

# Shifting paradigms: holistic and empowering approaches for adolescent HIV

**Guest Editors:** Moherndran Archary, Audrey E Pettifor, Elona Toska

**Supplement Editor:** Marlène Bras



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## EDITORIAL

# Adolescents and young people at the centre: global perspectives and approaches to transform HIV testing, treatment and care

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In this special issue of the *Journal of the International AIDS Society*, we focus on research and perspectives that put adolescents and young people at the centre of their HIV prevention and care. Globally over two million adolescents are living with HIV, while many more are at risk of HIV infection [1-3]. In contrast to reductions globally and in highest burden regions in the general population, estimates suggest that HIV incidence and mortality persist among adolescents and young people. Young people continue to be less likely to test for HIV, to link to care in a timely way and to stay engaged in care if they test HIV positive compared to adults [4-7]. Although, these disparities in access to HIV prevention and care have been documented over the last decade, the evidence base of models, programmes and tools to address the challenges young people face is limited [8-11]. This special issue documents a series of promising and effective approaches that support adolescents and young people, not only to access and use HIV prevention and care, but also to live whole and fulfilling lives. The articles in this issue bring together evidence and lessons learned from a number of global settings, unified by one clear message: young people need and want to be at the centre of their HIV prevention and care programmes.

Changes in HIV-related policies and guidelines can have a positive impact in HIV-related outcomes among adolescents and young people. The move to universal test and treat in 2016 for people living with HIV has had dramatic impacts on the number of people living with HIV who have started antiretroviral therapy (ART) and overall better treatment outcomes in many settings [18]. This is no different for adolescents. Analyses of national data from Thailand by Teeraananchai et al. investigate the impact of shifting from ART initiation based on CD4 values to immediate ART initiation upon HIV-positive test results [18]. Their analyses of data from over 51,000 15- to 24-year-old young people show that universal test-and-treat can improve linkages to care and reduce mortality among young people, compared to CD4-driven ART initiation.

Young people and adolescents have long demanded to be centrally involved in developing and implementing HIV research agendas, programmes and policies [12]. Adolescents and young people have different prevention and care needs based on their personal experiences, priorities and aspirations, developmental stages and the context they live in. The approaches in the HIV response need to acknowledge those differences and adapt accordingly [10]. In this issue, Rufurwadzo et al. – young people working with youth-led organizations and networks at the regional or global level – write about the importance of including adolescents and young people [13]. They give concrete examples of how young people are involved in the HIV response as advocates, educators, researchers and delivering services both within health facilities and through outreach activities. These examples are a start, but need to become the norm in our research and programming for adolescents.

One area in HIV prevention and care that acknowledges adolescents and young people's voices and needs is their inclusion in the provision of peer support. Mark et al. define peer support for adolescents living with HIV as “a part of adolescent friendly health services as a class of implementation strategies that can support adolescents to access, engage and sustain treatment” [14]. Bernays et al. present data from the Zvandiri peer support programme in Zimbabwe focusing on the experiences of peer supporters themselves. Their findings on research with a cohort of Community Action Treatment Supporters (CATS) highlight several key considerations that need to be addressed as peer support is ramped up as the preferred model for care and support for adolescents living with HIV, especially in high HIV-burden low-resource settings [15]. CATS encountered challenges such as the risk of occupational deductive disclosure and managing the emotional labour of providing care as a peer supporter, but these challenges were eased by the support of other peers and adult mentors. In another example from Thailand, Songtaweet et al. present

data from a randomized controlled trial (RCT) showing that young men who have sex with men and young transgender women in Thailand who were provided with youth-friendly pre-exposure prophylaxis (PrEP) services had good retention in care at six months (75%). The addition of an app to support adherence did not add to PrEP adherence compared to youth friendly services, underscoring the importance of youth-friendly service provision [16]. While the App was found to be acceptable to the young people, this small scale RCT may have been underpowered to detect improved outcomes when added to youth-friendly services. More work is needed on this topic given the often dynamic and unpredictable nature of adolescent sexuality and partnerships.

While adolescent-friendly and differentiated service provision is important to improve prevention and care outcomes for adolescents, it is essential to ensure that biomedical solutions which are accessible and available to adolescents and young people are developed and distributed. Amstutz et al. present findings from Lesotho demonstrating how HIV self-testing allows adolescents more flexibility in how, where and when they test for HIV thus improving the uptake of testing coverage, knowledge of HIV status and linkages to care [17]. HIV self-testing and mHealth solutions (apps or online platforms) could be critical to maintain our progress towards the global 95-95-95 targets among adolescents and young people, particularly in the context of the COVID-19 pandemic and its consequences on an overburdened health system. However, the evidence on both is emerging and additional research is needed to understand when such solutions work, but also when they do not work, so that adjusted and tailored versions can be tested and scaled up.

While specific interventions may be critical to the survival of adolescents and young people, their lives, needs and aspirations must be acknowledged holistically and comprehensively. As millions of adolescents and young people remain at risk of HIV infection or are living with HIV, testing, treatment and care services must be provided with a human-centred and life course approach. Two papers in this issue provide evidence on the complex needs that adolescent HIV programming must take into account. Bernays et al. discuss the complexities of transitioning to second-line treatment for adolescents and young people living with HIV and the need for a multi-faceted supported process [19]. Although immediate adherence improvements were reported, these could only be sustained through the development of “*adherence competencies*” in the context of a gradual transition processes supported by both caregivers and clinicians.

Programmes need to continue to aim to provide comprehensive care for the whole young person when they do engage with them for HIV prevention or care. This is particularly relevant in the context of COVID-19 pandemic when non-critical engagements with the healthcare system must be limited. Now more than ever it is clear that we need programmes and services that are adaptive to the needs of young people and that meet them where they are with what they need. Toska et al. present data from a survey among young women in South Africa – including adolescent mothers – highlighting the continued importance of young women’s sexual and reproductive health in addition to HIV prevention and care [20]. Even though nearly 95% of the pregnancies during adolescence among study participants were unintended, the use of hormonal contraception and condoms – dual protection

– was very low among young women, independent of their HIV status or whether they had already had a child. While these findings are similar to those of studies among adults, it is discouraging that – despite the dialogue on dual protection in the past two decades – there has not been considerable progress in this area. In another example in this issue, Chimbindi et al. report from experiences of scaling up and delivering a layered package of interventions for adolescent girls and young women: the DREAMS initiative, a partnership funded by the United States’ President’s Emergency Program for AIDS Relief, in a rural remote region of South Africa [21]. They report, much like Bernays and colleagues, that while many excellent programmes and practices exist for adolescent service delivery, there is limited documentation of what works, especially at scale. Additionally, experiences of scaling up a multi-component package like DREAMS highlights the tensions between local adaptation, adolescent engagement and ownership and maintaining fidelity to the original programmes. Despite the challenges, we must continue to learn how to best deliver combination and multi-dimensional programmes for youth.

This supplement was being prepared during the COVID-19 pandemic, though its content does not include data specific to COVID-19. Public health measure like physical distancing and limiting non-essential interactions with the healthcare system are raising challenges for access to services deemed non-essential in many settings, such as HIV testing, PrEP and contraception, as well as for essential services such as access to ART. However, the pandemic also may provide an opportunity to respond to these challenges with some of the adolescent-friendly and innovative interventions highlighted in this issue, such as the use of mobile health technology to augment adolescent- and youth-friendly services [16], HIV self-testing kits [17] and differentiated services [15,21]. The call by Rojo et al. for the development of long-acting antiretroviral drugs for adolescents can not only potentially improve acceptability and adherence but also limit the frequency of healthcare interactions [22].

## AVENUES FOR FUTURE RESEARCH

In addition to the work presented in this issue, two commentaries highlight several areas for future research and implementation [23,24], while another calls for stronger implementation science [25]. Laurenzi et al. call for more research evaluating the effects of interventions designed to improve the mental health of adolescents living with HIV (ALHIV) [23]. They highlight four priorities, including to generate more evidence about preventive mental health interventions for ALHIV, to include mental health outcomes in research on psychosocial interventions for ALHIV, to conduct intervention research that is sensitive to differences amongst ALHIV population, while ensuring that adolescents are involved in intervention design and testing. Stangl et al. focus on the needs of young women in the context of implementing partner notification in the context of HIV case indexing [24]. While partner notification is being implemented in some settings, additional research is needed not only to identify effective models but also to ensure potential social harms are identified and mitigated. Both commentaries call for implementation science to assess availability, accessibility, acceptability

and quality of programming for adolescent HIV interventions. Vorkoper and colleagues introduce the Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA) as a platform for promoting implementation science lessons learned and building capacity to design and conduct implementation science as it relates to adolescent HIV prevention and care in the African region [25]. Such research is critical to understand how evidence-based programmes can be implemented at scale rigorously, effectively and cost effectively.

For years, adolescent HIV prevention and care practitioners, advocates and researchers have been calling for the urgent need for more evidence-based interventions to reduce new HIV infections and improve HIV care outcomes for adolescents and young people. Often the disconnect between the research, programme and policy worlds results in proven interventions for adolescents not being implemented, or programmes not being evaluated to identify barriers to scale up. The content of this special issue provides emerging evidence about what works for young populations in different contexts with regard to improving testing, PrEP use and linkage to and adherence to treatment. As highlighted in the youth viewpoint by Rufurwadzo et al., there is a need for healthcare policy-makers and implementors to not be overly paternalistic, but to support and trust them to make good decisions through meaningful engagement [13]. Importantly, this supplement's content highlights that young people are often the best advocates and custodians of their care if they have the tools and the support they need to make safer and healthier choices. As adolescent HIV prevention and care specialists, providers and researchers, we support this positive trajectory and look forward to additional collaborations among policymakers, implementers and donor agencies to strengthen the evidence base and scale up programmes for adolescents and youth.

## COMPETING INTERESTS

The authors have no competing interests.

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## AUTHORS' CONTRIBUTIONS

MA, AEP and ET co-conceptualized this editorial and co-wrote it with feedback from the Journal of International AIDS Society editorial team. All authors have read and approved this.

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RESEARCH ARTICLE

# Rapid antiretroviral initiation among Thai youth living with HIV in the National AIDS programme in the era of treatment at any CD4 cell count: a national registry database study

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## Abstract

**Introduction:** The process indicators of ending the HIV epidemic include 90% of people living with HIV receiving antiretroviral therapy (ART). The population of youth, however, has less access to healthcare. We assessed ART initiation and attrition outcomes of the HIV continuum from HIV diagnosis to ART initiation in youth living with HIV (YLHIV) and factors associated with ART initiation.

**Methods:** We studied YLHIV aged 15 to 24 years who were registered on the National AIDS Program (NAP) from January 2008 to May 2019. The study period was divided into 2008 to 2013 (initiated ART by CD4-guided criteria) and 2014 to 2018 (initiate ART at any CD4). Date of registration was used as a surrogate for the diagnosis date and defined as the baseline. The database included ART prescription and laboratory results, and the vital status was linked daily with the National Death Registry. Competing risk methods were used to assess factors associated with accessing ART, with loss to follow-up (LTFU) and death considered as competing events. Logistic regression was used to assess factors associated with rapid ART initiation, defined as initiation  $\leq 1$  month after registration.

**Results:** Overall, 51,607 youth registered on the NAP (42% between 2008 and 2013). Median age was 21 (IQR 20 to 23) years; 64% were male. Overall ART initiation was 80% in the first period and 83% in the second. The ART initiation rate was higher among YLHIV aged 15 to 19 years (86%) than 20 to 24 years (82%) ( $p < 0.001$ ) in the second period. The proportion of youth starting rapid ART increased significantly from 27% to 52% between the two periods ( $p < 0.001$ ). Factors associated with ART initiation were age 15 to 19 years (aSHR 1.09, 95% CI 1.06 to 1.11), female (aSHR 1.26, 95% CI 1.23 to 1.29) and registration year 2014 to 2018 (aSHR 1.73, 95% CI 1.69 to 1.76). The cumulative incidence of LTFU/death prior to ART initiation at 12 months was 3.8% (95% CI 3.6% to 4.1%) in the first period and 1.9% (95% CI 1.8% to 2.1%) in the second period.

**Conclusions:** In the era of universal treatment of all at any CD4 level, 83% of YLHIV registered on the Thai National AIDS Program initiated ART. The majority initiated within one month of registration.

**Keywords:** youth living with HIV; antiretroviral therapy; universal coverage health programme; rapid ART; HIV cascade; loss to follow-up

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## 1 | INTRODUCTION

Treating 90% of people who know they are living with HIV by 2030, the second step in the HIV care cascade, is an important UNAIDS 90:90:90 target [1]. Studies indicate that loss to follow up (LTFU) is high before people start antiretroviral therapy (ART) and more likely in these pre-ART patients with high CD4 counts and less advanced clinical stage [2–4], due to waiting times for ART eligibility [5]. Youth living with HIV (YLHIV) have traditionally had poor outcomes, with high LTFU and death rates before ART initiation, and even lower proportions achieve the final endpoint of viral suppression in the cascade of care [6–8]. Evidence from Africa and Thailand

suggests that the rate of LTFU before ART initiation in young people (age 15 to 24 years) is higher than the rates observed in adults (age  $\geq 25$  years) and early adolescents (age  $< 15$  years) [3,9,10].

In Thailand, people living with HIV have been offered free HIV care and treatment through the universal coverage National AIDS Program (NAP) from the end of 2007 [11]. Since then, there have been successive updates in the CD4 thresholds set for starting ART (CD4  $< 200$  cell/mm<sup>3</sup> from 2008 to 2010, CD4  $< 350$  cells/mm<sup>3</sup> from 2011 to 2013, and any CD4 level since 2014) [12]. The updated HIV treatment guidelines have led to overall increases in the number of patients accessing ART: in 2017, 87% of all people living with



HIV registered on the NAP accessed ART and 69% were virally suppressed [13].

However, although the largest group of new HIV diagnoses is in young people who acquired HIV sexually, particularly young men who have sex with men [14–16], no outcome data along the care cascade are available for this group.

We sought to assess and compare outcomes for YLHIV treated through the Thai NAP at the second step of the care cascade, for 2008 to 2013 and for 2014 to 2018 when guidelines changed to ART initiation recommended at any CD4 count. Our primary aim was to assess changes in ART initiation and attrition cumulative incidence after HIV diagnosis in YLHIV. Our secondary aims were to assess factors associated with ART initiation and ART initiation within 30 days of registration on the NAP.

## 2 | METHODS

### 2.1 | Study cohort from national registry database

Briefly, health insurance programmes in Thailand consist of the Social Security Scheme for people working in the private sector, the Civil Servant Medical Benefit Schemes for people working in the public sector and the Universal Coverage Scheme for those not covered by either of the other two schemes. For HIV management, all these insurance systems were integrated as the NAP and have been administered by the National Health Security Office (NHSO) since 2007.

The NAP database was established in 2007 as a registration and reimbursement portal for HIV programmes. Hospitals and clinical sites enter laboratory results, clinical information and ART dispensing records into the database system at registration (HIV diagnosis) and all subsequent visits. CD4 tests are provided every six months and HIV-RNA is measured six months after starting ART and annually thereafter. ART is provided based on national HIV treatment guidelines [11]. Since site cost reimbursement is contingent on data being entered for services provided, the data are highly accurate. In addition, the database is linked with the national death registry, so patient vital status is updated daily.

More than 95% of YLHIV are covered by the Universal Coverage Scheme. An effective prevention of mother-to-child transmission (PMTCT) programme has seen vertical transmission decline to <1% of live births [17], but young people who acquired HIV sexually now account for the biggest number of new infections [18,19]. Accordingly, the concept of treating YLHIV has become more flexible, allowing YLHIV to start ART without parental consent, consistent with treating at any CD4 level. Moreover, YLHIV are cared for in paediatric clinics if they are younger than 18 years and then mostly transferred to an adult clinic at the age of 18 years.

This study was approved by the Institutional Review Board of the Institute for Development of Human Research Protection, Ministry of Public Health, Thailand. A waiver of consent was granted for this data analysis. The NAP database was de-identified by the NHSO before analysis.

### 2.2 | Study population

This study included YLHIV aged 15 to 24 years who registered on the NAP from January 2008 to May 2018. Follow-up

data were available until August 2019, providing at least a year of follow-up for all patients to assess outcomes, including an additional three months to account for possible delays in data entry. We excluded patients who were treated before enrolment into the NAP since no clinical information was available at the time of HIV diagnosis or ART initiation.

### 2.3 | Definitions and outcomes

Date of registration was used as a surrogate for diagnosis date and defined as the baseline.

The primary outcome was ART initiation, defined as patients starting ART after registration throughout the study period. Secondary outcomes were as follows:

- 1 Rapid ART initiation, defined as starting ART on the same day, within seven days and within one month of registration
- 2 Attrition outcomes (LTFU, mortality) from HIV diagnosis to ART initiation prior to ART initiation.

The study endpoints were ART initiation after HIV diagnosis, LTFU and death; those who did not start ART were censored at their last clinic visit. LTFU was defined as not starting ART and not attending clinic for 12 months after their previous appointment unless they subsequently returned to care before the final data transfer date. Patients who died without starting ART were classified as dead even if the patient was previously lost to follow-up. Patients who did not reach a study endpoint (starting ART, LTFU or death) were censored at the date of their most recent clinic visit. Baseline CD4 was taken as the closest result available to the date of registration within a window of six months before or after registration. Pre-ART CD4 results were defined as the closest results within a window 12 months before and up to two months after the date of ART initiation. Vital status was ascertained by linkage with death registry, which was updated daily.

### 2.4 | Statistical analysis

Baseline characteristics, including demographics, age (15 to 19 years were classified as older adolescents and 20 to 24 years as young adults [20]), year, region, history of opportunistic infection [20] and CD4 count level, were summarized using descriptive statistics by period of registration. The first period was defined as 2008 to 2013 and the second as 2014 to 2018. The outcomes along the HIV cascade from HIV diagnosis to ART initiation were reported as proportions by period of registration. The competing risk method of Fine and Gray [21] was used to calculate subdistribution hazard ratios (SHR), to assess associations between baseline characteristics and ART initiation, with LTFU and death considered as competing events.

From these analyses, the cumulative incidence of ART initiation and of LTFU/death was generated using competing risk estimators. Logistic regression was used to assess predictors of rapid ART initiation (within one month of registration). In this analysis, those starting ART within one month of registration were considered as successes and those who did not start within one month for any reason, including LTFU or death, were considered as failures. Covariates assessed in both logistic and competing risks models included baseline

age, gender, country region, year of registration and history of opportunistic infections.

Variables with  $p < 0.10$  were included in multivariate models. Statistical significance was identified using a two-sided  $p < 0.05$ . Statistical analysis was performed with SAS version 9.4 (SAS Institute Inc, Cary, NC, USA) and with Stata version 14 (Statacorp, College Station, TX, UAS).

## 3 | RESULTS

A total of 52,397 youth registered on the NAP from 2008 to 2018; 790 youth (2%) were excluded because they initiated ART in other facilities, such as private clinics and research programmes. Therefore 51,607 newly diagnosed patients were analysed, of whom 21,825 (42%) registered from 2008 to 2013 and 29,782 (58%) from 2014 to 2018.

### 3.1 | Patient characteristics

Baseline characteristics by period of registration are shown in Table 1. The median age was 21 (interquartile range [IQR] 20 to 23) years. Most patients (75%) enrolled at age 20 to 24 years versus age 15 to 19 years. The proportion of males increased from 50% to 74% from the first to the second period. A quarter of the YLHIV were from the northeast and the next highest proportions were from the northern and Bangkok regions. Fifty-one percent of YLHIV had CD4 counts available at registration and the median CD4 was 333 (IQR 171 to 491) cells/mm<sup>3</sup>. Only 48% of YLHIV who registered had pre-ART CD4 available: the median pre-ART CD4 count was 255 (IQR 81 to 395) cells/mm<sup>3</sup> in the first period and 318 (IQR 163 to 468) cells/mm<sup>3</sup> in the second period.

### 3.2 | Study outcomes

The percentage of YLHIV achieving outcomes along the HIV cascade from HIV diagnosis to ART initiation, by study period, is shown in Figure 1. The percentage initiating ART throughout the study increased from 80% to 83% from 2008-2013 to 2014-2018 ( $p < 0.001$ ). We found statistically significant improvements in the percentage of youth initiating ART on the same day, within seven days and within one month of registration in the first versus the second period. The percentage of deaths before ART initiation in the first period decreased from 4% to 2% in the second period ( $p < 0.001$ ). In the recent period where guidelines advocated starting ART at any CD4 count, the percentage of patients who were lost to follow-up prior to ART initiation reduced from 17% to 11% ( $p < 0.001$ ).

Moreover, the overall median duration from registration to ART initiation was 1.47 (IQR 0.37 to 12.18) months, with a total of 42,914 person-years. The median time from registration to ART initiation in 2008 to 2013 was six (IQR 0.8 to 25) months, significantly longer than in the second period [one (IQR 0.2 to 4) month,  $p < 0.001$ ]. The crude mortality rate was 3.52 (95% CI 3.35 to 3.70) per 100 person-years. The crude LTFU rate was 16.11 (95% CI 15.74 to 6.50) per 100 person-years.

The cumulative incidence of initiating ART for those who registered from 2008 to 2013 at one, three, six and 12 months was 26.9% (95% CI 26.3% to 27.5%), 40.6% (95%

CI 40.0% to 41.3%), 46.5% (95% CI 45.9% to 47.2%) and 51.4% (95% CI 50.8% to 52.1%) respectively. Among those who registered from 2014 to 2018, the cumulative incidence of ART initiation at one, three, six and 12 months was 51.5% (95% CI 51.0% to 52.1%), 68.8% (95% CI 68.3% to 69.4%), 73.8% (95% CI 73.3% to 74.3%) and 78.0% (95% CI 77.5% to 78.4%) respectively. The cumulative incidence of LTFU/death prior to ART initiation at 12 months was 3.8% (95% CI 3.6% to 4.1%) in the first period and 1.9% (95% CI 1.8% to 2.1%) in the second period (Figure 2).

