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Interventions addressing the adolescent HIV continuum of care in South Africa: a systematic review and modified Delphi analysis

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ABSTRACT

Introduction Compared with adults, adolescents in South Africa have larger gaps at each step of the HIV continuum of care resulting in low levels of viral suppression.

Methods We conducted a systematic review and modified Delphi analysis of interventions addressing the HIV continuum of care for adolescents in South Africa. We searched PubMed, Science Direct, and Google Scholar and online conference proceedings from the International AIDS Society, the International AIDS Conference, and the Conference on Retrovirology and Opportunistic Infections from 1 January 2010 to 30 September 2020. We then conducted a modified Delphi analysis with 29 researchers involved in the National Institutes of Health's Fogarty International-supported Adolescent HIV Implementation Science Alliance–South Africa to evaluate interventions for efficacy, feasibility and potential for scale-up.

Results We identified nine initial published articles containing interventions addressing the adolescent HIV continuum of care in South Africa, including five interventions focused on HIV diagnosis, two on antiretroviral therapy adherence and two on retention in care. No studies addressed linkage to care or transition from paediatric to adult care. Two studies discussed intervention costs. In-home and HIV self-testing, community-based adherence support, and provision of adolescent-friendly services were the most impactful and scalable interventions addressing the adolescent HIV continuum of care.

Conclusion Future interventions should work comprehensively across the adolescent HIV continuum of care and be tailored to the specific needs of adolescents.

Strengths and limitations of this study

► The Adolescent HIV Implementation Science Alliance–South Africa (AHI(SA)[2]) network includes highly experienced experts with key knowledge to evaluate interventions for adolescents and young adults living with HIV in South Africa.

► We evaluated interventions with quantifiable results addressing the full continuum of care for adolescents and young adults living with HIV in South Africa.

► The evaluation included interventions that were published in the literature and did not include studies that were in progress or planned.

► Not all AHI(SA)[2] members who were invited to participate completed the survey.

INTRODUCTION

South Africa has the highest burden of adolescents and young adults living with HIV (ALWH) in the world.[1] In the late 1990s and early 2000s, delays in access to HIV treatment and suboptimal HIV prevention tools contributed to more than 330 000 children being born with HIV through perinatal transmission.[2–5] These children are now ageing into adolescence and young adulthood. In addition, non-perinatal (typically sexual) transmission is a major concern among adolescents in South Africa. In 2017 alone, an estimated 50 200 adolescents aged 15–19 years contracted HIV, with the number of females (n=41 000) being more than four times higher than males (n=9200).[1] Despite growing recognition of the challenges in adolescent HIV prevention and care, HIV/AIDS remains the leading cause of death among all adolescents in South Africa.[6]

South Africa has the largest antiretroviral therapy (ART) programme in the world, and national ART guidelines support early initiation of ART with simple, potent and well-tolerated regimens.[7] ART scale-up has contributed to relatively high levels of viral suppression, low mortality rates and low HIV transmission among adults living with HIV in South Africa.[1 8 9] However, the continuum of care for ALWH (ie, from diagnosis to linkage to care and subsequent ART adherence, retention in care and viral suppression) has significant gaps at each step, resulting in

only 10% of adolescents who are living with HIV in South Africa being virally suppressed in a study conducted in 2016.[2] In addition, the process of transition from paediatric to adult care lacks evidence-based guidelines and has shown poor levels of retention in care and viral suppression after transition.[10–12]

While research is ongoing to support HIV treatment for ALWH in South Africa, the extent and efficacy of interventions have not been well defined, and evidence-based guidance is needed to direct future intervention development. Our objective was to use a network of researchers working to improve HIV care for ALWH in South Africa to identify promising interventions for wider implementation and future scale-up of successful interventions for this population. Here, we present the results of a systematic review and modified Delphi analysis of interventions addressing the adolescent and young adult HIV continuum of care in South Africa.

