

Recent Interventions to Improve Retention in HIV Care and Adherence to Antiretroviral Treatment Among Adolescents and Youth: A Systematic Review

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Abstract

Adolescents represent a growing proportion of people living with HIV worldwide and the highest risk population group for treatment attrition and AIDS-related mortality. There is an urgent need to design, implement, and test interventions that keep young people in HIV treatment and care. However, previous systematic reviews show scarce and inconclusive evidence of effective interventions for this age group. Recent years have seen an increase in focus on adolescent health and a rapidly changing programmatic environment. This systematic review article provides an evidence update by synthesizing empirical evaluations of interventions designed to improve antiretroviral therapy adherence and retention among adolescents (10–19) and youth (15–24) living with HIV, published between January 2016 and June 2018. A search of 11 health and humanities databases generated 2425 citations and 10 relevant studies, the large majority conducted in sub-Saharan Africa. These include six clinic-level interventions, one individual-level m-Health trial, and three community- or household-level interventions. Implications of their findings for future programming and research with young adults are discussed, in relation to previous reviews and the broader empirical evidence in this area. Findings highlight the need to further develop and test multi-faceted interventions that go beyond health facilities, to address broader social barriers to adherence and retention. In particular, further intervention studies with adolescents (10–19) should be a priority, if we are to retain these young people in treatment and care and aspire to achieve the United Nation's Sustainable Development Goals and 90-90-90 targets.

Keywords: systematic review, adolescents, youth, HIV treatment adherence, retention in HIV care

Introduction

THE FOCUS ON treatment and care for adolescents living with HIV has increased considerably in recent years, and with good reason. The number of adolescents living with HIV globally is around 1.8 million and growing, as a result of children with perinatally acquired HIV surviving into adolescence and high rates of adolescent HIV infection.^{1,2} This is especially the case in low- and middle-income countries (LMICs) highly affected by the epidemic; ~1.5 million or 85% of HIV-positive adolescents live in sub-Saharan Africa.²

Adolescents have the highest rates of attrition and loss to follow-up (LTFU) for HIV treatment and care at all stages of the treatment cascade.^{3–5} As a result they are a high-risk

population group for onward HIV transmission and AIDS-related mortality; in fact youth, 13–24 years of age represent the only population group with increasing AIDS-related mortality rates.⁶

The greater likelihood of detachment from health care among adolescents living with HIV may be partly explained by their unique psychological and medical needs^{7–9}; in particular, adolescents perinatally infected with HIV may face additional health and developmental challenges.^{1,10} It is clear that reaching the United Nation's health-related Sustainable Development Goals (SDGs) and 90-90-90 2020 treatment targets^{11,12} is going to be particularly challenging in this population group, unless we develop more effective and scalable approaches to increase timely HIV treatment

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initiation, and ensure treatment adherence and retention. There is an urgent need to design, implement, and test interventions and services that are effective at keeping young people in treatment and care, by responding to their particular risks and needs.

However, to date, the programmatic evidence on what works for this age group has been scarce. This is highlighted by a number of—in part overlapping—systematic reviews on interventions for antiretroviral therapy (ART) initiation, adherence, and retention, published over the past 4 years. These review articles provide a useful synthesis of the state of the evidence up until 2015. Some did not specifically focus on youth or adolescents, but included studies with adolescents within a broader population of adults and children.^{13,14} Moreover, most of these reviews limited their foci to specific types of interventions, for example, service delivery at health facilities,¹⁵ subgroups of adolescents, for example, vertically infected adolescents¹⁶ or groups of countries, for example, LMICs.^{13,14}

MacPherson et al. reviewed studies published between January 2001 and June 2014, evaluating the effectiveness of service delivery interventions to improve linkage from HIV diagnosis to ART initiation, retention in care and adherence to treatment for adolescents (10–19 years of age) living with HIV.¹⁵ The authors concluded that interventions such as individual and group education and counseling, financial incentives, youth-friendly clinic services, and increased accessibility to clinics showed promise; however, given the limited number (11) and low-to-moderate methodological quality of available studies, these approaches required further investigation. Moreover, most (8 out of 11) studies reviewed were conducted in high-income countries (HICs) and not in countries with generalized HIV epidemics.¹⁵

Two subsequent review articles, published in 2016, reinforced the potential effectiveness of phone-based, individual and family counseling approaches for ART adherence among youth 13–24 years of age,¹⁷ and interventions, such as psychosocial and peer support, and financial incentives, specifically for perinatally infected adolescents.¹⁶ Similar to the article by MacPherson et al., both 2016 reviews highlighted the predominance of studies deriving from HICs, mainly the United States, and the limited ability to generalize results from the low number of studies with small sample sizes and short follow-up periods.^{16,17} Moreover, Judd et al. exposed a gap in studies focusing on the transition period from pediatric to adult care, which appears to be the most vulnerable time for LTFU and nonadherence.^{3,16}

Two more recent systematic reviews report interventions to improve retention¹³ and ART adherence¹⁴ among adolescents and adults in LMICs; these include studies published during the 5 years between November 2010 and November 2015. Despite a specific interest in adolescents, these reviews found only four studies conducted with or disaggregating data for the 10–24 age group. Only two pilot studies—one working with adolescents 10–13¹⁸ and the other with youth 15–24¹⁹—pointed to the potential effectiveness of group counseling for adherence, incorporating HIV and ART information, psychosocial support, and empowerment.¹⁴ The reviews also identified interventions that showed promise with adults and would need to be further investigated for effectiveness with adolescents; these included decentralization of health care, task-shifting and community-based ad-

herence support, nutritional support, and differentiated care that targets resources toward high-risk patients.^{13,14} Overall, interventions that included community-based services provided the strongest evidence base for improved retention among adults.¹³ The authors recommended further investigation on youth-friendly services—a widely promoted and utilized approach, but not supported by adequate evidence—and an extension of the focus beyond health facilities, to individual-, community-, or policy-level interventions.¹³

While the systematic reviews cited above identify specific types of interventions that show promise for ART adherence and retention in care, they also highlight the very limited number and low quality of many studies on adolescent adherence and retention published up until 2015. There have been no published systematic reviews synthesizing evidence beyond 2015, notwithstanding the increase in focus on HIV-positive adolescents and the rapidly changing global policy, funding, and implementation environment in which HIV programming operates. An updated review, covering all types of interventions, would be useful to identify recent studies that may potentially reinforce the previous limited evidence for specific types of promising interventions, as well as broaden the synthesized knowledge base to include new and innovative interventions for this population group.

This systematic review aimed to (i) identify and synthesize empirical evaluations of interventions designed to improve ART adherence or retention in care among adolescents (10–19 years) and youth (15–24 years) published since January 2016, and (ii) discuss implications of these findings, in relation to previous reviews and empirical evidence, for future programming and research with adolescents and youth. Taking into account the expected limited number of studies with adolescents only, we extended the population age range to include youth; however, given the specific interest in adolescents, findings will be presented separately by age group (adolescents 10–19 years; youth 15–24 years; adolescents and youth 10–24 years), where age-disaggregated data are available. Moreover, this review was not limited to interventions at health facilities, but instead aimed to incorporate a broader range of initiatives, including community- and individual-level interventions.

Methods

The literature review was conducted between May and November 2018; the review protocol was registered with PROSPERO (Registration No. CRD42018110343). The systematic search strategy, including examples of search strings used, is illustrated in Table 1. We searched 11 health and humanities databases, including PubMed, ProQuest Health & Medical Complete, SocINDEX, and the Cochrane Library (see Table 1 for full list).

