [10,14,19]. Nevertheless, this multifaceted approach remains promising as it could, in theory, simultaneously tackle multiple barriers [9]. Future studies could combine interventions that have demonstrated improvements on linkage, such as supply-side interventions [13,15,23] and/or counseling interventions [12,16]. Together, the evidence base for these interventions suggests that, to date, combination intervention strategies integrating components such as POC CD4 testing, accelerated ART initiation (if CD4 ≤350), SMS messages, health education, and non- cash financial incentives, may not be effective at increasing linkage to care in Sub-Saharan Africa.

Conditional economic incentives did not have a clear effect on linkage to care in this review; however, only four of the fourteen studies [10,11,14,19] included a financial incentive, and of these, three were provided as a component of a larger, heterogeneous package [10,14,19]. Furthermore, the modality of the incentives (e.g., cash versus airtime) and the dose varied considerably, so it is difficult to draw definitive conclusions about the effectiveness of conditional economic incentives on linkage to HIV care other than that no strong effects were observed. Two of the four studies that used conditional economic interventions provided in-kind incentives (cellular air-time cards) [10,14], one provided mobile money as transport reimbursement [19], and another offered direct cash to participants [11]. Previous studies have illustrated that in-kind incentives (e.g., cellular air-time cards or food baskets) provide less autonomy than cash incentives and are often more expensive to implement [42,43]. Thus, conditional economic incentives should undergo additional evaluation to compare the effectiveness of different types (e.g., cash vs. in-kind), sizes (e.g., value), and delivery models (e.g., airtime, mobile banking, cash) on linkage to care.

Two non-traditional counseling interventions reported impressive improvements in linkage to care by utilizing home-based counseling [16] and structured phone calls to PLHIV

[12]. These studies potentially highlight the importance of meeting patients 'where they are' and using proven strategies such as motivational interviewing to better understand PLHIV's decision processes to seek and/or re-engage in care. Lastly, all three supply-side interventions included in the review were associated with improvements in linkage to care and, in general, had larger effect sizes compared to other intervention categories. Accelerated partner tracing [15], same-day ART initiation [13], and improved clinic training and capacity building [23] removed structural barriers to ART, such as a minimum number of appointments or counseling sessions required before starting treatment (some of which remain required of PLHIV even in the context of Treat All). These interventions did not rely on behavior change from PLHIV (such as counseling interventions), but instead worked to eliminate structural and/or policy- related constraints so that PLHIV could more easily access care. The relatively large effect sizes observed for these supply-side interventions could be the result of simple yet transformative interventions that can be scaled more rapidly and to a wider audience (e.g., an entire clinic) than interventions targeting individuals. Ultimately, supply-side interventions may have the potential to improve linkage on a larger scale through policies that affect the delivery of HIV care at the local, regional, or national level, yet only three of the fourteen papers included in the review targeted structural barriers, justifying future studies that address supply-side constraints.

Although there are too few studies to make definitive statements about the overall effectiveness of each strategy, some interesting hypotheses emerge from an examination of the interventions by their potential mechanism. Interventions that eliminated individual-level or structural barriers to HIV or CD4 testing through home or community-based testing did not improve linkage to care [17,18]. Allowing participants to test in their community or home improved convenience, mitigated transportation costs, and did not require PLHIV to miss work for testing; however, these strategies did not remove barriers to visiting an HIV care facility *after* testing (e.g., transport costs, stigma, and opportunity costs) which could explain the lack of an observed effect. In addition, this review did not find strong evidence that alleviating barriers to clinic transport and/or motivating attendance through conditional financial incentives was an effective strategy [10,11,14,19]. Previous research has demonstrated that conditional economic incentives operate via an income effect (i.e., increasing a person's income) or a price effect (i.e., reducing the price of attending a clinic through opportunity costs) [11]. Even though there were few studies of economic incentives [10,11,14,19], and they were diverse in intervention modality, size, and delivery method, these findings may imply that barriers to linkage were not adequately offset by the incentives as examined in those specific studies. Behavioral interventions [10,12,16–18,20–22] (such as counseling) also targeted individual-level barriers to linkage by appealing to one's innate desire to remain healthy. These behavior-change interventions varied considerably in terms of design and had mixed effects on linkage to care.