METHODS
Systematic review
We searched PubMed, Science Direct, and Google Scholar and online conference proceedings from the International AIDS Society, the International AIDS Conference, and the Conference on Retrovirology and Opportunistic Infections from 1 January 2010 to 30 September 2020. Keywords and medical subject headings relevant to age (ie, adolescent, adolescence, teen, young adult) were cross-referenced with terms associated with the HIV continuum of care (ie, diagnosis, linkage to care, retention, adherence and transition) (online supplemental file 1). Interventions addressing HIV prevention among adolescents and young adults were analysed separately and will be published separately. We reviewed literature published in English that reported interventions addressing the adolescent and young adult HIV continuum of care that were piloted or implemented in South Africa among adolescents and young adults. We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (online supplemental file 2).[13] Because of variability in reported age ranges, we included studies in our analysis with primary data on youth ages 10–24 years. We present age ranges as described by the original authors.

All identified studies were uploaded into Covidence, a non-profit website working with the Cochrane database to improve systematic reviews (www.covidence.org, Melbourne, Australia). Duplicate materials were removed. After initially screening the titles and abstracts, two authors (BZ and TR) independently reviewed potential studies. Conflicts were resolved by reviewing the full-text article and discussing the inclusion/exclusion criteria until consensus was reached. We included randomised controlled trials, pre–post evaluations and retrospective cohorts that evaluated interventions with primary outcomes addressing the adolescent HIV continuum of care in South Africa. We excluded review articles, study protocols, qualitative studies and studies that did not include an intervention, did not report primary data affecting the HIV continuum of care, or were targeting children or adults outside our specified age range of 10–24 years. We then extracted data including study population, location, design, intervention description, and outcomes from the full-text articles and created summarised tables organised by each step in the HIV continuum of care.

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) guidelines to assess the quality of the study, strength of evidence and bias for all included clinical trials and evaluated random sequence generation, allocation concealment, blinding, and outcome reporting.[14] Randomised controlled trials were considered less biased than pre–post evaluations, and prospective and retrospective observational studies. Observational studies were evaluated for bias using the GRADE guidelines and each article included an assessment of eligibility, controls, loss to follow-up and outcome consistency[15] (see online supplemental file 3 for quality assessment table).

Modified Delphi analysis
To identify the most effective, feasible and scalable interventions impacting the adolescent HIV continuum of care in South Africa, we engaged the National Institutes of Health's (NIH) Fogarty International-supported Adolescent HIV Implementation Science Alliance–South Africa (AHI(SA)^2) (www.ahisa2.org). Members of AHI(SA)^2 were selected by inviting (via email) researchers with current NIH funding and/or published first authors (and their research teams) addressing adolescent HIV prevention or the adolescent HIV continuum of care in South Africa. We uploaded summarised tables from our systematic review, along with links to the full-text articles and abstracts, into REDCap for participants to access.[16] We invited AHI(SA)^2 members to complete a questionnaire assessing the feasibility, efficacy, scalability and costing of each intervention (using 4-point Likert scales). We also asked members to assign an overall score (rating of 0–100) regarding the potential impact of the intervention on the continuum of care for ALWH in South Africa. We encouraged the participants to follow the GRADE guidelines in their assessment of the quality of the studies; however, participants did not have access to the GRADE table. AHI(SA)^2 leadership decided a priori that a score of 70 or greater would be a reasonable estimate of clinically meaningful effects and would be required to be included in the second-round analysis.

All AHI(SA)^2 members (n=42) received a secure link to the REDCap survey via email to complete the first-round questionnaire focused on intervention efficacy (24 August 2020–23 September 2020). Results were discussed at the first AHI(SA)^2 virtual meeting on 25 September 2020 with the 25 participants who attended. Interventions with a prespecified median overall impact score less than 70 or with an average efficacy score less than 3 (out of 4 on the Likert scale) were removed from the next-round

questionnaire. In preparation for the second round, we updated the literature search from 31 July 2020 to 30 September 2020 and invited AHI(SA)[2] members to nominate additional studies for inclusion. The REDCap questionnaire was updated and emailed to AHI(SA)[2] members who participated in the first-round questionnaire (n=29) to evaluate feasibility and scalability (25 September 2020–15 December 2020). We sought to formulate an expert consensus on the interventions for ALWH with highest potential to be taken to scale and to highlight areas in which future interventions are needed.[17 18]

Patient and public involvement

Patients or the public were not involved in the design or conduct of this study. The research questions were formulated by the AHI(SA)[2] leadership team. Results of this analysis were presented at regular AHI(SA)[2] (www.ahisa2.org) meetings.