Composite search strings were created using keywords to indicate the population of interest (adolescents and/or youth living with HIV and enrolled in an ART treatment program) and the outcomes of interest (HIV treatment adherence and retention in care), drawing from Cochrane Collaboration guidelines²⁰ and search strategies used by previous reviews.^{14,15} In particular, guidelines from the Cochrane Handbook for Systematic Reviews of Interventions were used to refine our review objectives and develop inclusion and exclusion criteria for studies.²⁰ The acronym PICO (Participants, Interventions,

TABLE 1. SYSTEMATIC REVIEW SEARCH STRATEGY

Search criteria (based on the Cochrane Collaboration's PICO criteria)	Population: adolescents (10–19) or youth (15–24) living with HIV enrolled in an HIV treatment program Intervention: any type of intervention or service aimed at increasing retention in care or treatment adherence Comparison: adolescents or youth living with HIV and enrolled in a treatment program, not receiving the intervention Outcomes: retention in care; treatment adherence; biomarkers such as CD4 count or viral load affected by treatment adherence
Search terms used for PubMed	HIV: (hiv[MeSH Terms] OR hiv[tw]) Adolescents or Youth: (Adolescent[MeSH Terms] OR youth[tw] OR young person [tw] OR young people [tw] OR young women [tw] OR young men [tw] OR pediatri*[tw] OR paediatric*[tw] OR teenag*[tw] OR child*[tw] OR adoles*[tw] OR young adult*[tw]) HIV treatment: (antiretroviral therapy[tw] OR anti-retroviral agents/therapeutic use[Mesh Terms] OR anti HIV agents[MeSH Terms] OR antiretroviral therapy, highly active[MeSH Terms] OR ART[tw] OR ARV*[tw] OR antiretroviral*[tw] OR anti-retroviral[tw] OR HAART[tw] OR cART[tw]) Adherence or Retention: (Medication Adherence[MeSH Terms] OR Patient Compliance[MeSH Terms] OR adher*[tw] OR complian*[tw] OR comply[tw] OR complied[tw] OR noncomplian*[tw] OR non-complian*[tw] OR non-adher*[tw] OR nonadher*[tw] OR adher*[tw] OR (loss to follow-up[tw] OR loss to follow up[tw] OR lost to follow-up[tw] OR lost to follow up[tw] OR loss-to-follow-up[tw] OR lost-to-follow-up[tw] OR retention[tw] OR retain*[tw] OR attrition[tw])
Search terms for EBSCOhost-linked databases, ProQuest and Cochrane Collaboration	HIV: (“hiv”) OR (“HIV”) OR (“human immunodeficiency virus”) OR (“human immunodeficiency virus”) HIV treatment: (“antiretroviral therapy”) OR (“anti-retroviral”) OR (“ART”) OR (“ARV”) OR (“HAART”) OR (“cART”) Adolescents or youth: (“youth”) OR (“young person”) OR (“young people”) OR (“young women”) OR (“young men”) OR (“pediatri*”) OR (“paediatric*”) OR (“teenag*”) OR (“child*”) OR (“adoles*”) OR (“young adult*”) Retention or adherence: (“loss to follow-up”) OR (“loss to follow up”) OR (“lost to follow-up”) OR (“lost to follow up”) OR (“loss-to-follow-up”) OR (“lost-to-follow-up”) OR (“retention”) OR (“retain*”) OR (“attrition”) OR (“noncomplian*”) OR (“non-complian*”) OR (“comply”) OR (“complied”) OR (“complian*”) OR (“non-adher*”) OR (“nonadher”) OR (“adher*”)
Databases searched	PubMed; ProQuest Health & Medical Complete; The Cochrane Library; Academic Search Complete; CINAHL Plus; Health Source: Nursing and Academic Edition; Humanities International Complete; Medline; Psychology and Behavioral Science Collection; PsychINFO; SocINDEX
Limiters	Published between January 1, 2016 and June 30, 2018 Peer-reviewed publications

PICO, Participants, Interventions, Comparisons, and Outcomes.

Comparisons, and Outcomes) refers to the following components of the research question that need to be specified to inform eligibility criteria for inclusion in a review: the types of population (participants), types of interventions (and comparisons), and the types of outcomes that are of interest.²⁰ These in turn inform the search strategy and search terms.

We identified the PICO components for this review and, after crosschecking with search terms used in similar previous reviews for completeness,^{14,15} developed composite search terms that included keywords for the population and outcomes of interest (Table 1). Also, in line with the Cochrane guidelines, we limited our primary outcomes of interest to a small number of outcomes identified as meaningful for this review (adherence to ART and retention in HIV care), and aimed to include studies with both adverse and beneficial outcomes.²⁰ However, given the potential wide range of interventions and low expected number of relevant studies, the search strategy did not include keywords for types of interventions; this was assessed manually. Also, no geographical or language limiters were used.

All references from the online databases were imported into Endnote, where duplicates were identified and removed. The authors independently examined titles and abstracts for inclusion. Full text of potentially relevant studies was retrieved and independently examined by the authors. Reference lists of articles deemed relevant were also hand searched to identify further potentially relevant studies. Summaries of each article were developed using a standardized form, similar to those used for previous reviews^{13–15} that extracted key information and characteristics of each study (Table 2).

Studies were considered eligible for inclusion in this review if they (i) evaluated the effects of or associations between an intervention and ART adherence or retention in care or related biomedical outcomes (e.g., viral suppression or CD4 count); (ii) reported quantitative measures of key outcomes; (iii) worked with or included samples of adolescents (10–19) and/or youth (15–24) living with HIV and enrolled in an HIV treatment and care program; and (iv) were published between January 1, 2016 and June 30, 2018. Given the limited research on this topic, we included randomized control trials (RCTs) as

TABLE 2. DESCRIPTION OF INTERVENTION TYPES AND SAMPLE AGE GROUPS

Type of intervention	Number of studies	Study	Intervention description	Adolescents (10–19)	Youth (15–24)	Adolescents and youth (10–24)
Clinic-based (six studies) Youth-friendly clinic services	5	MacKenzie et al. ²³ Ojwang' et al. ⁷ Reif et al. ⁵ Teasdale et al. ²⁶ Zanoni et al. ²⁷ Ingerski et al. ²⁸ Linnemayr et al. ²⁵ Fatti et al. ²⁹	Adolescent-centered differentiated care model comprising: dedicated weekend clinic time; sexual and reproductive health education; disclosure and ART adherence support; ART refill; individualized peer counseling and support and; peer interaction through sports, art, and games. Youth-orientated prevention, care, and treatment clinic. Dedicated adolescent clinic with youth-friendly services comprising: HIV-positive one-on-one and small group peer counseling; age-appropriate educational materials and extracurricular activities; family planning, STI testing, and counseling services for mental health and gender-based violence provided at the same clinic; clinic open until late afternoon to accommodate after-school hours. YAFS implemented in existing clinics, including: training and mentorship for health care providers on care for adolescents/youth; a monthly dedicated day for the adolescent/youth HIV clinic providing integrated sexual and reproductive health services; peer support groups and education programs. Saturday adolescent clinic within an existing clinic; services include ART dispensing, lunch, and scheduled counseling and recreational group activities. Prescription of placebo pills to practice taking HAART, with the same dosing frequency, pill size, and number of pills as the anticipated HAART medication regimen.	X	X	X
Individual-level (one study) mHealth Intervention	1	Bermudez et al. ²⁴	SMS reminder and check-in messages by means of one-way SMS (message only) or two-way SMS (message plus response option).	X		
Community- or household-based (three studies) Community-based health service delivery	1	Grimrud et al. ⁴	CBS intervention providing home-based ART- and sexual and reproductive health-related education, psychosocial support and referrals, nutritional security, screening for opportunistic infections, tracing of ART defaulters, and support with government grant access. Economic component including matched financial savings for medical expenses, income generation or education related expenses; financial management and life skills training. CACs with 25–30 participants per group, led by a community health worker and supported by a nurse. Includes group meetings every 2 months for group counseling, symptom screening, and distribution of prepacked ART.		X	X
Economic Empowerment	1			X		
Community-based ART adherence support groups	1					
Total	10			3	3	4

ART, antiretroviral therapy; CACs, community-based adherence clubs; CBS, community-based support; HAART, highly active antiretroviral therapy; SMS, Short Message Service; STI, sexually transmitted infection; YAFS, youth- and adolescent-friendly services.

well as nonrandomized studies (e.g., cohort studies, case-control studies, retrospective studies using routinely collected facility or program data, pre-post assessments).