### 3.3 | Factors associated with antiretroviral treatment initiation

We assessed factors associated with ART initiation after NAP registration. All covariates from univariate analysis were included in the multivariate analysis (Table 2). Patients aged 15 to 19 years who registered had a 9% higher chance of initiating ART compared with those aged 20 to 24 years who enrolled (aSHR 1.09, 95% CI 1.06 to 1.11). Females (aSHR 1.26, 95% CI 1.23 to 1.29) were more likely to initiate ART than males. Young people with no history of opportunistic infection were less likely to access ART (aSHR 0.95, 95% CI 0.91 to 0.98). In addition, youth who registered from 2014 had a higher chance (aSHR 1.73, 95% CI 1.69 to 1.76) of initiating ART versus those who registered before 2014. Patients living in the southern, eastern and western regions of Thailand had a lower chance of starting ART than those who lived in Bangkok Metropolitan area.

### 3.4 | Factors associated with rapid antiretroviral treatment initiation

In logistic regression analyses assessing starting ART within one month of registration (Table 3), all covariates tested in univariate models were included in the multivariate analysis. Patients aged 15 to 19 years who registered (aOR 1.14, 95% CI 1.10 to 1.19) were more likely to start ART within one month than those aged 20 to 24 years who enrolled. Females had 61% (aOR 1.61, 95% CI 1.54 to 1.68) higher odds of rapidly starting ART than males. Patients with no history of opportunistic infection were more likely to start ART within one month than those with history. The odds of starting ART rapidly increased threefold (aOR 3.20, 95% CI 3.07 to 3.33) in patients who registered in the period 2014 to 2018 versus those registered in 2008 to 2013. Patients living in the Bangkok Metropolitan area had higher odds of rapidly starting ART than other country regions.

## 4 | DISCUSSION

This study using the national registry database of the Thai National AIDS Program is the first to specifically address outcomes along the care cascade from HIV diagnosis to antiretroviral therapy initiation among young people aged 15 to 24 years. It reflects real-life practice and outcomes in a low-to middle-income country setting, where universal coverage is provided, in response to changes in national treatment guidelines. Our study showed that  $\geq 80\%$  of YLHIV initiated ART in both periods. The proportion initiating ART within one month

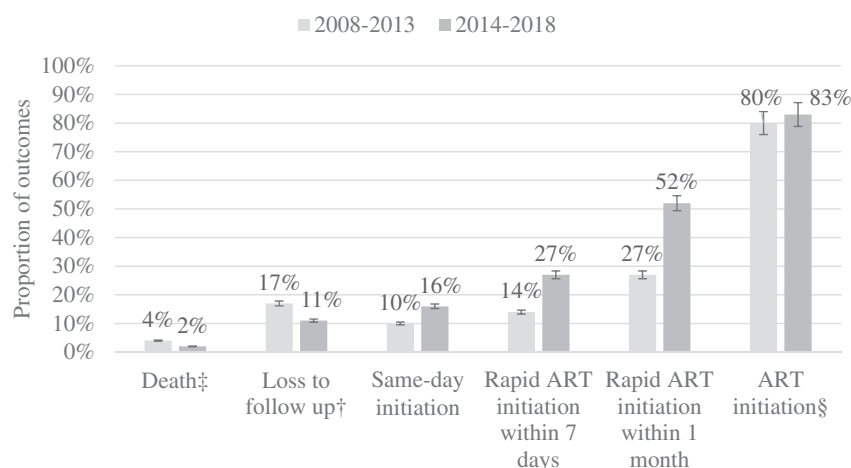


**Table 1. Baseline characteristics of youth living with HIV aged 15 to 24 years registered on the Thai National AIDS Program in 2008 to 2018**

Baseline characteristics <sup>a</sup>	2008 to 2013	2014 to 2018	Total	p <sup>b</sup>
N	21,825	29,782	51,607	
Median age at registration, years	22 (19 to 23)	21 (20 to 23)	21 (20 to 23)	<0.001
Age group				
15 to 19 years	5546 (25)	7333 (25)	12,879 (25)	<0.001
20 to 24 years	16,279 (75)	22,449 (75)	38,728 (75)	
Male	11,013 (50)	22,075 (74)	33,088 (64)	<0.001
History of opportunistic infection				
Yes	2105 (10)	1588 (5)	3693 (7)	<0.001
No	19,720 (90)	28,194 (95)	47,914 (93)	
CD4 available at registration	4682 (21)	21,612 (73)	26,294 (51)	
Median (IQR) CD4 at registration, cells/mm <sup>3</sup>	331 (156 to 492)	333 (175 to 491)	333 (171 to 491)	0.22
Pre-ART CD4 available	6626 (30)	17,900 (60)	24,526 (48)	
Median pre-ART CD4 count (cells/mm <sup>3</sup> )	255 (81 to 395)	318 (163 to 468)	300 (137 to 451)	<0.001
Geographical regions				
Bangkok metropolitan	2987 (14)	5609 (19)	8596 (17)	<0.001
Northeast	6015 (28)	7651 (26)	13,666 (26)	
North	3853 (18)	5079 (17)	8932 (17)	
Central	3397 (16)	5092 (17)	8489 (16)	
East	2225 (10)	2900 (10)	5125 (10)	
South	2440 (11)	2265 (8)	4705 (9)	
West	908 (4)	1186 (4)	2094 (4)	

ART, antiretroviral therapy.

<sup>a</sup>Presented as n (%) for categorical data and median (interquartile range) for continuous data; <sup>b</sup>The comparisons were performed using Pearson's Chi-square tests for categorical data, and a Wilcoxon rank sum test for continuous data.



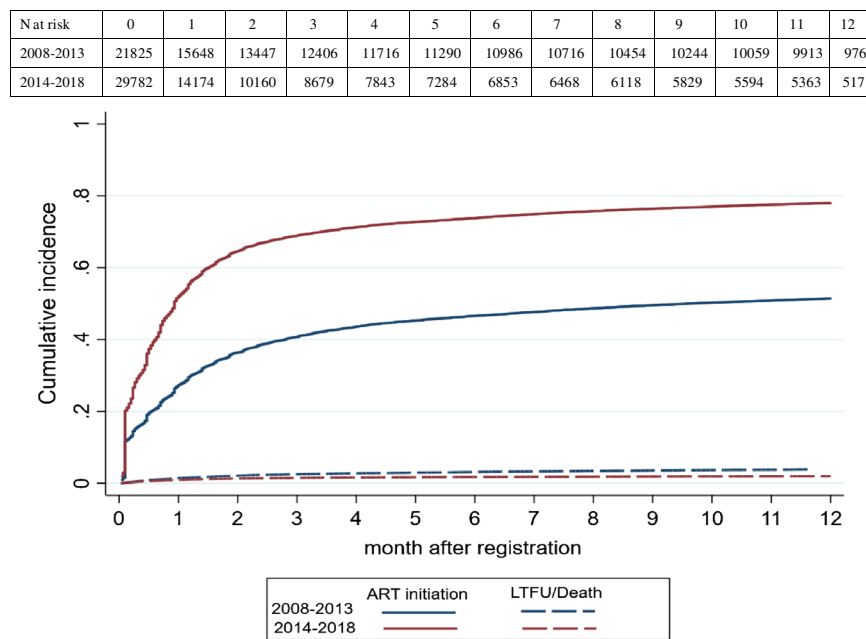
**Figure 1. Outcomes of youth living with HIV aged 15 to 24 years after registered on the Thai National AIDS Program.**

§ART initiation was defined as patients starting ART after registration throughout study period. †LTFU was defined as not starting ART and not attending clinic for 12 months after their previous appointment, unless they subsequently returned to care before the final data transfer date.

‡Patients who died without starting ART were classified as dead even if they were previously loss to follow-up. There were statistically significant differences in the percent of youth experiencing all outcomes in 2008 to 2013 compared with 2014 to 2018 ( $p < 0.001$ ). Formal comparisons were made using Pearson's Chi-square. Error bars represented 95% confidence interval. ART, antiretroviral therapy; LTFU, loss to follow up

of registration increased from 27% to 52%, and within six months of registration, it increased from 47% to 74%, coinciding with guidelines changing to starting ART at any CD4 count

[22]. This finding likely reflects the effect of the guideline change, in association with more experience in treatment sites and better infrastructure over the years.



**Figure 2. Cumulative incidence of accessing antiretroviral therapy among youth living with HIV on the Thai National AIDS Program, by period of registration.**

The cumulative incidence was calculated by competing risk models. ART, antiretroviral therapy; LTFU, loss to follow up.

Our study shows an increase in the trend of rapidly initiating ART in YLHIV during the study period. From 2014, more than 50% started ART within one month, increasing to 69% at three months and 78% at 12 months. This is higher than found by the International Epidemiology Databases to Evaluate AIDS (IeDEA) Global Cohort in young people aged 15 to 19 years (37.4% at one month, 62.2% at 12 months) [23]. Moreover, the median time from HIV diagnosis to ART initiation in our study decreased from six to one month after guidelines recommended starting ART irrespective of CD4 count levels. This finding is similar to a study from Zambia and South Africa in the period 2004 to 2015, where median time reduced after delivering an intervention to offer ART regardless of CD4 count (the HPTN 071, PopART, trial) from ten to six months [24].

The increase in cumulative incidence of ART initiation in YLHIV provides evidence of the changes in response to updates in the national HIV treatment guidelines. This finding is consistent with a meta-analysis that found the largest changes in cumulative incidence of ART initiation were in those who were ineligible under prior guidelines and in patients aged 16 to 24 years [25].

Our analysis of predictive factors for initiating ART and rapid ART showed that rates were especially high in those who were younger (15 to 19 years) and in females. This is similar to findings from an African study, where those who initiated same-day ART were younger, more likely to be female and presented with less advanced clinical disease [26,27]. With Thailand's PMTCT programme, all pregnant women are tested for HIV during pregnancy, so most female patients confirmed as HIV positive during pregnancy have prompt ART initiation; previous studies support evidence that rapid ART

initiation in pregnancy is effective in reducing mother to child transmission [3,27-29].

Furthermore, patients who lived in the Bangkok area were more likely to access ART than those in the southern, western and eastern regions. One possible explanation is that the central (including Bangkok), northeast and northern regions have the highest prevalence of HIV and were the earliest regions affected by the Thai HIV epidemic. They therefore have more experience in managing HIV patients and perhaps have more specialized HIV clinics. Previous studies from Zimbabwe and China support evidence that patients who live in urban areas can more easily access ART or treatment than those who live in rural areas [30,31].

While our findings are encouraging, they also show that further and more aggressive efforts are needed to achieve the second and third goals of the treatment cascade: 90% of people diagnosed with HIV receiving ART; and 90% of these ART-treated YLHIV virally suppressed. Integration of multiple effective approaches from policy, hospital services, healthcare centre services and community-led services are essential strategies to reach this ultimate goal.

Previous studies indicate that attrition rates are high during the period from HIV testing to ART initiation when eligibility criteria are based on CD4 thresholds, particularly in YLHIV [2-3,5,7,23,32]. Since guidelines have recommended immediately starting ART in all people living with HIV, high rates of patient attrition in the period between HIV diagnosis and ART initiation have reduced [2,33,34]. LTFU before ART initiation in our study reduced from 17% to 11% in the period of recommending treatment at any CD4 count.

Meanwhile, the IeDEA Global Cohort, which is comprised of cohorts with different infrastructures, reported that overall

**Table 2. Factors associated with accessing antiretroviral treatment from a competing risks regression model**

Characteristics (n = 51,607) <sup>a</sup>	Univariate SHR (95% CI)	p	Multivariate aSHR (95% CI)	p
Age group		<0.001		<0.001
15 to 19 years	1.10 (1.08 to 1.13)		1.09 (1.06 to 1.11)	
20 to 24 years	Reference		Reference	
Sex		<0.001		<0.001
Male	Reference		Reference	
Female	1.09 (1.06 to 1.11)		1.26 (1.23 to 1.29)	
History of opportunistic infection		0.04		0.001
Yes	Reference		Reference	
No	1.03 (1.01 to 1.07)		0.95 (0.91 to 0.98)	
Year of registration		<0.001		<0.001
2008 to 2013	Reference		Reference	
2014 to 2018	1.62 (1.59 to 1.66)		1.73 (1.69 to 1.76)	
Geographical region		<0.001		<0.001
Bangkok Metropolitan	Reference		Reference	
Northeastern	0.94 (0.91 to 0.97)		0.98 (0.94 to 1.01)	
Northern	0.93 (0.90 to 0.96)		0.97 (0.94 to 1.00)	
Central	0.95 (0.92 to 0.99)		0.97 (0.93 to 1.00)	
Southern	0.85 (0.82 to 0.88)		0.90 (0.86 to 0.93)	
Eastern	0.88 (0.85 to 0.92)		0.89 (0.86 to 0.93)	
Western	0.76 (0.72 to 0.80)		0.76 (0.72 to 0.81)	

aSHR, adjusted subdistribution hazard ratio; SHR, subdistribution hazard ratio.

<sup>a</sup>Characteristics were evaluated at baseline.

LTFU (defined as clinic absence of >6 months) before starting ART was 20.4%, but only 2.3% in the Asia-Pacific region [35]. The majority of Asian cohorts in the leDEA study were from research centres that specifically cater for YLHIV. These cohorts might therefore have a selection bias for better outcomes compared with the national registry database and with other world regions where LTFU is high due to undocumented mortality. However, similarly encouraging evidence was found by a Rwandan study where mortality and LTFU before ART initiation reduced after the change in Rwanda's national ART eligibility guidelines [36]. Offering ART immediately at diagnosis improves retention in care and mitigates LTFU in patients who are not ready to start ART [37].

There are a number of limitations to this study. First, we defined the date of registration with NAP as the surrogate for date of HIV diagnosis, which could create bias by shortening the perceived time from HIV diagnosis to ART initiation, as some patients may have been diagnosed at HIV testing centres or private clinics and re-tested at NAP registration. However, this seems unlikely because testing within the NAP is free and only 2% of NAP patients were known to be diagnosed outside the programme, indicating that our results are applicable to the vast majority of Thai youth diagnosed with HIV.

Second, the rate of initiating ART in the NAP may be lower than observed in our study since a small proportion of patients may access ART through research programmes and private clinics. We did not have detailed information about service delivery, whether hospitals had specialized HIV clinics,

or hospital size; we had information only on location of hospital. These factors might impact on ART access in young people living outside Bangkok. For this reason, we could not definitively establish whether these structural factors influenced the differences we noted between urban and rural areas. Third, we were unable to link PMTCT programme information with the NAP data, so we cannot present separate data about females who were diagnosed during pregnancy in the study period. We also did not have data on mode of infection in the database. We assume that the majority of YLHIV diagnosed with HIV aged 15 to 24 years acquired HIV through sexual transmission.

Fourth, approximately 50% of baseline CD4 counts were not available in this study. Fifth, the NHSO database does not record details about socio-economic factors, such as caregiver status, education status, occupation and income, so we were precluded from examining the effects of these factors which might also have an impact on access to ART.

Last, this is an observational study and it is possible that the outcomes in our study may be subject to unobservable biases and confounding. Regression discontinuity or interrupted time series analysis would allow exploration of temporal trends that may have already been underway in Thailand before the guidelines recommended treatment at any CD4 count.

Nevertheless, we believe that our method is also valid to assess changes related to treatment guidelines since no improvement trends were evident by calendar time prior to 2014. In addition, our model was able to assess the

**Table 3. Factors associated with rapid antiretroviral treatment initiation within one month after registration in the Thai National AIDS Program**

Characteristics <sup>a</sup> (n = 51,607)	Starting ART within one month, n (%)	Univariate <sup>b</sup> OR (95% CI)	p	Multivariate <sup>b</sup> aOR (95% CI)	p
Age group			<0.001		<0.001
15 to 19 years	5795 (27)	1.20 (1.15 to 1.25)		1.14 (1.10 to 1.19)	
20 to 24 years	15,684 (73)	Reference		Reference	
Sex			<0.001		<0.001
Male	13,330 (62)	Reference		Reference	
Female	8149 (38)	1.16 (1.12 to 1.21)		1.61 (1.54 to 1.68)	
History of opportunistic infection			<0.001		<0.001
Yes	1092 (5)	Reference		Reference	
No	20,387 (95)	1.76 (1.64 to 1.90)		1.43 (1.33 to 1.54)	
Year of registration			<0.001		<0.001
2008 to 2013	5971 (28)	Reference		Reference	
2014 to 2018	15508 (72)	2.88 (2.78 to 2.99)		3.20 (3.07 to 3.33)	
Geographical regions			<0.001		<0.001
Bangkok Metropolitan	4120 (17)	Reference		Reference	
Northeastern	5690 (26)	0.78 (0.73 to 0.82)		0.80 (0.76 to 0.85)	
Northern	3730 (17)	0.78 (0.73 to 0.83)		0.81 (0.76 to 0.86)	
Central	3555 (16)	0.78 (0.74 to 0.83)		0.76 (0.71 to 0.81)	
Eastern	2026 (10)	0.71 (0.66 to 0.76)		0.70 (0.65 to 0.75)	
Southern	1712 (9)	0.62 (0.58 to 0.67)		0.67 (0.62 to 0.72)	
Western	646 (4)	0.48 (0.44 to 0.54)		0.46 (0.42 to 0.51)	

aOR, adjusted odd ratio; OR, odd ratio.

<sup>a</sup>Characteristics were evaluated at baseline; <sup>b</sup>The analyses were performed using Logistic regression models.

cumulative incidence of ART initiation and attrition simultaneously in the same mode. Furthermore, the changes observed from our first to second study period coincided with a structural change in the National Treatment Guidelines on HIV/AIDS Treatment, affecting the entire country in a period with stable availability of antiretroviral agents, which lends support to the validity of our findings.

## 5 | CONCLUSIONS

In the period 2014 to 2018 when Thai guidelines advocated initiation of ART at any CD4 count, 83% of young people initiated ART and more than half of YLHIV initiated ART within one month of registration. This more rapid initiation also likely influenced the lower rates of mortality and LTFU prior to ART initiation seen in this period. Continued improvement in early access to ART is needed to reach the target of treating 90% of YLHIV with ART. Moreover, initiating ART rapidly can help control the HIV epidemic and optimize the health of people living with HIV.

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### COMPETING INTERESTS

KR received the Senior Research Scholarship from the Thailand Research Fund (TRF). He also received honoraria or consultation fees from Merck, Roche, Jensen-Cilag, Tibotec, Mylan and the Governmental Pharmaceutical Organization (GPO, Thailand). He has participated in a company-sponsored speaker's bureau from Abbott, Gilead, Bristol-Myers Squibb, Merck, Roche, Jensen-Cilag, GlaxoSmithKline and GPO. TP received a scholarship from the Anandamahidol Foundation and clinical research grant from ViiV. ST was funded as a CIPHER grantee from the International AIDS Society in 2018 to 2020.

### AUTHORS' CONTRIBUTIONS

ST, SK, KR and TP created the study concept and study design. ST, SK, PK and KR were responsible for data collection or oversaw programme implementation. ST conducted the analysis. SK, KR and TP advised on the analysis. ST, SK, PK, KR and TP interpreted the data. ST drafted the manuscript. All authors critically reviewed the manuscript and approved the manuscript for submission.

### ABBREVIATIONS

NAP, National AIDS Program; LTFU, loss to follow up; ART, antiretroviral therapy; aSHR, adjusted subdistribution hazard ratio; aOR, adjusted odds ratio; leDEA, the International Epidemiology Databases to Evaluate AIDS; IQR, interquartile range; PYFU, patient-years of follow-up; 95% CI, 95% confidence interval; PMTCT, prevention of mother-to-child transmission.

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## DISCLAIMER

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## VIEWPOINT

# Young people are experts and leaders in the HIV response

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**Keywords:** adolescents; young people; HIV; sexual and reproductive health and rights; peer support; advocacy; leadership

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It is 2020 and there are many examples of how young people are contributing to HIV prevention, treatment, support and care efforts globally. We do this as advocates, researchers, educators and service providers, among other roles.

This has not just happened overnight. We have had to push for meaningful leadership of young people in initiatives that affect our lives. In some contexts, we are still perceived as children who should stay quiet while adults and other experts say and do things for us. However, young people are increasingly taken seriously, as experts of our own lives, with clear ideas of what we are experiencing and need, as well as innovative ideas that respond to those needs.

Different factors have facilitated and supported our leadership, including organizations that believe in us and show it by funding and/or mentoring us, and programmes that enable us to be creative and deliver for our peers and for our communities. Processes and mechanisms placing young people at the table are critical to ensure that energies are spent taking up and making the most of these spaces.

There are a number of roles we play in the HIV response across advocacy, research, peer education and service delivery, using our experiences and skills to push change at community, national, regional and global levels.

## 1 | YOUNG PEOPLE AS ADVOCATES

We are the most effective advocates for our own health and wellbeing and that of our peers. We know the barriers and solutions to accessing health services. Some of these solutions, such as comprehensive sexuality education, may not be popular in some contexts. However, we push the conversation, even when it is uncomfortable, because it is important that we speak to our realities in order to propel change.

Examples of young people playing an effective role as advocates can be found in the Resilient and Empowered Adolescents and Young people (READY) movement [1], which supports adolescents and young people in our diversity to understand our

sexual and reproductive health rights and support our peers in making healthy choices. Most specifically, through the READY + project, and in line with research recommendations [2], networks of young people living with HIV in East and Southern Africa have been successfully advocating within parliamentary committees and technical working groups to lower the age of consent for HIV testing from 18 to 15 years. Elsewhere, READY advocates have brought the voices of young people to international conferences on HIV and to the UN to speak out on barriers to accessing healthcare [3].

## 2 | YOUNG PEOPLE AS RESEARCHERS

There are a number of studies that research our behaviours and investigate health outcomes of specific interventions. However, we are not only subjects of research. We are also researchers, helping answer complex questions.

For example in 2019 young researchers led a trial to evaluate the effectiveness of the Zvandiri model for HIV-related and psychosocial support services for adolescents living with HIV in rural districts of Zimbabwe [4]. The study found that adolescents receiving Zvandiri services and Ministry of Health and Child Care services were 42% more likely to be virologically suppressed than adolescents receiving Ministry of Health and Child Care services alone. Not only were young researchers involved in the rollout of the trial, they were also involved in taking up and using the findings to coordinate the successful implementation of the Zvandiri model within the intervention clinics at the rural district level.

## 3 | YOUNG PEOPLE AS EDUCATORS

Since the HIV response began, young people have played a role as peer educators, passing on information to our peers through support groups, after school clubs and other settings. These efforts are ongoing, and the content of education and



way young people educate their peers has evolved. Young people deliver sexuality education on sensitive topics such as same-sex relationships, intergenerational relationships, violence and safe abortion to respond to the real questions and experiences of young people so they can stay healthy and make informed life and health choices [5].