RESULTS
Systematic review

Our initial search yielded 273 relevant articles. Of these, 110 were removed due to duplicate publications or interventions, and 112 did not include interventions addressing the adolescent HIV continuum of care in South Africa, leaving 25 full-text articles for review. We excluded 16 of the 25 studies because 9 lacked an intervention, 3 focused on HIV primary prevention and 4 met one of the following exclusionary criteria: literature review only (n=1), no primary results (n=1), not focused on adolescents (n=1) or not conducted in South Africa (n=1). We did not find any additional unpublished studies in the review of conference abstracts. Overall, nine published papers with sufficient data were included in the first round of the modified Delphi analysis addressing the adolescent and young adult HIV continuum of care in South Africa.

Modified Delphi analysis
Participants

AHI(SA)[2] consisted of 42 eligible individuals involved in adolescent HIV research in South Africa. For the first round of the modified Delphi analysis, 29 (69%) participated in the REDCap survey. Participant characteristics are presented in table 1. Of the 29 who initiated the survey, 21 (72%) completed it. Of the 29 participants who were sent the second-round survey, 21 (72%) initiated it and 18 (62%) completed the survey.

Publications

Among the nine initial published articles containing interventions addressing the adolescent HIV continuum of care in South Africa, five interventions focused on HIV diagnosis, two on ART adherence and two on retention in care as indicated in online supplemental file 4. No studies addressed linkage to care or transition from paediatric to adult care. For study design, five studies were randomised

Table 1 Participant characteristics in two rounds of the modified Delphi Analysis

Demographics	First round (n=29) n (%)	Second round (n=21) n (%)
Profession		
Researcher	13 (45%)	12 (57%)
Clinician/researcher	6 (21%)	4 (19%)
Medical doctor	6 (21%)	3 (14%)
Healthcare provider	2 (7%)	1 (5%)
Student/fellow	2 (7%)	1 (5%)
Years working in adolescent HIV		
>10 years	14 (48%)	10 (48%)
6–10 years	6 (21%)	6 (29%)
1–5 years	8 (28%)	4 (19%)
<1 year	1 (3%)	1 (5%)
Highest Educational Degree		
PhD	11 (38%)	9 (43%)
MD or MBChB	5 (17%)	2 (10%)
MPH or other master's degree	5 (17%)	4 (19%)
MD/MBChB+PhD	3 (10%)	3 (14%)
MD/MBChB+master's degree	2 (7%)	3 (14%)
Other	3 (10%)	–
Primary residence		
South Africa	22 (76%)	15 (71%)
United States	6 (21%)	4 (19%)
United Kingdom	1 (3%)	1 (5%)

controlled trials, three were retrospective cohort analyses and one was a pre–post evaluation. Two studies of the nine discussed the cost of the intervention.

Intervention evaluation

Below we report summaries of the individual published interventions for ALWH in South Africa separated by steps in the continuum of care. Within each step, the interventions are listed beginning with the highest overall median impact rating in the modified Delphi analysis (online supplemental file 4 and table 2).

HIV diagnosis (n=5)

Five interventions addressed HIV diagnosis through expanded HIV testing among adolescents. Four of these were randomised controlled trials[19–22] and one was a pre–post evaluation.[23] Three of these studies met criteria for inclusion in both rounds of the modified Delphi analysis.[19 20 22] Two of the three studies showed high rates of HIV testing uptake and acceptability of in-home HIV testing and one showed strong short-term effects.

Shanaube et al reported on the 11 175 adolescents randomised to receive the full intervention of door-to-door

Table 2 Second round Delphi analysis of interventions to improve the continuum of care for adolescents living with HIV in South Africa