Examining the interventions by mechanism of action suggest that impediments to linkage persist even after reducing or eliminating some individual-level barriers. In contrast, this review identified that all three supply-side interventions [13,15,23] observed increases in linkage to care. The interventions described in the included manuscripts [13,15,23] reduced structural barriers to care rather than relying on individual behavior change. Given the substantial challenges that PLHIV face on both an individual and systemic scale, it is

important to explore diverse mechanistic pathways in future linkage studies. The field of implementation science focuses not only on what works – but *why* and *in what context* – and can help to accelerate the research-to-use pipeline for linkage to care [28–30]. Moving forward, framework's such as Proctor's [30] should be used to identify targeted questions, barriers, and bottlenecks related to high priority interventions that show promise for linkage to care or are ready for scale-up.

There are several limitations to this review, including the use of 2014 as a proxy for the "era of Treat All", as countries may or may not have adopted such procedures by this date. Additionally, we did not include any grey or unpublished literature to limit the review to peer-reviewed studies. Although we took caution to develop a comprehensive search strategy, there is still the possibility that our approach omitted potentially relevant studies. Lastly, not all of the studies reported the same linkage outcome or measure of association. For example, odds ratios reported by some of the papers [11,16,20] are known to overestimate the relative risk when the outcome is common [44]. For this reason, as well as heterogeneity in study approach, context, and population, we appropriately did not pool the results and conduct a meta-analysis.

V. Conclusions

The era of Treat All has provided an opportunity to expand linkage to care so that all PLHIV can receive ART, extend the length and quality of their life, and reduce and/or eliminate the risk of transmission to others. Yet, to achieve high ART uptake, multiple strategies will be required to link this much larger, more diverse group of PLHIV to care. Supply-side interventions and novel counseling interventions currently are supported by evidence that they may improve linkage to care in Sub-Saharan Africa. However, strategies targeting PLHIV who have disengaged from care have largely been ignored but will be critical in using treatment as prevention to end the HIV epidemic by 2030.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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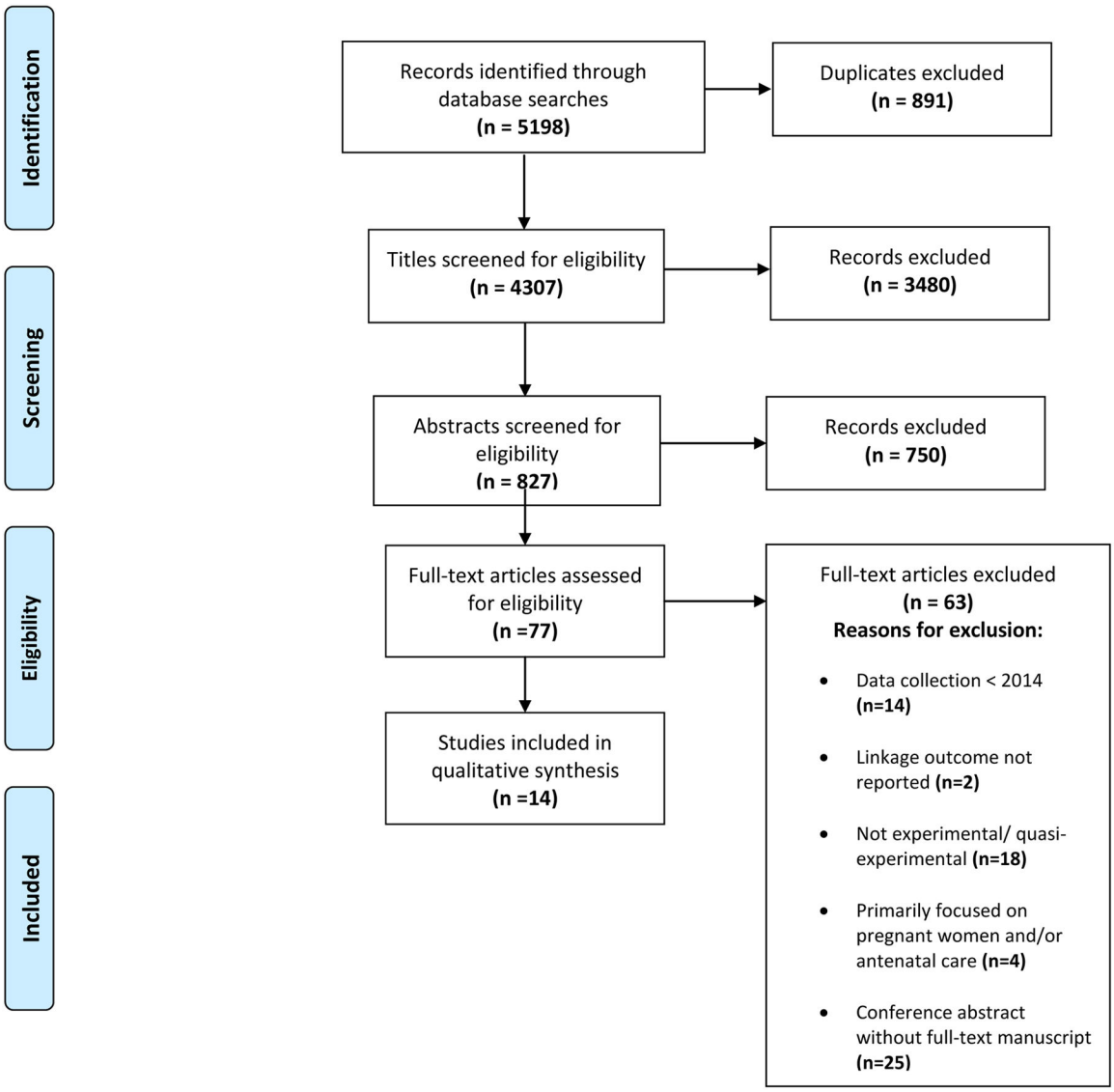