For example Youth LEAD [6], a network of young key populations in Asia and the South Pacific, has a number of programmes that support peer education through 14 youth-led organizations to share information they may have received at school or at home with their peers. This includes information about sexuality and sexual choices and behaviours. Knowledge is power – and that remains the case for young people who, like others, need to stay on top of research and developments, especially those on work towards achieving the sustainable development goals [7] in order to maximize our own health and care for peers.

## 4 | YOUNG PEOPLE AS SERVICE PROVIDERS

Young people are also no longer only recipients of care. We are active in service provision both within health facilities and through outreach activities [8]. There are innovative collaborations between youth networks and organizations and health facilities to deliver quality care to young people – care that is non-judgemental, competent and directly responds to the needs of young people.

For example the national network of young people living with HIV in Burundi (RNJ+) runs a youth centre which serves adolescents and young people living with HIV and from key populations [9]. The network has a clinic on site where young people both deliver and access HIV prevention, treatment and support services, such as counselling, health talks and HIV testing. The network has also integrated the use of information and communication technology to promote dialogue about sexual and reproductive health rights within the community and drive demand for services among young people.

While it is increasingly recognized that we are experts of our own lives [10], we must continue to push for greater investment in youth-initiated interventions and youth–adult collaborations. We need to inspire transformation at scale so it becomes the norm to expect a youth-led network or organization to be at the centre of large programmes for improving the health and wellbeing of adolescents and young people. The days of being on the side-lines are over. We must be at the centre of these initiatives – and the examples shared show we can deliver if well-resourced and mentored to do so.

Viva young people, viva!

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### COMPETING INTERESTS

None of the authors have a competing interests.

### AUTHORS' CONTRIBUTIONS

TR, AI, IN and SA contributed equally to this viewpoint. Each wrote sections of the initial draft, reviewed all revisions and approved the final version of the manuscript.

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### ABBREVIATIONS

HIV, human immuno-deficiency virus; ICT, information and communication technology; READY, Resilient Empowered Adolescents and Young People; RNJ+, Réseau National des Jeunes Vivant avec le VIH; SRHR, sexual and reproductive health and rights; UN, United Nations.

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### DISCLAIMER

None declared.

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RESEARCH ARTICLE

# Scaling up peer-led community-based differentiated support for adolescents living with HIV: keeping the needs of youth peer supporters in mind to sustain success

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## Abstract

**Introduction:** Low rates of viral suppression among adolescents living with HIV (ALHIV) indicate that more effective support is urgently required at scale. The provision of peer support has generated considerable enthusiasm because it has the potential to ameliorate the complex social and relational challenges which underpin suboptimal adherence. Little is known about the impact on young peer supporters themselves, which is the focus of this paper.

**Methods:** We present qualitative findings from the Zvandiri trial investigating the impact of a peer support intervention on the viral load for beneficiaries (ALHIV, aged 13 to 19 years) in Zimbabwe. The Zvandiri peer supporters aged 18 to 24 years, known as community adolescent treatment supporters (CATS), are themselves living with HIV. Individual in-depth interviews were conducted in late 2018 with 17 CATS exploring their experiences of delivering peer support and their own support needs. Interviews were analysed iteratively using thematic analysis.

**Results:** The CATS reported that being peer supporters improved their own adherence behaviour and contributed to an improved sense of self-worth. The social connections between the CATS were a source of comfort and enabled them to develop skills to manage the challenging aspects of their work. Two substantial challenges were identified. First, their work may reveal their HIV status. Second, managing the emotional labour of this caring work; given how commonly the complexity of the beneficiaries' needs mirrored the circumstances of their own difficult lives. Both challenges were ameliorated by the support the CATS provided to each other and ongoing supervision from the adult mentor. There was variation in whether they felt their roles were appropriately valued through the remuneration they received and within the health system. There was a consensus that their experience meant that they would graduate from being a CATS with transferable skills that could enhance their employability.

**Conclusions:** Their experiences illustrate the advantages and opportunities of being a CATS. To minimize potential harms, it is vital to ensure that they feel valued in their role, which can be demonstrated by the provision of appropriate remuneration, recognition and respect, and that there is continued investment in ongoing support through ongoing training and mentoring.

**Keywords:** HIV; adolescents; differentiated service delivery; peer support; community based; health systems

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## 1 | INTRODUCTION

A tenacious driver of the higher rates of morbidity and mortality amongst adolescents living with HIV (ALHIV) is suboptimal adherence to HIV treatment [1-4]. Although the global target is to get 95% of those on treatment to be virally suppressed, combined data from East and Southern African countries show that only 45% of adolescent girls living with HIV are virologically suppressed (vs. the goal of 86% under UNAIDS 95-95-95 targets for 2030) [5]. This makes them more vulnerable to treatment failure.

The provision of one-to-one peer support at scale has generated considerable enthusiasm because it has the potential to

ameliorate the complex social and relational challenges that are known to affect adolescents' capability to engage in sustained adherence to HIV treatment [6-9]. Peer support is predicated on the basis that sharing knowledge and experience can provide emotional, social and practical support [10-12]. The similarity in experiences between the adolescent beneficiaries and young peer supporters provide the opportunity for effective support. However, being responsible for helping others experiencing the same problems may also exacerbate the vulnerability of peer supporters.

Community-based peer support models have not proven to be consistently effective for children, adolescents and young people living with HIV [13]. However, the Zvandiri trial, a

cluster-randomized trial which evaluated a theoretically informed peer-led differentiated service delivery intervention on HIV in Zimbabwe [14,15], found 42% lower prevalence of virological failure or death at 96 weeks among participants receiving the Zvandiri intervention than among those solely receiving standard HIV care at rural clinics [16,17]. A detailed explanation of the intervention and trial is outlined in related publications [15,18]. The findings from this trial add to the growing body of evidence to support the scale-up of differentiated service delivery incorporating peer-supporters to support adolescents' antiretroviral treatment (ART) adherence and retention in care. With an emerging investment in peer support programmes [19], there is a clear need to address the knowledge gap that exists about the impact, value and risks of such interventions for the young peer supporters themselves. In this paper, we draw on qualitative research conducted with the peer-supporters, known as Community Adolescent Treatment Supporters (CATS), in the Zvandiri trial to explore their experiences of delivering peer support and to identify their own support needs.

## 2 | METHODS

### 2.1 | Study setting

The current HIV prevalence among those aged 15 to 49 years old in Zimbabwe is 12.7% [20-22]. The trial was conducted with public clinics in two rural districts (Bindura and Shamva) in Mashonaland Central province, Zimbabwe. The trial communities are characterized by high youth unemployment, a struggling economy, persistent stigma around HIV, faith healing and a stretched healthcare system with weak mental health provision.

### 2.2 | Data collection

We conducted individual in-depth interviews between November and December 2018 with 17 of the 18 CATS, aged 19 to 24 years, who were actively working in the intervention sites ( $n = 6$  female,  $n = 11$  male). The one active CATS not interviewed was temporarily away from the district during the fieldwork period. There were 29 CATS who had been trained but were no longer active in the trial by the time of data collection. After the initial recruitment, a large proportion left in the early stages of the trial as they found the work did not suit them. We outline, using the information available, the reasons that the 29 CATS were no longer working in Table 1.

We explored how the CATS considered that the intervention affected their lives, their experiences of being involved and their support needs. Individual interviews were conducted by one male and two female Zimbabwean researchers (AC, MT and KM) in private spaces in the public clinics and lasted approximately an hour. All the interviews were conducted in Shona, the participants' language.

With the participants' permission, the interviews were audio recorded. The interviewers listened back to the recordings and wrote up the interviews into detailed interview scripts [23,24]. Iterative data collection and analysis was conducted, in which the team discussed each interview in weekly analytical meetings. This informed the refinement

**Table 1. Reasons CATS had left the trial intervention**

Reason for attrition	Number of CATS
Relocated	5
Employment	2
Married	3
Pregnancy	1
Lack of engagement (competing priorities, limited time to commit to CATS' duties, inadequate commitment)	18
Total	29

CATS, Community Adolescent Treatment Supporters

of the topic guides. Our theoretical approach was informed by social constructionism with particular attention paid to relational agency, which is attentive to the restricted agency young people may have and how this is framed by their relationships, but is also fluid and so may be dynamic and transformative [25].

A thematic analytical approach was adopted, which involved SB, MT, AC and KM coding the scripts to develop a coding framework. Excel was used to organize the coding. Themes were developed through data-led analytical memos. Selected extracts were transcribed verbatim and translated for equivalent meaning in English. SB and WM provided analytical training to MT, AC and KM throughout 2018 and 2019.

Ethical approval was granted by the Medical Research Council of Zimbabwe (#2032) and the ethics committees of the London School of Hygiene & Tropical Medicine (London, UK; #11042) and University College London (London, UK; #2358/004). Written informed consent was collected prior to participation. Pseudonyms are used for all participants.

## 3 | RESULTS

### 3.1 | Feeling valuable: helping them, helps me

#### 3.1.1 | Changes in adherence behaviour

In general, the CATS reported that working as a CATS had brought them considerable opportunity and advantage, including improving their capacity to manage their HIV status. Although the remit of the CATS was to support other ALHIV, many of them themselves had been struggling with adhering to treatment: "Prior to being a CATS, I would take them any-time (ARVs). If I wasn't reminded at times I would skip." (Progress, female, aged 20). Many reported that the training and education which they received through the programme had improved their treatment literacy and galvanized their commitment to compliance: "I only got to know about all of this when I became a CATS." (Rudo, female, aged 24).

All of the CATS who had previously struggled with adherence described how the reminder structures they put in place for beneficiaries helped them too: "I send adolescents reminders, so there is no way that I won't also take my medication at seven o'clock." (Geoffrey, male, aged 20); "when you see the impact of those that are not taking their medication on time

and think about yourself who is taking on time you realise there is a difference." (Taurai, male, aged 21). These insights encouraged them to comply.

*"When I became a CATS and seeing others this gave me strength that even if I wanted to default I should know it's my own life being affected. From then, it has helped me to know that medication should be taken correctly and on time." (Rudo, female, aged 24)*

Overall the CATS considered their work fulfilling and were proud that the support they offered had a positive impact. The majority considered that the proximity of their own experiences to those of the beneficiaries enabled them to make a unique contribution, which underpinned why they were so effective:

*"This is work that I enjoy as I work with my age-mates. I am able to relate to them well... it may be difficult for adults to understand them." (Lisa, female, aged 20).*

Many of them reported that they had developed an increased sense of self-worth, which motivated their investment in their own health. Farai explained the mutual benefit of the peer support that he offered:

*"I find myself really happy because of the interaction with the adolescents, giving them support and sharing with them what I have gone through. I am able to motivate them. It is really helping me too because we share problems with the adolescent on what they are going through and what I am going through. We help each other." (Male, aged 22)*

### 3.1.2 | Gaining comfort and strength from the CATS' community

For most CATS their experience of living with HIV prior to engaging with the Zvandiri programme had been defined by solitude. They described having been burdened by anxiety about the anticipated loneliness and limited prospects that would characterize their futures. The CATS had regular and various opportunities to interact with each other through the coordination meetings and reported deriving significant benefits from engaging in a community of young people affected by HIV. Feeling accepted and connected transformed their expectations of what it meant to live with HIV: "I realised that I was letting myself down. This programme gave me confidence to love myself." (Lazarus, male, aged 20).

Sharing their experiences was also instrumental in developing their capacity to deliver their duties as CATS. They consistently emphasized the value of being able to collectively develop support strategies and resolve problems in the regular discussions they had with the other CATS and mentors. "We help each other and sharpen each other intellectually with ideas" (Tapiwa, male, aged 20). Progress reflected a widely held opinion: "I have learnt a lot including that if you face any challenge don't make it your own but share it with others so that you can help each other solve it." (Female, aged 20).

## 3.2 | Dilemmas in being "seen" as a CATS

The Zvandiri intervention was new to the districts in the trial. So the CATS were a new cohort and had no prior experience of the intervention. The youngest CATS to be recruited at the start of the trial were 18 years old. Many were still in the process of accepting their HIV status. Despite the internal progress made around self-acceptance, they were mindful of prevailing stigmatizing attitudes that persisted within their local communities. Consequently, the majority of CATS concealed the nature of their work from others in the community. As Lazarus explains:

*"I don't show them what the job entails, but they try to find out what I do. I am an open person but ... I am not able to do that (to talk about his status in public)." (Male, aged 20).*

Public disclosure of one's HIV status is not a requirement of being a CATS. For a significant minority the risk of their role, and consequently their HIV status, being discovered was a source of worry and stress. They described finding this difficult to manage, particularly in the first months of working as a CATS. Although the risk persisted, with support and guidance from other CATS and their mentors, their anxiety tended to ease over time as they became more robust in managing other people's questions. Geoffrey described a common pattern in his reaction to uncomfortable questions from those within the wider community:

*"This mainly happened in the first days... At first it pained me and you would really have so many different thoughts... (Fellow) CATS will then say to me 'my friend, I came across this numerous times. They are not people to listen to, what you need to do is just ride your bicycle and go'. I ended up doing that. Now I have a good relationship with them and no one asks me what I am doing." (Male, aged 20).*

There were two exceptional cases when individuals had less control over who knew about their status within the community. For one CATS his HIV-positive status had been widely presumed because as a child he had been known as a "sickling." In the second case a healthcare worker had disclosed a CATS' HIV-positive status to other patients at the clinic. Although this has been "a painful experience," it was attributed to a rare act of thoughtlessness by the healthcare worker. In general, the risk of deductive disclosure in which their HIV positive status was revealed by virtue of being eligible to work as a CATS appeared to be low and to be well managed by both the young people, their mentors and others involved.

## 3.3 | Critical support needs to offset risks of being a CATS

Events such as falling sick, struggling with their mental health or problems within their own households were rare, but did at times influence their capacity to fulfil the obligations of the role. In addition, hearing about the shared challenges they faced as young people growing up with HIV, contributed to the CATS' precarious vulnerability. The substantial support

offered by the CATS' mentors was a critical factor mediating the emotional burden which accompanied their work. On some occasions this involved the mentors needing to be flexible about an individual CATS' workload.

The Zvandiri mentors, adults with professional experience caring for adolescents living with HIV, provided training, as well as ongoing supervision to the CATS and took on the management of mental health referrals and support in complex cases. The counselling and personal support provided by the mentors played a pivotal role in enabling the CATS to continue to provide support, without being overwhelmed or risk "burn-out." Sarudzai recalled how her mentor "follows up every week to check on me" (female, aged 20), which acted as a safety net to manage the daily stresses that could otherwise disrupt the CATS' adherence and wellbeing. Practically, the mentors also focused on keeping the number of cases that a CATS was responsible for to fewer than ten and equipping them with bicycles so that they could cover the relatively long distances to complete the required number of home visits. These were pivotal management strategies to support the CATS in their work.

In the first few months of their role as CATS, young people had to absorb a lot of information, implement new skills and develop relationships with beneficiaries and caregivers. Concomitantly, having just finished school and entering the employment market, they were by definition very early on in their careers as caring professionals. In common with anyone embarking on a career in a caring profession, the CATS were still learning how to manage the burden of responsibility involved in their role. They praised the mentors and other CATS in supporting them through this early period. For example, the mentors commonly facilitated introductions of CATS to households where caregivers were initially reticent for their child to be engaged in the programme. Over time it became easier, but ongoing support remained critical:

*"I say it's easy (CATS work) because you are not left to work with the adolescents by yourself. In most cases I work with others and you are helped if you have any questions... It's the mentor that supports me."* (Lisa, female, aged 20)

Without exception the CATS reported feeling a keen sense of responsibility for the health and wellbeing of their beneficiaries. When beneficiaries received high viral load results it was not uncommon for the CATS to feel "hurt," "disappointed" and "worried." Chipso (female, aged 21) explains how in such instances, "I may blame myself and wonder if I am failing to do my work or is it the adolescent who is just not understanding." The impact was even more acute when a beneficiary died.

In general, the opportunity to engage the mentor when they were struggling and stressed was pivotal to CATS being able to manage the related stresses of complex cases. Part of this involved acknowledging that some of the problems that beneficiaries encountered were likely to be beyond the remit of what the CATS could be expected to influence. Managing their expectations was key: not all of the problems could be resolved, but with the intervention's support they might be ameliorated. "She was able to help with advice... well she was able to help to a certain level which made the situation lighter though this didn't completely solve the problem." (Chipso, female, aged 21).

Despite the pressures, the CATS were generally very positive about the consistency of the support that they received. There were only a few instances when the provision of support was considered to have been late or insufficient. The negative reactions of CATS when support was considered inadequate, although rare, further reinforces the importance of timely, responsive and proactive support to mitigate the risks of being a CATS.

### **3.4 | Being valued: the role of remuneration and recognition**

#### **3.4.1 | Competing commitments: working in my household and working doing home visits**

The CATS considered themselves to be both valuable and valued in their roles. The stipend they received for their work was welcomed by most of the CATS. Those who could generally spend it on their own needs consistently described it as helpful: "I have been able to do certain things like I managed to take my class four (driver's licence) as well as to make a part payment for a course (operating earth moving equipment)." (Tanatswa, male, aged 20). However, many CATS had additional responsibilities and needed income to support their dependents and they were more likely to describe the remuneration as insufficient. Some had contemplated quitting to take up work with better pay.

The relatively "low" remuneration (US\$20 a month) paid to the CATS created challenges in how their role was perceived within their own households, as well as within the clinics. For a minority, their limited earning was a source of household tension. The remuneration was considered inadequate to justify the time spent away from household chores.

*"At home I was not being treated well ... they were giving me a hard time. They would always say 'you are running away from doing chores, the money you are getting is peanuts. How can you work for only twenty dollars (US\$)?"* (Tinashe, male, aged 23).

The competing demands of contributing to their household and fulfilling their duties as a CATS was most apparent during farming seasons when the CATS often had to stay at home to work in the gardens: "I will be preoccupied with other household chores ... as I will be at home some of the time because I am the head of the house." (James, male, aged 22).

#### **3.4.2 | Recognition of skills to support transitioning on**

In the first few months of the intervention, healthcare workers reportedly expressed some ambivalence about the contribution that the CATS could make. However, over time most of the CATS described feeling recognized and valued within the clinics where they worked. "They (healthcare workers) say 'you are clever, you are doing your work well' ... I start to feel elated and I know that it is really working well." (Chipso, female, aged 20). The vast majority of the CATS articulated their hopes that the CATS' role would be formally recognized within the health system.

Being a CATS is a time limited role, with young people unable to continue once they are 25 years old. Many were

hoping that they would go on to be employed by the Zvandiri programme but recognized that this was a narrow option only available to a few. In general, the transferable skills they gained through their training and professional experience increased their employability. There were some challenges in describing their work experience because without a generic qualification, having to describe the precise nature of their role risked deductive disclosure. In some cases, CATS transitioned to taking on other roles in the clinics or benefitting directly from sponsorship opportunities:

*"I collected my school results (ordinary level) recently. There are subjects I am supposed to rewrite. The nurse from this clinic has offered to pay my examination fee to supplement these subjects that I want to write. So for me, there are many opportunities." (Farai, male, aged 22)*

## 4 | DISCUSSION

Increasing attention is now being paid to community-based peer-support programmes as a mechanism to improve clinical outcomes and wellbeing [19–21]. While the predominate focus of research on peer support for ALHIV has focused on the potential benefits to those receiving peer support [26], this study demonstrates that peer supporters themselves also benefit through improved adherence behaviours and self-confidence. But it was characterized as emotionally and at times physically gruelling work, resonating with existing research on other peer support programmes [19,27]. These findings illuminate the specific challenges and needs that might arise for young peer supporters providing HIV support in resource-stretched settings. Despite the celebration of the effects of peer support, the discursive emphasis on the “adolescent” and/or “youth” characteristic of the CATS may act as a glass ceiling, inadvertently justifying not adequately valuing the contribution that they make in their title or in their pay.

There needs to be a formalized recognition of their contribution within the health system. There is currently some tension in how they are seen. This could be overcome if they were described as paid lay counsellors, rather than volunteers who receive a stipend. The CATS are not acting in a peer educator or navigator role but operating as skilled peer counsellors. Equivalent adult cadres, ordinarily working in the role of primary counsellors, are remunerated more than they are; CATS currently receive marginally more than village health workers [28]. While the CATS entry qualifications may be less and their initial training shorter than the standard six-month duration for primary counsellors, the CATS as young adults receive training and supervision through the work that they are doing. To accelerate their integration, more emphasis needs to be placed on the initial preparatory work with healthcare workers in the clinic and caregivers within the households to assuage initial resistance. Given that many CATS described the resistance they encountered as dispiriting, this may be an opportunity to mitigate early attrition.

If there were more formal recognition of CATS as primary lay counsellors, for example where they graduated with a certified accreditation, this would also support their ability to demonstrate their impressive skillset once they transition on

from being a CATS. This would avoid the current deductive disclosure risks that accompany explaining their prior role as a CATS. Instead, it would equip them with neutral language to describe the skillset and experience that they have gained, enabling them to leverage the employment opportunities that their experience warrants; a need recognized but rarely actioned in HIV youth activities more generally [29].

Although many of the CATS' support needs relate to their age and shared HIV experiences, they also reflect those that would be required by anyone, regardless of age or HIV status, on their initiation into a professional caring role. To support the implementation of the intervention at scale, continuing to budget for intensive mentor support for new cohorts of CATS and investing in it as an integral principle of youth peer support is vital [26]. This would ensure that there is adequate support to ameliorate the cluster of challenges relating to stakeholder resistance, concerns around the occupational risks of deductive disclosure and related stigma [30,31] and under-appreciating the value of peer-supporters, which can occur upon initial roll out of the intervention within communities. The findings demonstrate the supportive value that the CATS gain from each other, in common with various manifestations of peer support [32], but also illustrate that this can be further reinforced by the opportunities to mentor and be mentored through the provision of ongoing training and coordination meetings with peers [17].