Studies were excluded if they were not conducted with the population age group of interest or did not disaggregate and report on data specifically for this age group (e.g., studies with children or adults, whether or not including youth/adolescents), if they did not test a specific intervention (e.g., correlational analyses), if they were not full peer-reviewed articles based on new empirical analyses (e.g., editorials, commentaries, reviews, abstracts), or if they focused only on pre-ART care or linkage to care.

The authors independently reviewed each included study for methodological quality; discrepancies in this assessment were resolved through discussion. This review applied the same quality assessment tools used by the systematic review of MacPherson et al.,¹⁵ in part to allow for greater consistency between quality assessments of earlier studies included in previous reviews and the (more recent) studies included in this review: these are the Cochrane Collaboration’s Tool for assessing Risk of Bias for randomized controlled trials,²¹ and

a modified version of the Newcastle–Ottawa Scale for non-randomized studies.^{15,22} A judgment of “UNCLEAR” was made for individual risk of bias items within these tools, where the study report did not provide adequate information. Each study was allocated a final quality of evidence rating of “low,” “moderate,” or “good” quality, based on the assessment of overall risk of bias.

Results

Figure 1 shows the PRISMA diagram illustrating the selection process for inclusion of studies. The review generated 2425 citations from the online databases, 1068 after duplicates. Ten studies were identified as relevant and eligible for inclusion in the review. Characteristics of these studies are summarized in Tables 1 and 2.

Characteristics of relevant studies

As illustrated in Table 1, three studies were conducted only with adolescents (between 10 and 19 years),^{5,23,24} three studies with youth (between 15 and 24 years),^{4,7,25} and four

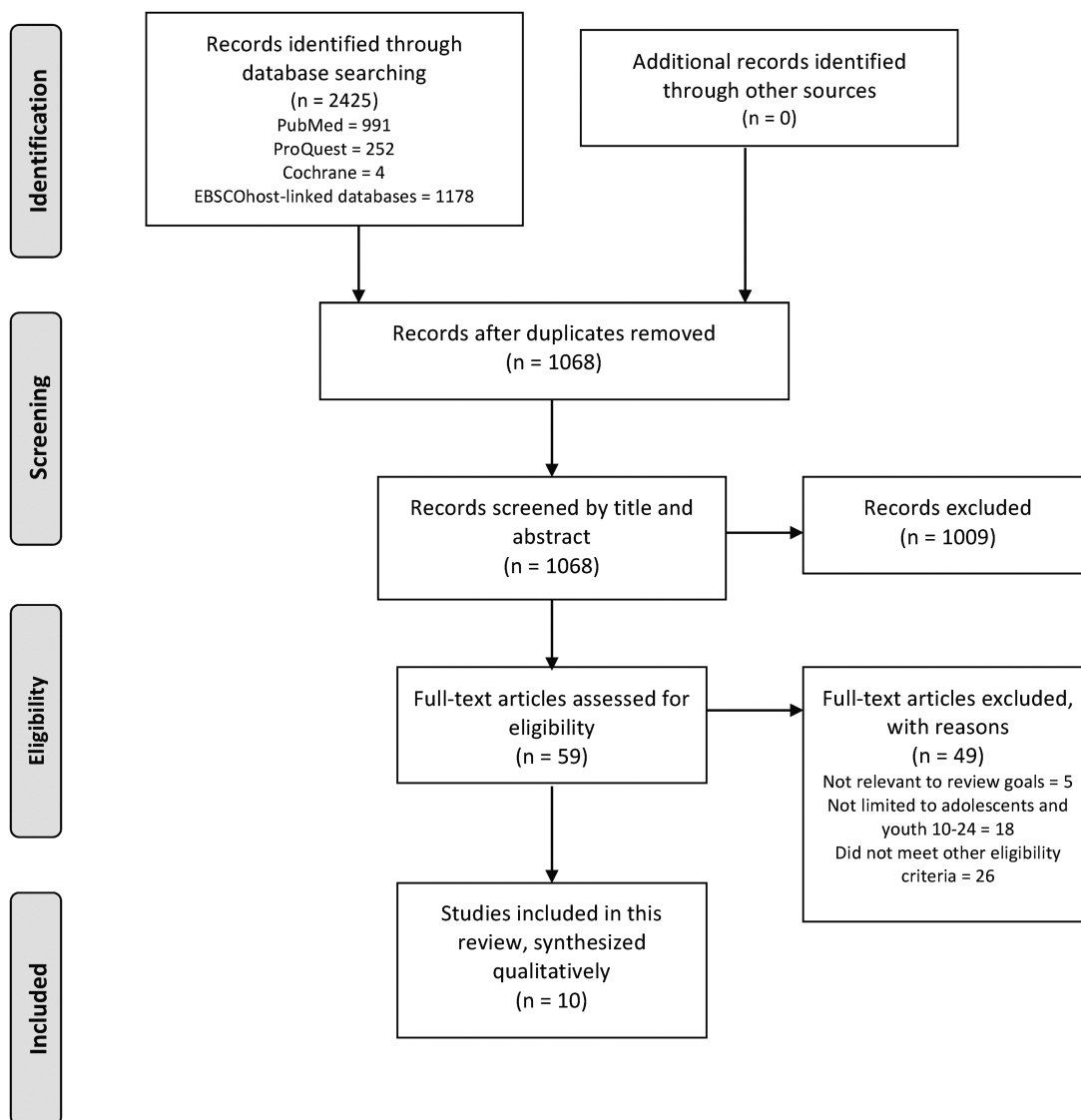


FIG. 1. Selection process for inclusion of studies.

studies with adolescents and youth (between 10 and 24 years).^{26–29} The large majority of studies (8) were conducted in sub-Saharan Africa (South Africa, Kenya, Uganda, and Malawi); of the remaining two studies, one was conducted in the United States²⁸ and one in Haiti.⁵ Two studies were identified as randomized controlled trials,^{24,25} one as a nested case–control study,²³ and the remaining seven as retrospective cohort studies.^{4,5,7,26–29} Total sample sizes ranged from 62²⁸ to 6706,²⁹ however, with the exception of the article by Ingerski et al., all studies worked with samples greater than 200.

As illustrated in Table 1, six studies were clinic based: five of these studies evaluated youth-friendly clinics or youth-friendly services^{5,7,23,26,27} and the sixth reported a placebo pill trial.²⁸ One study tested an individual-level mHealth mobile phone message intervention,²⁵ whereas the remaining three assessed family- or community-based initiatives, respectively, comprising: an economic empowerment intervention,²⁴ a community home-based health care intervention,²⁹ and community HIV treatment adherence club support groups.⁴

Key outcomes of interest and their measurement also differed across studies. One study measured treatment adherence through pill bottles with electronic monitoring systems, triangulated with self-reported adherence.²⁵ Four studies used some measure of retention in care or, conversely, LTFU, indicated by the patient's absence at the clinic or nonattendance of clinic visits over a given period of time, where possible, after checking for documented death or transfer.^{5,7,23,26} Three studies used some combination of LTFU and biomedical outcomes (e.g., viral suppression measured through viral load; CD4 counts).^{4,27,29} Lastly, two studies used only biomedical measures of CD4 count and/or viral load data as outcomes.^{24,28}

Given the small overall number of studies with these population groups, the range of different settings and populations, intervention types, outcomes, and outcome measurement approaches, we determined that meta-analysis of these studies' results would not be reliable. We have therefore provided a qualitative synthesis, whereby we discuss the types and modalities of interventions that have and have not shown success, and relate these to previous intervention evaluations among similar and broader population groups.

Findings of relevant studies

This section will describe findings of included studies in relation to their effectiveness for adherence and retention or related biomarkers. These will be described for each individual type of intervention, as per the categories indicated in Table 2, that is: youth-friendly clinics or services, the placebo pill trial intervention, the mHealth intervention, and household- or community-based interventions. Greater detail on the nature of each type of intervention and findings of each intervention study are provided in Tables 2 and 3.

