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## Systematic review of interventions aimed at improving HIV adherence to care in low- and middle-income countries in Sub-Saharan Africa

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### Abstract

Long-term adherence to antiretroviral medication continues to present as a challenge along the continuum of the HIV care cascade. HIV interventions and support programs are significantly threatened in resource-limited settings by challenges in maintaining long-term follow-up for ART adherence. We sought to complete a systematic review to comprehensively examine ART adherence and retention in care interventions in Sub-Saharan Africa and to report on the implementation of interventions in real-world settings to inform future health investments in HIV care. Interventions were grouped according to their impact on individual, community, and health-systems levels. While a vast majority of studies evaluated a combination of interventions, those studies that incorporated the community as a resource were most successful. In addition, providing education and behavior reminders proved effective and should be accompanied by community and peer efforts for best results. Multi-level interventions, such as combining individual and community-level interventions showed promising results for long term ART adherence.

### Keywords

Human immunodeficiency virus (HIV); adherence; systematic analysis; Sub-Saharan Africa

### Introduction

In 2014, UNAIDS launched an ambitious “9-90-90” goal and campaign to diagnose, treat, and suppress 90 percent of all human immunodeficiency virus (HIV) patients globally

by 2020 (1). However, by 2021, 75% percent of the 38.4 million people living with HIV (PLHIV) were receiving antiretroviral therapy (ART), a treatment gap of 5.9 million people (2). The high rates of patients lost to follow-up (LTFU) at each stage of the HIV care cascade (testing and diagnosis, linkage to care, ART initiation and adherence, and maintenance of therapy) make it difficult to achieve higher standards of care across health systems. Unfortunately, the most vulnerable step along the care cascade is long-term adherence. The WHO estimates retention rates 81% 12 months after initiating ART, 75% at 24 months, and 67% at 60 months, meaning that one-third of individuals have been lost by 5 years after beginning treatment (3). ART has the potential to dramatically reduce morbidity and mortality for PLHIV, however incomplete treatment adherence is the major cause of treatment failure, development of drug resistance, HIV disease progression, and death (4). Systematic reviews have demonstrated that long-term adherence to treatment in Sub-Saharan Africa is of particular concern, as one-third of adults in the region lose viral suppression at two years of treatment (5). As a result, a lack of adherence can help explain why increased access to ART in Sub-Saharan Africa has not produced positive outcomes to the extent that is expected (6). Adherence to ART is the critical determinant for HIV treatment outcomes, with adequate adherence predicting viral suppression and thus clinical outcomes (7–9).

Low- and middle-income countries (LMICs) in Sub-Saharan Africa account for over two-thirds of the global HIV burden (25.6 million), with an estimated 20.1 million on ARTs (2). However, in 2021 alone, an estimated 860 000 [660 000–1.2 million] people became newly infected with HIV, poor ART adherence is a key contributor to the ongoing incidence of HIV and this gap must be closed to reach zero new infections by 2030. A multitude of studies have evaluated the barriers and facilitators of adherence to ART (11). Many interventions to overcome these barriers, as well as interventions and approaches to simplify, streamline, and maximize the use of limited resources to optimize ART adherence have been implemented and studied across numerous settings. Although numerous interventions have been proposed to improve retention of patients, evaluations of these interventions are scarce (12–14). A synthesis of data, particularly under routine conditions, is needed to understand prioritization and investment in health programs for the future. This study seeks to comprehensively examine ART adherence interventions in Sub-Saharan Africa and to report on the success of interventions in real-world settings to inform future health investments in HIV care.

## Methods

We performed a systematic review of studies examining interventions along the HIV care cascade. This review was conducted in two parts, one for articles published between 2008 and 2018, and second updated review to identify articles published from 2018 to 2022. A query of search terms was completed in Pubmed, Embase, Scopus, Web of Science, and the Cochrane Library on June 7<sup>th</sup>, 2018, with an additional identical query conducted on February 24<sup>nd</sup>, 2022 to capture articles published between June 8<sup>th</sup>, 2018 and February 24<sup>nd</sup>, 2022. A four-concept search focused on HIV/AIDS, HIV Care Cascade, Service/Program delivery, and Sub-Saharan Africa was utilized. Search strategy concepts were developed in collaboration with a professional librarian (KL) and the Johns Hopkins University EAWA study team in accordance with PRISM guidelines. Only articles published from 2008 to 2022 were included. An overview of the complete search strategies is available

in the Appendix. Studies were categorized into one of the stages of the HIV care cascade (prevention, testing/diagnosis, linkage to care/antiretroviral initiation, or adherence), and each stage was treated as an independent, focused systematic review.

### **Study Inclusion Criteria**

Our objective was to evaluate studies that implemented an intervention to improve patient adherence to ART regimens. Interventions included pill counting, alarms, psychosocial interventions, mHealth/technology-based interventions, peer support, and other interventions.

### **Exclusions**

Studies were excluded if any of the following criteria were met: an intervention was not implemented, the study did not report results (e.g. study protocols, feasibility studies), PLHIV were not the focus of the study, the study did not occur in Sub-Saharan Africa, the intervention was not on the care cascade, or the study was a simulation and was not implemented in the field. Studies that were descriptive in nature were excluded, including those studies that were strictly qualitative.

### **Data extraction and synthesis for emergent themes**

Primary data was used for data extraction. Data extracted from the studies included: country of study, type of intervention implemented, and key findings and conclusions discussed by authors. Two authors screened each title and abstract for inclusion in this report. Authors completed further evaluation for a description of the intervention, data on the intervention, and conclusions about the effect(s) of the intervention.