A strength of this study was attending to the experiences of those providing peer support, making a valuable contribution to the emerging evidence-base that has generally focused narrowly on the recipients. However, by not interviewing those who had already left the programme, the results may be biased towards those with more positive experiences as peer supporters. Further research with those who work only briefly as peer supporters is required to understand the factors shaping attrition. However, a pertinent distinction should be drawn between peer supporters affected by attrition, who stop due to the effects of inadequate pay, support or poor health and *transition*, when individuals move onto other opportunities reflecting their successful growth in navigating considered decisions about becoming parents or seeking more sustainable employment opportunities. From the available information among the 29 inactive CATS, the latter was more common. Without further research there is a risk that attrition rates may be over-estimated. Peer supporters who move on before they exceed the age threshold may not represent an intervention failing, but instead indicate successful “graduation”.

## 5 | CONCLUSIONS

The experiences of the CATS demonstrate the considerable personal value that they gain from their work. To be able to maximize the benefits and minimize potential occupation harms over time, ongoing intensive and age-appropriate training and mentoring, as well as the establishment and maintenance of systems and remuneration which values the peer support role that CATS play, are integral to the success of peer support.

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## COMPETING INTERESTS

Authors declare no competing interests.

## AUTHORS'S CONTRIBUTIONS

SB was the lead social scientist, designing the process evaluation study with WM and FC which forms the basis of the data presented in this manuscript. MT, KM and AC collected the data with the support of SB, WM, NW and JM. All authors contributed to the overview of data collection and preliminary analysis for this paper through focused team discussions. SB, MT, KM, AC and WM conducted the data analysis. SB developed the manuscript with support from WM, MT, KM and AC. All authors read, reviewed and approved the final manuscript.

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RESEARCH ARTICLE

# Youth-friendly services and a mobile phone application to promote adherence to pre-exposure prophylaxis among adolescent men who have sex with men and transgender women at-risk for HIV in Thailand: a randomized control trial

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## Abstract

**Introduction:** Strategies are needed to curb the increasing HIV incidence in young men who have sex with men (YMSM) and transgender women (YTGW) worldwide. We assessed the impact of youth-friendly services (YFS) and a mobile phone application (app) on adherence to pre-exposure prophylaxis (PrEP) in YMSM and YTGW in Thailand.

**Methods:** A randomized control trial was conducted in YMSM and YTGW aged 15 to 19 years. Participants were provided daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC), condoms and randomized to receive either YFS or YFS plus a PrEP app (YFS + APP), whose features included self-assessment of HIV acquisition risk, point rewards and reminders for PrEP and clinic appointments. Clinic visits occurred at zero, one, three and six months and telephone contact at two, four and five months. HIV testing was performed at every clinic visit. PrEP adherence was evaluated with intracellular tenofovir diphosphate (TFV-DP) concentrations in dried blood spot (DBS) samples at months 3 and 6. The primary endpoint assessed was “PrEP adherence” defined as TFV-DP DBS concentrations  $\geq 700$  fmol/punch (equivalent to  $\geq 4$  doses of TDF/week).

**Results:** Between March 2018 and June 2019, 489 adolescents were screened at three centres in Bangkok. Twenty-seven (6%) adolescents tested positive for HIV and 200 (41%) adolescents participated in the study. Of these, 147 were YMSM (74%) and 53 YTGW (26%). At baseline, median age was 18 years (IQR 17 to 19), 66% reported inconsistent condom use in the past month. Sexually transmitted infection prevalence was 23%. Retention at six months was 73%. In the YFS + APP arm, median app use duration was three months (IQR 1 to 5). PrEP adherence at month 3 was 51% in YFS and 54% in YFS + APP ( $p$ -value 0.64) and at month 6 was 44% in YFS and 49% in YFS + APP ( $p$ -value 0.54). No HIV seroconversions occurred during 78 person years of follow-up.

**Conclusions:** Youth-friendly PrEP services enabled good adherence among half of adolescent PrEP users. However, the mobile phone application tested did not provide additional PrEP adherence benefit in this randomized trial. Adolescent risk behaviours are dynamic and require adaptive programmes that focus on “prevention-effective adherence.”

**Keywords:** adolescents; HIV prevention; pre-exposure prophylaxis (PrEP) adherence; men who have sex with men (MSM); transgender women (TGW)

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## 1 | INTRODUCTION

Adolescents and young men who have sex with men (YMSM) and young transgender women (YTGW) bear disproportionate burdens of HIV globally [1–4]. In Thailand, the HIV incidence among YMSM/YTGW has been consistently high, reported at 4 to 11 per 100 person years [3–7], similar to the United States where an estimated 14% of TGW are living with HIV

(US CDC 2019) and over a third of all new HIV infections are in YMSM [8,9]. The Thai epidemic among YMSM and YTGW is perpetuated by low rates of HIV test uptake, poor HIV knowledge and rates of condom use below 50% [10,11]. To achieve the ending of AIDS, comprehensive HIV prevention packages must be delivered to this key population [12]. Pre-exposure prophylaxis (PrEP) awareness in Thailand is low, reflected in national figures from December 2018, where only



an estimated 4% of PrEP-eligible YMSM and YTGW in Thailand received it, with one-quarter and one-third, respectively, accessing PrEP in Bangkok [13,14]. Only 2% of all PrEP prescribed in 2017 were to under 20s despite this age group having the highest national HIV incidence of 10 per 100 person years [13].

YMSM and YTGW at risk of HIV face a multitude of barriers in accessing and adhering to PrEP, including financial, third party consent laws, low perceived HIV risk, gender-based stigma and discrimination and lack of services that address their psychosocial needs [15–19]. Research studies from the United States emphasize the importance of regular contact to ensure good PrEP adherence in adolescents, with adherence dropping to less than half of PrEP users after monthly visits are extended to quarterly visits [20,21].

Thai YMSM and YTGW face considerable issues with low PrEP uptake and adherence. Among the 2,986 Thai adolescents and young adults aged 15 to 24 years who received counselling about PrEP between 2016 and 2020, only 24% accepted PrEP [22]. Among the 714 who have cumulatively initiated PrEP nationwide, only 22% continue to take PrEP since 2016 [22]. These uptake and retention challenges are similar to those seen with previous adolescent trials network (ATN) studies in adolescents aged 15 to 19 years, with PrEP discontinuation during ongoing HIV acquisition risk more likely (0.82 per 10-year increase in age) in younger individuals [23,24].

Mobile health (mHealth) technologies can facilitate task-shifting by utilizing its automation, widen availability, non-reliance on infrastructure development and ability to deliver personalized care [25]. As the information-motivation-behavioural (IMB) skills model has been validated and used previously for various HIV reduction interventions, it was utilized in this study to support engagement of adolescents in increasing self-risk awareness and consequently motivate behavioural risk reduction through *tailored information*: feedback of a calculated self-HIV risk level based on information of weekly risk behaviours, and *motivation*: point accumulation for mobile application use [26–28]. The goal of this study was to investigate whether use of a mobile phone application (app) in conjunction with youth-friendly services would improve PrEP adherence in YMSM and YTGW in Thailand.

## 2 | METHODS

### 2.1 | Study design and participants

This study was a prospective randomized controlled trial among young adolescents at risk of HIV acquisition in Bangkok, Thailand. Enrolment criteria included: (1) being YMSM or YTGW (assigned male sex at birth, self-reported sex with men, self-defined gender identity of being MSM or TGW for any period of time); (2) 15 to 19 years old; (3) self-reported risk behaviours, including inconsistent condom use; (4) being HIV negative. Participants could be new, previous or ongoing PrEP users, and were screened and recruited into the study at voluntary HIV testing centres at the Thai Red Cross AIDS Research Centre (TRCARC) and its community-based organization (CBO) branches, Rainbow Sky Association Thailand (RSAT) and Service Workers in Group Foundation (SWING), all located in Bangkok, Thailand via counsellors, online advertising, peer recruiters and word of mouth. Institutional Review

Board approval was granted by the Faculty of Medicine, Chulalongkorn University with a waiver for parental consent granted. This study was registered with ClinicalTrials.gov Identifier: NCT03778892.

### 2.2 | Study procedures

Participants were randomized (1:1) to receive youth friendly services (YFS) or YFS plus use of a PrEP adherence supporting mobile phone app (YFS + APP). Clinic visits occurred at months 0, 1, 3, 6 and telephone contact was made at months 2, 4 and 5. All participants were provided PrEP counselling, condoms and lubricants and daily oral tenofovir disoproxil fumarate (TDF) 300mg and emtricitabine (FTC) 200mg fixed-dose combination tablets; TenoEm (Thai Government Pharmaceutical Organization), Tenof-Em (Hetero Healthcare) or Ricovir-EM (Mylan). Sexually transmitted infection (STI) screening (*Neisseria gonorrhoea*, *Chlamydia trachomatis*) was performed on urine and anal swab samples and syphilis on blood samples at baseline and month 6 [29]. Surveys on sexual risk behaviours and perception were administered at baseline and monthly thereafter.

### 2.3 | Youth-friendly services only arm

YFS provided included ongoing counselling or support provided outside scheduled visits through online instant messaging or telephone calls with responses provided within 24 hours. Trained counsellors provided motivational interviewing focusing on risk reduction and adolescent self-empowerment through collaborative, non-judgemental discussions and positive reinforcement throughout the study [30,31]. Visits focused on building a fun and friendly atmosphere to build rapport with participants. Clinics were available out-of-office hours. Topics covered in counselling sessions were tailored to individual needs and included educational issues, lesbian, gay, bisexual, transgender (LGBT) stigma and discrimination, mental health and substance abuse issues, with specialist referrals where necessary. All clients had access to transgender counselling and gender-affirming related blood testing, and hormonal therapy.

### 2.4 | Youth-friendly services plus mobile phone application arm

In addition to YFS, the YFS + APP arm received an app for use, named “Project Raincoat” produced by Focal Intelligence Co., Ltd., which was designed based on use of the IMB skills model, specifically with information tailored to promote PrEP adherence and reduction of risk behaviours [26,28]. We conducted two adolescent YTGW and YMSM focus group discussions (FGDs) to inform design of the app. Focus groups of participants aged 15 to 19 years were conducted using a semi-structured interview guide with topics on desirable app functions, aesthetic designs and potential barriers and motivators for use. Key themes and subthemes were identified from a content analysis and utilized in informing app design, which included features supporting self-risk evaluation where users could input data once weekly on number of sex acts, sex partners, pills taken and condom use which was then used to calculate a feedback HIV risk of low, medium, high and very high risk. Points were rewarded in real time for data input

(maximum reward of 21 points per week) as well as responding to staff follow-up calls (5 points each), attendance of clinic visits (10 points each) and negative anti-HIV test results (50 points each). Points were exchangeable for cash, 100 points being exchangeable for 100 Thai Baht (3 USD). Users were able to customize self-reminders for medication and appointment reminders. Due to budgetary restraints the app was available on the Android operating system (OS) only and those using other OSs were loaned Android OS mobile phones.

## 2.5 | Data collection process

Behavioural surveys were completed by participants on paper forms at clinic visits. During scheduled telephone follow-up sessions, these were administered by staff. Participants completed monthly surveys asking about numbers of sexual partners, numbers of sex acts, condom use, numbers of PrEP pills taken each week and self-perceived HIV risk level. Self-perceived risk was determined by asking participants "in the last month, how would you rate your own risk of getting HIV?". Participants were able to select 1 from the 4 following possible responses: "low risk," "moderate risk," "high risk" and "extremely high risk." PrEP adherence was evaluated using tenofovir-diphosphate (TFV-DP) concentrations in dried blood spot (DBS) samples at months 3 and 6; with  $\geq 700$  fmol/punch equivalent to  $\geq 4$  TDF doses/week. App paradata including first and last entry into the app were collected [32].

## 2.6 | Laboratory assays

HIV antibody testing was performed using a chemiluminescent immunoassay (Architect HIV Ag/Ab Combo Reagent, Abbott Laboratories, Wiesbaden, Germany or Cobas HIV Combi Principle CMIA, 4<sup>th</sup> Generation). HIV testing at CBOs was performed using a rapid strip test (Alere Determine HIV-1/2, Alere International Limited, Ballybrit Galway, Ireland). STI screening was performed on urine and anal swab specimens for *Neisseria gonorrhea* (NG) and *Chlamydia trachomatis* (CT) with nucleic acid amplification (NAAT) testing using *in vitro* polymerase chain reaction (PCR) assays (Abbott RealTime CT/NG, Abbott Molecular, Inc., IL, USA). Syphilis testing at the TRCAC was performed using the electrochemiluminescence immunoassay analyser (ECLIA) and chemiluminescent magnetic microparticle immunoassay (CMIA). Syphilis testing at CBOs was performed using a solid phase immunochromatographic assay for the qualitative detection of antibodies of all isotypes (IgG, IgM, IgA) against *Treponema pallidum* (SD BIO-LINE Syphilis 3.0, Standard Diagnostics, Inc., Kyunggi-do, Korea). TFV-DP concentrations were measured from dried blood spot (DBS) samples collected onto Whatman Protein Saver 903 cards. Dried blood spots were stored at  $-70^{\circ}\text{C}$  until analysis. TFV-DP was analysed using liquid chromatography mass spectrometry (LC-MS/MS). The TFV-DP calibration curve range was 200 to 10,000 fmol/3mm punch [33,34].

## 2.7 | Sample size estimation

Estimating from results of previous adolescent PrEP trials, presuming that 45% of those in the YFS arm and 65% of those in the YFS + APP would have TFV-DP levels  $\geq 700$  fmol/punch with a power of test of  $>80\%$  and presumed

20% loss of cases to follow-up, a sample size of 100 for each arm was calculated, equating to a total of 200 participants needed for the trial [21,35].

## 2.8 | Statistical analysis

Primary outcome was PrEP adherence as measured via TFV-DP at months 3 and 6 follow-up. PrEP adherence was defined as those who had TFV-DP levels of  $\geq 700$  fmol/punch [36]. Secondary outcomes included rates of HIV infection, rates of study retention at month 6, associated factors with PrEP adherence and overall HIV acquisition risk protection (combined period with PrEP adherence or 100% consistent condom use).

Consistent condom use was defined as 100% condom use during all episodes of sexual intercourse. Substance use was defined as substances taken recreationally, including alcohol, sildenafil citrate, poppers and other illicit drugs (including amphetamine, ketamine and marijuana). Loss to follow-up was defined as no attendance for clinic visits or response to scheduled telephone calls for at least two consecutive months.

Associations of PrEP adherence with factors at enrolment was examined using univariable and multivariable logistic regression models. Associations were presented using odds ratios and 95% CI with *p*-values calculated utilizing the Z-test (Wald test). Factors where an association of  $p < 0.1$  in univariable analysis were selected for further multivariable analysis.

Age analysis was divided into 15 to 17 to represent "adolescence" and 18 to 19 to represent "young adulthood" [37]. To assess level of HIV protection from either PrEP adherence and/or 100% condom use, behavioural risk data were summarized into three-month blocks of risk periods prior to TFV-DP collection. Stata/SE 13.0 was used for all data analyses.

# 3 | RESULTS

## 3.1 | Characteristics at baseline and month 6

Between March 2018 and June 2019, 489 adolescents were screened, 27 (6%) tested positive for HIV and 200 (41%) enrolled to the study. There were 147 were YMSM (74%) and 53 YTGW (26%). Baseline characteristics between the YFS and YFS + APP arms were similar (Table 1). Median (IQR) age was 18 years (17-19) at enrolment. Median (IQR) age of sexual debut was 16 (15-17) years. Of those sexually active within the past month, 34% reported consistent condom use. Laboratory diagnosed STI prevalence at enrolment was 23%. Thirteen percent of participants overall reported substance use in the last three months. Self-reported substance use included alcohol (6%), amphetamines or methamphetamines (4%), ketamine (0.5%), poppers (volatile alkyl nitrites) (5%), marijuana (2%) and sildenafil citrate (4%).

An overall six-month retention rate of 73% was observed at six-month follow-up, 72% in the YFS arm and 73% in the YFS + APP arm ( $p = 0.87$ ). No characteristics were found to be associated with month 6 retention (Table 2). Consistent condom use in the past month among sexually active adolescents increased from 34% (95% CI, 25 to 43) at baseline to 58% (95% CI, 49 to 68) at month 3 ( $p < 0.001$ ) and remained a similar level at month 6 (52%; 95% CI, 41 to

**Table 1. Baseline characteristics of adolescents taking once daily HIV pre-exposure prophylaxis**

	Overall, n = 200 (%)	YFS, n = 100	YFS + APP, n = 100
Gender identity			
MSM	147 (74%)	71 (71%)	76 (76%)
TGW	53 (26%)	29 (29%)	24 (24%)
Age at enrolment median (IQR)	18 (17, 19)	18 (17, 19)	18 (17,19)
15 to 17 years	63 (32%)	32 (32%)	31 (31%)
18 to 19 years	137 (68%)	68 (68%)	69 (69%)
Age sexual debut (years)	16 (15, 17)	16 (15, 17)	16 (15, 17)
Sexually transmitted infections <sup>a</sup>	45 (23%)	19 (19%)	26 (26%)
No. of sex partners in the past month			
0	57 (29%)	29 (29%)	28 (28%)
1	87 (44%)	41 (41%)	46 (46%)
≥2	56 (28%)	30 (30%)	26 (26%)
Condom use in the past month in sexually active (N = 143)			
Inconsistent	94 (66%)	46 (65%)	48 (67%)
Consistent	49 (34%)	25 (35%)	24 (33%)
Substance use in the past 3 months <sup>b</sup>	26 (13%)	8* (8%)	18* (18%)
Self-perceived risk (N = 197)			
Low risk	121 (61%)	62 (63%)	59 (60%)
Moderate risk	66 (34%)	29 (30%)	37 (37%)
High- extremely high risk	10 (5%)	7 (7%)	3 (3%)

Consistent condom use = 100% condom use. MSM, men who have sex with men; TGW, transgender women; YFS, youth-friendly services; YFS + APP, youth-friendly services plus pre-exposure prophylaxis adherence motivation mobile phone application use.

<sup>a</sup>Sexually transmitted infections were laboratory confirmed and included syphilis, *Neisseria gonorrhoea* and *Chlamydia trachomatis*, the latter 2 from anal swabs and urine samples.

<sup>b</sup>Substance use included alcohol, amphetamines, methamphetamines, ketamine, poppers (volatile alkyl nitrates), marijuana and sildenafil citrate

\* $p < 0.05$  with Pearson's chi-squared test.

62). No evidence of reduced condom use was seen with good PrEP adherence (Table 3). STI incidence was 25.2 per 100 patient years during the study. In the 78 person-years of follow-up, there were no incidence cases of HIV seroconversion.

### 3.2 | Mobile application use

Of the 100 participants assigned to use the app, 62% had their own phone and the remaining 38% were loaned phones. Eighty-seven percent of participants used the app more than once and median duration of app use was three months (IQR 1 to 5). Approximately 75% of participants completed self-risk assessments in the first two weeks, dropping to 50% in six weeks and 25% by week 12. For point rewards, 60% of adolescents earned 100 to 199 points in the app, with a median of 120 points earned (IQR 60 to 205). One third (32%) redeemed their cash rewards at their month 3 visit and the remaining at their month 6 closing visit.

### 3.3 | Assessment of TDF adherence using TFV-DP DBS concentrations

A total of 294 TFV-DP samples were collected from 164 participants, 155 at month 3 and 139 at month 6. An additional seven timepoints (5 clients at month 3 and 2 clients at month 6) were added in the analysis as undetectable TFV-DP levels,

where blood samples were not taken due to self-reporting of no PrEP use in the preceding month. A total of 301 risk periods were therefore analysed. PrEP adherence by TFV-DP level was 52% (95% CI 45 to 60) at month 3 and 48% (95% CI 39 to 55) at month 6. PrEP adherence at month 3 was 51% in the YFS arm and 54% in the YFS + APP arm ( $p = 0.64$ ) and at month 6 was 44% in the YFS arm and 49% in the YFS + APP arm ( $p = 0.54$ ) (Figure 1).

### 3.4 | Associated factors with PrEP adherence

Variables with significant association ( $p < 0.1$ ) in univariable analysis to PrEP adherence were included in a further multivariable analysis, which included: gender identity, age, number of sex partners, self-perceived risk for HIV infection and study arm. Education was not included due to its collinearity with age. Multivariable analysis showed only gender identity remained significantly associated with PrEP adherence at month 3, with YMSM being associated with greater odds of PrEP adherence compared to YTGW (OR 3.1, 95% CI 1.3 to 7.6,  $p < 0.01$ ), but not at month 6 (OR = 2.4, 95% CI 1.0 to 6.2,  $p = 0.06$ ) (Table 4).

### 3.5 | Overall HIV acquisition risk protection

A total of 296 risk period blocks for analysis were available (145 in YFS, 151 in YFS + APP, 5 of 301 available TFV levels

**Table 2. Characteristics associated with retention<sup>a</sup> at 6 months**

Characteristics	No	Retention (%)	Unadjusted odds ratio (95% CI)	Wald test <i>p</i> -value
Gender identity				
MSM	147	109 (74.2)	1.35 (0.68, 2.69)	0.39
TGW	53	36 (67.9)	1	
Age at enrolment (years)				
15 to 17	63	44 (69.8)	1	0.57
18 to 19	137	101 (73.7)	1.21 (0.63, 2.34)	
Education				
≤Junior high school	87	65 (74.7)	1	0.54
≥Senior high school	113	80 (70.8)	0.82 (0.44, 1.54)	
Number of sex partners in last month				
0	57	43 (75.4)	1	0.69
1	87	63 (72.4)	0.85 (0.04, 1.84)	
≥2	56	39 (69.6)	0.75 (0.33, 1.71)	0.49
Condom use in last month among sexually active (N = 143)				
100% condom use	49	34 (69.4)	1	0.71
Inconsistent condom use	94	68 (72.3)	1.15 (0.54, 2.46)	
Substance use in last three months <sup>b</sup>				
No	174	122 (70.1)	1	0.06
Yes	26	23 (88.5)	3.27 (0.94, 11.36)	
Self-perceived risk (N = 197)				
Felt at low risk	121	92 (76.0)	1	0.33
Felt at moderate-extremely high risk	76	53 (69.7)	0.72 (0.38, 1.38)	
Intervention arm				
YFS	100	72 (72.0)	1	0.87
YFS + APP	100	73 (73.0)	1.05 (0.56, 1.96)	

MSM, men who have sex with men; TGW, transgender women; YFS, youth-friendly services; YFS + APP, youth-friendly services and mobile phone application.

