Community-Based Interventions to Improve and Sustain Antiretroviral Therapy Adherence, Retention in HIV Care and Clinical Outcomes in Low- and Middle-Income Countries for Achieving the UNAIDS 90-90-90 Targets

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Abstract

Little is known about the effect of community versus health facility-based interventions to improve and sustain antiretroviral therapy (ART) adherence, virologic suppression, and retention in care among HIV-infected individuals in low-and middle-income countries (LMICs). We systematically searched four electronic databases for all available randomized controlled trials (RCTs) and comparative cohort studies in LMICs comparing community versus health facility-based interventions. Relative risks (RRs) for pre-defined adherence, treatment engagement (linkage and

retention in care), and relevant clinical outcomes were pooled using random effect models. Eleven cohort studies and eleven RCTs (N = 97,657) were included. Meta-analysis of the included RCTs comparing community- versus health facility-based interventions found comparable outcomes in terms of ART adherence (RR = 1.02, 95 % CI 0.99 to 1.04), virologic suppression (RR = 1.00, 95 % CI 0.98 to 1.03), and all-cause mortality (RR = 0.93, 95 % CI 0.73 to 1.18). The result of pooled analysis from the RCTs (RR = 1.03, 95 % CI 1.01 to 1.06) and cohort studies (RR = 1.09, 95 % CI 1.03 to 1.15) found that participants assigned to community-based interventions had statistically significantly higher rates of treatment engagement. Two studies found community-based ART delivery model either cost-saving or cost-effective. Community- versus facility-based models of ART delivery resulted in at least comparable outcomes for clinically stable HIV-infected patients on treatment in LMICs and are likely to be cost-effective.

Introduction

The number of people living with HIV (PLWH) who have started life-saving antiretroviral therapy (ART) has markedly increased in low- and middle-income countries (LMICs) [1]. This impressive development, however, has led to overcrowding in health care facilities, longer waiting times during visits, and reduced time for counseling and clinical care of newly enrolled patients. In most public sector clinics in LMICs, it has also restricted the workforce's capacity to provide ongoing adherence support and monitor patients who do not remain engaged in care (treatment engagement) to ensure optimal ART-related benefits on patient health and community HIV prevention [2]. Further, in July 2014, UNAIDS called for a global scale-up of treatment as prevention and efforts to meet the following "90-90-90" targets by 2030: (1) 90 % of all people living with HIV should know their HIV status (90 % diagnosed); (2) 90 % of all people diagnosed with HIV infection should receive ART (90 % on treatment); and (3) 90 % of all people receiving ART should achieve viral suppression [3]. This ambitious target for 73 % of all PLWH with documented undetectable viral load is expected to be associated with a significant decrease in HIV-related morbidity and mortality, lowest risk of sexual transmission, and decrease in HIV incidence at population level as well as supported by the latest World Health Organization (WHO) guidelines recommending treating all PLWH irrespective of immune status [4•]. It implies that an additional 21 million people are in need for treatment as of 2015 and underscores the importance of strengthening health systems' capacity to meet the growing health needs within communities [4•].

Emerging data from both resource rich and limited settings have demonstrated that a substantial reduction in patient retention in clinical care occurs between each stage of the HIV treatment continuum from diagnosis and linkage to care, assessment of ART readiness to acceptability, receipt of initial ART, adherence and long-term retention in care, and treatment success as reflected by virologic suppression [5, 6, 7•, 8]. A systematic review reported that retention of PLWH on ART at 36 months in LMICs averages only 65 to 70 % [9•]. This proportion is markedly lower in patients who present to hospitals with advanced

HIV. Success along the HIV treatment cascade is even worse in key populations, namely, pregnant women, children and adolescents, sex workers, people who inject drugs, and men who have sex with men, and they are at high risk of acquiring as well as transmitting HIV to others, thus experiencing poor clinical and public health outcomes [10–15]. Against this background, it is critical to determine how effective interventions are at every level of the treatment cascade to prevent new infections and promote health outcomes to achieve the goal of an AIDS-free generation [7•].

In LMICs, selected approaches to reducing loss at every stage of the HIV treatment cascade include decentralization of services and task-shifting aspects of care to nurses and to nonclinical staff, including lay counselors who may be patients themselves. These approaches have been found to be feasible, effective, and results in good clinical outcomes [16–18]. Task shifting is now recommended and being scaled up in LMICs [16–19]. Such facility-based strategies, however, are reaching their limits as increasing numbers of patients initiate ART. Recently, suggestions have been made to expand accessible and flexible community-based ART service delivery, differentiating the needs of clinically ill patients starting ART or in need of significant adherence counseling from the needs of clinically stable patients with documented optimal ART adherence. This transition from facility- to community-based treatment has been identified as an important strategies for maintaining retention in HIV care and improving ART adherence, and viral suppression, but without reducing quality of care [16].