“Youth-friendly” clinics or services. As indicated above, the most frequent types of interventions tested were youth-friendly clinics or youth-friendly clinic services within existing facilities. There was considerable heterogeneity in the “basket” of services and characteristics included within the definition of “youth- or adolescent-friendly.” These included combinations of services, such as HIV- or other

health-related education, psychosocial support and counseling, referrals, screening for sexually transmitted or opportunistic diseases, defaulter tracing and adherence support, recreational activities, and characteristics such as accessibility of clinic location and hours, the nature of the clinic environment, and the youth-specific knowledge or competency of clinic health workers. All of the five studies in this category focused on retention as an outcome, whereas one study also assessed differences in viral suppression.²⁷ These intervention evaluations showed mixed results, with two studies suggesting a positive impact on retention^{23,27} and one of these also on viral suppression,²⁷ and the other three showing no significant effects on retention.^{5,7,26}

Placebo trial intervention. The last clinic-based intervention was a placebo pill trial, through which participants were prescribed pills with an inert substance mimicking the HAART regimen, to allow them to practice taking HAART and identify possible barriers to adherence.²⁸ This intervention did not show evidence of effectiveness, as biomarkers (viral load and CD4 count readings) for youth who received one or more trials were not significantly different from those who did not a year postintervention.²⁸

mHealth intervention. The one individual-level intervention evaluated, the mHealth study, did not find significant differences in adherence between youth receiving reminder SMS (Short Message Service; text) messages and those who were not, over a 48-week period.²⁵ This was the case for both the one-way and two-way messaging intervention groups.

Community- or household-based interventions. Instead two household-based interventions provided evidence of better outcomes among young people who received the intervention: Bermudez et al. found higher odds of viral suppression at both 12 and 24 months among adolescents who participated in their savings-led economic empowerment intervention, compared with controls.²⁴ Fatti et al. found the receipt of a home-based health and support intervention to be associated with lower LTFU (higher retention) and mortality rates 5 years after the intervention.²⁹ Lastly, the study evaluating community-based adherence clubs found significantly lower LTFU after 1 year for adults in the intervention group, but not for the population of interest for this review, that is, youth 16–24 living with HIV.⁴

Study quality and risk of bias assessment

Most of the studies included in this review were judged to be of moderate quality (Tables 4 and 5); three studies achieved a “good” rating (one of which was an RCT) and one received a “low” rating. For the two RCTs it would not have been possible to prevent knowledge of allocation to the intervention recipients or implementers, given the nature of the interventions.^{24,25} Quality concerns among the non-randomized studies included lack of clear or adequate information on intervention and control group selection criteria,^{4,5,28} the consistency of the intervention's application to all participants,^{7,23,26} and how missing data were addressed in the analyses.^{4,23,26,28}

Other concerns for specific studies were short follow-up time,²⁶ small sample size and not controlling for potential

TABLE 3. CHARACTERISTICS OF INCLUDED STUDIES

Citation	Country	Study design	Participants	Intervention	Control/comparison	Outcome measures and definitions	Key findings
1 Bermudez et al. ²⁴	Uganda	Longitudinal cluster randomized trial	Total sample: 702 adolescents 10–16 enrolled for ARV treatment across 39 clinics in 4 districts of Southern Uganda, participating in 3 waves of the <i>Suubi-Adherence</i> project between 2012 and 2017. Intervention: 20 clinics and 358 adolescents. Control: 19 clinics and 344 adolescents	Bolstered standard of care and savings-led economic empowerment intervention. Economic component included (i) a CSA, matched at a rate of 1:1 and from which financial savings could be used for medical related expenses, family small business development or education related expenses; (ii) four workshops blending financial management and life skills with topics including asset building, small business development, goal setting, and risk mitigation.	Bolstered standard of care: 8 information sessions on adherence to ART, using evidence-based print cartoons.	Viral suppression, as measured through undetectable viral load (HIV RNA viral load <40 copies/mL) and the reduced mean log of VL.	Intervention adolescents had significantly lower odds of a detectable VL at both 12 months (OR 0.42; $p < 0.01$) and 24 months (OR 0.3; $p < 0.001$) postintervention initiation, whereas no significant differences were found across time for the control group. There was also a significant reduction in log ₁₀ VL at 12 months in the intervention group (mean difference = -0.36; $p < 0.05$).
2 Fatti et al. ²⁹	South Africa	Retrospective cohort study	Total sample: 6706 adolescents and youth 10–24 who initiated ART between January 2004 and September 2010 at 47 public ART facilities across 4 South African provinces. Intervention: 2100 youth. Control: 4606 youth	Standard clinic based care and a CBS intervention provided by lay workers, including: home-based ART- and sexual and reproductive health-related education, psychosocial support, referrals for psychosocial problems and nutritional security, screening for opportunistic infections, tracing of defaulters and support accessing government grants.	Standard clinic-based care.	Primary outcomes: All-cause mortality and LTFU after ART initiation. Secondary outcomes: (i) Adherence to ART, measured using Medication Possession Ratios derived from pharmacy refill data (number of days of dispensed medication divided by the number of days between the first and last pharmacy refill during the study period); (ii) CD4 cell count increases between months 0 and 36 after starting ART; (iii) CD4 count slope (mean change in CD4 count per month) between months 0–6 and 6–60; and (iv) the proportion of patients not achieving virological suppression after 3 years and during the fifth year of ART.	CBS was associated with substantially reduced attrition, including 40% less LTFU (aHR = 0.60; $p < 0.001$) and reduced mortality 5 years after the intervention (aHR = 0.52; $p < 0.001$). The proportion of youth who failed to achieve viral load suppression at 5 years was higher in the control group (aOR 0.24; 95% CI: 0.06–1.03), although this was marginally significant. The intervention also appeared to be cost-effective, with an ~50\$ cost per year and \$600 to \$776 cost per patient loss averted.

(continued)

TABLE 3. (CONTINUED)

Citation	Country	Study design	Participants	Intervention	Control/comparison	Outcome measures and definitions	Key findings
3 Grimsrud et al. ⁴	South Africa	Retrospective cohort study	Total sample: 884 youth 16–24, from a larger sample of 8150 individuals initiating ART Intervention: 156 youth Control: 728 youth	CACs, a community health worker led and nurse supported model of care supporting groups of 25–30. Includes group meetings every two months for group counseling, symptom screening and distribution of prepacked ART.	Patients attending a CHC, a large primary health care facility typical of urban public sector ART services across the region, based on South African national program criteria for ART.	LTFU (no visit in the first 12 weeks of 2014) and viral rebound (a single viral load measurement >1000 copies/mL after previous suppression).	For youth 16–24 years of age LTFU for CACs was not significantly different from that of CHCs (aHR = 0.68; $p = 0.197$). For all other age groups in the study, participation in CACs was instead associated with a decreased risk of LTFU, compared with CHC attendance (aHR = 0.33; 95% CIs: 0.27–0.40).
4 Ingerski et al. ²⁸	US	Retrospective study using systematic medical record review	Total sample: 62 youth 13–24 with horizontally acquired HIV, initiating HAART in a clinic setting. Intervention: 72% (45 youth) received one or more placebo trials before HAART, and 27% (17 youth) two or more. Control: remaining 17 youth that did not receive a trial	Receipt of one or more placebo trials before HAART initiation. Placebo pills, containing lactose sugar, were prescribed using a regimen with the same dosing frequency, pill size, and number of pills as the anticipated HAART medication regimen.	Youth who did not receive a placebo trial before HAART initiation.	Viral load and CD4 count readings, abstracted from participants' electronic medical record.	No significant differences were found in disease markers at 12 months between youth receiving a placebo trial post-HAART initiation and youth who did not ($p > 0.01$). Youth receiving multiple trials were more likely to have lower CD4 count 9 months post-HAART initiation, suggesting this may serve as a method to identify most at-risk adolescents.
5 Linnemayr et al. ²⁵	Uganda	Individually randomized parallel multi-site controlled trial	Total sample: 332 HIV-positive 15–22 year olds attending one of two study HIV clinics in Kampala, Uganda. Participants randomly assigned by simple randomization in a 1:1:1 ratio to control group or 1 of 2 intervention groups. Intervention group 1 (one-way SMS messaging): 110 youth Intervention group 2 (two-way SMS messaging): 110 Control group: 112	SMS reminder messages by means of one-way SMS (message only) or two-way SMS (message plus response option). Message for both groups was "We hope you are feeling well today." For the two-way SMS group respondents were asked to reply "1 if well, 2 if unwell"; they received a call from a study coordinator within 24 h if the response was "unwell."	Usual standard of care.	Primary outcome: mean HIV treatment adherence over a 48-week period (number of recorded bottle openings divided by the number of prescribed bottle openings, measured by means of a pill bottle with an electronic MEMS). Secondary outcomes: at least 90% adherence; self-reported adherence for the previous month; binary indicator of whether treatment was interrupted for 48 or more hours.	No significant differences in mean adherence [67% in the control group, 64% in the one-way SMS group (95% CI = 0.77–1.14), and 61% in the two-way SMS group (95% CI = 0.75–1.12)] or secondary outcomes found across the 3 groups.