### **Conceptual Framework**

We grouped and categorized interventions based on a conceptual framework (Figure 2) which focused on understanding patients and providers as individuals living in unique social and cultural contexts within broader health systems, all of which affect ART adherence. We developed a framework previously theorized and used by others to categorize interventions acting at individual, community, and structural health system levels (15–18). We adapted the adherence models shown in Mukumbang et al.'s 2017 review of antiretroviral adherence theories (17). Our modification of this model categorized interventions into groups according to the level of care that they addressed: those aimed directly at promoting individual adherence behavior, those promoting adherence by focusing on interpersonal support and relationships in the community and within group settings, and those addressing structural issues at the organizational and systemic levels of the care cascade. We integrated these frameworks after identifying themes throughout intervention types which aimed to target different levels of society while also targeting different aspects of human behavior that impact adherence.

Using the conceptual framework shown above (Figure 2), we categorized each intervention found in the literature review. Each study intervention was categorized by target of intervention and level of action. An intervention was categorized as individual if it involved only the intervention and patient or provider involved in care; group or team interventions

community members that were not the target of the intervention but could provide support such as, organizational interventions involved reorganization of the providers or services involved in the care of patients, and systems or environment interventions focused on changes to the clinic or healthcare system delivery. Direct comparison among studies was sometimes compounded by the heterogeneous definitions of adherence as a primary outcome measure. Adherence was most often defined by appointment attendance, viral load, or CD4+ count, though these measured endpoints varied across studies.

## Results

### Study Characteristics

From 7940 unique titles identified, 1020 studies described the implementation and evaluation of an HIV care cascade intervention and underwent full text review. Of these, 409 met the inclusion criteria and 158 focused on the adherence to treatment phase of the HIV care cascade in Sub-Saharan Africa. These articles include studies conducted in 18 unique countries, listed as follows: Burkina Faso, Cameroon, Ethiopia, Ghana, Kenya, Lesotho, Malawi, Mozambique, Nigeria, Rwanda, Sierra Leone, South Africa, Swaziland, Tanzania, Uganda, Zambia, and Zimbabwe. One study conducted a multi-site analysis. Of the 158 studies, South Africa is featured most prominently, recurring as the setting in 37 (27%) articles. After South Africa, Uganda with 24 (18%) and Kenya with 19 (14%) were the next most commonly featured. Study design types included randomized control trials, retrospective cohort studies, and prospective cohort studies, among others. Studies varied by the number of interventions implemented: 101 studies examined single component interventions, while 36 studies assessed multiple component interventions.

### Composition of Interventions

Of the 186 unique adherence strategies interventions applied within the 137 selected studies, 108 (63%) interventions were at the level of the individual, 30 (17%) were focused on community or peers as resources, and 34 (20%) were organization-based. Notably, many of the studies implemented multi-level intervention, for example streamlining care and changing clinic practices were most often accompanied by counseling, as were short messaging systems (SMS) focused interventions.

Structurally-focused interventions such as financial and nutrition assistance were most often combined with education but could accompany any intervention type. Support groups often included patient education components. Twelve interventions included more comprehensive services involving three or more intervention categories. Wraparound services were successfully provided both in the clinic setting and in the community through community based adherence clubs. Overall, these interventions had a high rate of improvements in adherence success as measured within each study 10/13 (77%).

Comparisons between these studies are difficult due to the application of multiple interventions simultaneously. In Table 1 we provide a count of the studies by intervention type. We then identify the number of studies that analyze the intervention independently, and of those how many identified a positive result when accounting for other covariates.

For example, patient education was reported to fare well when evaluated as part of a bundle of interventions (number of positive studies 11/15 (73%), but it was not successful when evaluated independently. The reverse was true for peer support interventions, in-person pill count and streamlining care who seem to perform better on independent analysis.

### Adherence Success by Intervention Type

**Individual Interventions**—Individual interventions most often worked to increase the act of pill-taking without focusing on other aspects of adherence such as motivation or structural factors. These interventions include SMS reminders, alarm reminders, directly observed therapy (DOT), pill counting, and electronic adherence monitoring. These interventions were often low cost, with the exception of DOT, but they produced mixed results especially when not provided with additional services. Overall, 108 (63%) interventions had at least one component focused on the individual level. These reminder interventions produced mixed results, with DOT, pill counts, and SMS reminders each showing significantly positive result rates of around 50% (Table 1).

Directly observed therapy was found to be effective about 50% of the time (Table 1), but was described as a high resource intervention, which will impact sustainability in a real-world setting. Pill counts, including electronic pill boxes and other technology-based interventions demonstrated mixed results in the literature. Electronic pill boxes were found to be slightly less effective than unannounced pill counts at clinic visits and may be more expensive and challenging to implement. SMS reminder messages were low cost but also demonstrated mixed results. In 9/16 (56%) SMS reminder studies, results showed significant increases in medication adherence. One study which compared the effect of SMS reminders on care retention in rural versus urban settings found the text messages were only effective for urban participants (19). The majority of text studies sent weekly reminders, but frequency went as high as daily. Notably these interventions excluded individuals who did not have consistent mobile phone access and who were not able to read and respond to texts.

While 24/108 (22%) interventions included a patient education component, none utilized patient education alone as an intervention, and these efforts were often used as a comparison group in studies comparing patient education alone with more intensive interventions in combination with patient education. Although low-cost, patient education alone does not seem to be adequate to independently produce differences in adherence level. Limited studies from the current review have assessed the individual effect of patient education.

Nine interventions examined moderating factors such as cash transfers, food packets, financial counseling, or home assessments. Financial assistance performed well alongside other interventions such as counseling or support groups and showed adherence improvements in 6/7 (83%) studies (22–28). Out of five studies which provided direct financial assistance through cash transfer, food assistance, and transportation support, four showed significant results, with the greatest impact resulting from cash transfer. One study found that food and cash transfers improved adherence at 6 and 12 months, noting that short-term transfers may be most beneficial to improving ART adherence among patients who are poorer and most recently diagnosed, among whom stronger effects were observed, compared to higher-income and patients with longer time to ART initiation from diagnosis (27).