Community-based programs to promote retention in HIV care and/or ART adherence are now increasingly being recognized as an important and sustainable approach that could contribute significantly toward the UNAIDS 90-90-90 target and ultimately an AIDS-free generation [20–27, 28•, 29–32]. Such approaches are also seen as an essential mechanism of service delivery, including dispensing of ART, and a means of decongesting traditional health services, rather than being purely an adherence adjunct. Furthermore, such interventions are likely to be cost-effective from a societal perspective by offering a shift of certain tasks from overburdened and high-cost health care settings directly into communities and para-professional staff, reducing also transportation costs for patients [33, 34].

We conducted a systematic review and meta-analysis to compare the effect of community-based ART delivery on treatment engagement, ART adherence, virologic suppression, and all-cause mortality among PLWH in LMICs against results obtained from patients treated in traditional health care facilities.

Methods

Protocol

The study background, rationale, and methods were specified in advance and documented in a study protocol registered in the PROSPERO database (CRD42016034114).

Study Inclusion Criteria

In order to be eligible for inclusion in the review, studies had to report on adherence, virologic suppression, and treatment engagement outcomes after initiation of ART. The following selection criteria were used to identify potential studies:

- *Study design*: observational and experimental studies with primary data using cross-sectional, case–control, and cohort (prospective and retrospective) and randomized controlled trial (RCT) designs.

- *Study population*: HIV-infected individuals initiated on ART.

- *Intervention*: community-based ART delivery. Models could include the following: (1) home-based interventions (e.g., friends or family-centered approaches); (2) peer- or HIV patients-led interventions; community ART distribution points (with or without involving primary level formal or informal health facilities); (3) community-based ART adherence clubs (with or without involving primary level formal or informal health facilities); (4) community ART groups (CAGs)

- *Comparator*: traditional health care facility (e.g., hospital or clinics)

- *Outcomes*: primary: (1) proportion of PLH with optimal ART adherence levels* (>80 %); (2) proportion of PLH with virologic suppression (as defined by the studies) at 12 and/or 24 months after ART initiation. Secondary: (1) treatment engagement (combining linkage and retention in HIV care) as proportion of patients retained in care at 12 and/or 24 months post-ART initiation; (2) all-cause mortality; (3) reported stigma; and (4) cost to patient and provider and cost-effectiveness.

Data Sources and Searches

We conducted a systematic literature search using the following databases: Medline (PubMed), Scopus, SCI Web of Science, and Cochrane Central Register of Controlled Trials (CENTRAL) through January 2016. In addition, abstracts from major HIV/AIDS or infectious disease conferences such as the Conference on Retrovirus and Opportunistic Infections (CROI), International AIDS Society (IAS), International AIDS Conference, and Infectious Diseases Society of America (IDSA) were reviewed for inclusion. Our search terms included the following: "community"; "home-based care"; "health facilities"; "hospital"; "clinic"; "adherence"; "virologic suppression"; "adherence club"; "retention in care"; "retention"; "loss to follow up", "attrition", "antiretroviral therapy"; "HIV"; "community volunteers"; "treatment supporter"; "DOT"; "DAART"; "cost"; "cost-effectiveness".

Study Selection and Data Extraction

Two of the authors (JBN and OA) screened the search outputs using titles and abstracts and independently reviewed the full text of all potentially eligible studies to assess whether they met the inclusion criteria. Discrepancies in the choice of included studies between the two authors were resolved through discussion and consensus. For all eligible studies, the same

authors reviewed extracted information regarding publication date, study setting, study design, methods, patient population, study intervention, and outcomes.

Risk of Bias (Quality) Assessment

To appraise the risk of bias for included studies, a tool was adapted from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (Appendix) [35]. Briefly, the risk of bias was assessed as low risk, unclear risk, or high risk for each of the following domains: selection (sample population), selection (participation rate), performance bias (outcome assessment), performance bias (analytical methods to control for bias), and other forms of bias. We used the Cochrane Collaboration's tool for assessing the risk of bias for quality assessment of the included studies [36]. The studies were graded based on the following: (i) sequence generation, (ii) blinding of outcome assessor, (iii) incomplete outcome data, (iv) selective outcome reporting, and (v) other sources of bias.

Measures of Treatment Effect and Unit of Analysis

We used relative risks (RR) for the calculation of dichotomous data (such as adherence and retention in care). All results are presented with 95 % confidence intervals (CI).

Data Synthesis

In the absence of statistical heterogeneity, we used a fixed effect model, and we used a random effect model where we detected moderate heterogeneity and it was deemed still reasonable to combine trials. We assessed the presence of statistical heterogeneity in the meta-analyses by visual inspection of the forest plot and applying a Chi-squared test for heterogeneity with a threshold P value of 0.10 to determine statistical significance. Inconsistency was quantified across studies using the I^2 value. We used Review Manager 5.3 [37] to conduct analyses and analyzed results for trials and cohort studies separately and also pooled these data. This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [38].