Figure 1.

PRISMA flow diagram describing the search strategy for linkage to care interventions, 2014–2018 [36]

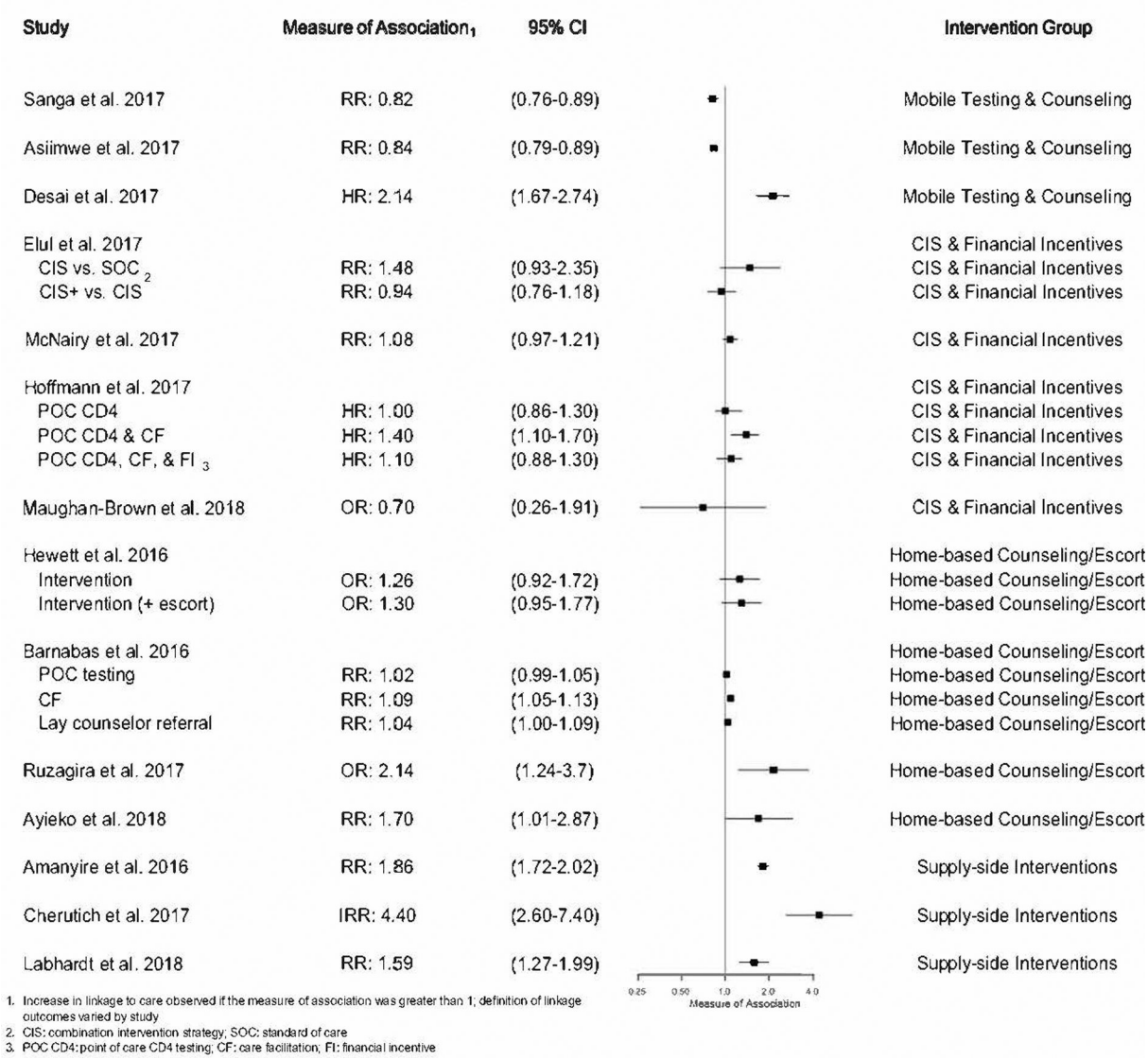

Figure 2.