Authors	Title	Publication and date	Step in continuum of care	Costing	Feasibility mean score	Efficacy mean score	Scalability mean score	Overall median impact score
Zanoni, et al[11]	Higher Retention and Viral Suppression with Adolescent-Focused HIV Clinic in South Africa	PLoS One 2017	Retention	$1.25 per adolescent per clinic visit	3.34	3.28	3.17	80
Fatti, et al[27]	The Effectiveness and Cost-Effectiveness of Community-Based Support for Adolescents Receiving Antiretroviral Treatment: An Operational Research Study in South Africa	Journal of the International AIDS Society 2018	Retention	Cost of intervention was US$49.50/patient/year. Incremental cost per patient-loss averted was US$600 and US$776 after 1 and 2 years, respectively.	3.00	2.83	3.11	76
Shanaube, et al[22]	Community Intervention Improves Knowledge of HIV Status of Adolescents in Zambia: Findings from HPTN 071-PopART for Youth Study	AIDS 2017	HIV Diagnosis	Not evaluated	3.39	3.11	3.00	75
Pettifor, et al[20]	HIV Self-testing among Young Women in Rural South Africa: A randomised controlled trial comparing clinic-based HIV testing to the choice of either clinic testing or HIV self-testing with secondary distribution to peers and partners	EClinical Medicine 2020	HIV Diagnosis	Not evaluated	3.06	2.76	3.00	72
Cluver, et al[25]	Achieving Equity in HIV-Treatment Outcomes: Can Social Protection Improve Adolescent ART-Adherence in South Africa?	AIDS Care 2016	ART Adherence	Not evaluated	3.00	2.94	2.67	68
Doherty, et al[19]	Effect of Home-Based HIV Counselling and Testing Intervention in Rural South Africa: Cluster Randomised Trial	BMJ 2013	HIV Diagnosis	Not evaluated	3.17	3.06	2.94	65

HIV testing and counselling with support for linkage to care delivered by community health workers compared with standard of care in the Zambia PopART for Youth Study.[22] HIV testing was done for 80% of participants with awareness of a positive HIV test increased by a threefold by the third round of interventions and a median time to ART linkage of 5 months; however, there was no reported comparison with standard of care for HIV testing. Doherty *et al* performed a cluster randomised clinical trial among adolescents evaluating door-to-door home-based HIV testing performed by lay counsellors compared with standard of care.[19] HIV testing was significantly higher among adolescents receiving home-based testing (69%) compared with standard of care (47%) (prevalence ratio 1.54, 95% CI 1.32 to 1.81). Pettifor *et al* showed high uptake of HIV self-testing among young women. This study randomised 287 young women aged 18–26 years to choose between HIV self-testing kits and receive clinic-based HIV testing compared with HIV testing in government clinics.[20] In the choice arm, 95% chose self-testing. After 3 months, 92% of the choice arm and 43% of the standard of care arm reported HIV testing a difference of 49%. By 9 months, the difference reduced to 25%.

The remaining two studies did not meet the threshold to continue to the second round of the modified Delphi analysis due to lack of demonstrated efficacy as determined by the first round of the modified Delphi analysis; both used soccer as a means to increase HIV testing. Hershow *et al* conducted a pre–post analysis of the SKILLZ Street intervention by Grassroot Soccer where female coaches delivered afterschool education programme consisting of 10 2-hour biweekly sessions with 1953 female adolescents aged 12–16 years.[23] Among the participants, 69% tested for HIV by the end of the intervention. There was no control group or comparison with baseline testing. Rotheram-Borus *et al* randomised 142 male adolescents between the ages of 18 and 25 years to immediately participate in Grassroot Soccer with trained coaches, rapid HIV testing and vocational training compared with delayed participation in the control group.[21] There was no significant difference in HIV testing among the immediate group (29%) compared with the delayed uptake group (24%) after the intervention.

ART adherence (n=2)
Two studies evaluated interventions designed to improve adolescent ART adherence.[24 25] Both were included in the first round of the modified Delphi analysis, but only one continued to the second round due to lack of perceived efficacy. Cluver *et al* evaluated the provision of social protection on adherence among 1059 adolescents aged 10–19 years in an observational cohort.[25] They found that food provision (adjusted OR (aOR) 0.57, 95% CI 0.42 to 0.76), attendance at HIV support groups (aOR 0.60, 95% CI 0.40 to 0.91) and parental supervision (aOR 0.46, 95% CI 0.43 to 0.73) were associated with lower rates of self-reported non-adherence to ART in the prior week. Bhana *et al*'s VUKA Family Program was not included in

the second round of the modified Delphi analysis due to lack of clear efficacy. The intervention consisted of 10 sessions over 3 months and used a culturally tailored cartoon storyline of step-by-step guidance for problem-solving skills and facilitated family discussions.[24] ART adherence (last time missed medication) increased over time from baseline to completion of the study, but there was no comparison with standard of care.