However, the largest study, which evaluated unconditional cash transfers alone, failed to see improvement over the long term (22). The limited number of studies in this category limits generalizability; however, barrier assessments and cash transfers demonstrated promise across settings.

**Community/Peer Support Interventions**—Of the three intervention groups, community or peer-focused interventions were the second-most frequently used after individual-based interventions. Community and peer interventions primarily focused on the motivational aspects of behavior change. Community and peer intervention programs had the highest rates of success of any intervention type.

Peer interventions included peer support programs (10 programs), CHW home visits (11 programs), and counseling (31 programs). Peer support was particularly effective. Among 7 studies which analyzed one-on-one peer support programs, 6 (86%) showed a significant improvement in adherence. Allowing the participant to choose their own treatment partner from family or friends was also effective. Home visit programs were found to be effective in 9/12 studies (75%); they were also often included in wraparound interventions that included multiple services. CHW home visits were most likely to overlap with directly observed therapy, counseling, and peer support. Peer HIV+ health workers (PHWs) were able to combine the elements of a lay health worker and a peer support program.

Counseling was analyzed independently in 13/31 (42%) interventions which included a counseling component but was regularly used to provide education and determine factors such as additional needs. 5/13 (38%) saw significant results, including three which found motivational counseling specifically to improve adherence, while two additional studies reported that participants in the counseling intervention were less likely to be lost to follow up in care, but did not measure or identify significant differences in adherence (20,21). Overall, counselling appears to be potentially effective, but direct comparison between studies is challenging due to variability in the specific goals and implementation of counseling programs.

Adherence clubs, community based adherence support groups, and peer support groups have all been shown to have a positive impact on treatment adherence. Community-based support groups, rather than those directed through a clinic, were better for maintaining treatment success in those already adhering to ART (29). Clinic-based groups with a trained counselor or CHW were most effective in general and may be particularly important for at-risk groups or those not already adhering to ART. A study in South Africa of 3861 patients over 8 years showed a sustained decrease in LTFU with (HR 0.74 (95% CI: 0.66–0.84;  $p < 0.0001$ ) among those receiving community based adherence support (30). Although partner education and partner directly observed therapy were both studied, neither showed significant results (31,32).

Peer support groups were found in various studies to increase adherence as well as HIV-related knowledge. In rural Ethiopia, peer support was found to decrease internalized HIV-related stigma by 97% ( $P = 0.001$ ), increase HIV-related knowledge (17% increase,  $p=0.001$ ), while maintaining high adherence (adherence rate 94% (95% CI = 89%–97) (33).

Peer support may be particularly effective for marginalized groups or those for whom HIV stigma is playing an important role in adherence. Among adolescents, both peer support groups and group family counseling were found to be effective, and family counseling was also effective in decreasing HIV-related social stigma and increasing comfort with discussing sensitive topics among adolescents in South Africa ( $p < 0.002$ ) (34). Peer support is a particularly popular intervention among adolescents and has been shown to be effective in that population through adherence clubs (24,35). However, peer support groups were equally effective among adults. In a cohort study with 8150 participants, community based adherence clubs decreased the risk of LTFU by 67% aHR: 0.33, 95% CI: 0.27 to 0.40) (36).

Community education programs involved those interventions which addressed family education for living with PLHIV and education for treatment partners or others in the community helping to support and monitor patient adherence. None of these programs were analyzed independently of other intervention components.

Community support groups were used more often than peer, family, and friend support. Further, community support programs were more often associated with positive adherence outcomes compared to other support programs. Out of 14 studies which examined community support groups, 12/14 (86%) found significant increases in adherence; some studies alternatively measured loss to follow up or retention in care (37–39).

**Organizational Interventions**—Health system changes included several modalities, including task shifting, care integration, alternative distribution, changes to treatment provision guidelines, and changes to patient follow-up. This category of intervention was used less often than other interventions and also demonstrated the least amount of standardization across clinics with different interventions used to streamline or improve care delivery. Patient follow-up may improve identification of nonadherent patients but has not been consistently shown to increase adherence itself. One study of pregnant women with HIV in Kenya found that an active defaulter tracing system in which women were repeatedly contacted by social work after missing an appointment decreased LTFU (40). Integration of care, either with chronic disease care or maternal-child care had other benefits such increasing new HIV diagnosis and may increase convenience for families but was not shown to increase ART adherence. Task shifting from doctors to nurses for ART follow-up visits was shown in multiple studies to be non-inferior to physician visits. A study of 10,112 patients in rural Malawi found no significant difference in attrition when ART was administered by a nurse (aIRR=1.18, 95% CI 0.95–1.47) (41). Shifting specific tasks to CHWs was also found to be effective to maintain care for adults who were clinically stable in Kenya, with patients who received CHW home visits maintaining equal disease control with half as many clinic visits as controls ( $p > .001$ ) (42). Task-shifting is not typically used to increase adherence but rather to decrease cost without decreasing adherence success. The exception was for peer health workers living with HIV, who were able to increase adherence and decrease HIV-related stigma among women in Ethiopia (43) through task-shifting.

## Discussion

There is an opportunity and need to identify strategies to improve ART adherence in PLHIV. Studies that specifically quantified the adherence gap estimate show wide variability; a study in Bata, Equatorial Guinea, quantified adherence using the CEAT-VIH score and estimated that 55% of clients had low or insufficient adherence(44), But there is hope, a recent study in Tanzania that showed a pharmacy refill intervention, not only demonstrated high adherence (71%) but also that the majority of patients attained undetectable viral load 6 months after using DTG based regime (45) and a study in South Africa that paired TB and HIV treatment, demonstrating 5-year treatment success at 89.3% (46).