Results

Study Selection and Characteristics of Included Studies

The process of study identification and selection is shown in Fig. 1. The literature search yielded 7950 citations after removing duplicates. After review of title and abstract, 37 full text articles were selected for critical review. A total of 11 RCTs were included [21, 25, 26, 29, 30, 36, 39, 40•, 41–44] and 11 cohort studies [27, 36, 39, 45–48, 49•, 50, 51, 52•, 53, 54] with a total of 5861 and 89,388 participants, respectively. These studies were conducted in eight different sub-Saharan African countries: Botswana, Zimbabwe, South Africa, Nigeria, Uganda, Kenya, Tanzania, and Zambia. Other studies were conducted in other LMICs like Brazil, Haiti, Peru, and Thailand. See additional details in Table 1. We excluded 17 studies [44], three studies were excluded due to non-inclusion of community-based data [55–57] while seven studies were excluded because the studies were non-comparative [19, 58–62]. One study was also excluded because only baseline data were reported [63] while four did not show outcome data for different arms of the studies [17, 64–66].

Risk of Bias in Included Studies

The risk of bias of included cohort studies is summarized in Table 2. All the included studies had low risk of bias with respect to the selection of sample population and explaining the rationale for case and control selection while the included cohort studies were at risk of bias for sample selection ambiguity and having samples that were unlikely to be representative. All the studies had a high participation rate (>70–85 %). In terms of outcome assessment, seven of the included studies had objective measures of adherence such as "pill count," while two had high risk of bias by measuring the outcome using self-reporting format. All the RCTs and cohort studies used one or more analytical methods to control for bias in individual studies. The risk of bias in the included studies was highest from other forms of bias, followed by selection of sample population, and lowest from participation rates and analytical methods to control for bias.

The risk of bias of included trials is shown in Table 3. Allocation sequence generation was adequate in all the 11 trials. Allocation concealment was adequate in nine trials and unclear in the remaining two trials. Masking of outcome assessors was not clear in all the nine trials. Potential risk of bias due to selective reporting and other bias was low in all 11 trials.

Optimal ART Adherence

Seven RCTs and three cohort studies reported optimal adherence as an outcome. Individual and pooled RRs for optimal adherence are shown in Fig. 2. The result of pooled analysis from the RCTs showed no statistically significant difference in optimal adherence outcomes between the two treatment groups (pooled $RR = 1.02$, 95 % CI 0.99 to 1.04, $I^2 = 68$ %), such that among 6358 participants randomized to community-based ART, 5827 (91.7 %) achieved optimal ART adherence compared with 4083 of 4619 in the facility-based ART group (88.4 %). Three cohort studies, however, provided evidence that participants in community-based ART had statistically significant higher optimal adherence outcomes compared to patients in the facility-based ART programs ($RR = 1.80$, 95 % CI 1.04 to 3.13), such that among 274 participants in the community-based ART, 295 (92.9 %) achieved optimal ART adherence compared with 196 (68.1 %) of 288 in the facility-based ART group.

Virologic Suppression

Eight RCTs and eight cohort studies reported virologic suppression as an outcome. Individual and pooled RRs for virologic suppression are shown in Fig. 3. The result of pooled analysis from the RCTs showed no statistically significant difference in virologic suppression rates between the two treatment groups (pooled $RR = 1.00$, 95 % CI 0.97 to 1.03), with evidence of no statistically significant heterogeneity between studies ($I^2 = 0$ %, $p = 0.49$). Similarly, the result of pooled analysis from the cohort studies showed no statistically significant difference in virologic suppression rates between the two treatment groups (pooled $RR = 1.06$, 95 % CI 0.77 to 1.46), with evidence of statistically significant substantial heterogeneity between studies ($I^2 = 100$ %, $p < 0.00001$).

Treatment Engagement (Linkage and/or Retention in Care)

Seven RCTs and four cohort studies reported retention in care as an outcome. Individual and pooled RRs for retention in care are shown in Fig. 4. The result of pooled analysis from the

RCTs showed that participants assigned to community-based ART (80.3 % [3157 of 3931]) had statistically significant higher rates of treatment engagement than those in facility-based ART (75.9 % [2334 of 3074]) at the end of the follow-up period (RR = 1.03, 95 % CI 1.01 to 1.06, I^2 = 0 %). Similarly, the result of pooled analysis from the cohort studies showed that participants assigned to community-based ART (89.4 % [1074 of 1203]) had statistically significant higher rates of treatment engagement than those in facility-based ART (84.9 % [2578 of 3038]) at the end of the follow-up period (RR = 1.09, 95 % CI 1.03 to 1.15, I^2 = 69%)

All-Cause Mortality

Ten RCTs and eight cohort studies reported all-cause mortality as an outcome. Individual and pooled RRs for all-cause mortality are shown in Fig. 5. The result of pooled analysis from the RCTs showed that there was no statistically significant difference in rates of all-cause mortality in assigned to community-based ART (9.3 % [388 of 4160]) than to those assigned to facility-based ART (10.3 % [338 of 3272]) at the end of the follow-up period (RR = 0.93, 95 % CI 0.73 to 1.18, I^2 = 38 %). Similarly, the result of pooled analysis from the cohort studies showed that there was no statistically significant difference in rates of all-cause mortality in assigned to community-based ART (4.2 % [1075 of 25,506]) than those assigned to facility-based ART (6.0 % [3299 of 54,708]) at the end of the follow-up period (RR = 0.44, 95 % CI 0.19 to 1.02, I^2 = 96 %).