Retention in care (n=2)
Two studies were designed to improve retention in care, and both were included in the first and second rounds of the modified Delphi analysis. Zanoni *et al* evaluated a weekend-based, adolescent-focused clinic that offered peer support, group activities, counselling and meals compared with standard of care in a retrospective cohort analysis.[26] Retention in care and viral suppression were higher among adolescents who attended the adolescent-friendly clinic (95% and 91%, respectively) compared with standard of care (85% and 80%, respectively; aOR 3.5, 95% CI 1.2 to 11.1; p=0.018 and aOR 2.5, 95% CI 1.1 to 5.8; p=0.028, respectively). The second study by Fatti *et al* evaluated community-based support that included home-based ART education, psychosocial support, opportunistic infection screening and access to government grants compared with standard of care among 6706 adolescents aged 10–24 years.[27] Cumulative loss to follow-up was lower in the intervention group (30%) compared with standard of care (39%; adjusted HR 0.60; 95% CI 0.51 to 0.71; p<0.0001). Although there was no statistically significant difference in viral failure after 3 or 5 years, 8.8% in the intervention group had viral failure compared with 37.2% in the standard of care group (aOR 0.24, 95% CI 0.06 to 1.03); the difference may be clinically meaningful.

DISCUSSION
In our systematic review and modified Delphi analysis of interventions addressing the adolescent HIV continuum of care, we found five feasible and effective interventions with high potential for scale-up to improve adolescent HIV outcomes in South Africa. To improve HIV diagnosis among ALWH in South Africa, in-home HIV testing[20] and HIV self-testing[22] were promising interventions. However, there was a lack of demonstrated efficacy in targeting successful linkage to care after HIV testing. Adherence to ART among adolescents improved with the provision of food support, attendance in HIV support groups and parental supervision.[25] Two interventions improved retention in care: one focused on adolescent-friendly services by providing an afterschool hours clinic with peer support, counselling and meals,[26] and the other by providing in-home support for HIV education, psychosocial support and assistance with applications to governmental grants.[27] Unfortunately, no interventions addressed transition from paediatric to adult-based care for ALWH in South Africa.

Although adolescents and young adults have the highest incidence of new HIV infections in South Africa, they often do not present to health centres for HIV testing. Structural barriers such as school, transportation or finances; psychosocial barriers such as the feelings of invincibility; or clinical factors such as the lack of clinical symptoms all contribute to poor engagement in care.[1 6] Therefore, traditional methods including clinic-based opt-out testing are not ideal for this population. Non-traditional methods of intensified case finding are required to identify adolescents living with undiagnosed HIV. In-home HIV testing provided by lay counsellors offers a solution to the issues of adolescents not attending health centres. Although this process can be labour-intensive and costly, it also offers a mechanism to improve linkage to care once adolescents are diagnosed with HIV. Another potential solution to low HIV testing rates among adolescents and young adults is self-testing which has shown acceptability and uptake but requires interventions to provide counselling to newly diagnosed individuals and facilitate linkage to care.

Adolescents living with HIV commonly suffer poor adherence to ART.[28 29] Direct interventions addressing adherence among adolescents living with HIV often require considerable effort and resources and have variable efficacy.[30 31] Indirect measures that improve food and economic security, psychosocial support and supervision appear to improve adherence among adolescents.[25] Future interventions to address adherence should include economic and psychosocial support. In addition, addressing barriers such as depression and substance use, which has improved ART adherence in adults, may also benefit adolescents and young adults.[32]

Afterschool hours clinics, peer support and improved connection to clinical staff have been shown to improve retention in care among adolescents living with HIV.[33] As recommended by the WHO, the provision of adolescent-friendly services and reimagining of clinical care delivery for adolescents and young adults can strengthen retention.[34] For example, many of these services can be provided outside of clinic space and time. In-home or virtual clinical services could be expanded to improve adolescent retention in care.

Interventions require resources in time, personnel and funding, but only two interventions in this review presented cost analyses. For implementors and policymakers to adequately assess intervention scale-up, costing and cost-effectiveness analyses are required. Future interventions addressing the adolescent HIV continuum of care should evaluate cost.