### Best Practices

The most commonly used interventions utilized across Sub-Saharan Africa focused on individual, community and peer interventions focused on support and motivation for behavior change. Multi-level interventions, such as combining individual and community-level interventions were found to be the most likely to improve adherence. In particular, providing education and behavioral reminders should both be accompanied by additional support interventions for best results. Community-based support groups and participant-chosen supporters are cost effective interventions.

One-on-one peer support and community support groups were both found to be effective across multiple settings. Adherence clubs, led by CHWs (community health workers or PHWs (peer health workers living with HIV) were both found to be effective, although qualitatively participants appreciated PHWs more (47). Adherence clubs are also good opportunities to provide more wraparound services such as education and learn about opportunities for additional support such as food insecurity. Interventions with support groups combined various additional services including education, pill counting, and home visits. In addition to the benefits provided by the group itself, it also provided interventions with knowledge on who had stopped attending and some studies used this for closer follow-up, such as sending a home visit (48). The availability of peer support in these interventions further allows especially vulnerable patients with other comorbidities and behavioral factors to receive counseling tailored to their individual circumstances (49).

Results in individual-focused methods were more mixed. Directly observed therapy was found to be successful in the clinic setting but not when done by a patient-selected treatment partner. DOT is only practical for a subset of high-risk patients due to the high burden of time and expense. Reminder systems were more effective when paired with motivational programs. SMS reminders sent after a dose was missed, as tracked by a pill counter or electronic adherence system, were not effective in any context, suggesting that reminders need to be proactive rather than reactive. Overall, reminder systems such as SMS are the easiest to implement and therefore are applicable on a wide scale. However, more research is needed to determine which populations are most likely to succeed with reminders alone compared to additional counseling or peer support, and which frequency, text content, and setting allows SMS messages to be most effective. Adherence counseling appears to be an effective strategy across different settings, though there remain opportunities to improve this approach (50). Standardization of adherence counseling may help to improve content



delivery to individual patients by ensuring a baseline level of knowledge and organization in the counseling process (51,52). With the use of electronic adherence tools and text reminder systems, coupling these interventions with standardized mobile device counseling applications may prove particularly effective in settings where this technology is accessible and can increase access to these service in rural areas (53).

Organizational interventions also produced mixed results. Streamlining care such as fast-tracking appointments and increasing prescription length for stable patients increased medication refills and clinic attendance. Integrated care systems such as treating families together were found to be effective about half of the time. Certain health systems interventions were also successful at reducing costs and ensuring non-inferiority of adherence, such as task-shifting from nurses to doctors or nurses to CHWs.

### Important Considerations

Key considerations for implementing adherence interventions include cost, time intensiveness, location, target population, available resources, and long-term sustainability of the intervention.

**Location**—The effectiveness of interventions varies by region, resources, and population density. Therefore, the considerations for determining the application of certain interventions varies in rural vs. urban settings. In rural areas, studies demonstrate that technology-based interventions produce limited benefit in ART adherence and have limited lasting impact. These interventions, including electronic adherence monitoring, are in large part ineffective due to their associated technical limitations. Instead, interventions may choose task-shifting roles to health care workers with less training than physicians in order to increase time spent with the provider and improve relationships between patients and their providers. Rural areas with limited health access may also do well with clinic reorganization interventions such as making appointment scheduling easier, scheduling families together, and increasing lengths of prescription. By contrast, urban centers may have more access to health centers but benefit from peer relationships and community based support. Text messaging reminders can be effective in both contexts, given adequate cell phone coverage.

**Cost**—Many studies did not explicitly state the cost per intervention; however, more resource-intensive interventions involved significant human capital such as CHW home visits, counseling, directly observed therapy, and support groups. Lowest cost interventions include individual reminder interventions such as SMS reminders and task-shifting care from clinicians to nurse and community health care providers.

**Target population**—Many studies specifically focused on groups which had already failed at least one round of ART and thus targeted more vulnerable patients and those at higher risk of repeat treatment failure. Others studied the interventions only in groups that had been established in care. Further work is needed to assess interventions that prevent the first round of treatment failure or in clinics with a wide variety of patients to evaluate whether interventions should be focused among certain groups compared to implemented for all ART adherences. For example, facility-based support groups were found

to be effective in several contexts, but not among mothers. On the other hand, intensive follow-up tracing was found to be ineffective in most studies but was effective in preventing MTCT in Kenya (54). There is some evidence that interventions vary by gender in terms of their effectiveness, with support groups improving outcomes among cisgender women even greater than the effect seen in men (55). Another study assigned 2000 participants a “treatment buddy” for peer support, which increased ART adherence only among women (56).

Many of the individual programs studied in the literature primarily focused on behavioral change and monitoring of adherence rather than addressing the underlying motivations for or barriers to adherence to care. In interventions such as electronic adherence monitoring, adherence is externally monitored with little done to address the underlying problems that impact individual adherence. These technology-based interventions can prove prohibitively expensive, and the technical limitations associated with device failure and disrupted service in rural areas in particular have prevented any long-term benefit from these interventions. In contrast, community programs in rural areas are associated with a lower cost and seek to address individual support to maintain successful viral suppression. Importantly, individual empowerment and support for socioeconomic activity among HIV care patients and their families remain important factors in contributing to medication adherence and retention in care (57,58).

**Timing of Intervention Initiation**—The timing of intervention initiation significantly impacts adherence outcomes. Several of the reviewed studies demonstrated that adherence interventions must be initiated at the time of linkage to care in order to maximize their effectiveness. Studies showed that beginning ART later after diagnosis is less likely to lead to successful adherence (59). Therefore, starting interventions after patients had already enrolled in care decreased the effectiveness of some interventions.