Relative change in linkage to care associated with each intervention, Sub-Saharam Africa 2014–2018

Table 1.

Characteristics of included studies, stratified by target group of PLHIV

Target Group: Newly Diagnosed			
Author	**Year**	**Study design**	**Country**
Cherutich et al. [15]	2017	Cluster randomized controlled trial	Kenya
Elul et al. [14]	2017	Cluster randomized controlled trial	Mozambique
McNairy et al. [10]	2017	Cluster randomized controlled trial	Swaziland
Sanga et al. [18]	2017	Prospective cohort	Tanzania
Target Group: Not Currently in Care or on ART			
Author	**Year**	**Study design**	**Country**
Barnabas et al. [21]	2016	Individual randomized controlled trial	South Africa, Uganda
Desai et al. [22]	2017	Cluster randomized controlled trial	Kenya
Hoffmann et al. [19]	2017	Individual randomized controlled trial	South Africa
Ayieko et al. [12]	2018	Individual randomized controlled trial	Kenya
Target Group: Never on ART or Never Received HIV Care			
Author	**Year**	**Study design**	**Country**
Amanyire et al. [23]	2016	Stepped-wedge cluster randomized controlled trial	Uganda
Ruzagira et al. [16]	2017	Cluster randomized controlled trial	Uganda
Labhardt et al. [13]	2018	Individual randomized controlled trial	Lesotho
Maughan-Brown et al. [11]	2018	Individual randomized controlled trial	South Africa
Target Group: Not Specified			
Author	**Year**	**Study design**	**Country**
Hewett et al. [20]	2016	Individual randomized controlled trial	Zambia
Asiimwe et al. [17]	2017	Prospective cohort	Uganda

Table 2.

ART eligibility & results of included studies, stratified by intervention approach