We identified several interventions that could be scaled to improve the adolescent HIV continuum of care in South Africa; however, several gaps remain. Improving HIV diagnosis is critical to improve the continuum of care, but without linkage to care, adolescents cannot access ART and achieve viral suppression. Interventions to improve adolescent HIV testing should include linkage to care, and adolescents require additional support to achieve and maintain viral suppression. Moreover, children initiating ART under the care of paediatricians will eventually require transition to adult care; however, we did not find any published interventions addressing transitional care for ALWH in South Africa highlighting a key area for future research.

Future interventions addressing the adolescent HIV continuum of care should build on the promising results from the highlighted studies and perhaps include a combination of the most effective strategies to optimise outcomes. Additionally, acceptability of the interventions by adolescents is critical for continued success of potential interventions.[35] Using participant-centred design and direct input from adolescents early in intervention development can likely increase acceptability and improve likelihood of intervention success.[36]

This systematic review and modified Delphi analysis has several limitations. First, we only identified interventions that were published in the literature and did not include studies that were in progress or planned. In addition, the modified Delphi analysis did not include researchers who were not yet published, received non-NIH funding or did not respond to email invitations. However, the AHI(SA)^2 network includes highly experienced experts with key knowledge to evaluate interventions in South Africa. In addition, not all AHI(SA)^2 members who were invited to participate completed the survey. We experienced drop-out rates of 28% and 38% in rounds one and two of the modified Delphi analysis due to strict completion deadlines prior to scheduled AHI(SA)^2 meetings. Although participants were encouraged to consider the GRADE guidelines in considering the quality of the studies, they did not have access to the final GRADE table. However, this review highlights published interventions with quantifiable results addressing the continuum of care for adolescents and young adults evaluated by scholars with interest in this population.

CONCLUSION

No single intervention exists to improve each step of the continuum of care for ALWH in South Africa. However, we highlight several promising interventions, specifically in-home HIV testing and self-testing to increase the proportion of ALWH who know their diagnosis and economic support and food support to increase ART adherence. These interventions should be further evaluated as they are implemented to improve adolescent outcomes in the HIV care cascade. Future interventions should work comprehensively across the adolescent HIV continuum of care and be tailored to the specific needs of adolescents.

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Supplement 1: Search terms used for systematic review:

Pubmed search strategy:

((adolescent[MeSH Terms]) OR (teen*) OR (youth*) OR (adoles*) AND ((HIV infection[MeSH Terms]) OR (acquired immune deficiency syndrome[MeSH Terms]) OR (HIV[TIAB]) OR ("AIDS"[TIAB]) OR ("acquired immune deficiency syndrome"[TIAB]) OR ("acquired immunodeficiency syndrome"[TIAB])) AND ("south africa"[TIAB]) AND ((intervention[TIAB])

Google scholar search strategy:
"adolescen* HIV intervention South Africa"

ScienceDierect search strategy:
Key words: "Adolescent HIV intervention South Africa"

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Supplement 2 | PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a literature review.	Title page 1
ABSTRACT			
Abstract	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings. See the PRISMA 2020 for Abstracts checklist for the complete list.	Abstract page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge, i.e., what is already known about your topic.	Page 2, lines 23 - 29
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Pages 2 – 3, lines 25 - 29
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses with study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 3, lines 33 - 46
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 3, lines 33 - 39
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Appendix 1
Selection process	8	State the process for selecting studies (i.e., screening, eligibility). Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Pages 3 – 4, lines 48 - 59
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4, lines 61 - 66
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Pages 5 – 6, lines 99 - 107
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were	N/A

Supplement 2 | PRISMA Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		excluded.	
Study characteristics	17	Cite each included study and present its characteristics (e.g., study size, PICOS, follow-up period).	Table 1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 4, lines 61 - 66
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table 1
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Pages 9 - 12
	23b	Discuss any limitations of the evidence included in the review.	Page 12, lines 267 - 277
	23c	Discuss any limitations of the review processes used.	Page 12, lines 267 - 277
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12, lins 280 - 286
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Not prepared
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	None
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Supplementary information
Competing interests	26	Declare any competing interests of review authors.	Supplementary information
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Supplementary information