### Future research

Several specific areas where additional research is needed arose throughout the course of this analysis. Many interventions incorporate multiple components. This practice increases the likelihood of intervention success, but without analyzing components separately it is impossible to determine which aspects were necessary and which were not. Studies focused on best practices for specific population groups would be particularly helpful. Support groups and family counseling were found to be useful with adolescents, while text messages did not show a significant difference. Out of four interventions targeted specifically at mothers, only one was found to be effective (an integrated postpartum clinic).

Additionally, more descriptions of sustainability are needed. A minority of studies ran past one year, but ART adherence matters throughout the lifespan. Studies that were specifically designed to be low-cost or reduce costs reported their expense per participant, but many studies did not describe the cost of their intervention. More transparency on the cost of these studies is necessary to cross-compare them in the future. Similarly, standardizing best practices among interventions would allow for better cross-comparison. Defining intervention components clearly and analyzing components separately would help with this.

Nine studies (10%) included lacked an adequate comparison group, and an additional six (7%) studies only reported point estimates rather than statistical significance.

### Limitations

A key limitation of this study is the lack of ability to compare intervention types quantitatively. Due to the heterogeneity of intervention designs, and the fact that many interventions were multifactorial, no direct cross-comparison or multivariable analysis was possible, and nor were we able to quantify regional variation in adherence success.

### Conclusions

Significant innovations in implementation research in ART adherence interventions have been made, and bundled interventions that include a combination of behavioral support and infrastructure support demonstrated the most promise.