(continued)

TABLE 3. (CONTINUED)

Citation	Country	Study design	Participants	Intervention	Control/comparison	Outcome measures and definitions	Key findings
6 MacKenzie et al. ²³	Malawi	Nested case-control study	Total sample: 617 adolescents 10–19, who were ART patients participating in the Zomba District <i>Observational Cohort Study</i> at a tertiary urban referral hospital in Zomba and started ART during or after March 2010. From this population, 135 nonretained cases and 405 retained controls were selected. Intervention: 302 adolescents Control: 238 adolescents	An adolescent-centered differentiated care model (“Teen Club”), comprising: dedicated weekend clinic time; sexual and reproductive health education; disclosure and ART adherence support; ART refill; individualized peer counseling and support; peer interaction through sports, art, and games.	Usual standard of care.	Nonretention in ART care, defined as patients who were lost to follow-up (patient did not return to the clinic within 2 months after (s)he was expected to have run out of ART and is not known to have transferred out or stopped treatment); “stopped” (the patient is known to have stopped treatment for any reason) or; “died” (the patient is known to have died, based on report by guardians, health facility staff, or from routine LTFU tracing by facility staff).	Adolescents exposed to Teen Club were more likely to be retained than those without exposure (aOR for nonexposure: 0.27; 95% CIs: 0.16–0.45). Attrition was higher among older adolescents (15–19) compared with the 10–14 age group (aOR 2.14; 95% CIs: 1.12–4.11).
7 Ojwang et al. ⁷	Kenya	Retrospective cohort analysis	Total sample: 924 HIV-positive patients 15–21 years of age enrolled in care at a Youth Center or Health Center in Kisumu, Kenya, between July 2007 and September 2010. Intervention: 584 at the youth-specific clinic Control: 340 at the family-oriented clinic.	Youth-orientated prevention, care, and treatment clinic. Similarly to the family clinic, fees are not charged and defaulter tracing is conducted (NOTE: no further description of the youth-friendly clinic and its characteristics is provided).	Family oriented clinic, offering free services and including an active defaulter program to contact patients that miss appointments. Includes assisted disclosure, identification, and enrollment of other HIV-positive family members and family counseling.	LTFU (patients missed his/her last appointment by ≥4 months).	The clinic of enrollment was not associated with LTFU (aHR=1.09; <i>p</i> =0.56). LTFU was very high, over 50% (52.9/100 person-years).
8 Reif et al. ⁵	Haiti	Retrospective analysis using programmatic clinic patient-level data	Total sample: 554 adolescents 13–19 years of age (of the 1672 who tested positive for HIV) that initiated ART at a public HIV clinic in Port-au-Prince between January 2003 and December 2012. Intervention: 305 who initiated post the adolescent clinic 2009 intervention. Comparison: 249 who initiated preclinic	Implementation of a dedicated adolescent clinic. Over and above standard clinic services, youth-friendly HIV services included: HIV-positive one-on-one and small group peer counseling; age-appropriate educational materials and extracurricular activities, such as projects and games to promote retention; family planning and STI testing provided at the same clinic; counseling services for mental health and gender-based violence at the clinic; clinic hours from 8 am to 5 pm to accommodate after school hours.	Standard pediatric services (for ages 10–13) or adult clinic services (for ages 14–19). Services for adolescents in the adult clinic included counseling by HIV-positive peer educators, reminder phone calls for appointments, and transport support. Family planning and treatment for STIs were provided in separate clinics at the same site.	Attrition, defined as dead or lost-to-follow-up (no clinic or pharmacy visit for 6 months with no documented transfer or death).	Retention after ART initiation was not significantly lower in the preclinic (comparison group (aHR = 0.83; <i>p</i> = 0.2), although the study showed higher rates of pre-ART attrition at 12 months from testing in the preclinic group (aHR = 1.44; <i>p</i> < 0.001).

(continued)

TABLE 3. (CONTINUED)

Citation	Country	Study design	Participants	Intervention	Control/comparison	Outcome measures and definitions	Key findings
9 Teasdale et al. ²⁶	Kenya	Retrospective cohort study	HIV-positive youth 10–24 enrolled for ART at a health facility participating in the Optimal Models for HIV care in Africa study in the Nyanza region of Kenya, either during the preintervention period (March to December 2011) or postintervention period (March to December 2013). Intervention: 304 youth enrolled during postintervention period at 6 intervention facilities Control groups: 426 youth enrolled in preintervention period at 6 intervention facilities; 1017 enrolled in the preintervention period and 304 postintervention at 28 control facilities. Analysis of LTFU in the 6 months after initiation included 274 adolescents from intervention facilities (172 pre and 102 post) and 576 from the control facilities (410 pre and 166 post).	Implementation of YAFS in 6 health facilities from March 2013. The intervention comprised: (i) training and mentorship for health care providers on care for adolescents/youth; (ii) a dedicated day for adolescent/youth HIV clinic at least once monthly, which provided integrated sexual and reproductive health services; and (iii) support groups and education programs run by youth and adult peer educators.	Standard HIV services as per Kenyan national guidelines.	Incidence of LTFU in the first 12 months after ART enrollment (LTFU before ART initiation was defined as not attending visits over the 12 months and not recorded as dead or transferred to another facility; LTFU after initiation was assessed for patients who started treatment at least 6 months before the end of data collection).	No significant differences were found in post-ART LTFU before and after YAFS implementation at intervention facilities ($p=0.19$). There were also no significant differences in LTFU in patients on ART between the YAFS and non-YAFS facilities in either the pre- ($p=0.73$) or post-YAFS ($p=0.77$) periods. The intervention did not improve retention either before ART or in the 6 months after treatment initiation.
10 Zanoni et al. ²⁷	South Africa	Retrospective cohort study	Total sample: 241 perinatally HIV-infected adolescents and young adults 13–24 who received at least 1 prescription of ART at a hospital-based ART clinic in KZN, SA, between April 2007 and November 2015 Intervention: 88 youth Controls: 153 youth	Saturday adolescent clinic opened within an existing clinic. Services included ART dispensing, lunch, and scheduled group activities (e.g., dancing, soccer, education, counseling).	Standard pediatric clinic care at the same site.	Primary outcomes: retention in care (one clinic visit and/or ART dispensing in the 6 months before data extraction) and viral suppression (viral load of <400 copies/mL from the most recent test within previous 6 months). Secondary outcome: composite outcome of retention and suppression (one clinic visit, pharmacy refill, and viral load <400 copies/mL within the previous 12 months).	Retention and viral suppression (previous 6 months), respectively, were higher among youth attending the dedicated adolescent clinic versus the standard pediatric clinic (Retention: aOR 8.5; $p<0.01$. Viral suppression: aOR 3.8; $p<0.01$). Retention with viral suppression (past 12 months) was also higher among youth attending the adolescent clinic (aOR 8.4; $p<0.0001$).

CHC, community health center; CSA, Child Savings Account; LTFU, loss to follow-up; MEMS, medication event monitoring system; VL, viral load.