Supplement 3: Evaluation of the quality of evidence using the GRADE guidelines

STUDY	DESIGN	QUALITY	CONSISTENCY	DIRECTNESS	MODIFYING FACTORS	POPULATION
HIV TESTING						
DOHERTY, ET AL.	Randomized controlled trial	No serious limitation	No important inconsistency	Direct	Cluster randomized	4,154 adolescent and adults
ROTHERAM-BORRUS, ET AL	Randomized controlled trial	No serious limitation	No important inconsistency	No effect of intervention	Cluster randomized 2 sites only	142 adolescent males
HERSHOW, ET AL.	Observational	No control group	No important inconsistency	Direct without comparison	None	1,953 adolescent females
SHANAUBE, ET AL.	Randomized clinical trial	Single arm reported	No important inconsistency	Direct without comparison	None	11,175 adolescents
PETTIFOR, ET AL.	Randomized controlled trial	No serious limitation	No important inconsistency	Direct	Decreased effect over time	287 young women
ADHERENCE						
BHANA, ET AL.	Randomized controlled trial	No serious limitation	No important inconsistency	Indirect measure of adherence	Self-reported adherence	65 adolescents
CLUVER, ET AL.	Observational	No serious limitation	No important inconsistency	Indirect measure of adherence	Self-reported adherence	1,059 adolescents
RETENTION IN CARE						
FATTI, ET AL.	Observational	No serious limitations	No important inconsistency	Direct	None	6,706 adolescents
ZANONI, ET AL.	Observational	No serious limitation	No important inconsistency	Direct	Large effect size Propensity score matching	254 adolescents

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Supplement 4: Interventions to improve the continuum of care for adolescents and young adults living with HIV in South Africa

Authors	Title	Publication and Date	Location	Number of Subjects	Ages (Target Population)	Study Type	Intervention Description	Overall Results	Median Overall Score Round 1
Adolescent HIV Testing									
Doherty, et al.	Effect of Home-Based HIV Counseling and Testing Intervention in Rural South Africa: Cluster Randomised Trial	*BMJ* 2013	uMzimkhulu subdistrict, KwaZulu-Natal, South Africa	4154 Adolescents and Adults	14-17, 18+ Adult Guardians	Cluster Randomized Controlled Trial; Door-to-Door Testing	Door-to-door home-based HIV testing (HBT) performed by lay counselors compared to standard of care HIV counseling and testing at local clinics.	Testing completed in 69% of HBT compared to 47% in control (PR 1.54 95% CI 1.32 to 1.81)	72.5
Rotheram-Borus, et al.	Feasibility of Using Soccer and Job Training to Prevent Drug Abuse and HIV	*AIDS and Behavior* 2016	South Africa	142 Adolescents	18-25 Unemployed Males	Community Randomized Controlled Trial	Randomized neighborhoods to immediate intervention or delayed control; Intervention: Grassroot Soccer program with trained coaches, random rapid diagnostic tests for alcohol/drugs, and vocational training.	29% testing in immediate vs. 24% in delayed (no significant difference)	50
Hershow, et al.	Using Soccer to Build Confidence and Increase HCT Uptake Among Adolescent Girls	*Sport in Society* 2015	South Africa	1953 Adolescents	12-16 (Females Only)	Pre-Post Evaluation	Survey before and after participation in SKILLZ Street intervention developed by Grassroot Soccer (GRS). SKILLZ Street female coaches delivered an afterschool education program consisting of 10, two hour bi-weekly sessions.	69% tested for HIV No control group.	63
Shanaube, et al.	Community Intervention Improves Knowledge of HIV Status of Adolescents in Zambia: Findings from HPTN 071-PopART for Youth Study	*AIDS* 2017	Results from Zambia only; Intervention also conducted in South Africa	11 175 Adolescents	15-19	Community-Randomized Clinical Trial	**HPTN 071 (PopART)** Door-to-door HIV prevention package delivered by community health workers. Intervention included in-home HIV Counseling and Testing (HCT), support for linkage to care for individuals identified living with HIV, ART adherence support, referrals for voluntary medical male circumcision	HCT uptake 80% (8,707/10,809) and awareness of an HIV-positive status tripled from 75 to 210. Home visits from providers saw the percentage of ALWH aware of their HIV status rise from 27.6% to 88.5%. No comparison with standard care.	76