<sup>a</sup>Retention defined as engagement with PrEP prevention services throughout six-month study period with no more than 1 period of disengagement for no longer than 2 consecutive months. PrEP, pre-exposure prophylaxis

<sup>b</sup>Substance use defined as alcohol, amphetamines, methamphetamines, ketamine, poppers (volatile alkyl nitrates), marijuana and sildenafil citrate.

had risk data missing so were excluded from this part of the analysis). In addition to the 51% of risk periods protected from HIV with PrEP, an additional 18% of risk periods were protected with self-reported consistent condom use, achieving a presumed total of 69% protection against HIV (Figure 2). Of the 67 % of risk periods with inconsistent condom use reported, 54% of these were protected with PrEP.

## 4 | DISCUSSION

To our knowledge, this is the first study in the Asia Pacific region that provides insights of youth-friendly PrEP service implementation in YMSM and YTGW aged 15 to 19 years with an innovative approach using a mobile phone application to support adherence. This study demonstrated that youth-friendly service integration to a PrEP programme enabled retention of three-quarters of adolescent clients and HIV protective TFV-DP levels of ≥700 fmol/punch among half of adolescent PrEP users during six months of follow-up. However, the mobile application used did not provide additional PrEP adherence benefit in this randomized trial. For Thailand,

lessons learned in this study are particularly valuable in supporting nationwide PrEP services for key populations including youth under its universal health coverage scheme as of October 2019, considerable progress from Thailand's first fee-based PrEP services in 2014 [29,38-41].

TFV-DP DBS concentrations ≥700 fmol/punch, deemed to be protective from HIV for the preceding 30 days [42] in this study was found in 46% to 52% of participants at both three and six months, similar figures to those seen in US adolescent studies conducted between 2013 and 2014 (30% to 50%) at the same time points [21,35]. An earlier adolescent study in 2010 that saw protective levels of only 20% by six months [43], a trend of improved adherence in newer studies also observed in adult studies, presumed to be due to higher general knowledge in PrEP efficacy and better informed and more motivated study participants in PrEP studies [44,45]. The fact that all aforementioned studies including this study did not see any HIV seroconversions despite imperfect PrEP adherence may have been due to PrEP use being effectively used in an event-driven fashion during risky events. Encouraging "prevention-effective adherence," the use of PrEP during periods of risk exposure to effectively protect against HIV acquisition

**Table 3. Proportions of adolescents with 100% condom use over time stratified by PrEP adherence at months 3 and 6**

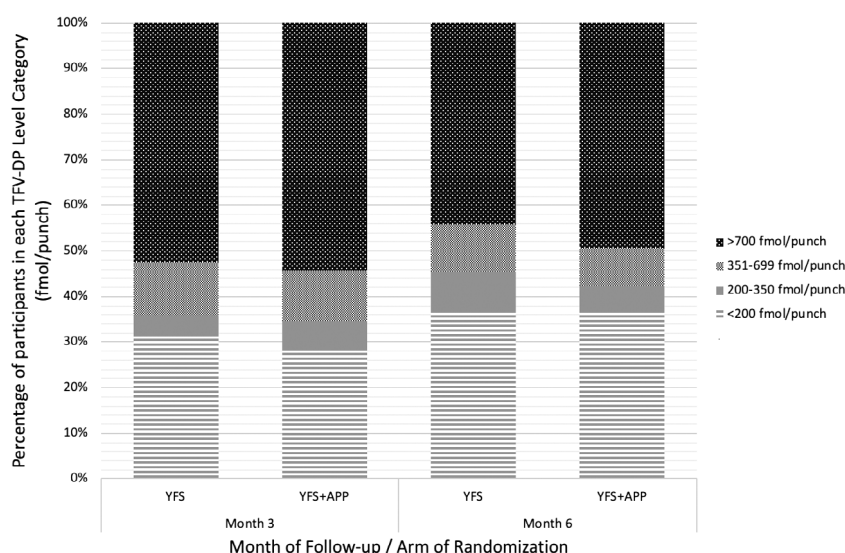
	Baseline <sup>a</sup>	Month 3 visit	p-value	Baseline <sup>a</sup>	Month 6 visit	p-value
Overall <sup>b,c</sup>	38 (34%, 25 to 43)	66 (58%, 49 to 68)	0.0002	33 (33%, 24 to 42)	48 (52%, 41 to 62)	0.008
PrEP adherent <sup>d</sup>	21/67 (31%, 20 to 42)	36/60 (60%, 48 to 72)		17/50 (34%, 21 to 47)	27/49 (55% 41 to 69)	
Non-PrEP adherent	17/45 (38%, 24 to 52)	30/53 (57%, 43 to 70)		16/50 (32% 19 to 45)	21/44 (48%, 33 to 62)	

<sup>a</sup>Baseline figures based on availability of TFV-DP results to match with self-reported condom use data for corresponding follow-up month analysed.

<sup>b</sup>p-value of Z-test for proportions comparing % of consistent condom use between month 3 versus month 6 = 0.329.

<sup>c</sup>No p-values calculated from Z-test for proportions comparing % of consistent condom use between PrEP adherent versus non-adherent groups within visits reached 0.05.

<sup>d</sup>PrEP adherent defined as tenofovir-diphosphate levels  $\geq 700$  fmol/punch.



**Figure 1. Adherence to once daily oral HIV pre-exposure 3 prophylaxis at months 3 and 6 of follow-up by randomization arm. YFS, Youth-friendly services; YFS + APP, Youth-friendly services plus mobile phone application use.**

is important because it acknowledges the dynamic pattern of HIV risk acquisition behaviours and the use of alternate HIV prevention strategies [46]. This may be a more appropriate goal to aim for in adolescents where the expectation of perfect adherence may become a barrier for those who would otherwise benefit from PrEP [44,46]. We believe that in this study, a mix of few sex acts, use of alternate HIV protection methods such as condoms and reduced perceived risk of situations driven by incomplete neurocognitive development typical of the adolescence phase of growth contributed to the inconsistent PrEP use seen [44-45,47]. This emphasises the need to combine PrEP with condoms and other HIV prevention modalities as a package to protect adolescents against HIV. It is encouraging that approximately 50% of participants had "high" adherence based on TFV-DP DBS concentrations of  $\geq 700$  fmol/punch and in combination with self-reported consistent condom use increased the overall protection to 68%. This cohort showed that with service delivery of an HIV prevention package, an increase in proportion of condom use was seen, contrary to speculated concerns of PrEP reducing condom use [48]. However, it is acknowledged that condom use can only be measured by self-report. We believe that recall bias was minimized by surveys at monthly intervals,

although it should be kept in mind this may still have been offset with a degree of reporting bias due to social desirability bias.

The vulnerability to HIV infection of the population investigated was reflected by the high rates of self-reported inconsistent condom use (66%) and laboratory diagnosed STIs at baseline of 23%, similar figures to those seen in the ATN studies 110 and 113 [21,35]. This was in contrast to the majority of participants who felt at low or moderate risk of HIV infection. This suggests that HIV prevention services for adolescents may be better justified to offer services based on risk behaviours rather than self-perceived risk. This cohort of adolescents had a relatively lower number of sex acts (2 to 3/month) and partners in the preceding month compared to much higher numbers (8 to 10/month) in the seminal ANRS Ipergay trial in adult MSM. This highlights the unique context of young people being at high risk of HIV acquisition for reasons such as lower rates of condom use and access to PrEP services, rather than number of sexual exposures [49]. For this reason, event-driven PrEP may be more suited to adolescents, further studies are needed [50].

There are studies in adolescent HIV prevention research with preliminary data suggesting the feasibility and

**Table 4. Associated factors with PrEP adherence<sup>a</sup>, 4A at month 3 of follow-up 4B at month 6**

	N	PrEP adherent <sup>a</sup>		Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
	N	N	%				
Characteristics (Total N = 160)							
Month 3 follow-up							
Total	160	84	52.5				
Gender identity							
MSM	120	74	61.7	4.83 (2.16, 10.79)	<b>0.003</b>	3.13 (1.30, 7.55)	0.01
TGW	40	10	25.0	1			
Age at enrolment (years)							
15 to 17	49	17	34.7	1			
18 to 19	111	67	60.4	2.87 (1.42, 5.77)	<b>0.003</b>	1.91 (0.87, 4.20)	0.11
Education							
≤Junior high school	70	30	42.9	1			
≥Senior high school	90	54	60.0	2.00 (1.06, 3.77)	<b>0.03</b>		
No. of sex partners in past month							
0	48	17	35.4	1			
1	70	40	57.1	2.43 (1.14, 5.20)	<b>0.02</b>	1.62 (0.69, 3.79)	0.26
≥2	42	27	64.3	3.28 (1.38, 7.80)	<b>0.007</b>	1.74 (0.66, 4.63)	0.26
Condom use in past month (N = 112)							
Consistent use	38	21	55.3	1			
Inconsistent use	74	46	62.2	1.33 (0.66, 2.94)	0.48		
Substance use in past three months <sup>b</sup>							
No	137	70	51.1	1			
Yes	23	14	60.9	1.49 (0.60, 3.67)	0.39		
Self-perceived HIV acquisition risk (N = 157)							
Not at risk	96	42	43.8	1			
At risk	61	40	65.6	2.45 (1.26, 4.76)	<b>0.008</b>	1.74 (0.84, 3.63)	0.14
Laboratory diagnosed STI at baseline							
No	123	63	51.2	1			
Yes	37	21	56.8	1.25 (0.60, 2.62)	0.56		
Intervention							
YFS	79	40	50.6	1			
YFS + APP	81	44	54.3	1.16 (0.62, 2.16)	0.64	1.08 (0.54, 2.16)	0.82
Characteristics (total N = 141)							
Month 6 follow-up							
Total	141	66	46.8				
Gender identity							
MSM	105	57	54.3	3.56 (1.53, 8.30)	<b>0.003</b>	2.44 (0.96, 6.20)	0.06
TGW	36	9	25.0	1			
Age at enrolment (years)							
15 to 17	42	12	28.6	1			
18 to 19	99	54	54.6	3.00 (1.38, 6.53)	<b>0.006</b>	1.89 (0.80, 4.50)	0.15
Education							
≤Junior high school	63	23	36.5	1			
≥Senior high school	78	43	55.1	2.14 (1.08, 4.22)	<b>0.03</b>		
No. of sex partners in past month							
0	41	16	39.0	1			
1	62	25	40.3	1.06 (0.47, 2.37)	0.90	0.80 (0.33, 1.91)	0.61
≥2	38	25	65.8	3.00 (1.20, 7.52)	<b>0.02</b>	1.94 (0.71, 5.30)	0.20



**Table 4.** (Continued)

	N	PrEP adherent <sup>a</sup>		Unadjusted odds ratio (95% CI)	p-value	Adjusted odds ratio (95% CI)	p-value
		N	%				
Condom use in past month (N = 100)							
Consistent use	33	17	51.5	1			
Inconsistent use	67	33	49.2	0.91 (0.40, 2.10)	0.83		
Substance use in past three months <sup>b</sup>							
No	118	57	48.3	1			
Yes	23	9	39.1	0.69 (0.28, 1.71)	0.42		
Self-perceived HIV acquisition risk							
Not at risk	89	37	41.6	1			
At risk	52	29	55.8	1.77 (0.89, 3.54)	<b>0.10</b>	1.28 (0.60, 2.76)	0.52
Laboratory diagnosed STI at baseline							
No	107	51	47.7	1			
Yes	34	15	44.1	0.87 (0.40, 1.88)	0.72		
Intervention							
YFS	68	30	44.1	1			
YFS + APP	73	36	49.3	1.23 (0.64, 2.39)	0.54	1.18 (0.58, 2.42)	0.64

fmol/punch, femtomoles per 3 mm punch; MSM, men who have sex with men; TGW, transgender women; STI, sexually transmitted infection, laboratory confirmed and included syphilis, *Neisseria gonorrhoea* and *Chlamydia trachomatis*, the latter 2 from anal swab and urine samples; TFV-DP DBS, tenofovir diphosphate dried blood spots; YFS, Youth-friendly services; YFS + APP, Youth-friendly services plus mobile phone application.

<sup>a</sup>“PrEP adherent” defined as TFV-DP DBS concentrations  $\geq 700$  fmol/punch [equivalent to  $\geq 4$  doses of TDF/week].

<sup>b</sup>“substance use” defined as alcohol, sildenafil citrate and other recreational and illicit drug use including alcohol, amphetamines, methamphetamines, ketamine, poppers (volatile alkyl nitrates), marijuana and sildenafil citrate.

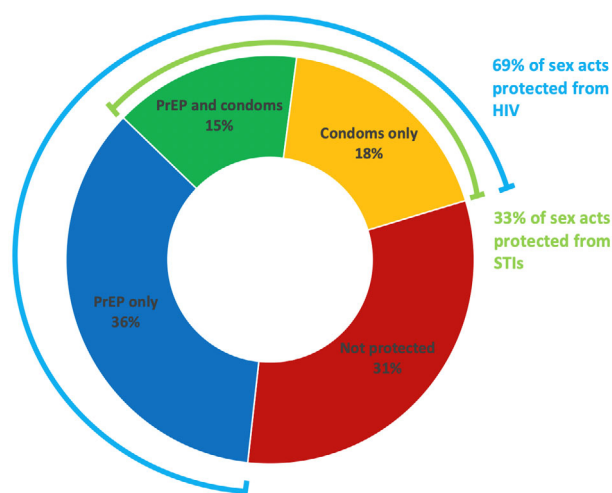
acceptability of apps in supporting PrEP adherence, however, trial results on efficacy are pending [51–54]. The “Raincoat” app used in this trial did not show efficacy in PrEP adherence or service retention. The median time of app use was only three months out the total six months of the study, substantially lower than in an adult study where >60% continued to use a PrEP adherence app at by six months [55]. This may have been due to (1) lack of social networking features such as chat boards or a leader board, (2) lack of ongoing new features over the six-month period contributing to boredom (3) availability on only one operating system (Android), meaning one-third of participants had to borrow phones to use the app, which may have been inconvenient. Retention could further be addressed with more adaptive designs to service delivery, which include (1) *convenience* – more accessibility and flexibility of services, self-testing for HIV and postal delivery of PrEP, (2) *adaptability to medication needs* – adolescent sexual activity changes over time and may be more suited to event-driven PrEP, (3) *technological developments* to add interactive activity such as leader boards, and chat boards to increase engagement or sense of community.

There are some data to suggest risk perception influences risk behaviours in adult MSM [56,57], and has similarly been described in a Thai YMSM study. We designed “Project Raincoat” based on the assumption that self-risk assessment would lead to increased adherence. Findings from studies have been mixed with some evidence to suggest risk perception has some relation to reduced risk behaviours [58,59], whereas in others despite risk perception, risk reduction was unaffected

[60]. It could be argued that although there is evidence to suggest low perceived risk is associated with poor adherence in YMSM [61], this does not mean the opposite is necessarily true. It is important to point out that risk perception was part of a spectrum of other factors influencing risk taking behaviours not explicitly addressed by the intervention in this arm, such as addressing of barriers to condom use and alcohol use which may explain the outcomes observed in this study [62]. At the time of this study, there were no universally accepted validity tools available for the effectiveness of mobile applications prior to taking them to randomized trials. There is acknowledgement that multiple factors influence whether a mobile application is effective, including participant demographics, intervention factors (intensity, components), technology used (video, infographics, text) and behavioural change intervention used, only some of which were possible to investigate in this trial [63]. More understanding is also needed on whether and how point rewards influence YMSM behaviour. A qualitative component of this study is underway.

Retention in HIV prevention services was fairly high at 73% by six months, similar to figures seen in the ATN 110/113 studies, with no clear differences between YMSM and YTGW in contrast to previous experience in Thailand suggesting TGW have poorer retention rates in HIV prevention care [64]. This may have been related to comprehensive care including gender affirming hormone therapy [65]. High overall retention rates suggest that the approach to counselling and multidisciplinary care taken in this study were important in engaging and retaining adolescents in HIV prevention services as has been previously found [12].





**Figure 2.** Mode of protection of risk periods against HIV and STIs seen in Thai adolescents. “PrEP protection” defined as  $\geq 700$  fmol/punch, “condom protection” defined as 100% condom use. PrEP, pre-exposure prophylaxis; STIs, sexually transmitted infections.

The strength of this study was it provided youth-friendly services that focused on adolescents between 15 and 19 years. This study was made possible through Thailand's policies that allow adolescents aged 13 to 18 years to access to HIV and STI testing and treatment without parental consent and approval of parental consent exemption by an ethics committee. It was further supported by the Princess PrEP Program led by HRH Princess Somsawali, recently appointed UNAIDS Goodwill Ambassador for HIV Prevention in Asia and the Pacific (2019) that funded our PrEP supply in accordance with HIV acquisition risks regardless of age or gender identity [66]. These strengths of Thailand exemplify the advances possible in HIV prevention efforts through giving importance to the overcoming of legal and structural barriers. Finally, this study is continuing with qualitative data collection on the mobile phone application used, which will provide information to improve future designs.

Our study also had a number of limitations. The mobile application was only available on the Android platform. Additionally, this study was not specifically designed to focus on YTGW, who are increasingly recognised as a distinct group with unique needs and therefore it could be argued that a separate gender-specific study with tailored interventions for YTGW is more appropriate [67]. The relatively short six-month duration of follow-up was also a limitation. Although this study looked at PrEP “execution,” further study is needed to address PrEP “persistence” in order to study ongoing HIV risk adolescents have over time [46]. We currently have an ongoing open-label extension study following up participants to look at PrEP persistence. It must also be noted that the comprehensive YFS offered in this study is not routinely offered across Thailand and other middle-income countries in the region, which may have negated any effects the mobile app had on PrEP adherence on the intervention arm of this study. Self-reported measures regarding sex acts, sex partners or condom use may have been subject to reporting bias. Finally, this study may have been underpowered to detect

differences in study arms due to a higher than expected dropout rate.

## 5 | CONCLUSIONS

Using youth-friendly service delivery, we were able to achieve retention in three-quarters of our clients at six months and good adherence among half of adolescent PrEP users, with no seroconversions. However, the mobile phone application tested did not provide additional PrEP adherence benefit to comprehensive YFS in this randomized trial. Adolescent HIV risk behaviours are dynamic and require adaptive programmes that focus on “prevention-effective adherence.” Further research is required on how improved adherence may be programmatically supported in adolescents both short and long-term through further qualitative and PrEP persistence studies.

## AUTHORS' AFFILIATIONS

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## COMPETING INTERESTS

The authors have no conflicts of interest to declare.

## AUTHORS' CONTRIBUTIONS

WNS was responsible for writing the initial version of the manuscript. SK did the data analysis. TP supervised the overall manuscript writing process and content. NP and TC oversaw PrEP operations at the TRCARC. TRC led TFV-DP laboratory analysis. PW coordinated this study and did the data collection. CS oversaw holistic care of study participants. SJ and DL oversaw PrEP operations at community-based organisations. All authors have read and approved the final version of this manuscript.

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RESEARCH ARTICLE

# “If it is left, it becomes easy for me to get tested”: use of oral self-tests and community health workers to maximize the potential of home-based HIV testing among adolescents in Lesotho

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## Abstract

**Introduction:** Home-based HIV testing fails to reach high coverage among adolescents and young adults (AYA), mainly because they are often absent during the day of home-based testing. ADORE (ADolescent ORal tEsting) is a mixed-method nested study among AYA in rural Lesotho, measuring the effect of home-based secondary distribution of oral HIV self-tests (HIVST) on coverage, as well as exploring how AYA perceive this HIV self-testing model.

**Methods:** ADORE study was nested in a cluster-randomized trial. In intervention village-clusters, oral HIVST were left for household members who were absent or declined testing during a testing campaign. One present household member was trained on HIVST use. Distributed HIVST were followed up by village health workers (VHW). In control clusters no self-tests were distributed. The quantitative outcome was testing coverage among AYA (age 12 to 24) within 120 days, defined as a confirmed HIV test result or known status, using adjusted random-effects logistic regression on the intention-to-treat population. Qualitatively, we conducted in-depth interviews among both AYA who used and did not use the distributed HIVST.

**Results:** From July 2018 to December 2018, 49 and 57 villages with 1471 and 1620 consenting households and 1236 and 1445 AYA in the control and intervention arm, respectively, were enrolled. On the day of the home-visit, a testing coverage of 37% (461/1236) and 41% (596/1445) in the control and the intervention arm, respectively, were achieved. During the 120 days follow-up period, an additional 23 and 490 AYA in control and intervention clusters, respectively, knew their status. This resulted in a testing coverage of 484/1236 (39%) in the control versus 1086/1445 (75%) in the intervention arm (aOR 8.80 [95% CI 5.81 to 13.32];  $p < 0.001$ ). 21 interviews were performed. Personal assistance after the secondary distribution emerged as a key theme and VHWs were generally seen as a trusted cadre.

**Conclusions:** Secondary distribution of HIVST for AYA absent or refusing to test during home-based testing in Lesotho resulted in an absolute 36% increase in coverage. Distribution should, however, go along with clear instructions on the use of the HIVST and a possibility to easily access more personal support.

**Keywords:** HIV; adolescent; oral self-test; Lesotho; HIVST; secondary distribution

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## 1 | INTRODUCTION

In Southern Africa, adolescents and young adults (AYA) experience high HIV transmission rates as access to HIV prevention, testing and care services remains low among AYA [1–4]. In 2016, UNICEF estimated that only 13% of adolescent girls and 9% of adolescent boys aged 15 to 19 in Southern Africa have been included in HIV testing services in the previous 12 months [5].

In high HIV incidence settings, community-based HIV testing tailored to the needs of AYA are seen as one important

pillar to reduce HIV incidence, morbidity and mortality in this age group [4]. However, while uptake is usually at 90% during home-based testing, the testing coverage remains low due to a large number of household members being absent at the time of the campaign, mainly men, adolescents and young adults [6–9]. In a previous study from Lesotho, more than 40% of young men aged 15 years and older could not be reached through home visits during week nor weekend days [7]. A promising approach to reach higher testing coverage during home-based HIV testing may be the use of HIV self-testing (HIVST). Oral-fluid rapid HIVST has been shown to increase

uptake, particularly among young people, in facility- and home-based testing models across the region [10–12].

One approach to increase testing coverage using oral HIVST may be its secondary distribution for household members not present during a home-based testing campaign. The HOSENG (HOMe-based SELF-testiNG) trial assessed the increase in testing coverage through secondary HIVST distribution to household members, all ages, absent or refusing to test during a home-based testing campaign in rural Lesotho [13]. Overall, 58% of HIVST distributed were used and returned within 120 days, resulting in an overall HIV testing coverage of 81%, more than 20% higher than in the standard of care arm where no HIVST were distributed [14].