TABLE 4. METHODOLOGICAL QUALITY AND RISK OF BIAS ASSESSMENT FOR RANDOMIZED CONTROLLED TRIALS

Study	Sequence generation		Blinding of participants and outcome assessors	Incomplete outcome data	Selective outcome reporting	Other sources of potential bias	Overall quality of study
	Was the allocation sequence adequately generated?	Was allocation adequately concealed?	Was knowledge of the allocated intervention adequately prevented during the study?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study free of other problems that could put it at a high risk of bias?	
Bermudez et al. ²⁴	Unclear	Unclear	No	Yes	Yes	No	Moderate
Linnemayr et al. ²⁵	Yes	Yes	No	Yes	Yes	No	Good

confounding factors,²⁸ insufficient detail on the nature of the intervention,⁷ and changing composition of the intervention and control groups throughout the duration of the study.^{5,23} Several studies also indicate high risk of selection bias inherent in the allocation of participants to the intervention versus control groups;^{4,27–29} examples of selection bias include exclusion from the intervention group based on the participant's health status, access to the intervention service, or a maximum cutoff number for the intervention.

Discussion

This review highlights several positive developments in studies focusing on adolescent and youth ART adherence and retention in care interventions post 2016. First, there appears to have been a shift in geographical focus since the publication of previous reviews,^{14,15} from HICs to lower-income countries most affected by generalized HIV epidemics; 9 of the 10 studies identified in this review were in fact conducted in LMICs, and 8 in sub-Saharan Africa.

Second, while it is difficult to confidently make direct comparisons between study quality assessments of different reviews (due to different foci and an element of subjectivity inherent in assessments made by different groups of individuals), it appears there has been a quality improvement in RCTs conducted in recent years with adolescents and youth (noting that all RCTs in the review of studies by MacPherson et al. before 2014 were graded as low).

Third, there has been a clear increase in sample sizes and follow-up periods: intervention group sizes for most of the studies included in this review were over 200, whereas intervention group sizes for the large majority of studies in previous reviews ranged between 10 and 50 participants;^{14,15} with the exception of one study, all studies identified in this review had follow-up periods of 12 months or more, whereas many studies included in previous reviews with youth had follow-up periods below 6 months.^{14,15}

Studies included in this review provide further evidence for previously tested approaches with youth and adolescents, and extend the evidence base to new approaches with this population group. Below, we discuss the implications of findings for each type of intervention study included in this review, in relation to the broader empirical literature.

Youth friendly clinics and services

This review shows an increase in the number of adolescent- or youth-friendly clinic intervention evaluations, as had been advocated by previous review articles.^{13,15} These interventions likely draw from WHO recommendations that

adolescent-friendly services be accessible, acceptable, equitable, appropriate, and effective,³⁰ by aiming to improve the physical space and social environment.^{27,31} However, despite high hopes, studies evaluating youth-friendly approaches in this review show mixed results.

When considering this finding, it is of course important to take into account the heterogeneity in youth-friendly models across studies and the methodological limitations of studies, both described above. It is possible that certain components or services may be more strongly associated with better outcomes than others, and that this may differ in different contexts. In fact, a recent cross-sectional study, conducted across multiple (12) clinics in the United States, found retention in HIV care among youth to be associated with some youth-friendly components of care, such as clinic waiting areas intentionally designed for youth, evening hours, and providers with training in adolescent health, but not with others, such as clinic location or accessibility.³² However, we were not able to identify clear commonalities in the models adopted among studies in this review that showed effectiveness, or differences between those that did and did not.

It is also worth noting that, while most of the facility-level studies included in this review were conducted at public clinics, they were either based at one clinic or groups of clinics participating in existing interventions or networks; it is therefore unclear whether these could be considered representative of youth accessing health services nationally or even in the study area.

Evidently, further research and consideration are required to better understand why youth friendly approaches may work in some cases and not in others. Well-designed and reported implementation science methodologies could be employed to identify which aspects or components of specific youth friendly interventions may be working or not working well, and why.^{33,34} Moreover, implementation research could compare the effectiveness and cost-effectiveness of different youth-friendly clinic models. It could be particularly useful to disaggregate and assess specific characteristics of interventions, for example, individual intervention components, intervention timing and dose, implementers, target population, and outcomes.³⁵ This research could be informed by qualitative studies conducted with health providers and young people that explore perceived facilitators and barriers to care, to strengthen health service implementation and uptake.^{34–36}

Placebo trial intervention

The placebo pill intervention did not show positive impact with adolescents and youth in the United States.²⁸ These

TABLE 5. METHODOLOGICAL QUALITY AND RISK OF BIAS ASSESSMENT FOR NONRANDOMIZED STUDIES

Study	Participant selection		Exposure to intervention		Comparability		Assessment of outcomes		Other potential sources of bias		
	Were participants selected to be representative of the target population?	Were there clear participant selection criteria (for both exposed and control group) avoiding inappropriate exclusions?	Was a comparator/control group assessed?	Was the intervention being studied applied consistently to all eligible participants?	Were potential confounders identified and appropriately adjusted for?	Were procedures for assessment of outcome sufficient to satisfy confirmation of presence of condition of interest?	Was follow-up long enough for outcome to occur?	Were incomplete outcome data adequately addressed?	Are reports of the study free of suggestion of selective outcome reporting?	Was the study free of other problems that could put it at a high risk of bias?	Overall quality of study
Fatti et al. ²⁹	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	No	Good
Grimstad et al. ⁴	No	No	Yes	Unclear	Yes	Yes	Yes	Unclear	No	No	Moderate
Ingerski et al. ²⁸	Yes	No	Yes	No	No	Yes	Yes	Unclear	No	No	Low
MacKenzie et al. ²³	Yes	Yes	Yes	No	Yes	Yes	Yes	Unclear	Yes	No	Moderate
Ojwang et al. ⁷	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Good
Reif et al. ⁵	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No	Moderate
Teasdale et al. ²⁶	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	No	Moderate
Zanoni et al. ²⁷	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No	Moderate

types of trials applied to ART among young adults are in their early stage, and it should be noted that the quality of the study by Ingerski et al. was assessed as low in this review, in part because of the small sample size. Nevertheless, it is unclear whether there would be value in further investigating this type of intervention in LMICs most affected by the HIV epidemic, where coexisting social and economic factors may present greater obstacles to adherence⁵ than knowledge and discipline linked to pill taking.

mHealth intervention

The only study in this review evaluating an mHealth intervention did not provide evidence of effectiveness.²⁵ Although this was the first known study to report effects of a mobile phone text message reminder intervention on ART adherence among adolescents and young adults, previous studies testing similar interventions with HIV-positive adults in Africa and India have shown mixed results.^{37–40}

While enthusiasm for interventions that take advantage of increasingly accessible mobile technology is understandable, this clearly needs to be tempered with more reasonable expectations as to what text messages alone can achieve.²⁵ The content of the intervention reported in the study by Linne-mayr et al. (standardized messages that asked whether the participant felt well or unwell) was very limited and may not have been sufficient to have significant impact. We also need to consider that text messages alone may not be particularly effective for adolescents in some of today's societies, given increasing volumes of messaging, and also lower cellphone network coverage in rural and remote areas within Africa.

Future mobile technology interventions should explore additional functionality, such as adherence feedback, or integration into broader m-Health approaches.^{14,25} For example, a recent US study with 91 young men who have sex with men showed the preliminary success of an intervention utilizing multiple social media (including Facebook, texting, and GPS-based mobile social and sexual networking) in increasing retention in HIV care and viral load suppression.⁴¹ Further testing of similar initiatives with larger samples among general adolescent and youth populations in LMICs would be very useful.