Costs and Cost-Effectiveness

Jaffar et al. [25] reported costs to access care per patient including transport, lunch, child care costs, and lost work time. The average total cost per patient in the first year was US $29 among the community-based participants compared to the US $60 facility-based patients. In terms of health-service costs, the same study reported average cost per patient per year to be US$793 among the community-based participants compared to US$838 among facility-based patients in Jinja, Uganda. Also, Bango and colleagues reported from South Africa that ART adherence clubs (AAC) were most cost-effective than standard of care (SOC), with a cost per patient year of $296 for AAC versus $374 for SOC. Retention in care at 1 year was 95 % (95 % CI 94.88–95.86) for SOC and 98 % for ACC (95 % CI 97.6–98.3) [67].

Discussion

This review found no statistical difference in optimal ART adherence, virologic suppression, all-cause mortality, and loss to follow-up between those participants assigned to community-based ART and facility-based ART, when the analysis was restricted to RCTs. In the pooled analysis from both RCTs and cohort studies, however, we documented that participants assigned to community-based ART had significantly higher rates of retention in care than those in facility-based ART at the end of the follow-up period.

The above results corroborate the fact that providing patient support and education programs at the community level are equal and certainly not inferior compared to facility-based ones and may in fact be superior when it comes to selected outcomes such as retention in HIV care. Of note, our analysis may be underpowered to show superiority on selected outcomes

such as virologic outcomes and all-cause mortality. Of note, ascertainment of selected outcomes such as all-cause mortality is better in the community than in the facility-based settings due to the fact that mortality in facility-based studies may be under-ascertained, which will make mortality in the community looks higher [68]. At the same time, silent health facility-based patient transfer (patients are being seen at other clinics, but the clinic-of-origin staff think that they are disengaged in care) will likely be under-captured, thus making health facility-based retention in care worse [68].

In building decentralized ART delivery, adherence, and retention in care support, community-based ART programs encourage patient autonomy, build social networks, and minimize the structural barriers, such as cost of transport to the clinic, which in turn appear to result in better outcomes [69]. Such community-based interventions are likely to have more impact since they tend to involve trained community health workers, peers, volunteers, or patient's own social network members (e.g., family and friends) who assist with ART adherence counseling and support. In addition, there is evidence that they may provide material, instrumental, and emotional support, as well as promote other healthy behaviors, such as decreased alcohol and drug use, leading to better health outcomes—including survival [14, 24, 29, 32]. Furthermore, enhancing certain aspects of the patient–supporter relationships—such as trust, supporter availability, communication, reciprocity of support, and medication assistance—in a manner consistent with patients' expectations may help to optimize the relationship and its positive impact on patient health [14, 24, 70].

Our study complements the findings of a previous review that assessed the effect of home-based interventions on viral outcomes in sub-Saharan Africa; this review found that there were insufficient data to be conclusive [70]. Another recent review summarized the evidence supporting different models of community participation for ART care or community-based ART in resource-limited settings; these community ART programs made treatment readily accessible and affordable [71]. In Uganda and Kenya, community health workers or volunteers delivered ART at home [41, 62], while in Tete, Mozambique, a demonstration project of people living with HIV/AIDS used self-formed community-based ART groups to deliver ART in the community [19]. Also, in South Africa, *Médecins Sans Frontières* piloted ART adherence clubs with promising results [27]. These clubs may provide some adherence counseling and peer support, as well as enable a "fast track" refill mechanisms. Patients are placed in groups of approximately six patients, and one member of the group (rotating each month) is permitted to obtain refills for all of the patients in his or her group. These approaches decrease the patient burden on health facilities, reduce transportation costs and waiting times for patients, and help overcome structural barriers. They also reduce treatment fatigue and loss to follow-up, increase disclosure and treatment education, and may help patients develop necessary social ties. While supportive of community-based interventions, these evaluations used observational study designs with possibility of selection and observational bias as well as confounding, and most of them did not have a valid comparator and could not be included in our meta-analysis.

We also investigated as secondary outcomes two potential concerns related to community-based ART adherence and retention programs, including reported stigma and low quality of care which could result in an increased all-cause mortality. In terms of stigma, an RCT

reported that only 3 % of patients refused to participate in the home-based ART program due to stigma [25]. Furthermore, it has even been suggested that involvement of community-health care workers in HIV care reduced stigma [72] and being part of peer groups has been found to decrease the perception of social stigma [73].

Our results have important clinical and public health implications in the context of reaching the 2030 UNAIDS 90-90-90 targets toward an AIDS-free generation. While this systematic review and meta-analysis did not examine the first step of the HIV treatment cascade, HIV diagnosis, it did examine the next two. Importantly, community-based interventions aim to conveniently deliver a package of essential ART care functions that extend beyond the clinic into the community such as ART refills, monitoring of treatment adherence and outcomes, and detection of sick patients linked to rapid referral to care. This, in turn, frees up capacity within the clinic-based medical workforce to be able to focus on complicated tasks such as clinical care for sick patients, training and supervision of lay health care workers, and management of health care services. Of note, task shifting is somewhat limited in selected LMICs (e.g., Brazil, Argentina, Mexico, and Puerto Rico), because a physician always needs to be present, at the very least to sign off every single prescription. Second, community-based ART delivery and adherence monitoring and support models for clinically stable patients with documented virologic suppression hold the potential of enabling countries to build sustainable, cost-effective, and equitable HIV care for populations in countries with a scarce health care workforce. Indeed, a cost-effectiveness study by Marseille and colleagues concluded that a home-based ART program in rural Africa may be more cost-effective than most previous estimates for facility-based ART programs [74]. Only three cohort studies involved children [46, 49•, 52•]. The outcomes reported by these studies were virologic suppression, mortality, and loss to follow-up, and all of these were not different from what was obtainable in the adult population. These studies were conducted in South Africa and Uganda.