Mobile or Home-based Testing & Counseling				
Author	**Year**	**Intervention**	**Outcome**	**ART eligibility at the time of data collection**
Sanga et al. [18]	2017	Mobile HIV testing vs. facility testing	Linkage to care was significantly higher in the facility-based arm (RR: 0.82, 95% CI: 0.76–0.89; HR: 0.56, 95% CI: 0.48–0.66)	CD4 count ≤350 cells/mm^3
Asiimwe et al. [17]	2017	Home-based HIV testing, counseling, & referral vs. facility-based testing	Linkage to care was significantly higher in the facility-based arm (RR: 0.84, 95% CI: 0.79–0.89)	CD4 count ≤500 cells/mm^3 [37]
Desai et al. [22]	2017	Home-based POC CD4 testing & counseling vs. standard referral following home-based HIV testing	The intervention arm had significantly higher linkage to care at 6 months (HR: 2.14, 95% CI: 1.67–2.74; RR: 1.72, 95% CI: 1.44–2.05)	CD4 count ≤350 cells/mm^3
Combination Intervention Strategies (CIS) & Financial Incentives				
Author	**Year**	**Intervention**	**Outcome**	**ART eligibility at the time of data collection**
Elul et al. [14]	2017	1. Combination Intervention Strategy (CIS): POC CD4 testing & referral with accelerated ART if CD4 ≤350; SMS messages 2. CIS+: CIS plus conditional financial incentives	Compared to the SOC, the CIS arm had a significantly higher combined outcome of linkage at 1 month & retention at 12 months (RR: 1.55, 95% CI: 1.07–2.25) as well as individual same-day linkage, linkage at 12 months, & retention outcomes. Linkage was not higher in the CIS arm at 1 week or 1 month (RR: 2.43, 0.70–8.41; RR: 1.48, 0.93–2.35, respectively). Outcomes did not vary between the CIS and CIS+ arms (RR=0.94, 95% CI: 0.76–1.18)	CD4 count ≤350 cells/mm^3 and/or WHO stage 3/4
McNairy et al. [10]	2017	POC CD4 testing with accelerated ART if CD4 ≤350, SMS appointment reminders, health education, & financial incentive	The intervention arm had a higher combined outcome of linkage at 1 month and retention at 12 months (RR: 1.50, 95% CI: 1.12–1.99) as well as retention at 12 months. Linkage to care (RR: 1.08, 95% CI: 0.97–1.21) and viral suppression did not differ from the control arm	CD4 count ≤500 cells/mm^3
Hoffmann et al. [19]	2017	1. POC CD4 testing; 2. POC & care facilitation (CF); 3. POC, CF & transport reimbursement	Only care facilitation (arm 2) significantly increased clinic-verified linkage within 90 days (HR: 1.4, 95% CI: 1.1–1.7)	CD4 count ≤350 cells/mm^3
Maughan-Brown et al. [11]	2018	Redeemable voucher conditional on ART initiation	The intervention did not increase linkage to care or ART initiation within 3 months (OR: 0.70, 95% CI: 0.26–1.91; OR: 0.67, 95% CI: 0.26–1.78). However, the intervention arm linked to care and ART faster than the comparison group, but this result was not statistically significant	CD4 count ≤500 cells/mm^3
Home-based Counseling and/or Clinic Escort				
Author	**Year**	**Intervention**	**Outcome**	**ART eligibility at the time of data collection**
Hewett et al. [20]	2016	1. Enhanced counseling, referral, & follow-up; 2. Added escort to the clinic	The intervention did not increase linkage to care for either intervention arm (OR: 1.26, 0.92–1.72; OR: 1.3, 95% CI: 0.95–1.77), but the authors note that ART initiation was higher in the intervention groups at 6 months	Originally, CD4 count ≤350 cells/mm^3 but changed to ≤500 cells/mm^3 during the study [38]
Barnabas et al. [21]	2016	POC CD4 testing & either: 1. home counseling, or 2. escort to the clinic	POC testing & home counseling did not increase linkage (RR: 1.02, 95% CI: 0.99–1.05; RR: 1.04, 95% CI: 1.0–1.09, respectively) but escort to the clinic marginally	Originally, CD4 count ≤350 cells/mm^3 but changed to ≤500 cells/mm^3 during the study

Mobile or Home-based Testing & Counseling				
Author	**Year**	**Intervention**	**Outcome**	**ART eligibility at the time of data collection**
			did (RR: 1.09, 95% CI: 1.05–1.13), plus there were high rates of linkage overall (>90%)	
Ruzagira et al. [16]	2017	Home-based counseling 1 & 2 months post-test	The odds of linkage at 6 months were higher in the intervention group (OR: 2.14, 95% CI: 1.24–3.7). The probability of linkage did not differ in the first two months, but was significantly higher in the intervention arm at 6 months (HR: 1.62, 95% CI: 1.12–2.33)	CD4 count ≤500 cells/mm^3
Ayieko et al. [12]	2018	Phone call from a clinic officer within 1 hour of post-test counseling	The intervention group had higher a relative risk of linkage at 30 days (RR: 1.70, 95% CI: 1.01–2.87), but was not significant at 7 days (RR: 1.82, 95% CI: 1.00–3.33). The intervention arm had a higher relative hazard of linkage at 30 days, but this was not significant (HR: 1.86, 95% CI: 0.99–3.48)	Treat All
Supply-side Interventions				
Author	**Year**	**Intervention**	**Outcome**	**ART eligibility at the time of data collection**
Amanyire et al. [23]	2016	Clinic staff training, rapid CD4 testing, & facility feedback	ART initiation in the intervention arm was significantly higher at all time points (14 day RR: 1.86, 95% CI: 1.72–2.02), but decreased over time. Retention did not vary between the two groups, but viral suppression was significantly higher in the intervention arm	Originally, CD4 count ≤350 cells/mm^3 or WHO stage 3/4 but changed to ≤500 cells/mm^3 during the study
Cherutich et al. [15]	2017	Immediately attempted contact with sex partners and offered HIV testing vs. delayed contact	The intervention group had a significantly higher rate of partners linked to care at 6 weeks (IRR: 4.4, 95% CI: 2.6–7.4)	Originally, CD4 count ≤350 cells/mm^3 but changed to ≤500 cells/mm^3 during the study [39,40]
Labhardt et al. [13]	2018	Same-day ART initiation & counseling with modified appointment schedule vs. standard referral & procedures	The intervention arm had a significantly higher risk of linkage at 90 days (RR: 1.59, 95% CI: 1.27–1.99) and viral suppression at 12 months	Treat All