Household- or community-based interventions

Two studies in this review provide evidence of potential effectiveness of community interventions with adolescents and youth, including home-based health care and broader economic empowerment initiatives such as savings mechanisms and financial management education.^{24,29} The study results from Fatti et al. extend findings of previous studies showing positive effects of community support interventions on retention among adults and children,^{42,43} and a recent RCT showing improvements in viral suppression and mortality among children (6–15 years) whose caregivers received structured support from community health workers.⁴⁴

The study by Bermudez et al., instead, is the first known evaluation of an economic empowerment intervention aimed at improving HIV treatment adherence among adolescents (a previous pilot study showed promise but tested a combination of motivational interviewing and financial incentives and worked with a very small sample of 11 adolescents⁴⁵).

However, the importance of economic support is not surprising, as transportation costs and food insecurity have been identified as the greatest challenges to adolescent treatment and care in sub-Saharan Africa.⁴⁶ Recent cross-sectional analyses with over 1000 ART-initiated adolescents in South Africa's Eastern Cape province found SDG-related provisions—such as access to basic necessities, food security, government cash transfers, and household employment—to be associated with reduced mortality risk [indicated by lack of viral suppression and/or symptomatic untreated tuberculosis (TB)]; moreover results showed a strongly graded reduction in risk in the presence of multiple provisions.⁴⁷ In addition, there is prior evidence pointing to the usefulness of economic strengthening initiatives with HIV-positive adults in LMICs; for example, an agricultural and microfinance intervention in Kenya was found to improve viral suppression, CD4 counts, and food security.⁴⁸

The promising findings of family-based and economic empowerment initiatives reinforce the need to move beyond the health facility or possibly even health sector, to further investigate broader and multi-faceted interventions that address social and economic barriers to treatment adherence. While it is important to better align clinic facilities to the needs of adolescents and youth, a number of studies now indicate that this may have limited impact on long-term retention post-ART initiation without also addressing socio-economic, family, and community factors.⁵ Suggested potential foci include developing and testing interventions that encourage family disclosure and support, strengthen adolescents' social networks, reduce stigma, and provide community-based services, including transport.^{5,16}

Nonetheless, positive findings of community- and family-based initiatives should be considered with caution, since the evidence base with youth and adolescents is still small: this review only identified one study for these types of interventions and each was the first of its kind to be tested within this population group. Further evaluations are clearly needed both to determine the effectiveness of these interventions and the various mechanisms through which this may occur. For example, a home-based intervention offering multiple services could positively impact HIV treatment retention through one or more factors, including referrals and clinic linkages, better health care, better mental health, and self-management skills.^{29,49}

From a research and programmatic perspective, it would be important to be able to disaggregate and separately test individual components of multi-component interventions, to determine which aspects of these programs are (more or less) effective. This was reported as a challenge by previous authors when reviewing interventions.¹⁴

Lastly, the study evaluating community-based adherence clubs found a reduction in LTFU for adults (in line with previous studies with HIV-positive adults⁴²) but not for youth 16–24.⁴ This finding highlights the fact that interventions with positive impact for adult populations may not always work for adolescents and youth, a group with particular difficulties and needs. It reinforces the need to develop interventions and conduct rigorous evaluation studies specifically with adolescents and youth in mind, preferably soliciting their feedback on intervention design and barriers to retention²³ through qualitative or mixed methods research.³⁶

Concluding thoughts

Despite a notable increase in the relative number and quality of studies published over the past two and a half years, the current pace of intervention research with young people living with HIV remains highly disproportionate to their needs.¹⁷ The overall number of studies for each type of intervention is still small, quality across studies is inconsistent, and—even for interventions with more available evidence—findings are inconclusive. In particular, this and previous reviews highlight the very small number of studies conducted specifically with the 10–19 (adolescent) age group, despite this being the potentially most vulnerable age group in need of effective support and adherence interventions.^{2,3}

We clearly need more, more representative and higher quality studies focused on youth and, more specifically, adolescents 10–19, or that disaggregate findings for these particular age groups. Moreover, there may be good reason to disaggregate even further based on subgroups identified by previous studies as potentially high risk for LTFU and poor biomedical outcomes, for example, older (15- to 19-year-old) adolescents²³ and adolescents transitioning from pediatric to adult care.¹⁶ These particular groups of young people can fall through the cracks of existing systems and may require specific programming and transition protocols.¹⁶

A greater focus on specific groups of youth speaks in part to the concept of “differentiated care,” which has gained traction in the recent HIV treatment adherence debate.⁵⁰ Certainly, focusing a greater proportion of health worker time and other health resources on more at-risk patients can potentially lead to higher retention among these critical groups, as well as efficiency gains and lower health worker needs.^{13,50} However, possible long-term effects on adherence across various groups, as well as gains at facility level, are issues that require further investigation.

Lastly, while beyond the scope of this review, it is important to consider the replicability and potential sustainability of interventions, as well as their effectiveness. Many of the studies included in the 2015 review of MacPherson et al. comprised resource-intensive approaches such as individual counseling, education, and therapy. As argued by the review authors, these interventions may not be generalizable or sufficient to overcome the structural and systemic obstacles facing adolescents.¹⁵ This may be all the more the case in LMICs in sub-Saharan Africa with generalized epidemics. The recent increase in studies conducted in LMICs in Africa is encouraging. However, it is important to consider whether these initiatives could be feasibly scaled up in the absence of large amounts of external donor funding or technical support and implemented within the (health worker and other) constraints of existing national health and social systems.⁴⁹

In this respect, operations research and cost-effectiveness analyses would be particularly useful to prioritize resources and monitor impact within the health system,^{23,51} and determine the cost and feasibility of scaling up interventions beyond the health system (e.g., community-based interventions). Only one study included in this review,²⁹ conducted in South Africa, assessed costs and benefits (expressed as patient-loss averted) of the community-based support intervention tested, and found it to be cost effective. As argued by previous authors,¹⁵ the public health benefits of expanding ART access to adolescents through universal treatment can

only materialize when cost-effective and sustainable service delivery interventions are widely implemented.

UNAIDS treatment targets aim to eliminate new HIV infections by the year 2020; these targets include 90% of all people living with HIV knowing their HIV status, 90% of all people with diagnosed HIV infection receiving sustained ART, and 90% of all people receiving ART having suppressed viral loads.¹² While some progress has been made globally, we are still very far from achieving these goals among adolescents and youth, particularly in those parts of the world where most affected young people reside, such as sub-Saharan Africa.²

This highlights the pressing need for interventions and service models among these specific population groups that are effective in increasing HIV testing and timely treatment uptake, as well as retention and treatment adherence to ensure viral suppression. To achieve these global public health goals, interventions and services will not only need to be effective, but also acceptable and accessible to young people, financially and operationally viable for scale-up, and sustainable in the medium to long term.

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References

1. Lowenthal E, Bakeera-Kitaka S, Marukutira T, et al. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: A review of emerging challenges. *Lancet Infect Dis* 2014;14:627–639.
2. UNICEF. Turning the Tide Against AIDS Will Require More Concentrated Focus on Adolescents and Young People. 2018. Available at: <https://data.unicef.org/topic/adolescents/hiv-aids> (Last accessed August 5, 2018).
3. Adejumo O, Malee K, Ryscavage P, et al. Contemporary issues on the epidemiology and antiretroviral adherence of HIV-infected adolescents in sub-Saharan Africa: A narrative review. *J Int AIDS Soc* 2015;18:20049.