The ADORE (ADolescent ORal tEsting) study is a mixed-method study nested within HOSENG trial, investigating the effectiveness and perception of secondary oral HIVST distribution with a follow-up by village health workers (VHWs) among AYA 12 to 24 years old.

## 2 | METHODS

### 2.1 | Study design, participants and recruitment

The ADORE study is a predefined mixed-method nested study embedded in the HOSENG trial, a cluster-randomized trial conducted in 106 rural villages in the catchment area of 20 health facilities of two districts in Lesotho. The randomization was stratified by district (Butha-Buthe vs. Mokhotlong), village size ( $\geq 30$  vs.  $< 30$  households) and access to the nearest health facility (easy vs. hard to reach, defined as needing to cross a mountain or river or  $> 10$  km away from a health facility). An independent statistician was responsible for the computer-generated randomization list. The study protocol of HOSENG including the nested study ADORE has been published [13]. In short, the trial assessed the increase in HIV testing coverage in intervention clusters through secondary HIVST distribution for household members absent or refusing to test during the day of the home-based testing campaign compared to control clusters, where no HIVST were distributed during the home-based testing campaign. Before cluster-randomization and trial start, the study team obtained verbal consent from all involved village chiefs by attending the village chiefs' councils and presenting the project. On the day of the HIV testing campaign, the study campaign team, consisting of counsellors and a nurse, obtained a written consent from each household head (or representative aged 18 years or older), to collect household data on all absent and present household members and to propose HIV testing. If the household consented to participate, then the study team enumerated all household members, offered blood-based HIV testing and counselling plus multi-disease screening (tuberculosis, alcohol) and HIV prevention (voluntary medical male circumcision referral, condom provision). The counsellors obtained from each household member written informed consent for HIV testing, following national testing guidelines [15]. According to national guidelines individuals aged 12 years or older can consent to HIV testing. For HIVST no written consent was obtained as the act of self-testing itself represents consent.

In control villages, during the home-based testing campaign household members with unknown HIV status and absent or refusing to test were encouraged to get tested at the nearest facility.

In intervention arm, study teams offered to leave an oral HIVST (OraQuick®) to household members with unknown HIV status and absent or refusing to test if they were 12 years or older. One present household member was trained and tested with the HIVST by a personal step-by-step explanation along with the written instruction in Sesotho (the local language). Prior to the campaign, the VHW from intervention villages were trained on the use and interpretation of the HIVST. During the campaign, these VHWs received a list of all household members for whom an HIVST was dispensed and were instructed to visit the households two to four weeks after the campaign to collect the oral HIVST if it was not returned to them before. In the case of a reactive HIVST, the VHW coordinated further blood-based testing to confirm the outcome.

The qualitative part included 12 to 24 years old participants who refused to use the secondary distributed HIVST and those who used the secondary distributed HIVST, stratified by two pre-defined factors: male versus female; age 12 to 15 versus 16 to 24 years. They were recruited using purposive sampling, following the concept of saturation [16]. Eligible participants provided written informed consent. Illiterate participants provided a thumb print after a literate witness of their choice read, explained and co-signed the form, and participants below 18 years chose a caregiver to co-sign.

This study was approved by the National Health Research and Ethics Committee of the Ministry of Health of Lesotho (ID06-2018) and the Ethics committee in Switzerland (Ethikkommission Nordwest- und Zentralschweiz; 2018-00283).

### 2.2 | Data collection and outcomes

Data collection for the quantitative part of the ADORE study was launched with the start of HOSENG trial on 26 July 2018 in both districts simultaneously. Recruitment lasted for five months. Details about data collection are published elsewhere [13]. The quantitative outcome of ADORE study was testing coverage among AYA (age 12 to 24) within 120 days after home-based testing, defined as the proportion of all individuals aged 12 to 24 years living in a household of the surveyed area with a confirmed HIV test result. A follow-up period of 120 days allowed sufficient time for absent members to return to their households, conduct the self-test, and return it to the VHW. The VHWs re-read the result of the oral HIVST strip and documented the outcome on a study-specific form. Furthermore, at all health facilities in both study districts, the study team searched through the testing registers to collect testing outcomes for those participants who decided to come to the clinic for testing instead. Twelve years was chosen as lower age-limit for oral self-testing because it is the legal age for providing HIV testing consent in Lesotho [17] and by then available evidence supported the use of the oral HIVST for individuals 12 years of age and older [18]. We defined confirmed HIV test results as (i) known HIV-positive with documentation (in the health booklet or the national testing register), (ii) known HIV-negative (tested within previous 4 weeks with documentation in the health booklet or the national testing register), or (iii) confirmed HIV test result during the study period according to the national HIV testing guidelines [15]. We classified a reactive oral HIVST as confirmed only if follow-up blood-based testing was performed.



After assessment of the quantitative outcome, one-on-one in-depth interviews were conducted from February 02, 2019 until 14 May 2019, by one trained interviewer. The interviews lasted approximately 20 minutes and were conducted in Sesotho in a private space at participants' home. The interviewer used a semi-structured interview questionnaire tailored to participants who refused versus who used the HIVST. The questionnaire covered socio-demographic characteristics, HIV testing preferences, their individual views on the secondary distribution of HIVST, perceptions about the optimal support needed during usage of HIVST and the follow-up of distributed HIVST. Two qualitative research objectives were defined:

- 1 *How do AYA (12 to 24 years old) perceive the use of an oral HIVST that was left for them because they were absent during the day of the HIV testing campaign or because they refused blood-based HIV testing?*
- 2 *How do AYA (12 to 24 years old) perceive the involvement of the village health worker in the follow-up of the distributed oral HIVST?*

## 2.3 | Data analysis

The quantitative outcome was analysed following an intention-to-treat approach with clusters as unit of randomization and individuals as unit of analysis, using multi-level logistic regression models including village and household as random effects. The model was adjusted for the pre-specified randomization stratification factors. Results are presented as adjusted odds ratios (aOR) and 95% confidence intervals (CI). As pre-defined subgroup analyses, the potential effect modification of sex (male, female) was assessed and intervention effects calculated separately in the case of significant effect modification. All analyses were done using Stata (version 15, Stata Corporation, Austin, TX, USA) and all tests used two-sided *p*-values with alpha 0.05 level of significance.

Regarding the qualitative data, audio recordings were translated and transcribed into English, and the analysis process determined according to the Framework Method [19]. A codebook was developed by the qualitative study team, deducting themes and codes from the two qualitative research objectives. Three researchers coded the transcripts independently, line by line and regularly met to compare the coding. In parallel to the rollout of the interviews, a working analytical framework was developed, and the codebook was constantly updated, adding more detailed codes inductively. A matrix was developed to systematically compare relevant responses across participants. Similarities and differences in findings by the stratified groups were identified, and illustrative quotes were selected.

## 3 | RESULTS

### 3.1 | Quantitative results

#### 3.1.1 | Participant characteristics

From July 26, 2018, until December 12, 2018, 49 and 57 villages with 1471 and 1620 consenting households and 1236 and 1445 enumerated AYA in the control and intervention

arm, respectively, were enrolled. 843 (68%) AYA in the control arm and 911 (63%) AYA in the intervention arm were absent. Table 1 summarizes the demographic information of all enumerated participants.

#### 3.1.2 | Testing coverage among AYA

Figure 1 displays the HIV testing coverage among the study participants in detail. Applying the outcome definitions of a confirmed HIV test results (see above), a testing coverage on the day of the home-visit of 37% (461/1236) and 41% (596/1445) in the control and the intervention arm, respectively, was achieved. In intervention clusters, overall, 785 oral HIVST were left for AYA who were absent (*n* = 771) or refused testing (*n* = 14) during the home-visit. Uptake of the distributed HIVST was 62% (487/785). At completion of the 120 days follow-up period after the HIV testing campaign, in the intervention clusters 490 additional AYA – who were initially absent or refused to test during the campaign – knew their HIV status: 99% (487) through usage of the distributed oral HIVST and 1% (3) through testing at a health facility. In the control arm, 23 AYA initially absent or refusing to test attended the health facility for testing within the follow-up period.

Overall, this resulted in a HIV testing coverage among AYA within 120 days after the home visit of 484/1236 (39%) in the control arm versus 1086/1445 (75%) in the intervention (aOR 8.80 [95% CI 5.81 to 13.32]; *p* < 0.001; Table 2). The intervention effect was greater in male AYA (70% vs. 25%; aOR 16.40 [CI 8.35 to 32.24]) than female AYA (80% vs. 52%; aOR 5.78 [CI 3.55 to 9.41], *p*-interaction <0.001; Table 2). Linkage to care data will be published separately.

## 3.2 | Qualitative results

### 3.2.1 | Interviewee characteristics

Overall 21 participants from intervention village-clusters were interviewed: 11 who refused to use the HIVST and 10 who did use HIVST. On average, the participants had completed 10 years of schooling, showed moderate HIV/AIDS-related knowledge and low HIV/AIDS-related stigma. Over 80% of the participants reported having tested for HIV before (all blood-based) and 80% in the HIVST user group and 60% in the HIVST non-user group reported oral-based testing as preferred test specimen (Table 3).

### 3.2.2 | Perceptions about secondary distribution of HIVST

Many participants thought secondary distribution was acceptable; "Because if a person wants to test if they were not at home they would miss to test if it was not left" (female, 14 years, HIVST user) Some emphasized that it was a convenient way of getting tested; "I think it's a good thing because I do not go to the doctor, so I do not have many opportunities to get tested so when it is left it becomes easy for me to get tested" (female, 18 years, HIVST user); whereas others pointed out the confidentiality of testing; "I think it's a good thing, because a person is sometimes scared to use while another person is present but if it is left for them that will be easy" (male, 15 years, HIVST user).



**Table 1. Characteristics of study participants by study arm**

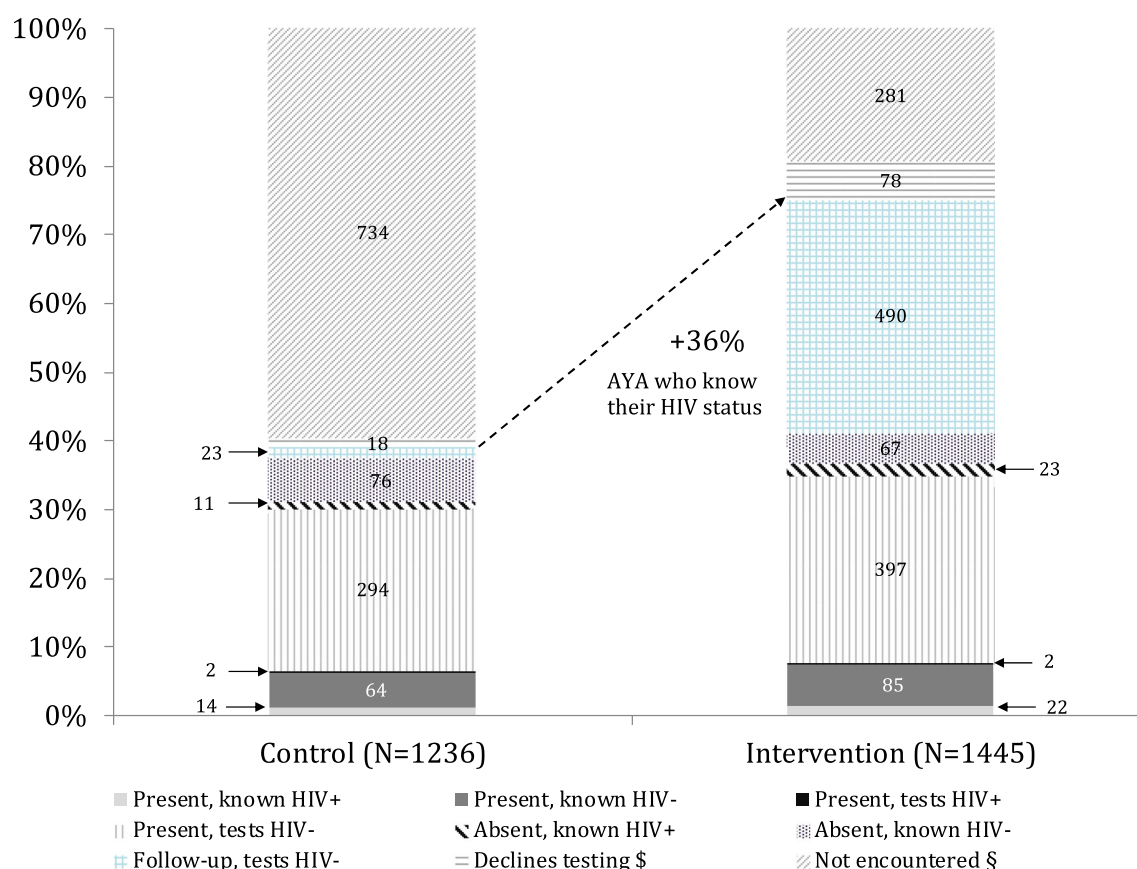
	Control	Intervention	Total
N	1236 (100)	1445 (100)	2681 (100)
Absent			
Yes	843 (68.2)	911 (63.0)	1754 (65.4)
No	393 (31.8)	534 (37.0)	927 (34.6)
Reason for being absent			
Work	51 (6.0)	63 (6.9)	114 (6.5)
School	503 (59.4)	466 (50.9)	969 (55.0)
Within the village	109 (12.9)	151 (16.5)	260 (14.8)
Outside the village	166 (19.6)	226 (24.7)	392 (22.2)
Unknown	10 (1.2)	8 (0.9)	18 (1.0)
Other reasons	8 (0.9)	1 (0.1)	9 (0.5)
Age	17.0 (14.0 to 21.0)	18.0 (15.0 to 21.0)	18.0 (15.0 to 21.0)
Gender			
Female	652 (52.8)	776 (53.7)	1428 (53.3)
Male	584 (47.2)	668 (46.3)	1252 (46.7)
Pregnant <sup>a</sup>			
Yes	18 (3.3)	35 (5.0)	53 (4.3)
No	522 (96.7)	662 (95.0)	1184 (95.7)
Main caregiver for the child <sup>b</sup>			
Mother	337 (56.8)	368 (56.1)	705 (56.4)
Father	51 (8.6)	74 (11.3)	125 (10.0)
Other family member	204 (34.4)	213 (32.5)	417 (33.4)
Friend	1 (0.2)	0 (0.0)	1 (0.1)
Neighbour	0 (0.0)	1 (0.2)	1 (0.1)
Orphan <sup>b</sup>			
Yes, single orphan	130 (21.9)	126 (19.4)	256 (20.6)
Yes, double orphan	46 (7.7)	42 (6.5)	88 (7.1)
No	418 (70.4)	481 (74.1)	899 (72.3)
Years of schooling	7.0 (5.0 to 8.0)	7.0 (6.0 to 9.0)	7.0 (5.0 to 9.0)
Work			
Employed in Lesotho	55 (4.5)	79 (5.5)	134 (5.0)
Employed in RSA	17 (1.4)	14 (1.0)	31 (1.2)
Self-employed	24 (2.0)	28 (2.0)	52 (2.0)
Subsistence farming	71 (5.8)	63 (4.4)	134 (5.0)
No regular income/employment	305 (24.8)	365 (25.5)	670 (25.2)
Housewife	81 (6.6)	121 (8.4)	202 (7.6)
Student	665 (54.2)	753 (52.5)	1418 (53.3)
Child	10 (0.8)	10 (0.7)	20 (0.8)

<sup>a</sup>Only asked among female participants; <sup>b</sup>Only asked among participants below 16 years of age. RSA, Republic of South Africa.

A few participants also raised concerns, mainly challenges related to pre-test counselling. Specifically, some noted that they did not feel ready to test; “I believe I need to think a lot before I can use it, so that I am ready to use the test. No, they did not prepare me in any way” (female, 20 years, HIVST non-user) or were afraid of the outcome; “I decided not to use it because I am afraid. If I find that I have the infection I would be stressed” (male, 15 years, HIVST non-user). Others added that no pre-test counselling happened at all; “I was not able to use it and it was not explained to me how it is used, so I was only told that it is there but I was not explained how

it is used when I get home” (female, 15 years, HIVST non-user).

Both groups were asked about what kind of additional support they would have wished to perform the HIVST that was left for them. A few mentioned better written instructions and adding audio assistance; “That we are left with something to listen to that explains how it is used” (male, 14 years, HIVST user). Someone suggested to hold a public gathering after the distribution; “I recommend that the next time there should be a public gathering, so as to inform people on how to use it, and how it will help them.” (female, 17 years, HIVST user).



**Figure 1. Testing coverage by cluster arm.**<sup>\$</sup>They declined testing during home visit and no follow-up testing outcome available. <sup>§</sup>They were absent during home visit and no follow-up testing outcome available. AYA, adolescents and young adults.

However, most wished more adequate personal assistance by various personnel; “I could have said the village health worker should help me, to help me test for HIV” (female, 15 years, HIVST non-user); “...when it is a nurse who explains to me how this tool is used, and what it is used for” (female, 14 years, HIVST non-user); “If I had at least got it from the people who have left it or the people from the ministry I believe I could get the right support” (male, 21, HIVST user); “It is that I get assisted by my mother” (female, 16 years, HIVST non-user).

### 3.2.3 | Views on VHW involvement

Both groups were interviewed about their view to involve the VHW in the follow-up of secondary distributed HIVST. The participants overwhelmingly expressed positive views. Some participants highlighted that the VHW can offer additional support and counselling; “This is a good idea because the village health worker can also be able to explain to people the use and results to them” (male, 21 years, HIVST user) and clarification; “I think it’s good because we’re going to make

**Table 2. Quantitative outcome and subgroup analysis**

	Control	Intervention	Adjusted odds ratio <sup>a</sup> (95% CI)	p-value
ADORE quantitative outcome				
HIV testing coverage among AYA <sup>b</sup>	484/1236 (39%)	1086/1445 (75%)	8.80 (5.81 to 13.32)	<0.001
Subgroup analysis on ADORE quantitative outcome				
Gender				
Male	148/584 (25%)	467/668 (70%)	16.40 (8.35 to 32.24)	<0.001
Female	336/652 (52%)	618/776 (80%)	5.78 (3.55 to 9.41)	<0.001

CI, confidence interval. AYA, adolescents and young adults.

<sup>a</sup>Multi-level logistic regression models adjusted for clustering (village and household as random effects) and stratification factors (district, village size, and access to health facility as fixed effects); <sup>b</sup>Within 120 days of the home visit.

**Table 3. Characteristics of interviewees**

	HIVST users	HIVST non-users	Total
N	10	11	21
Age, median (IQR)	15.5 (13 to 17)	15 (14 to 19)	15 (14 to 19)
Female sex, n (%)	5 (50)	7 (64)	12 (57)
Years of schooling, median (IQR)	10 (8 to 12)	9 (8 to 12)	10 (8 to 12)
Single marital status, n (%)	10 (100)	11 (100)	21 (100)
HIV/AIDS-related knowledge, mean (SD) <sup>a</sup>	5.78 (1.39) <sup>c</sup>	6.09 (1.14)	5.95 (1.23)
HIV/AIDS-related stigma, mean (SD) <sup>b</sup>	0.56 (0.88) <sup>c</sup>	0.64 (0.81)	0.6 (0.82)
Ever tested for HIV before, n (%)	8 (80)	9 (82)	17 (81)
Prefer blood-based testing (vs. oral-based)	2 (20)	4 (40)	6 (29)

<sup>a</sup>10 items, 1 point each, the higher the better knowledge, using a validated questionnaire (Bowen et al. BMC Public Health (2016) 16:70);

<sup>b</sup>8 items, 1 point each, the higher the more stigma, using a validated questionnaire (Bowen et al. BMC Public Health (2016) 16:70); <sup>c</sup>1 missing data.

mistakes then she can come back to help and show us we have to do this and that" (female, 18 years, HIVST user). Others emphasized the aspect of confidentiality; "Yes [the VHW] could pick them up, it's best because if it is one of those in our teens or young people they are likely to look at others but if it is an elderly person it is much better" (female, 20 years, HIVST non-user) and convenience; "Yes, [the VHW can] take them back to the people who distributed them" (male, 13 years, HIVST non-user).

However, one participant expressed major concerns. She argued that the VHW could disclose the status of the tested person, thus leading to discrimination in the village;

*"To give to them? No. because in the village as I previously mentioned when a person has tested themselves and discovers that they are positive, since they will have to take it to the village health worker, they might think that when he meets you on the road here they may humiliate or tell other people, and then you will end up living in fear without self-esteem."* (female, 20 years, HIVST non-user)

## 4 | DISCUSSION

In sub-Saharan Africa HIV transmission remains disproportionately high among AYA. [4] Many national programmes for HIV testing appear not to address enough the needs and demands of AYA, resulting in low testing coverage and delayed access to care. [20] Using quantitative and qualitative methods, the ADORE study contributes to the literature on how to better

reach AYA during home-based testing in rural Lesotho: Secondary distribution of oral HIV self-tests and subsequent follow-up by a VHW for AYA, who were initially absent or refused to test during a testing campaign, increased testing coverage within a period of four months by 36%. The existence of a long-standing VHW network in Lesotho – similar to many other sub-Saharan African countries – makes this model feasible and scalable with little additional costs. Findings from the qualitative research suggest that AYA perceived oral HIVST as a convenient and confidential way for getting tested, and that in general, VHWs appear to be a trusted lay cadre for the follow-up of HIVST.

As a caveat, even though distribution of oral HIVST increased testing coverage among AYA to 75%, it still fell short of the targeted 90% coverage, and 38% of the AYA who received a HIVST through secondary distribution did not use it. As stated during the in-depth interviews, a few AYA felt uncomfortable in doing the test alone, others stated, generally not being ready to test as they were afraid of the result. During the 4-month follow-up no HIV-positive test result was recorded. We may have to assume that a number of individuals who had a reactive HIVST result did not bring the test kit back to the VHW or the facility – at least not within the set outcome window. These caveats emphasize the importance of differentiated service deliveries for AYA – in line with current policies from international HIV agencies and the WHO [21,22].