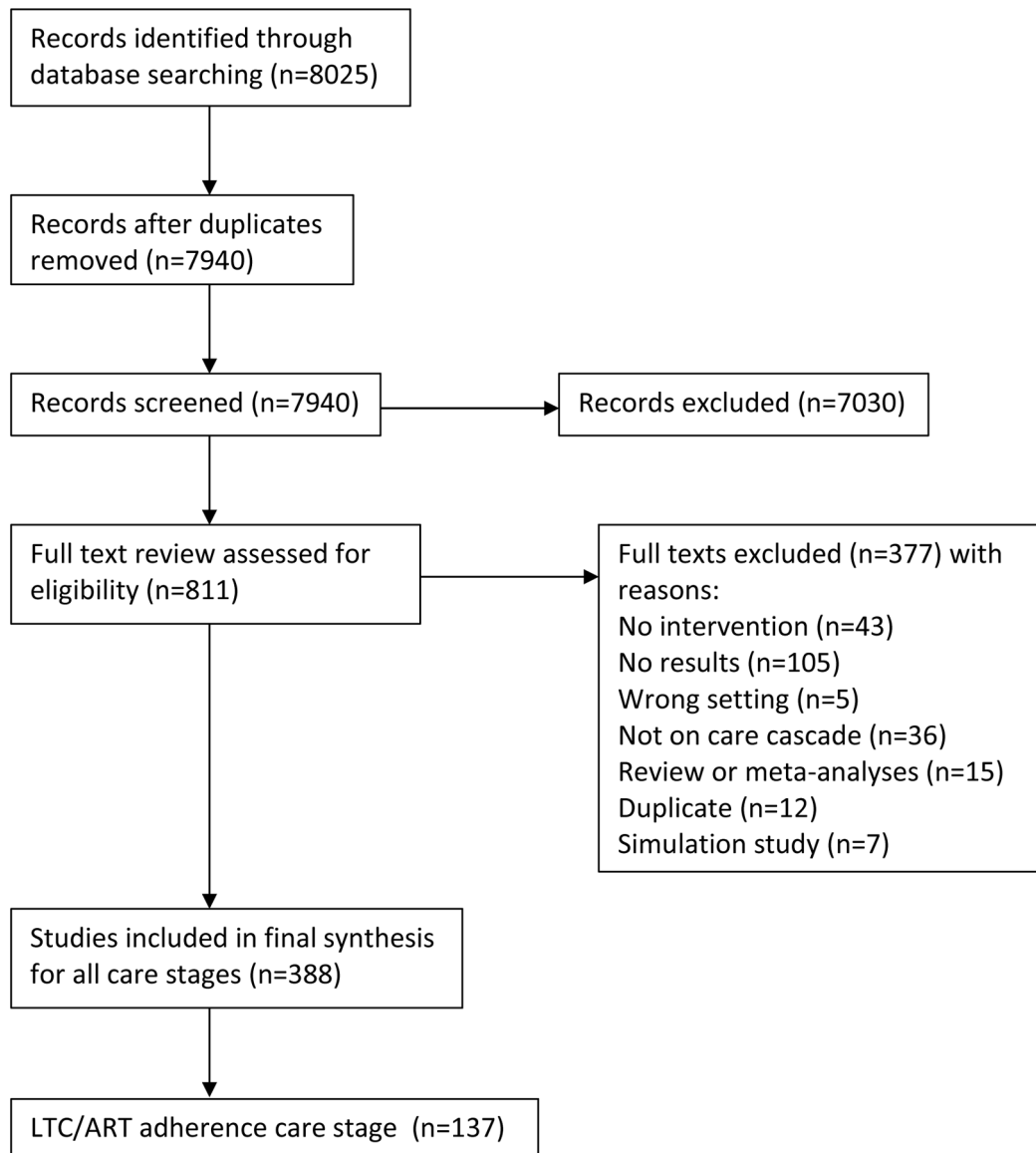
### References

1. UNAIDS. 90–90–90 An ambitious treatment target to help end the AIDS epidemic 2014 Geneva: UNAIDS; 2014.
2. WHO | Data and statistics (n.d.). WHO; World Health Organization. Retrieved July 2, 2020, from <http://www.who.int/hiv/data/en/>
3. World Health Organization (WHO) (2013) Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection
4. Nachega JB, Marconi VC, van Zyl GU et al. HIV treatment adherence, drug resistance, virologic failure: evolving concepts. *Infect Disord Drug Targets* 2011;11(2):167–174. [PubMed: 21406048]
5. Barth RE, van der Loeff MFS, Schuurman R, Hoepelman AI, Wensing AM. Virological follow-up of adult patients in antiretroviral treatment programmes in sub-Saharan Africa: a systematic review. *Lancet Infect Dis* 2010;10(3):155–166. [PubMed: 20185094]
6. Soomro N, Fitzgerald G, Seeley J, Schatz E, Nachega JB, Negin J. Comparison of antiretroviral therapy adherence among HIV-infected older adults with younger adults in Africa: systematic review and meta-analysis. *AIDS Behav* 2019;23(2):445–458. [PubMed: 29971732]
7. Nachega JB, Marconi VC, van Zyl GU et al. HIV treatment adherence, drug resistance, virologic failure: evolving concepts. *Infect Disord Drug Targets* 2011;11(2):167–174. [PubMed: 21406048]
8. Paterson DL, Swindells S, Mohr J et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000;133(1):21–30. [PubMed: 1087736]
9. Bangsberg DR, Perry S, Charlebois ED et al. Non-adherence to highly active antiretroviral therapy predicts progression to AIDS. *AIDS* 2001;15(9):1181–1183. [PubMed: 11416722]
10. Holzman CW, Brady KA, Yehia BR. Retention in care and medication adherence: current challenges to antiretroviral therapy success. *Drugs* 2016;75(5):445–454.
11. Bärnighausen T, Chaiyachati K, Chimbindi N, Peoples A, Haberer J, Newell ML. Interventions to increase antiretroviral adherence in sub-Saharan Africa: a systematic review of evaluation studies. *The Lancet infectious diseases* 2011 Dec 1;11(12):942–51. [PubMed: 22030332]
12. MacPherson P, Munthali C, Ferguson J et al. Service delivery interventions to improve adolescents' linkage, retention and adherence to antiretroviral therapy and HIV care. *Trop Med Int Heal* 2015;20: 1015–1032.
13. 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;11:855–867. [PubMed: 22035614]
14. Wynberg E, Cooke G, Shroufi A, Reid S, Ford N. Impact of point-of-care CD4 testing on linkage to HIV care: a systematic review. *J Int AIDS Soc* 2014;17(1):18809. [PubMed: 24447595]

15. Bijker R, Jiamsakul A, Kityo C et al. Adherence to antiretroviral therapy for HIV in sub-Saharan Africa and Asia: a comparative analysis of two regional cohorts. *J Int AIDS Soc* 2017;20(1):21218. [PubMed: 28362063]
16. Fisher JD, Fisher WA. Changing AIDS-risk behavior. *Psychol Bull* 1992;111:455–74. [PubMed: 1594721]
17. Mukumbang FC, Belle SV, Marchal B, Wyk BV. Exploring ‘generative mechanisms’ of the antiretroviral adherence club intervention using the realist approach: A scoping review of research-based antiretroviral treatment adherence theories. *BMC Public Health* 2017;17(1).
18. Haberer JE, Sabin L, Amico KR et al. Improving antiretroviral therapy adherence in resource-limited settings at scale: A discussion of interventions and recommendations. *J Int AIDS Soc* 2017;20(1).
19. Davey JD, Nhavoto JA, Augusto O et al. Evaluating mobile phone text reminders to improve retention in HIV care for patients on antiretroviral therapy in Mozambique. *J Acquir Immune Defic Syndr* 2016;73(2):e23–30. [PubMed: 27632147]
20. Igumbor JO, Scheepers E, Ebrahim R, Jason A, Grimwood A. An evaluation of the impact of a community-based adherence support programme on ART outcomes in selected government HIV treatment sites in South Africa. *AIDS Care* 2011;23(2):231–6. [PubMed: 21259136]
21. Sarna A, Saraswati LR, Okal J et al. Cell phone counseling improves retention of mothers with HIV infection in care and infant HIV testing in Kisumu, Kenya: a randomized controlled study. *Glob Health Sci Pract* 2019;7(2):171–188. [PubMed: 31142546]
22. Mills EJ, Adhvaru A, Jakiela P et al. Unconditional cash transfers for clinical and economic outcomes among HIV-affected Ugandan households. *AIDS* 2018;32(14):2023–2031. [PubMed: 29847330]
23. Bezabih T, Weiser SD, Menbere MS, Negash A, Grede N. Comparison of treatment adherence outcome among PLHIV enrolled in economic strengthening program with community control. *AIDS Care* 2018;30(3):369–377. [PubMed: 28859495]
24. MacKenzie RK, van Lettow M, Gondwe C et al. Greater retention in care among adolescents on antiretroviral treatment accessing “Teen Club” an adolescent-centred differentiated care model compared with standard of care: a nested case-control study at a tertiary referral hospital in Malawi. *J Int AIDS Soc* 2017;20(3):e25028. [PubMed: 29178197]
25. Franke MF, Kaigamba F, Socci AR et al. Improved retention associated with community-based accompaniment for antiretroviral therapy delivery in rural Rwanda. *Clin Infect Dis* 2013;56(9):1319–26. [PubMed: 23249611]
26. McCoy SI, Njau PF, Fahey C et al. Cash vs. food assistance to improve adherence to antiretroviral therapy among HIV-infected adults in Tanzania. *AIDS* 2017;31(6):815–825. [PubMed: 28107221]
27. Kadota JL, Fahey CA, Njau PF et al. The heterogeneous effect of short-term transfers for improving ART adherence among HIV-infected Tanzanian adults. *AIDS Care* 2018;30(Suppl 3):18–26.
28. Galárraga O, Enimil A, Bosomtwe D, Cao W, Barker DH. Group-based economic incentives to improve adherence to antiretroviral therapy among youth living with HIV: safety and preliminary efficacy from a pilot trial. *Vulnerable Child Youth Stud* 2020;15(3):257–268. [PubMed: 33281920]
29. Luque-Fernandez MA, Van Cutsem G, Goemaere E et al. Effectiveness of patient adherence groups as a model of care for stable patients on antiretroviral therapy in Khayelitsha, Cape Town, South Africa. *PLoS One* 2013;8(2):e56088. [PubMed: 23418518]
30. Fatti G, Mothibi E, Shaikh N, Grimwood A. Improved long-term antiretroviral treatment outcomes amongst patients receiving community-based adherence support in South Africa. *AIDS Care* 2016;28(11):1365–72. [PubMed: 27251459]
31. Gross R, Zheng L, La Rosa A et al. Partner-based adherence intervention for second-line antiretroviral therapy (ACTG A5234): a multinational randomised trial. *Lancet HIV* 2015;2(1):e12–9. [PubMed: 26424232]
32. Nakigozi G, Makumbi FE, Bwanika JB et al. Impact of patient-selected care buddies on adherence to HIV care, disease progression, and conduct of daily life among pre-antiretroviral HIV-infected patients in Rakai, Uganda: a randomized controlled trial. *J Acquir Immune Defic Syndr* 2015;70(1):75–82. [PubMed: 26039929]

