


# BMJ Open 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.

## INTRODUCTION

South Africa has the highest burden of adolescents and young adults living with HIV (ALWH) in the world.<sup>1</sup> 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.<sup>2–5</sup> These children are now ageing into adolescence and young adulthood. In

## Strengths and limitations of this study

- The Adolescent HIV Implementation Science Alliance–South Africa (AHI(SA)<sup>2</sup>) 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)<sup>2</sup> members who were invited to participate completed the survey.

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).<sup>1</sup> 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.<sup>6</sup>

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.<sup>7</sup> 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.<sup>1 8 9</sup> 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.<sup>2</sup> 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.<sup>10–12</sup>

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).<sup>13</sup> 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](http://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.<sup>14</sup> 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<sup>15</sup> (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)<sup>2</sup>) ([www.ahisa2.org](http://www.ahisa2.org)). Members of AHI(SA)<sup>2</sup> 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.<sup>16</sup> We invited AHI(SA)<sup>2</sup> 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)<sup>2</sup> 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)<sup>2</sup> 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)<sup>2</sup> 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)<sup>2</sup> members to nominate additional studies for inclusion. The REDCap questionnaire was updated and emailed to AHI(SA)<sup>2</sup> 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.<sup>17 18</sup>

### 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)<sup>2</sup> leadership team. Results of this analysis were presented at regular AHI(SA)<sup>2</sup> (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)<sup>2</sup> 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

	First round (n=29)	Second round (n=21)
Demographics	n (%)	n (%)
<b>Profession</b>		
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%)
<b>Years working in adolescent HIV</b>		
>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%)
<b>Highest Educational Degree</b>		
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%)	–
<b>Primary residence</b>		
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<sup>19–22</sup> and one was a pre–post evaluation.<sup>23</sup> Three of these studies met criteria for inclusion in both rounds of the modified Delphi analysis.<sup>19 20 22</sup> 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 care	Costing	Feasibility		Efficacy		Scalability		Overall median impact score
					mean score	score	mean score	score	mean score	score	
Zanoni, et al <sup>11</sup>	Higher Retention and Viral Suppression with Adolescent-Focused HIV Clinic in South Africa	<i>PLoS One</i> 2017	Retention	\$1.25 per adolescent per clinic visit	3.34	3.28	3.17	3.00	3.11	3.17	80
Fatti, et al <sup>27</sup>	The Effectiveness and Cost-Effectiveness of Community-Based Support for Adolescents Receiving Antiretroviral Treatment: An Operational Research Study in South Africa	<i>Journal of the International AIDS Society</i> 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	3.00	3.11	3.11	76
Shanaube, et al <sup>22</sup>	Community Intervention Improves Knowledge of HIV Status of Adolescents in Zambia: Findings from HPTN 071-PopART for Youth Study	<i>AIDS</i> 2017	HIV Diagnosis	Not evaluated	3.39	3.11	3.00	3.39	3.00	3.00	75
Pettifor, et al <sup>20</sup>	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	<i>EClinical Medicine</i> 2020	HIV Diagnosis	Not evaluated	3.06	2.76	3.00	3.06	3.00	3.00	72
Cluver, et al <sup>25</sup>	Achieving Equity in HIV-Treatment Outcomes: Can Social Protection Improve Adolescent ART-Adherence in South Africa?	<i>AIDS Care</i> 2016	ART Adherence	Not evaluated	3.00	2.94	2.67	3.00	2.67	2.67	68
Doherty, et al <sup>19</sup>	Effect of Home-Based HIV Counselling and Testing Intervention in Rural South Africa: Cluster Randomised Trial	<i>BMJ</i> 2013	HIV Diagnosis	Not evaluated	3.17	3.06	2.94	3.17	2.94	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.<sup>22</sup> 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.<sup>19</sup> 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.<sup>20</sup> 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. Hershov *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.<sup>23</sup> 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.<sup>21</sup> 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.<sup>24,25</sup> 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.<sup>25</sup> 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.<sup>24</sup> 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.<sup>26</sup> 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.<sup>27</sup> 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<sup>20</sup> and HIV self-testing<sup>22</sup> 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.<sup>25</sup> Two interventions improved retention in care: one focused on adolescent-friendly services by providing an afterschool hours clinic with peer support, counselling and meals,<sup>26</sup> and the other by providing in-home support for HIV education, psychosocial support and assistance with applications to governmental grants.<sup>27</sup> 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.<sup>16</sup> 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.<sup>28 29</sup> Direct interventions addressing adherence among adolescents living with HIV often require considerable effort and resources and have variable efficacy.<sup>30 31</sup> Indirect measures that improve food and economic security, psychosocial support and supervision appear to improve adherence among adolescents.<sup>25</sup> 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.<sup>32</sup>

Afterschool hours clinics, peer support and improved connection to clinical staff have been shown to improve retention in care among adolescents living with HIV.<sup>33</sup> 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.<sup>34</sup> 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 policy-makers 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.<sup>35</sup> Using participant-centred design and direct input from adolescents early in intervention development can likely increase acceptability and improve likelihood of intervention success.<sup>36</sup>

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)<sup>2</sup> network includes highly experienced experts with key knowledge to evaluate interventions in South Africa. In addition, not all AHI(SA)<sup>2</sup> 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)<sup>2</sup> 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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