Direct (i.e. primary) distribution of HIVST in sub-Saharan Africa has shown to successfully reach high testing rates among AYA across various testing modalities [23–26]. However, to our knowledge, ADORE is among the first studies exploring secondary distribution of HIVST during home-based HIV testing in AYA. A nested trial within HPTN 071 (PopART) investigated primary as well as secondary HIVST distribution during a door-to-door testing campaign [27]. This led to a moderate increase in coverage rates from 65% to 68% overall, and from 70% to 74% among young adults aged 16 to 29 years old. The authors, however, were not able to assess if the positive effect on coverage was driven by the primary or secondary distribution.

The benefit of secondary oral HIVST distribution in ADORE study was particularly high among male AYA, although overall testing coverage achieved remained below the coverage rate of female AYA. Among male AYA, testing coverage increased from 25% to 70% (Table 2). Given the generally lower access to HIV testing among men, particularly young men, this finding encourages national programmes to include secondary distribution of oral HIVST into any community-based HIV testing campaign. The PopArt nested study reported similar findings but with different effect sizes: By distributing HIVST in the intervention arm, the coverage significantly increased by 6% among male AYA, but only by 1% among female AYA [27]. The gender difference may be driven by the fact that more male AYA than female AYA are usually absent during home-based HIV testing [7]. In our study male AYA made up 57% (991/1754) of all absent household members. On the other hand, a recent cross-sectional study from the Democratic Republic of the Congo assessed preferences of HIV testing among 600 adolescents and concluded that home-based HIVST was preferred over facility-based testing, especially among male adolescents [28]. The fact of having more control over the testing

process thanks to self-testing is particularly appealing to young men and may explain high uptake of testing [29].

During the global roll-out of HIVST concerns have been raised that HIVST may lead to unintended social harm. However, a systematic review [30], as well as a large-scale assessment within the STAR initiative [31] found little evidence to support this concern. During the follow-up of HIVST our VHW did not report any serious adverse events related to HIVST, nor did our interviewees.

Rather surprisingly, in our study interviewed AYA were almost unanimously in favour of integrating the VHW in the post-test process, which may indicate that the engagement of VHW in the HIV/AIDS response is acceptable for AYA in this setting. This is an encouraging finding in light of the UNAIDS 2017 initiative to recruit two million African community health workers ensuring an effective and sustainable response to the HIV/AIDS epidemic in Africa [32]. On the other hand, universal home-based testing may become less frequent in future as its yield of new HIV diagnoses has become extremely low and donors may reduce funding for such approaches.

Our study has several limitations. First, calculation of HIV testing coverage considered only those who either had a proof of recent testing (within the last four weeks) or tested within the study. Some individuals, particularly among those absent, may have tested for HIV at a different occasion or at facilities outside the study districts. Second, some may have used the test but did not return it to the VHW. Both factors would lead to an underestimation of the actual testing coverage. Third, purposive sampling for the qualitative interviews may have resulted in an interviewee population generally more open to healthcare services than individuals who could not be reached for or refused interviews. On the other hand, half of the interviewed participants did not make use of our intervention and thus may have contributed to a comprehensive picture. Overall, the qualitative data has insufficient depth with only 21 interviews but may still give a hint why the intervention worked. Fourth, a more extensive interview design would have been needed to thoroughly explore social harm of our intervention. Fifth, due to the design of the study we were not able to explore other follow-up methods after HIVST usage than by the VHW. Future research should investigate the optimal training of the present household member as well as the VHW, include phone numbers of nearby health personnel and VHW that can assist, and explore new technologies, such as audio and video instructions, for conducting the follow-up after secondary HIVST distribution.

## 5 | CONCLUSIONS

The ADORE study, conducted in Lesotho, Southern Africa, shows that secondary distribution of oral HIVST for AYA absent or refusing to test during home-based HIV testing results in an absolute 36% increase in testing coverage. Based on these findings we encourage secondary HIVST distribution for AYA who cannot be reached during testing campaigns. Secondary distribution should, however, go along with clear instructions on the use of oral HIVST and a possibility for AYA to easily access support if they wish so. In our study, village health workers who are mainly older female members of the community appear to be a trusted cadre for the follow-up

of distributed HIVST among AYA, as long as confidentiality is ensured.

## AUTHORS' AFFILIATIONS

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## COMPETING INTERESTS

The authors declare that they have no competing interests.

## AUTHORS' CONTRIBUTIONS

AA, JM, MK, NDL, TIL and TRG conceptualized and designed the study. AA and NDL drafted the first version of the manuscript. MK is the study coordinator and conducted the interviews. LK and MKa coordinated quantitative data collection. AA, MK and TIL analysed qualitative data. TRG analysed quantitative data. JM provided technical support. All authors read, critically revised and approved the final manuscript.

## ABBREVIATIONS

AYA, Adolescents and Young Adults; ADORE, ADolescent ORal sELf-testing; CI, Confidence Interval; HIV, Human Immunodeficiency Virus; HIVST, HIV Self-Test (ing); HOSENG, HOme-based SELF-testiNG; IQR, Interquartile Range; OR, Odds Ratio; VHW, Village Health Worker; WHO, World Health Organization.

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RESEARCH ARTICLE

# “Because we all have to grow up”: supporting adolescents in Uganda to develop core competencies to transition towards managing their HIV more independently

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## Abstract

**Introduction:** Sustaining optimal adherence is the major challenge facing adolescents living with HIV (ALHIV), particularly in low-resource settings, where “second-line” is often the last accessible treatment option. We explored the knowledge and skills adolescents need in order to maintain improved adherence behaviours, and the specific ways clinicians and caregivers may support young people to do so more independently.

**Methods:** We conducted individual, in-depth interviews with 20 ALHIV aged 10 to 18 years in Uganda in 2017 to 2018. All participants had recently commenced second-line treatment as part of a clinical trial. We used thematic qualitative analysis to examine adherence experiences and challenges while on first-line therapy, as well as specific supports necessary to optimise treatment-taking longer-term.

**Results:** Adherence difficulties are exacerbated by relatively rapid shifts from caregiver-led approaches during childhood, to an expectation of autonomous treatment-taking with onset of adolescence. For many participants this shift compounded their ongoing struggles managing physical side effects and poor treatment literacy. Switching to second-line typically prompted reversion back to supervised adherence, with positive impacts on self-reported adherence in the immediate term. However, this measure is unlikely to be sustainable for caregivers due to significant caregiver burden (as on first line), and provided little opportunity for clinicians to guide and develop young people's capacity to successfully adopt responsibility for their own treatment-taking.

**Conclusions:** As ALHIV in sub-Saharan Africa are attributed increasing responsibility for treatment adherence and HIV management, they must be equipped with the core knowledge and skills required for successful, self-directed care. Young people need to be relationally supported to develop necessary “*adherence competencies*” within the supportive framework of a gradual “transition” period. Clinic conversations during this period should be adolescent-focussed and collaborative, and treatment-taking strategies situated within the context of their lived environments and support networks, to facilitate sustained adherence. The disclosure of adherence difficulties must be encouraged so that issues can be identified and addressed prior to treatment failure.

**Keywords:** adolescents; transition; paediatric; adherence; psychosocial support; viral suppression; HIV

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## 1 | INTRODUCTION

With vast improvements in survival resulting from effective prevention of mother-to-child transmission (PMTCT) and antiretroviral treatment (ART) for HIV in high-burden, resource-stretched countries, adolescence has emerged as a critical priority area for HIV care [1–3]. Limited improvements in survival have been observed among this age-group relative to their paediatric and adult counterparts [3,4], and morbidity

rates among adolescents in sub-Saharan Africa are not declining at the same pace as other age groups [3]. As for other chronic conditions, provision of HIV care during adolescence is characterised by unique management challenges as major cognitive, psychosocial, physical and sexual developmental changes take place [5–8]. This is illustrated by relatively poorer HIV-care outcomes with high rates of attrition from clinical care services [9–11] and compromised ART adherence [10,12,13]. Accompanied by exploration of risk-associated



sexual behaviours [14,15], this has far-reaching consequences for individuals and public health outcomes alike [16,17].

Importantly, adolescence involves the shift of responsibility for HIV care, from caregiver to adolescent [18]. To support the development of mechanisms which enable independent self-management of treatment compliance and health literacy among adolescents, there is a need to characterise the process of successful transition among adolescents, including development of evidence-based approaches to guide clinicians [10,19]. In high-burden, resource-stretched settings, the transition to adult care may not be demarcated by a discrete movement between paediatric and adult facilities as occurs in developed settings [20–23]. Thus, contextually appropriate approaches to formalising this process are needed to facilitate intentional adolescent capacity-development and treatment continuity [9,24].

In this paper, we conceptualise “transition” as being the shift young people make away from caregiver-driven (or “mediated”) to increasingly autonomous, self-directed treatment-taking and HIV care; accompanying the broader, contemporaneous developmental transition toward independence. Our applied approach is grounded in the social-ecological theory for transition preparedness [25,26]; incorporating both individual elements of transition preparedness and consideration of the influential role of the surrounding physical and social environments and support systems [25,27]. We investigated the challenges encountered by ALHIV during the adolescent transition period, particularly those related to treatment-taking, and identified core competencies required to manage their health independently. And secondly, the specific ways in which clinicians and caregivers may equip ALHIV with the knowledge and skills required for successful transition to “adult” HIV care.

## 2 | METHODS

We present the results of a qualitative study conducted among 20 ALHIV (aged 10 to 18 years) attending a leading HIV clinic in Kampala, Uganda. The clinic is well-resourced, and offers separate paediatric and adult care. Transfer to adult care typically occurs once a young person is in their early twenties. This study was conducted over a 12-month time period: 2017 to 2018.

The study is a qualitative sub-study of the ongoing “ODYSSEY” trial (Once-daily DTG based ART in Young people versus Standard thErapY) (NCT NCT02259127) [28]. The clinical trial is an open-label, randomised, non-inferiority, basket trial evaluating the efficacy and safety of DTG plus 2 nucleos(t)ides (NRTIs) versus standard of care in HIV-positive adolescents age <18 years starting first-line ART (ODYSSEY A) or switching to second-line (ODYSSEY B).

We recruited ALHIV who had experienced treatment failure (ODYSSEY B), as identified by high viral load or morbidity. These participants were presumed to be encountering adherence challenges and had recently commenced second-line treatment through the clinical trial. All clinical trial participants who were eligible to take part in the qualitative study were invited to do so, with the final five participants recruited purposively to ensure a representative balance of age and gender across the sample.

Data were collected using in-depth, semi-structured interviews, which were conducted by trained local researchers in a private room within the paediatric clinic (caregivers were not present). The interview guide was developed based on knowledge from both the existing literature and the authors’ previous research, but primarily focused on generating detailed accounts of individual experiences of treatment-taking within its broader context. It was then revised and adapted in light of emerging analytical areas of interest; including experiences of growing up with HIV; ART-adherence; expectations of adulthood and “adult” models of care; management of relationships and onward disclosure. We present findings from the first wave of interviews, in which participants reflected on their treatment experiences on first-line therapy, prior to switching.

All participants were aware of their HIV status prior to recruitment. Appropriate national and institutional ethics approvals were obtained, specifically, from the London School of Hygiene and Tropical Medicine and the Joint Clinical Research Centre, Uganda. Participant consent or assent were obtained, and caregiver consent obtained for assenting participants aged younger than 18 years.

Audio-recorded interview data were transcribed verbatim and then translated into English for analysis. Participant identifying details were removed and pseudonyms applied. Transcript coding was done individually (manually) by the first and last author. These initial codes were discussed and reconciled into a Codebook. The Codebook was reviewed by the second and third author, who were familiar with the data. A thematic qualitative analysis was conducted, with emerging themes discussed between the authors to ensure the integrity of inductive data interpretation (including understanding of nuances specific to the local context). Deviant case analyses were conducted to attain representative depth of analysis.

## 3 | RESULTS

Table 1 presents participant characteristics. The experiences of participants reflected a range of diverse situations which shaped their capacity to adhere to their HIV treatment. However, all participants had recently been moved onto second-line ART, and all reported experiencing some challenges maintaining optimal adherence.

### 3.1 | Individual-level (adolescent) considerations

#### 3.1.1 | Evolving models of care

Our findings suggest adolescents are attributed more responsibility for their treatment-taking with increasing age, with dwindling involvement from their caregivers. Although participants anticipated becoming “fully responsible” for treatment-taking “when [they] grow older” (George, male, age 10), we argue this expectation often faltered in reality as they were not adequately equipped with necessary accompanying knowledge and strategies to successfully navigate and sustain the complex demands of transition to self-care.

For several of our participants, the time period during which they had assumed responsibility for their own treatment-taking predated them being disclosed to regarding their diagnosis

**Table 1. Participant characteristics (n = 20)**

Sex	12 male, 8 female
Median age (age range)	14.5 years (10 to 18 years)
Mode of HIV infection	All participants had vertically acquired HIV
Antiretroviral therapy	All participants were receiving second-line ART therapy
Living situation/caregiver/s	13 were living with parent/s and 7 were living with wider family
Education and employment	17 were attending school, 2 were technical apprentices, 1 was employed
Clinical care centre	All were receiving care from the same paediatric HIV clinic

ART, antiretroviral therapy.

and understanding the necessity of consistent treatment-taking [29,30]. Dennis, male, age 14, shared how this knowledge deficit proved problematic for him:

*“There were some problems, because there came a situation when I didn’t know why I was taking this medicine, they took long to tell me... I was not taking them because I didn’t know what they were for so I asked myself why I had to since I was young... I used to ask my mother many times but she would just say that you must take them... So when I stopped, on coming here the viral load went high to about 2000, and we went to the counsellor and they asked if I knew, and it was my mum to tell me... Before I knew that I had HIV it was difficult because I just didn’t understand why I had to yet others were not taking.”*

**3.1.2 | Knowledge deficits as a barrier to self-management**

Aligned with study inclusion criteria, all participants were aware of their HIV-positive status. At the time of data collection, however, HIV and related treatment literacy remained variable and frequently limited. Participants described garnering HIV-related information from non-specialist sources such as radio, television and overheard conversations between laypeople, and tended to absorb overly simplistic, blunt and often distressing messages. Zack male, age 15, recalls his reaction upon learning of his diagnosis in this way:

*“I got so scared... I knew that I was going to die. Why did you think that you were going to die? They used to say that HIV kills. Where did you hear this? Over the radio and even amongst people.”*

Relevant information is typically provided in clinic visits. However, this appeared not to have been understood and integrated into the young people’s knowledge. Thus, ambiguous explanations given during childhood often persisted unamended [31] rather than increasing in sophistication with maturity. Sophia, female, age 17, shared simply, “I was born

with HIV.” Some appeared unaware of their sizeable knowledge gaps and did not know to enquire. When prompted, however, many participants had specific questions related to their illness which had not yet been voiced. Representative of this issue, Denna, male, age 11, disclosed:

*“Do you perhaps have any questions about your illness? Yes, I have always wanted to know where HIV came from. Have you ever asked your mother about this? Sometimes she is too busy so I get scared to ask. What about at the clinic? I fear the health care workers also. What do you think will happen if you asked them? I don’t know but I fear and sometimes I forget.”*

Generally, understanding of specific administration requirements for treatment taking, such as appropriate timing, were hazy. When asked the time he was meant to take his medication, Mark, male, age 12, responded, “any time that I want.” Jasmine, female, aged 17, shared a different concern:

*“Sometimes I would find myself late and I would give up because I know that day is wasted... They told us that we can only take the medication at most five minutes passed the scheduled time.”*

Others were aware that they needed to take treatment every day, but struggled due to side-effects such as “headache and nausea” (Zack, male, age 15), presuming these to be unavoidable.

**3.1.3 | Individual adherence strategies**

At the time of being interviewed, all knew why they were taking treatment, and the majority had grasped that adherence was important. Sam, male, age 12, shared, “I want to take my medication for my survival.” Similarly frightened by the prospect of switching, Denna, male, age 11, resolved he would “make an extra effort to take medication at all the times [he was] supposed to take them.” However, renewed commitment in the absence of additional support may be less likely to succeed. A handful of participants had devised individual strategies to support adherence. Teddy, female, age 14, and Ethan, male, age 18, set alarms to prompt them to take their treatment; Lazarus, male, age 18, took his at the time of a particular television programme, and Mariam, female, age 14, upon Muslim call to prayer. Jasmine, female, age 17, initiated changing the time of administration to facilitate adherence:

*“I would wake up late but I had to go to school and yet I had not yet showered, so before I know it is getting to 7am yet I have not yet taken my medication, so I decided to change it.”*

The development and use of these individual adherence strategies indicates a willingness and evolving capacity to self-care, however, these self-driven, apparently autonomous approaches were exceptional; and the need for additional support is evidenced by their need to transition to second-line therapy despite their individual efforts.

## 3.2 | Interpersonal-level considerations (caregivers, schools, workplaces)

### 3.2.1 | Caregiver-mediated treatment-taking

During childhood and early adolescence, capacity for self-care exists within the framework of caregiver-dependence and support. Dan, male, age 17, shared; “they (grandparents) are the ones who give me the money for transport to come to the clinic, they also ensure that I have juice or milk to take with my medication.” In later adolescence, some participants continued to benefit from caregiver support in contingency management. Sheena, female, age 17, explained; “if I don’t feel well, I let her (mother) know and she finds a solution.” Extended family and siblings assisted with providing support for several participants. In other accounts, however, caregivers were unsure how to respond to concerns and crisis situations arising in the home environment. Their capacity to respond appeared to be determined by the extent to which they had been equipped by healthcare workers with accessible resources and strategies.

### 3.2.2 | Transfer, rather than transition, of responsibility

Caregivers frequently struggled to juggle work and caring commitments. Denna, male, age 11, shared his impression that his mother was “too busy” to respond to questions about his illness. Ethan, male, age 18, similarly explained his grandmother “is usually busy, so she may not know that I take my medicine.” Given these limitations, transfer of responsibility for treatment-taking may have necessarily occurred in an unplanned, abrupt manner, rather than being implemented gradually; leaving young people with unreliable treatment supporters, or for some, “no people to remind or to help them” (Sophia, female, age 17).

Being moved to second-line treatment prompted more intensive adherence support, as Bob, male, age 15, recalls: “because I was missing, they (caregivers) started to give me my medication.” While reverting to caregiver-mediated treatment taking may be initially helpful, this approach fails to address underlying causes of non-adherence, and previous difficulties encountered by caregivers are likely to resurface; making this unlikely to be a sustainable model of support.

### 3.2.3 | Caregiver-mediated competency development

A handful of participants shared strategies implemented by their caregivers which developed their ability to self-manage treatment-taking, evolving to a model of “supporting” rather than “delivering” treatment. For example, Zack, male, aged 15, reported; “I take my medication at the same time with mother, so if one of us has forgotten we remind each other.” Dan, male, aged 17, shared; “I keep my medicine in their (grandparents) bedroom on a table, so in the evenings I go with my milk to their bedroom then I show them [that I] take the medicine.” In both scenarios, the adolescent is encouraged to initiate taking treatment on time, but within a protective net of indirect caregiver supervision. Other caregivers provided psychological support for their children with notable benefit. Jasmine, female, age 17, shared:

*“I told him that I was fed up of taking the medication every day, but he (father) told me that I have to take my medication, and I insisted and told him that I was fed up, then he encouraged me.”*

### 3.2.4 | Role of schools and workplaces

The benefit of collaboration with schools (and for older adolescents, workplaces) also proved to be an essential aspect of navigating impediments to treatment. For example, by approving absences necessary to attend HIV clinic appointments, providing education (“they taught us about HIV in class;” Sheena, female, age 17), combatting stigma when teachers “treat us (HIV-positive children) just like the other children” (Teddy, female, age 14), and discreetly storing and distributing ART medication.

We found that maintaining the confidentiality of HIV status was a universal priority, in light of significant concerns about bullying and stigma, and yet many participants lacked strategies to manage their treatment-taking discreetly in their school, workplace and (for some) HIV-discordant home environments. This issue created critical difficulties within boarding school contexts (in the absence of necessary support) as Saidat, female, age 16, recalls:

*“When I was in boarding school, I would be afraid to remove my medication to take it in the presence of the other students... because they will make fun of me or feel disgusted by me, like they do with the other children.”*

Lazarus, male, age 18, also avoided taking medication to work because “the pills were too big, as soon as someone else saw them they would instantly know... that I am sick.” Not always verbalised, these issues persisted unacknowledged; and in Saidat’s particular case, resulted in a period of compromised adherence totalling “three years.”

## 3.3 | Organization-level considerations (providers, clinicians)

### 3.3.1 | Adolescent-centred clinical interactions

The role of clinicians is central to the facilitation of transitions towards inter-dependent self-management of treatment adherence, however, we observed occasions where the structure of clinical interactions posed a significant barrier to their potential effectiveness. We found that caregivers rather than adolescents were often positioned at the centre of consultations, and that this had not necessarily evolved as they aged (particularly for those who had attended the clinic since childhood). Mariam, female, age 14, described a recent appointment where she was not addressed directly by the clinician:

*“Sometimes (the counsellor) speaks to me, but many times she speaks to Mummy. Today what did you speak about with the counsellor? She was writing in the file and Mummy was answering her.”*

Inadvertent exclusion of adolescents from clinical interactions appeared to limit the development of their health

literacy and ability to self-care, and emerged as being particularly problematic when caregiver support was withdrawn. Despite these challenges, enthusiasm to engage with clinicians and in health education persisted. Teddy, female, age 14, shared her (yet unmet) desire to learn more about HIV; "I like coming here because I am keen to know about my health. Do they tell you about your health when you come here? No they do not tell me, but I would like to know."

### 3.3.2 | Clinician-mediated competency development

It is revealing that participants were very responsive to instances when clinicians had initiated discussion and provided counselling. Jasmine, female, age 17, demonstrated how fostering disclosure of adherence difficulties can lead to their timely resolution, such as through joint problem solving;

*"I told a health care worker that I take my medication in the morning at 7am and when I come back from school at 6pm... but I told her that time is sometimes challenging for me. The counsellor told me that I could choose a time that was more convenient for me, and from that time I started to choose the time when to take my medication myself."*

In an environment where disclosure of HIV-positive status remains complex and challenging in the community setting, clinicians may be the only contacts other than the primary caregiver or immediate family to be aware of an adolescent's HIV-positive status. Sheena, female, age 17, shared:

*"I want to tell people what it is like for me taking the medicine, I would like them to encourage me. Mainly things to do with my treatment... I would like to speak to a friend."*

Clinicians have a potentially vital role to play as key supporters of psychological as well as physical wellbeing; central to holistic care and adolescent resilience. Teddy, female, age 14, shared the benefit she received by partaking in the clinical trial: "the study helps encourage us to take our medication well, and not feel sad and isolate ourselves."