33. Lifson AR, Workneh S, Hailemichael A, Demisse W, Slater L, Shenie T. Implementation of a peer HIV community support worker program in rural Ethiopia to promote retention in care. *J Int Assoc Provid AIDS Care* 2017;16(1):75–80. [PubMed: 26518590]
34. Bhana A, Mellins CA, Petersen I et al. The VUKA family program: piloting a family-based psychosocial intervention to promote health and mental health among HIV infected early adolescents in South Africa. *AIDS Care* 2014;26(1):1–11. [PubMed: 23767772]
35. Fatti G, Jackson D, Goga AE et al. The effectiveness and cost-effectiveness of community-based support for adolescents receiving antiretroviral treatment: an operational research study in South Africa. *J Int AIDS Soc* 2018;21 Suppl 1(Suppl Suppl 1):e25041. [PubMed: 29485714]
36. Grimsrud A, Lesosky M, Kalombo C, Bekker LG, Myer L. Implementation and operational research: community-based adherence clubs for the management of stable antiretroviral therapy patients in Cape Town, South Africa: a cohort study. *J Acquir Immune Defic Syndr* 2016;71(1):e16–23. [PubMed: 26473798]
37. Bock P, Gunst C, Maschilla L et al. Retention in care and factors critical for effectively implementing antiretroviral adherence clubs in a rural district in South Africa. *J Int AIDS Soc* 2019;22(10):e25396. [PubMed: 31588668]
38. Hanrahan CF, Schwartz SR, Mudavanhu M et al. The impact of community- versus clinic-based adherence clubs on loss from care and viral suppression for antiretroviral therapy patients: findings from a pragmatic randomized controlled trial in South Africa. *PLoS Med* 2019;16(5):e1002808. [PubMed: 31112543]
39. Ibiloye O, Decroo T, Eyona N, Eze P, Agada P. Characteristics and early clinical outcomes of key populations attending comprehensive community-based HIV care: experiences from Nasarawa State, Nigeria. *PLoS One* 2018;13(12):e0209477. [PubMed: 30571744]
40. Thomson KA, Cheti EO, Reid T. Implementation and outcomes of an active defaulter tracing system for HIV, prevention of mother to child transmission of HIV (PMTCT), and TB patients in Kibera, Nairobi, Kenya. *Trans R Soc Trop Med Hyg* 2011;105(6):320–6. [PubMed: 21511317]
41. McGuire M, Ben Farhat J, Pedrono G et al. Task-sharing of HIV care and ART initiation: evaluation of a mixed-care non-physician provider model for ART delivery in rural Malawi. *PLoS One* 2013;8(9):e74090. [PubMed: 24066099]
42. Selke HM, Kimaiyo S, Sidle JE et al. Task-shifting of antiretroviral delivery from health care workers to persons living with HIV/AIDS: clinical outcomes of a community-based program in Kenya. *J Acquir Immune Defic Syndr* 2010;55(4):483–90. [PubMed: 20683336]
43. Lifson AR, Workneh S, Hailemichael A et al. Implementation of a Peer HIV Community Support Worker Program in Rural Ethiopia to Promote Retention in Care. *J Int Assoc Provid AIDS Care* 2017;16(1):75–80. [PubMed: 26518590]
44. Salmanton-García J, Herrador Z, Ruiz-Seco P, Nzang-Esono J, Bendomo V, Bashmakovic E, Nseng-Nchama G, Benito A, Aparicio P. Self-reported adherence to antiretroviral therapy in HIV+ population from Bata, Equatorial Guinea. *AIDS care* 2016 May 3;28(5):543–53. [PubMed: 26698540]
45. Mutagonda RF, Mlyuka HJ, Maganda BA, Kamuhabwa AAR. Adherence, Effectiveness and Safety of Dolutegravir Based Antiretroviral Regimens among HIV Infected Children and Adolescents in Tanzania. *Journal of the International Association of Providers of AIDS Care (JIAPAC)* January 2022. doi:10.1177/23259582221109613
46. Moosa A, Gengiah TN, Lewis L, Naidoo K. Long-term adherence to antiretroviral therapy in a South African adult patient cohort: a retrospective study. *BMC infectious diseases* 2019 Dec;19(1):1–2. [PubMed: 30606108]
47. Arem H, Nakyanjo N, Kagaayi J et al. Peer health workers and AIDS care in Rakai, Uganda: a mixed methods operations research evaluation of a cluster-randomized trial. *AIDS Patient Care STDS* 2011;25(12):719–724. [PubMed: 21391828]
48. Chang LW, Kagaayi J, Nakigozi G et al. Effect of peer health workers on AIDS care in Rakai, Uganda: a cluster-randomized trial. *PLoS One* 2010;5(6):e10923. [PubMed: 20532194]
49. Magidson JF, Joska JA, Belus JM et al. Project Khanya: results from a pilot randomized type 1 hybrid effectiveness-implementation trial of a peer-delivered behavioral intervention for ART