Surprisingly, we found only two eligible studies to inform cost or cost-effectiveness outcomes. Clearly, more research using economic outcomes is needed. Available data suggest that community-based ART services even if they are equivalent to, but not superior to clinic-based programs, may be more cost-effective from a societal perspective because personnel, operational, and utility costs are likely to be lower, and transportation costs for patients will also be lower; these facts, added to the increased effectiveness in terms of retention, are likely to make community-based ART much more cost-effective and sustainable in the long run. In addition, as mentioned, community-based approaches also make use of community health workers, and an overall community health model that will enable a transformation of the health system from the current vertical siloes to a more integrated approach where community-based HIV care may be further combined with care for other chronic conditions, including non-communicable diseases such as cardiovascular and metabolic diseases which are becoming more prevalent in LMICs as these countries experience the epidemiological and demographic transitions.

Our study has several strengths. We performed a comprehensive search of several databases and sources to identify eligible cohorts and RCTs with the latter providing the highest quality of evidence. Two authors independently evaluated each study for inclusion and data

extraction. Regarding limitations, inclusion of cohort study designs may bias the overall estimate of effects due to unmeasured confounding not adjusted for in multivariate analyses. Indeed, the fact that we are observing a difference between RCTs and observational studies for the ART adherence outcome may reflect that in many if not all of these community-based interventions, the patients who end up in the intervention, if it is not randomized, are likely to be quite a bit different—selected somehow—for stability even if not measured. However, in the context of implementation science, observational studies often provide strong signals of important direction of effect. Also, as mentioned earlier, facility-based treatment engagement may have been underestimated since such outcome does not account for silent transfers, and which therefore may not completely capture retention in care [68]. Finally, with only 11 RCTs, we may be underpowered to show superiority of either type interventions.

In summary, community- versus facility-based models of ART delivery resulted in at least comparable outcomes for clinically stable HIV-infected patients on treatment in LMICs and are likely to be cost-effective. As ART rollout expands in LMICs, health systems need to continually adjust to accommodate further expansion. Community-based ART delivery for stable patients hold the promise of enabling countries to build sustainable, cost- effective, and equitable HIV care for populations in settings with a scarce health workforce. Further research with well-powered studies may be needed to further explore effectiveness and cost-effectiveness of such community-based ART programs, particularly in under-represented patient groups such as HIV-infected children, adolescents, and pregnant women to sustain optimal outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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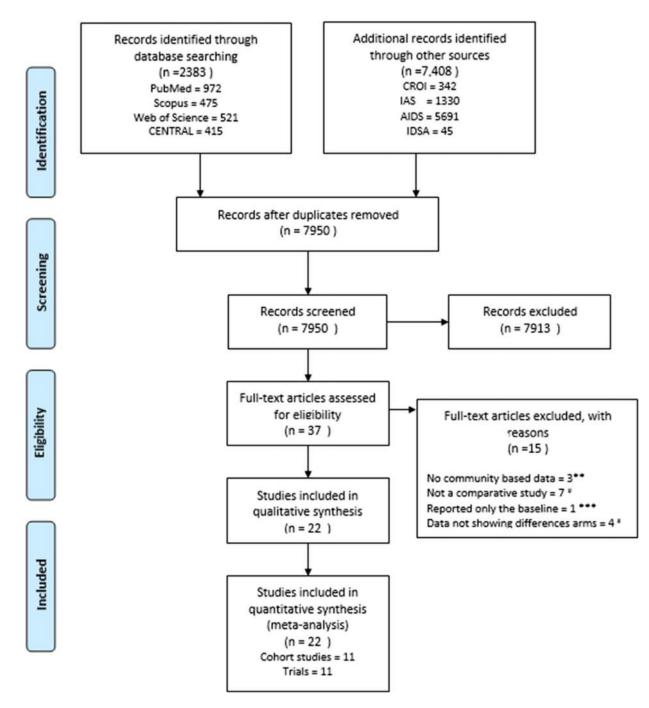
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Fig. 1.
PRISMA flow for study selection