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Pettifor, et al	HIVself-testing among young women in rural South Africa: A randomized reported controlled trial comparing clinic-based HIVtesting to the choice of ei-therclinict esting or HIVself-testing with second-ary distribution to peers andart-ners	*EClinical Medicine* 2020	Mpumlanga, SouthAfrica	287 women	18 - 26	Randomized Cotrolled Trial	Standard of care HIV counseling and testing (HCT) at government clinics vs. choice of clinic based HCT or HIV self-testing kits. +referrals for peers to receive clinic based HCT or HIV self-testing kits	146 randomized to HCT and 141 to choice. In the choice arm 95% (n=135) chose HIV self testing kits. After 3 months a significantly higher percent (92%) of participants in the choice arm reported HIV testing compared to (43%) the HCT arm with a difference of 43% (95% CI 40% - 58%). By 9 months the difference decreased to 25% (95% CI 17% - 33%). Participants in the choice arm were more likely to invite peers or partners to test (94% vs. 76%)	70
Adherence									
Bhana, et al.	The VUKA Family Pro-gram: Piloting a Family-Based Psychosocial Intervention to Promote Health and Mental Health Among HIV Infected Early Adolescents in South Africa	*AIDS Care* Jan 2014	KwaZulu-Natal, South Africa	65 Adolescents and Their Fam-ily Members	10-13	Randomized Controlled Trial	**VUKA Family Program** Inspired by CHAMP, the interven-tion consisted of 3 months and ten sessions involving a culturally-tai-lored cartoon storyline and curricu-lum. The curriculum follows the story and provdes step-by-step guid-ance for problem solving and facili-tating discussions. ALWH were as-sessed for feelings of stigma, knowledge of ART, adherence de-pression and caregiver support.	ART adherence: Intervention (I) 1.10, Control (C) -. 43 at baseline; Follow-up, $p < .05$. Caregiver/child communication: (I) .41, (C) -.07, $p < .09$. Youth knowledge of HIV treatment: (I) .27; (C) -.74, $p < .08$.	68.5
Cluver, et al.	Achieving Eq-uity in HIV-Treatment Out-comes: Can So-cial Protection Improve Ado-lescent ART-Adherence in South Africa?	*AIDS Care* 2016	Eastern Cape, South Africa	1059 Adoles-cents	10-19	Observational Cohort	Evaluated the provision of social protections on adherence. Social provisions included government cash transfers, food security, school fees/materials, school feeding, and clothing; HIV support group, sports groups, choir/art groups, positive parenting and parental supervi-sion/monitoring.	Three social protection provisions were associated with reduced non-adher-ence: Food provision (aOR .57, CI .42–.76, p < .001); HIV support group attendance (aOR .60, CI .40–.91, p < .02); High paren-tal/caregiver supervision (aOR .56, CI .43–.73, p < .001).	75
Retention in Care									

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| Fatti, et al. | The Effectiveness and Cost-Effectiveness of Community-Based Support for Adolescents Receiving Antiretroviral Treatment: An Operational Research Study in South Africa | *Journal of the International AIDS Society* 2018 | KwaZulu-Natal/Western Cape/Eastern Cape/Mpumalanga, South Africa | 6706 Adolescents | 10-24 | Retrospective Cohort Study | Community based support (CBS) included home-based ART-related education, psychosocial support, symptom screening for opportunistic infections and support to access government grants. CBS was compared to standard of care. | Cumulative LTFU was 40% lower amongst participants receiving CBS (29.9%) compared to participants without CBS (38.9%), aHR = 0.60 (95% CI: 0.51 to 0.71); p < 0.0001).

 Viral failure: at 3 years – no difference; at five years 18.8% CBS participants versus 37.2% non-CBS participants had viral failure, adjusted odds ratio = 0.24 (95% CI: 0.06 to 1.03). | 80 |
| Zanoni, et al. | Higher Retention and Viral Suppression with Adolescent-Focused HIV Clinic in South Africa | *PLoS One* 2017 | KwaZulu-Natal, South Africa | 254 HIV+ Adolescents | 13-24 | Retrospective Cohort Analysis | Weekend adolescent-focused clinic with peer support, group activities, counseling, and meals compared to standard of care. | Retention: 95% in adolescent-friendly clinic vs. 85% in standard clinic (OR 3.5; 95% CI 1.2 – 11.1; p=0.018).

 Viral Suppression: 91% adolescent-friendly clinic vs. 80% in standard clinic. (OR 2.5; 95% CI 1.1 – 5.8; p=0.028 | 88 |