- adherence and substance use in HIV care in South Africa. *J Int AIDS Soc* 2021;24 Suppl 2:e25720. [PubMed: 34164935]
50. Kikaire B, Ssemanda M, Asiimwe A et al. HIV viral load suppression following intensive adherence counseling among people living with HIV on treatment at military-managed health facilities in Uganda. *Int J Infect Dis* 2021;112:45–51. [PubMed: 34481969]
51. McCreesh-Toselli S, Torline J, Gouse H et al. Staff perceptions of preimplementation barriers and facilitators to a mobile health antiretroviral therapy adherence counseling intervention in South Africa: qualitative study. *JMIR Mhealth Uhealth* 2021;9(4):e23280. [PubMed: 33821806]
52. Twimukye A, Naggirinya AB, Parkes-Ratanshi R et al. Acceptability of a mobile phone support tool (Call for Life Uganda) for promoting adherence to antiretroviral therapy among young adults in a randomized controlled trial: exploratory qualitative study. *JMIR Mhealth Uhealth* 2021; 9(6):e17418. [PubMed: 34121665]
53. Comulada WS, Wynn A, van Rooyen H et al. Using mHealth to deliver a home-based testing and counseling program to improve linkage to care and ART adherence in rural South Africa. *Prev Sci* 2019;20(1):126–136. [PubMed: 30259235]
54. Thomson KA, Cheti EO, Reid T. Implementation and outcomes of an active defaulter tracing system for HIV, prevention of mother to child transmission of HIV (PMTCT), and TB patients in Kibera, Nairobi, Kenya. *Trans R Soc Trop Med Hyg* 2011;105(6):320–6. [PubMed: 21511317]
55. Decroo T, Koole O, Remartinez D, et al. Four-year retention and risk factors for attrition among members of community ART groups in Tete, Mozambique. *Trop Med Int Health* 2014;19:514–521. [PubMed: 24898272]
56. Kibaara C, Blat C, Lewis-Kulzer J et al. Treatment buddies improve clinic attendance among women but not men on antiretroviral therapy in the Nyanza region of Kenya. *AIDS Res Treat* 2016;9124541. [PubMed: 27092271]
57. Ssewamala FM, Dvalishvili D, Mellins CA et al. The long-term effects of a family based economic empowerment intervention (Suubi+Adherence) on suppression of HIV viral loads among adolescents with HIV in southern Uganda: findings from 5-year cluster randomized trial. *PLoS One* 2020; 15(2):e0228370. [PubMed: 32040523]
58. Mazambara F, Chagwena D, Mudzviti T et al. Utility of HIV support groups in advancing implementation research in resource-limited settings: experiences from an urban-setting HIV support group in Zimbabwe. *AIDS Res Ther* 2022;19(1):7. [PubMed: 35164769]
59. Ibiloye O, Decroo T, Eyona N, Eze P, Agada P. Characteristics and early clinical outcomes of key populations attending comprehensive community-based HIV care: experiences from Nasarawa State, Nigeria. *PLoS One* 2018;13(12):e0209477. [PubMed: 30571744]



**Figure 1.**  
PRISMA diagram of systematic review flow.



**Figure 2.**  
Adherence interventions framework.

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**Table 1.**

Results by intervention.

Intervention	Number of Studies with the Intervention	Number of Studies with Positive Results	Number of Studies that Analyzed the Intervention Independently	Number of Studies with a Positive Result when Analyzed Independently
Text messages	19	12/19 (63%)	11/18 (61%)	7/11 (64%)
Counseling	31	18/31 (58%)	12/31 (39%)	7/12 (58%)
Patient education	15	11/15 (73%)	1/12 (8%)	0/1 (0%)
CHW home visits	12	9/12 (75%)	6/12 (50%)	5/6 (83%)
Support group	16	14/16 (88%)	9/16 (56%)	7/9 (78%)
Peer support	13	9/13 (69%)	10/13 (77%)	9/10 (90%)
Directly observed therapy	6	2/6 (33%)	5/6 (83%)	2/5 (40%)
In-person pill counts	3	2/3 (67%)	2/3 (67%)	2/2 (100%)
Technology-based pill counter	4	2/4 (50%)	4/4 (100%)	2/4 (50%)
Financial assistance	7	4/7 (67%)	3/7 (43%)	1/3 (33%)
Partner/family education	6	4/6 (67%)	0/6 (0%)	N/A
Patient follow-up	13	7/13 (54%)	6/13 (46%)	3/6 (50%)
Task shifting	10	4/10 (40%)	6/10 (60%)	4/6 (67%)
Streamlining care	18	10/18 (56%)	12/18 (67%)	8/11 (73%)
Integrated intervention (>3 components)	13	10/13 (77%)	N/A	N/A
<b>TOTAL N</b>	<b>186</b>	<b>118/186 (63%)</b>	<b>87/169 (51%)</b>	<b>57/86 (66%)</b>