Study or Subgroup	Community-based Events	Total	Facility-based Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.1.1 RCT subgroup							
Chang 2010	862	874	322	330	25.5%	1.01 [0.99, 1.03]	
Jaffar 2009	3698	3951	2527	2768	27.0%	1.03 [1.01, 1.04]	
Kunutsor 2011	80	87	71	87	4.3%	1.13 [1.00, 1.27]	
Mfinanga 2015	451	509	429	481	16.2%	0.99 [0.95, 1.04]	
Nakigozi 2015	458	605	470	604	11.2%	0.97 [0.91, 1.04]	
Selke 2010	79	84	95	98	10.7%	0.97 [0.91, 1.03]	
Taiwo 2014	199	248	169	251	5.1%	1.19 [1.07, 1.33]	
Subtotal (95% CI)		6358		4619	100.0%	1.02 [0.99, 1.04]	
Total events	5827		4083				

Heterogeneity: Tau² = 0.00; Chi² = 18.78, df = 6 (P = 0.005); I² = 68%
Test for overall effect: Z = 1.20 (P = 0.23)

	Community-based Events	Total	Facility-based Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	
1.1.2 Cohort subgroup							
Johnston 2012	209	212	165	205	41.3%	1.22 [1.14, 1.31]	
Kaihin 2014	19	23	5	23	22.3%	3.80 [1.71, 8.44]	
Munoz 2011	46	60	26	60	36.4%	1.77 [1.28, 2.44]	
Subtotal (95% CI)		295		288	100.0%	1.80 [1.04, 3.13]	
Total events	274		196				

Heterogeneity: Tau² = 0.19; Chi² = 17.79, df = 2 (P = 0.0001); I² = 89%
Test for overall effect: Z = 2.09 (P = 0.04)

Test for subgroup differences: Chi² = 4.12, df = 1 (P = 0.04), I² = 75.7%

[Favors facility-based] [Favors community-based]

Fig. 2.
Forest plot of optimal ART adherence comparing community-based ART versus facility-based ART

Study or Subgroup	Community-based Events	Total	Facility-based Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 RCT sub-group						
Chang 2010	417	462	155	173	27.0%	1.01 [0.95, 1.07]
Coker 2015 (a)	91	107	87	99	8.1%	0.97 [0.87, 1.08]
Coker 2015 (b)	86	107	87	99	6.7%	0.91 [0.81, 1.03]
Gross 2015	95	129	105	128	5.5%	0.90 [0.79, 1.02]
Jaffar 2009	615	729	403	483	36.8%	1.01 [0.96, 1.06]
Kiweewa 2013	99	136	93	136	4.0%	1.06 [0.91, 1.24]
Nachega 2010	77	86	83	96	8.2%	1.04 [0.93, 1.15]
Selke 2010	38	43	29	32	3.9%	0.98 [0.83, 1.14]
Subtotal (95% CI)		1799		1246	100.0%	1.00 [0.97, 1.03]
Total events	1518		1042			

Heterogeneity: Tau² = 0.00; Chi² = 6.44, df = 7 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.80)

Study or Subgroup	Community-based Events	Total	Facility-based Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.2 Cohort sub-group						
Fatti 2012	4004	6087	8271	14813	12.8%	1.18 [1.15, 1.21]
Fatti 2014	161	238	704	1105	12.7%	1.06 [0.96, 1.17]
Franke 2014	252	304	235	306	12.7%	1.08 [1.00, 1.17]
Grimsrud 2016	2677	6037	1762	2113	12.8%	0.53 [0.51, 0.55]
Grimwood 2012	87	108	753	959	12.7%	1.03 [0.93, 1.13]
Johnston 2012	152	211	98	203	12.4%	1.49 [1.26, 1.76]
Kipp 2012	120	185	124	200	12.5%	1.05 [0.90, 1.22]
Munoz 2011	40	60	28	60	11.4%	1.43 [1.03, 1.98]
Subtotal (95% CI)		13230		19759	100.0%	1.06 [0.77, 1.46]
Total events	7493		11975			

Heterogeneity: Tau² = 0.21; Chi² = 1510.55, df = 7 (P < 0.00001); I² = 100%
Test for overall effect: Z = 0.34 (P = 0.73)

Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%

[Favors facility-based] [Favors community-based]

Fig. 3.
Forest plot of virologic suppression comparing community-based ART versus facility-based ART

Study or Subgroup	Community-based Events	Total	Facility-based Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.3.1 RCT sub-group							
Chang 2010	859	970	320	366	26.5%	1.01 [0.97, 1.06]	
Coker 2015 (a)	107	200	99	200	1.5%	1.08 [0.89, 1.31]	
Coker 2015 (b)	107	200	99	200	1.5%	1.08 [0.89, 1.31]	
Jaffar 2009	662	859	441	594	15.0%	1.04 [0.98, 1.10]	
Mfinanga 2015	842	1001	794	998	31.2%	1.06 [1.01, 1.10]	
Nakigozi 2015	493	605	479	604	17.2%	1.03 [0.97, 1.09]	
Selke 2010	87	96	102	112	7.1%	1.00 [0.91, 1.09]	
Subtotal (95% CI)		3931		3074	100.0%	1.03 [1.01, 1.06]	
Total events	3157		2334				

Heterogeneity: Tau² = 0.00; Chi² = 3.37, df = 6 (P = 0.76); I² = 0%
Test for overall effect: Z = 2.80 (P = 0.005)