4. Grimsrud A, Lesosky M, Kalombo C, et al. 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:e16–e23.
5. Reif LK, Bertrand R, Benedict C, et al. Impact of a youth-friendly HIV clinic: 10 years of adolescent outcomes in Port-au-Prince, Haiti. *J Int AIDS Soc* 2016;19:20859.
6. UNICEF. For Every Child, End AIDS: Seventh Stock-taking Report. New York: UNICEF, 2016.
7. Ojwang VO, Penner J, Blat C, et al. Loss to follow-up among youth accessing outpatient HIV care and treatment services in Kisumu, Kenya. *AIDS Care* 2016;28:500–507.
8. Mutumba M, Musiime V, Lepkowski JM, et al. Examining the relationship between psychological distress and adherence to anti-retroviral therapy among Ugandan adolescents living with HIV. *AIDS Care* 2016;28:807–815.
9. World Health Organisation. Health for the world's adolescents: A second chance in the second decade. 2014. Available at: www.who.int/maternal_child_adolescent/documents/second-decade/en (Last accessed June 20, 2018).
10. Ferrand RA, Bandason T, Musvaire P, et al. Causes of acute hospitalization in adolescence: Burden and spectrum of HIV-related morbidity in a country with an early-onset and severe HIV epidemic: A prospective survey. *PLoS Med* 2010;7:e1000178.
11. Global Burden of Disease SDG Collaborators. Measuring the health-related Sustainable Development Goals in 188 countries: A baseline analysis from the Global Burden of Disease Study 2015. *Lancet* 2016;388:1813–1850.
12. UNAIDS. 90–90–90—An Ambitious Treatment Target to Help End the AIDS Epidemic. Geneva: UNAIDS, 2014.
13. Murray KR, Dulli LS, Ridgeway K, et al. Improving retention in HIV care among adolescents and adults in low- and middle-income countries: A systematic review of the literature. *PLoS One* 2017;12:e0184879.
14. Ridgeway K, Dulli LS, Murray KR, et al. Interventions to improve antiretroviral therapy adherence among adolescents in low- and middle-income countries: A systematic review of the literature. *PLoS One* 2018;13:e0189770.
15. 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 Health* 2015;20:1015–1032.
16. Judd A, Sohn AH, Collins IJ. Interventions to improve treatment, retention and survival outcomes for adolescents with perinatal HIV-1 transitioning to adult care: Moving on up. *Curr Opin HIV AIDS* 2016;11:477–486.
17. Shaw S, Amico KR. Antiretroviral therapy adherence enhancing interventions for adolescents and young adults 13–24 years of age: A review of the evidence base. *J Acquir Immune Defic Syndr* 2016;72:387–399.
18. Bhana A, Mellins C, 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;26:1–11.
19. Kaihin R, Kasatpibal N, Chitreechuer J, Grimes RM. Effect of an empowerment intervention on antiretroviral drug adherence in Thai youth. *Behav Med* 2015;41:186–194.
20. O' Connor D, Green S, Higgins J. Defining the review question and developing criteria for including studies. In: Higgins J, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions*: Cochrane Book Series. London: Cochrane Collaboration, 2011.
21. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
22. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomised studies in meta-analyses. 2000. Available at: www.ohri.ca/programs/clinical_epidemiology/oxford.asp (Last accessed June 1, 2018).
23. 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:DOI:10.1002/jia1002.25028.
24. Bermudez LG, Ssewamala FM, Neilands TB, et al. Does economic strengthening improve viral suppression among adolescents living with HIV? Results from a cluster randomized trial in Uganda. *AIDS Behav* 2018;22:3763–3772.
25. Linnemayr S, Huang H, Luoto J, et al. Text messaging for improving antiretroviral therapy adherence: No effects after 1 year in a randomized controlled trial among adolescents and young adults. *Am J Public Health* 2017;107:1944–1950.
26. Teasdale CA, Alwar T, Chege D, et al. Impact of youth and adolescent friendly services on retention of 10-24-year-olds in HIV care and treatment programs in Nyanza, Kenya. *J Acquir Immune Defic Syndr* 2016;71:e56–e59.
27. Zanoni BC, Sibaya T, Cairns C, et al. Higher retention and viral suppression with adolescent-focused HIV clinic in South Africa. *PLoS One* 2017;12:e0190260.
28. Ingerski LM, Wilkins ML, Rach AM, et al. Use of placebo pills before treatment initiation in youth with HIV: Are they ready? *J Int Assoc Provid AIDS Care* 2017;16:412–417.
29. 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):e25041.
30. WHO. Making Health Services Adolescent Friendly: Developing National Quality Standards for Adolescent-Friendly Health Services. Geneva, Switzerland: World Health Organisation, 2012.
31. Tanner AE, Philbin MM, Duval A, et al. “Youth friendly” clinics: Considerations for linking and engaging HIV-infected adolescents into care. *AIDS Care* 2014;26:199–205.
32. Lee L, Yehia BR, Gaur AH, et al. The impact of youth-friendly structures of care on retention among HIV-infected youth. *AIDS Patient Care STDS* 2016;30:170–177.
33. Hickey, M, Odeny T, Petersen, M, et al. Specification of implementation interventions to address the cascade of HIV care and treatment in resource-limited settings: A systematic review. *Implement Sci* 2017;12:102.
34. Schackman, B. Implementation science for the prevention and treatment of HIV/AIDS. *J Acquir Immune Defic Syndr* 2010;55(Suppl 1):S27–S31.
35. Beach L, Greene G, Lindeman P, et al. Barriers and facilitators to seeking HIV services in Chicago among young men who have sex with men: Perspectives of HIV service providers. *AIDS Patient Care STDS* 2018;32:468–476.
36. Grieb S, Kerrigan D, Tepper V, et al. The clinic environment as a form of social support for adolescents and young

- adults living with HIV. *AIDS Patient Care STDS* 2018;32:208–213.
37. Lester RT, Ritvo P, Mills EJ, et al. Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): A randomised trial. *Lancet* 2011;376:1838–1845.
 38. Pop-Eleches C, Thirumurthy H, Habyarimana JP, et al. Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: A randomized controlled trial of text message reminders. *AIDS* 2011;25:825–834.
 39. Mbuagbaw L, Thabane L, Ongolo-Zogo P, et al. The Cameroon Mobile Phone SMS (CAMPS) trial: A randomized trial of text messaging versus usual care for adherence to antiretroviral therapy. *PLoS One* 2012;7:e46909.
 40. Shet A, De Costa A, Kumarasamy N, et al. Effect of mobile telephone reminders on treatment outcome in HIV: Evidence from a randomised controlled trial in India. *BMJ* 2014;349:g5978.
 41. Tanner A, Song E, Mann-Jackson L, et al. Preliminary impact of the *weCare* social media intervention to support health for young men who have sex with men and transgender women with HIV. *AIDS Patient Care STDS* 2018;32:450–458.
 42. Wouters E, Van Damme W, Van Loon F, et al. Public-sector ART in the Free State Province, South Africa: Community support as an important determinant of outcome. *Soc Sci Med* 2009;69:1177–1185.
 43. Grimwood A, Fatti G, Mothibi E, et al. Community adherence support improves programme retention in children on antiretroviral treatment: A multicentre cohort study in South Africa. *J Int AIDS Soc* 2012;15:17381.
 44. Ferrand R, Simms V, Dauya E, et al. The effect of community-based support for caregivers on the risk of virological failure in children and adolescents with HIV in Harare, Zimbabwe (ZENITH): An open-label, randomised controlled trial. *Lancet Child Adolesc Health* 2017;1:175–183.
 45. Foster C, McDonald S, Frize G, et al. “Payment by Results”—Financial incentives and motivational interviewing, adherence interventions in young adults with perinatally acquired HIV-1 infection: A pilot program. *AIDS Patient Care STDS* 2014;28:28–32.
 46. Soeters H, Pediatric AIDS Treatment for Africa, World Health Organization. Adolescent Africa: A Situational Analysis of Adolescent HIV-Treatment and Care in Sub-Saharan Africa. Cape Town, South Africa: PATA, 2015.
 47. Cluver L, Pantelic M, Orkin M, et al. Sustainable survival for adolescents living with HIV: Do SDG-aligned provisions reduce potential mortality risk? *J Int AIDS Soc* 2018;21(Suppl 1):25056.
 48. Weiser SD, Bukusi EA, Steinfeld RL, et al. Shamba Maisha: Randomized controlled trial of an agricultural and finance intervention to improve HIV health outcomes in Kenya. *AIDS* 2015;29:1889–1894.
 49. Judd A, Violari A. Does community support help children take their ART? *Lancet* 2017;1:160–161.
 50. Dutta A, Barker C, Kallarakal A. The HIV treatment gap: Estimates of the financial resources needed versus available for scale-up of antiretroviral therapy in 97 countries from 2015 to 2020. *PLoS Med* 2015;12:e1001907.
 51. 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;20:21371.

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