Study or Subgroup	Community-based Events	Total	Facility-based Events	Total	Weight	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
1.3.2 Cohort sub-group							
Franke 2014	280	304	267	306	30.0%	1.06 [1.00, 1.11]	
Johnston 2012	179	212	151	205	18.0%	1.15 [1.04, 1.27]	
Kipp 2012	129	185	142	200	13.0%	0.98 [0.86, 1.12]	
Luque-Fernandez 2013	488	502	2018	2327	39.0%	1.12 [1.10, 1.15]	
Subtotal (95% CI)		1203		3038	100.0%	1.09 [1.03, 1.15]	
Total events	1076		2578				

Heterogeneity: Tau² = 0.00; Chi² = 9.63, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 2.88 (P = 0.004)

Test for subgroup differences: Chi² = 2.57, df = 1 (P = 0.11), I² = 61.1%

0.1 0.2 0.5 1 2 5 10
[Favors facility-based] [Favors community-based]

Fig. 4.
Forest plot of retention in care comparing community-based ART versus facility-based ART

Study or Subgroup	Community-based Events	Total	Facility-based Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.1 RCT sub-group						
Chang 2010	90	970	31	366	18.3%	1.10 [0.74, 1.62]
Coker 2015 (a)	11	200	11	200	7.0%	1.00 [0.44, 2.25]
Coker 2015 (b)	18	200	11	200	8.3%	1.64 [0.79, 3.38]
Gross 2015	4	129	3	129	2.4%	1.33 [0.30, 5.84]
Jaffar 2009	117	859	80	594	24.9%	1.01 [0.78, 1.32]
Kunutsor 2011	2	87	0	87	0.6%	5.00 [0.24, 102.66]
Mfinanga 2015	134	877	180	843	28.5%	0.72 [0.58, 0.88]
Nachega 2010	9	137	20	137	7.9%	0.45 [0.21, 0.95]
Nakigozi 2015	2	605	2	604	1.4%	1.00 [0.14, 7.06]
Selke 2010	1	96	0	112	0.6%	3.49 [0.14, 84.81]
Subtotal (95% CI)		4160		3272	100.0%	0.93 [0.73, 1.18]
Total events	388		338			

Heterogeneity: Tau² = 0.04; Chi² = 14.53, df = 9 (P = 0.10); I² = 38%
Test for overall effect: Z = 0.61 (P = 0.54)

Study or Subgroup	Community-based Events	Total	Facility-based Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.5.2 Cohort sub-group						
Fatti 2012	970	19668	2968	47285	14.2%	0.79 [0.73, 0.84]
Fatti 2014	22	3871	116	982	13.7%	0.05 [0.03, 0.08]
Franke 2014	13	304	22	306	13.1%	0.59 [0.31, 1.16]
Grimwood 2012	4	323	106	3240	11.9%	0.38 [0.14, 1.02]
Johnston 2012	12	212	12	205	12.7%	0.97 [0.44, 2.10]
Kipp 2012	32	185	23	200	13.6%	1.50 [0.91, 2.47]
Luque-Fernandez 2013	1	502	39	2327	7.9%	0.12 [0.02, 0.86]
Massavon 2014	21	441	13	163	13.1%	0.60 [0.31, 1.16]
Subtotal (95% CI)		25506		54708	100.0%	0.44 [0.19, 1.02]
Total events	1075		3299			

Heterogeneity: Tau² = 1.27; Chi² = 159.26, df = 7 (P < 0.00001); I² = 96%
Test for overall effect: Z = 1.92 (P = 0.05)

Test for subgroup differences: Chi² = 2.82, df = 1 (P = 0.09), I² = 64.6%

Fig. 5.
Forest plot of all-cause mortality comparing community-based ART versus facility-based ART

Table of included studies

Table 1

Study	Type	Age-median (years)		Countries included	Duration of study	Sample size (*n*)	Participants/health care service description	
		Intervention	Comparator				Intervention	Comparator
Chang et al. [21]	Cluster-randomized trial	35.5	34.0	South Africa	27 months; May 2006–July 2008	1336	Patients with Community-based peer health workers	Control group-accessing standard of care
Fatti et al. [45]	Cohort	35.1	34.6	South Africa	69 months; January 2004–September 2010	66,953	Patients who received community-based adherence support	Patients without community-based adherence support
Fatti et al. [46]	Cohort	6.3	6.6	South Africa	69 months; January 2004–September 2010	4,853	Patients who received community-based adherence support	Patients without community-based adherence support
Franke et al. [47]	Prospective cohort	37.0	37.0	Rwanda	15 months; June 2007 to August 2008	610	Community-Based Accompaniment	Clinic-Based Care
Grimsrud et al. [48]	Cohort	33.9	33.2	South Africa	20 months; May 2012–December 2013	8,150	Community based adherence club	Community Health Centre
Grimwood et al. [49•]	Cohort	6.8	6.2	South Africa	57 months; January 2004–September 2009	3,563	Children with patient advocates	Children without patient advocates
Jaffar et al. [25]	Cluster-randomized equivalence trial	37.0	38.0	Uganda	48 months; February 2005–January 2009	1,453	Home-based care	Facility based care
Johnston et al. [50]	Retrospective cohort	36.0	43.0	South Africa	75 months; January 2003–March 2010	417	Community cohort	Workplace cohort
Kipp et al. [51]	Cohort	36.8	34.8	Uganda	15 months; March 2006–May 2007	385	Centre/Community-based cohort	Hospital-based cohort
Kiweewa et al. [39]	Randomized controlled trial	27.0	27.8	Uganda	29 months; May 2007–September 2009	92	Nurse-Peer model	Doctor-Counsellor model
Luque-Fernandez et al. [27]	Cohort	Not reported	Not reported	South Africa	40 months; November 2007–February 2011	2,834	Adherence clubs	Traditional clinic-based care
Massavon et al. [52•]	Retrospective cohort	91.0 months	45.9 months	Uganda	2003–2010	1,623	Community home-based care approach	Facility-based family-centred approach
Mfinanga et al. [40•]	Open-label, randomized controlled trial	38.0 35.0	37.0 35.0	Tanzania Zambia	19 months; February, 2012–September, 2013	1,999	Clinic plus community support	Standard care

Study	Type	Age-median (years) Intervention	Age-median (years) Comparator	Countries included	Duration of study	Sample size (*n*)	Participants/health care service description Intervention	Comparator
Nachega et al. [29]	Open-label, randomized controlled trial	35.7	36.7	South Africa	42 months; February 2005–July 2008	274	Directly observed therapy (DOT-ART) arm	Self-administered ART (Self-ART arm)
Selke et al. [41]	Cluster randomized controlled clinical trial	38.7	37.5	Kenya	26 months; March 2006–April 2008.	208	Community Care Coordinators arm patients	Standard of Care arm patients
Taiwo et al. [42]	Randomized controlled trial	Not reported	Not reported	Nigeria	19 months; June 2006–December 2007	499	Treatment partner-assisted ART	Patient-administered standard of care ART
Gross et al. [44]	Randomized controlled trial	38	37	Botswana, Brazil, Haiti, Peru, South Africa, Uganda, Zambia, Zimbabwe	30 months; April 2009–September 2011	259	Partner-based modified directly observed therapy	Standard of care
Nakigozi et al. [30]	Randomized controlled trial	37.6	37	Uganda	15 months; October 2010–January 2012	1,209	Patient-selected care buddy	Standard of care
Kaihin et al. [53]	Cohort	18.2	19.4	Thailand	4 months; April-July 2011	46	Experimental Group (Empowerment Intervention)	Control
Kunutsor et al. [26]	Randomized controlled trial	39.1	39.2	Uganda	8 months; March-September 2010	174	Standard adherence intervention package plus treatment supporter intervention	Standard intervention package
Munoz et al. [54]	Cohort	31.7	31.9	Peru	17 months; December 2005–April 2007	120	Community-based accompaniment with supervised antiretrovirals	Control
Coker et al. [43]a	Randomized controlled trial	Not reported	Not reported	Nigeria	18 months; August 2006–January 2008	400	Peer educators arm	Standard of care
Coker et al. [43]b	Randomized controlled trial	Not reported	Not reported	Nigeria	18 months; August 2006–January 2008	400	Home visits and peer educators arm	Standard of care

Table 2

Risk of bias in included studies of cohort studies

Study	Selection (sample population)	Selection (participation rate)	Performance bias (outcome assessment)	Performance bias (analytical methods to control for bias)	Other form of bias
Fatti et al. [45]	High	Low	Unclear	Low	High
Fatti et al. [46]	High	Low	Unclear	Low	High
Franke et al. [47]	High	Low	Unclear	Low	High
Grimsrud et al. [48]	High	Low	Low	Low	High
Grimwood et al. [49•]	High	Low	Unclear	Low	High
Johnston et al. [50]	High	Low	Unclear	Low	High
Kipp et al. [51]	High	Low	Low	Low	High
Luque-Fernandez et al. [27]	High	Low	Unclear	Low	High
Massavon et al. [52•]	High	Low	Low	Low	High
Kaihin et al. [53]	High	Low	Low	Low	High
Munoz et al. [54]	High	Low	Low	Low	High

Table 3

Risk of bias in included studies of randomized controlled trials

Study	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of outcome assessors (performance bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chang et al. [21]	Low	Unclear	Unclear	Low	Low	Low
Jaffar et al. [25]	Low	Low	Unclear	Low	Low	Low
Kiweewa et al. [39]	Low	Low	Unclear	Low	Low	Low
Mfinanga et al. [40•]	Low	Low	Unclear	Low	Low	Low
Nachega et al. [29]	Low	Low	Unclear	Low	Low	Low
Selke et al. [41]	Low	Low	Unclear	Low	Low	Low
Taiwo et al. [42]	Low	Unclear	Unclear	Low	Low	Low
Gross et al. [44]	Low	Low	Low	Low	Low	Low
Nakigozi et al. [30]	Low	Low	High	Low	Low	Low
Kunutsor et al. [26]	Low	Low	Unclear	Low	Low	Low
Coker et al. [43]	Low	Low	Unclear	High	Low	Low
	Low	Unclear	Unclear	High	Low	High