## 4 | DISCUSSION

In accordance with the wider chronic disease literature describing best practice management during adolescence, our findings indicate that a deliberate "transitional" period in HIV care is required to facilitate successful transfer of HIV-management responsibility, from caregiver to adolescent [7,22-23,32]. We suggest adopting a social-ecological approach to the evolving model of care provision during this life-stage [25], incorporating both individual elements of transition preparedness, and harnessing the influential role of surrounding physical and social environments and available support systems [25,27].

Individuals must be equipped with core competencies required to engage with, and manage, the transition to autonomous treatment-taking and HIV care; for example, HIV literacy, self-efficacy and skill-acquisition, beliefs, goals and expectations, and psychosocial wellbeing [25,27]. The nature

and implications of their diagnosis, rationale and window of opportunity to take treatment daily, and strategies to manage missed doses and medication side-effects are essential to adherence counselling. For this purpose, established "transition checklists" may provide a valuable tool to broadly establish the extent of individual transition preparedness and guide ongoing care (where adapted, contextually suitable checklists are available [33,34]). We suggest that HIV-counselling content increase in sophistication pre-emptively with evolving maturity [35-37]. Ultimately, the optimal timing and rate of adolescent transition should be tailored to the neurocognitive developmental status of the individual, based on longitudinal assessment and contemporaneous understanding of individual capacity [25,38], rather than chronological age [39].

As young people mature, the relational influence of caregivers (who typically determine the success of HIV care during childhood) remains integral. However, the onset of adolescence should herald the onset of a deliberate, developmentally appropriate transition period which increasingly supports adolescents to partner with their treating clinicians directly [23,40]. Schools and workplaces may facilitate the transition process by providing supportive environments; in particular, by offering logistical assistance such as discreet treatment storage and medical leave.

This approach emphasizes that effective care during the transitional adolescent period entails a joint approach, which actively involves clinician, caregiver and adolescent collaboratively in the therapeutic process [7,25,38]. Aligned with the core foundation of social-ecological theory as pioneered by Bronfenbrenner [41], the adolescent should be positioned at the centre of the transition framework, and more specifically, at the centre of clinical interactions. Such encounters should foster an environment of uninhibited discussion, collaboration and support [11,29,40,42]. We found that treatment regimens were far more likely to be successful when they were developed in consultation with individual young people themselves [6,21,23,43]. This may be achieved by eliciting and seriously considering the priorities of ALHIV, such as preserving secrecy of their HIV-positive status, engaging in education and employment opportunities, establishing peer and intimate relationships, and maintaining realistic hope for the future [42,44-47]. Treatment plans should be adapted to contextual factors [6,8,23], such as by tailoring scheduled times for treatment-taking to prevent conflict with school and work commitments. In this way, regimen tolerability may be optimised, adherence incentivized and barriers to adherence pre-emptively addressed [39,48,49]. Similarly, when adherence is compromised, rather than conceptualising a young person as having "failed" in this regard (which may limit disclosure of future adherence challenges [29,48]), they should be re-framed as being the expert on their own individual circumstances [48,50]. Thereby, encouraging the adolescent to engage with caregivers and clinicians alike to identify their specific support needs [13,37,39,48]. Provision of training for healthcare professionals in the delivery of adolescent-centred care is likely to convey benefit to HIV-care outcomes by optimising the efficacy of therapeutic encounters [9,21,23,40]. Clinical interventions should be paired with strategic engagement of caregivers and relevant stakeholders (including teachers and employers) to foster supportive environments; integral to adolescent success during the transition period.



## 4.1 | Strengths and limitations

Previous qualitative research conducted among children and adolescents in similar settings has demonstrated their tendency to ration the candour with which they speak about adherence challenges, due to a desire to protect themselves and their relationships with others; given the moralized nature of discussions surrounding adherence [29,31,42]. A significant strength of this study is the recruitment of participants who had recently transitioned to second-line therapy. This provided us with a unique opportunity to discuss adherence challenges as being in the past, after they had been acknowledged; thereby facilitating greater transparency in participants' accounts.

A potential limitation of this study is that the clinic in which it was conducted is a relatively well-resourced speciality HIV centre, as such, our findings risk over-estimating the resources available in smaller, more remote settings. Conscious of this, we have focussed on transition as primarily taking place in community settings (homes and schools) with clinician guidance provided only during scheduled clinic appointments; an approach which should be replicable.

## 5 | CONCLUSIONS

As ALHIV are attributed greater responsibility for their treatment-taking and management, they must be equipped with the essential knowledge and capabilities required. Our findings suggest improved HIV outcomes in high-burden, resource-stretched settings may be achieved through the implementation of an intentional "transition period" in HIV care, incrementally supporting adolescents toward sustainable, autonomous management. We suggest adopting a social-ecological approach to transition care, whereby ALHIV are relationally supported in clinic, home, school and workplace environments to develop necessary "*adherence competencies*," specifically, through ongoing dialogue about HIV treatment literacy; routine management; identification of contingency strategies should social or physical environmental factors impede treatment taking; and disclosure of adherence difficulties as standard practice (allowing barriers to be addressed early). The proposed approach acknowledges the evolving relationship between adolescent, caregiver and clinician, and fosters efficacious collaboration in relation to HIV care throughout the dynamic transition process.

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### COMPETING INTERESTS

The authors have no competing interest to declare.

### AUTHORS' CONTRIBUTIONS

SB and JS designed the study which forms the basis of the data presented in this manuscript, with the support of SP and VM. SN collected the data with the supervision and support of SB and JS. VM contributed to the overview of data collection with JS and SB. Data analysis and drafting of the manuscript was done by CL and SB with support provided by JS, SN and SP. HN and CM contributed to data management and early contributions to data analysis. AT and VM contributed to the development of the manuscript. All authors read, reviewed and approved the final manuscript.

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## SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

**Appendix S1. ODYSSEY TRIAL TEAM\***



## SHORT REPORT

# Reproductive aspirations, contraception use and dual protection among adolescent girls and young women: the effect of motherhood and HIV status

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## Abstract

**Introduction:** There is a growing interest in adolescent motherhood and HIV among policymakers and programme implementers. To better shape services and health outcomes, we need evidence on reproductive aspirations and contraception use in this high-risk group, including the effect of motherhood and HIV status. We report data from a large survey of adolescent girls and young women conducted in a mixed rural-urban district in South Africa.

**Methods:** Quantitative interviews were conducted with 1712 adolescent girls and young women (ages 10 to 24): 336 adolescent mothers living with HIV (AMLHIV), 454 nulliparous adolescent girls living with HIV (ALHIV), 744 HIV-negative adolescent mothers (control adolescent mothers) and 178 HIV-negative nulliparous adolescent girls (nulliparous controls) in 2018 to 2019. Standardized questionnaires included socio-demographic measures, reproductive health and contraception experiences. Reproductive aspirations were measured as the number of children participants wanted to have. Dual protection was computed as use of both hormonal and barrier contraception or abstinence. Multivariate logistic regression and marginal effects models in STATA 15 were used to test associations between HIV status, adolescent motherhood and outcomes of reproductive aspirations, contraception use and dual protection, controlling for covariates.

**Results and discussion:** Nearly 95% of first pregnancies were unintended. Over two-thirds of all participants wanted two or more children. Hormonal contraception, condom use and dual protection were low across all groups. In multivariate regression modelling, ALHIV were less likely to report hormonal contraception use (aOR 0.55 95% CI 0.43 to 0.70  $p \leq 0.001$ ). In marginal effects modelling, adolescent mothers – independent of HIV status – were least likely to report condom use at last sex. Despite higher probabilities of using hormonal contraception, rates of dual protection were low: 17.1% among control adolescent mothers and 12.4% among AMLHIV. Adolescent mothers had the highest probabilities of not using any contraceptive method: 29.0% among control mothers and 23.5% among AMLHIV.

**Conclusions:** Among adolescent girls and young women in HIV-endemic communities, reproductive aspirations and contraceptive practices affect HIV risk and infection. Tailored adolescent-responsive health services could help young women plan their pregnancies for when they are healthy and well-supported, and help interrupt the cycle of HIV transmission by supporting them to practice dual protection.

**Keywords:** adolescents; motherhood; HIV; contraception; dual protection; South Africa

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## 1 | INTRODUCTION

More than 50% of all births in sub-Saharan Africa are to 15-to-19-year-old women [1]. By 2030, there will be nearly 1.5 million adolescent and young mothers living with HIV worldwide [2]. The majority of these pregnancies are unintended, and may result from violent and inequitable relationships [3-6]. Despite these difficult first pregnancies, qualitative research from sub-Saharan Africa suggests that adolescent

girls and young women have strong reproductive aspirations, regardless of their HIV status. To date, no quantitative research has examined the effect of HIV status and motherhood on reproductive aspirations and practices.

The children of adolescent mothers have higher risks of preterm birth, low birthweight and mortality [7-10]. Adolescent mothers are less likely to access contraception services and use postpartum contraception [11]. Nearly half of all unintended pregnancies among adolescent mothers end with

terminations of pregnancy, most of which are unsafe [12,13]. Moreover, in several sub-Saharan African countries, many adolescent girls and young women report more than one pregnancy before age 20 [14], including adolescent girls living with HIV (ALHIV) [10,17,18]. Rapid repeat pregnancies within adolescence may pose further biological, developmental and economic risks for both the mother and her children.

The risks facing adolescent mothers are amplified for those living with HIV, who face additional vulnerabilities [17–19]. Adolescents living with HIV who become pregnant experience less consistent engagement in antenatal and HIV care, intermittent viral suppression [20–22], delayed initiation of antiretroviral therapy (ART) [23] and poorer access to infant HIV testing [24–26]. Consequently, adolescent mothers living with HIV (AMLHIV) in sub-Saharan Africa are likelier than older mothers with HIV to transmit HIV to their children [26], despite global reductions in vertical HIV transmission [27].

More evidence about the syndemic of adolescent pregnancy and HIV is needed to inform future programming [18]. We present initial findings from a large study of adolescent mothers living with and without HIV, with comparison groups of nulliparous adolescent girls (N = 1712). This study addresses two important questions: First, how do reproductive aspirations, contraception use and dual protection practices of adolescent girls and young women vary by motherhood? Second, do experiences differ by adolescent mothers' HIV status?

## 2 | METHODS

The study was conducted in a mixed urban-rural health district of the Eastern Cape Province, South Africa. We interviewed n = 1712 adolescent girls and young women between March 2018 to July 2019, of whom n = 1027 had delivered their first child before age 20. We utilized six parallel sampling strategies to reach adolescent mothers (independent of their HIV status), alongside nulliparous adolescent girls with matched demographic profiles. An advisory group of adolescent mothers co-developed these recruitment methods with the research team for hard-to-reach adolescent mothers. For each recruitment channel, we recorded refusals and consenting adolescents. First, we included all district health facilities (n = 73). In health facilities, we searched all patient files of adolescent girls (10 to 19 years) who had ever initiated HIV treatment (whether still in HIV care or not) and interviewed them at home – 97% enrolled. Second, we used case files at all maternity obstetric units (n = 9) to identify all adolescent mothers (including AMLHIV) who were contacted through nurses, community healthcare workers in person or over the phone – 95% enrolled. Third, we randomly selected district secondary schools (n = 43) and interviewed adolescent girls who had recently given birth or dropped out of school due to pregnancy or motherhood – 98% enrolled. Fourth, we interviewed neighbouring adolescent girls of those approached through clinic files, which reduced any unintended stigmatization and provided a demographically matched control group. Fifth, we used referrals by social workers and NGO service providers to identify adolescent mothers who may be especially vulnerable – all eligible enrolled in the study (n = 95). Lastly, we included community referrals by adolescent mothers themselves – important in contexts where many

adolescents do not access any services – all those eligible enrolled (n = 51).

Voluntary informed consent was obtained from adolescents and their caregivers when adolescents were under 18, following international and national guidelines for consent among vulnerable populations. Data collection tools were piloted with n = 25 ALHIV and nine adolescent mothers. Ethical approvals were obtained from the Universities of Oxford (R48876/RE001,SSD/CUREC2/12–21) and Cape Town (HREC226/2017,CSSR2013/4), Eastern Cape Departments of Health and Basic Education and participating health and educational facilities. Participants did not receive financial remuneration, but were awarded a participation certificate and small gift pack selected by our Teen Advisory Group, including toiletries for adolescents and infants.

We used measures and scales validated in South Africa, where possible. *Socio-demographic* items (age, residence type (rural/urban), housing (formal/informal), household poverty and food insecurity) have been reported in detail elsewhere [19,28]. *Age at first parity* was measured through self-report and validated with oldest child age from children's medical records. *Unintended first pregnancy* was measured by assessing whether the pregnancy resulting in the first child was unwanted or unplanned. *Reproductive aspiration* was measured by asking how many children participants desire and was dichotomized for analyses (1 = want 2 or more children; 0 = wants none or 1 child). *Hormonal contraception* was computed from three variables: current self-reported use of oral contraceptives, injectables or implant: participants reporting using any form was coded as 1. *Condom use at last sex* was defined as using a condom for the entire duration of the most recent sexual act. *Dual protection* was computed by combining adolescents reporting both hormonal contraception and condom use at last sex. Abstinent adolescents were marked as dually protected. Participants were coded as having *no protection* if they reported no hormonal contraception nor condom use, and were not abstinent. *Current ART use* was defined as self-reported ART use during the interview. Relationship factors included: *relationship status* (yes/no), *partner type* (boyfriend/girlfriend/husband/wife vs. casual), *partner HIV status knowledge* (unknown, HIV negative, HIV positive), all self-reported by participants.

All analyses were conducted using STATA 15. First, socio-demographic characteristics, reproductive aspirations, contraception and dual protection frequencies were computed for the full sample and for four sub-groups by HIV status and motherhood: (1) AMLHIV, (2) adolescent girls and young women living with HIV who have not initiated childbearing (*nulliparous ALHIV*), (3) HIV-negative adolescent mothers (*control adolescent mothers*), and (4) HIV-negative adolescent girls and young women who have not initiated childbearing (*nulliparous controls*). Second, pairwise correlations among socio-demographics and relationship variables were computed to check collinearity and to determine which factors were included in additional analyses. Third, associations between HIV status and motherhood on outcomes were explored using multivariate logistic regression models, controlling for socio-demographic variables that were significantly different across four sub-groups. *p*-values were adjusted for multiple outcome testing using the Benjamini–Hochberg approach [29]. Fourth, predicted probabilities of reporting each outcome for the four

sub-groups were computed, holding all included socio-demographic factors at their mean values.

## 3 | RESULTS AND DISCUSSION

### 3.1 | Participant characteristics

Table 1 presents frequencies of socio-demographic characteristics and reproductive aspirations and experiences for the full sample (N = 1712) and four sub-groups defined above: (i) AMLHIV (n = 336, 20%), (ii) nulliparous ALHIV (n = 454, 27%), (iii) control adolescent mothers (n = 734, 44%) and (iv) nulliparous controls (n = 188, 10%). Participants' mean age was 17.6 years (IQR 16 to 19 years, SD = 2.6), and average age at first child among n = 1045 mothers was 16.5 (SD 1.8). AMLHIV, on average, had their first child slightly later at 17.3 years (SD 2.2,  $p \leq 0.001$ ). One-quarter of participants lived in rural areas. AMLHIV were more likely to live in informal housing ( $p \leq 0.001$ ). One-quarter of participants reported

past-week food insecurity. The study's participants live in challenging socio-economic environments, reflecting the living situations of most adolescents in the region.

Nearly all adolescent mothers – independent of HIV status – had at least one sexual partner in the last year, with over half reporting being in a relationship. A third of all participants knew their partner's HIV status, with three-quarter of control adolescent moms reporting they knew this (almost all partners were reported as HIV negative).

On average, participants wanted to have two children (mean 1.9, IQR, SD = 1.0). Over two-thirds of all participants wanted to have at least two children, though almost 95% of all first childbearing pregnancies were unintended. Just under half of the participants reported using hormonal contraception, 31.5% of sexually active participants reported condom use at last intercourse, and 16.7% reported using both condoms and hormonal contraception for dual protection. Twenty percent reported using no methods of contraception or HIV prevention at last sex.

**Table 1. Socio-demographic and relationship characteristics of adolescent girls and young women by HIV and motherhood**

Characteristics	AMLHIV (n = 336)	Nulliparous ALHIV (n = 454)	Control adolescent mothers (n = 744)	Nulliparous controls (n = 178)	All participants (n = 1712)	p-value
Age (mean, SD)	19.8 (1.9)	16.3 (2.9)	17.8 (1.5)	16.3 (3.0)	17.6 (2.6)	$\leq 0.001$
Age at first child (mean, SD) <sup>a</sup>	17.3 (2.2)		16.3 (1.6)		16.5 (1.8)	$\leq 0.001$
Rural residence (n, %)	86 (25.4)	109 (24.3)	223 (30.0)	47 (26.4)	465 (27.2)	0.141
Informal housing (n, %)	80 (23.6)	63 (14.0)	155 (20.8)	15 (8.4)	313 (18.3)	$\leq 0.001$
Household poverty (n, %)	276 (81.4)	315 (69.8)	591 (79.4)	110 (61.8)	1292 (75.5)	$\leq 0.001$
Food insecurity (n, %)	99 (29.2)	98 (21.7)	195 (26.2)	43 (24.2)	435 (25.4)	0.102
Currently on ART (n, %)	291 (85.8)	409 (90.7)	NA	NA	700 (88.6)	0.034
Sexually active in the past year (N, %)	318 (93.8)	111 (24.6)	696 (93.6)	73 (41.0)	1198 (70.0)	$\leq 0.001$
In a relationship (n, %)	246 (74.1)	113 (25.2)	477 (64.5)	74 (41.8)	910 (53.6)	$\leq 0.001$
Partner HIV status (n, %)						$\leq 0.001$
Unknown	124 (49.0)	72 (62.6)	126 (26.2)	32 (42.7)	354 (38.3)	
HIV-negative	62 (24.8)	35 (29.7)	352 (73.2)	43 (57.3)	492 (53.3)	
HIV-positive	67 (26.7)	8 (6.8)	3 (0.6)	0 (0)	78 (8.4)	
Last sexual partner casual (n, %)	87 (25.7)	337 (74.7)	268 (36.0)	106 (59.6)	798 (46.6)	$\leq 0.001$
Reproductive aspirations, contraception and dual protection						
Aspirations (mean, SD)	2.0 (0.8)	1.8 (0.9)	1.8 (0.8)	2.2 (1.7)	1.9 (1.0)	$\leq 0.001$
Aspirations – want 2 or more children (n, %)	252 (74.3)	303 (67.2)	480 (64.5)	145 (81.5)	1180 (68.9)	$\leq 0.001$
First child pregnancy unintended (n, %) <sup>a</sup>		274 (93.2)		716 (95.2)	990 (94.7)	0.193
Hormonal contraception (n, %)	214 (63.1)	81 (18.0)	474 (63.7)	55 (30.9)	824 (48.1)	$\leq 0.001$
Condom use at last sex (n, %) <sup>b</sup>	99 (31.1)	61 (55.0)	178 (25.6)	39 (53.4)	377 (31.5)	$\leq 0.001$
Dual protection (n, %)	72 (21.2)	46 (10.2)	136 (18.3)	32 (18.0)	286 (16.7)	$\leq 0.001$
No protection (n, %)	93 (27.4)	34 (7.5)	218 (29.3)	22 (12.4)	367 (21.4)	$\leq 0.001$

<sup>a</sup>Data available for n = 1045 adolescent mothers only

<sup>b</sup>Among sexually active participants only n = 1198.

AMLHIV, adolescent mothers living with HIV; SD, standard deviation; ART, antiretroviral therapy.

### 3.2 | Effect of HIV and motherhood on reproductive practices

Results of multivariate regressions for each of the five outcomes adjusted for socio-demographic variables are included in Table 2, with predicted probabilities of reporting the outcomes in Figure 1. All the rates reported below are adjusted predicted probabilities of each outcome being reported, holding age, informal housing and poverty at their mean values. Independent of HIV status, adolescent mothers were less likely to report wanting >2 children (aOR 0.57, CI 0.43 to 0.75), possibly due to the challenges already experienced [30]. Predicted probabilities – adjusted to take into account age, informal housing and poverty – showed that aspirations for two or more children were lowest among AMLHIV (62.9%) and highest among nulliparous controls (77.4%).

Hormonal contraception showed differences by both adolescent motherhood and HIV status. Adolescent motherhood was associated with substantially higher rates of hormonal contraception use (aOR 3.37, 95% CI 2.58 to 4.40) compared to nulliparous girls. Amongst adolescent mothers, AMLHIV had a lower predicted probability of reporting hormonal contraceptive use (48.4% vs. 63.1% amongst control adolescent mothers). The opposite pattern was observed for condom use at last sex among sexually active participants (aOR 0.34, 95% CI 0.29 to 0.47), with higher rates amongst adolescents who had not yet had children: 52.5% among controls and 53.9% among ALHIV. Adolescent motherhood rates of condom use were slightly higher amongst ALMHIV (28.2%) than adolescent mother controls (26.3%). Dual protection, recommended for all adolescent girls and mothers in national guidelines, remained extremely low (16.7%). ALHIV who had not yet had children had lowest rates of dual protection (10.2%).

Adolescent mothers were more likely to report no protection at last sex (aOR 3.21, 95% CI 2.25 to 4.58). The likelihood of reporting no protection was highest among control adolescent mothers (29.0%).

### 3.3 | Implications for service provision and research

These findings highlight important paradigm shifts that are needed to provide effective health and social services to adolescents and young women. First, they highlight the importance of responding to adolescent girls' parenthood aspirations and needs, not only their risk profiles. Adolescent girls and young women – regardless of HIV status – aspire to have families, with over two-thirds of them wanting two or more children. If acknowledged in respectful and age-appropriate ways, these aspirations provide an opportunity to engage adolescents in integrated sexual and reproductive health (SRH) services, including safe conception, into HIV care and treatment services. Rates of dual protection – protection from sexually transmitted infections (STIs) and access to family planning – were low among all participants, only slightly higher than the rates of dual protection documented among young women in two South African studies over a decade ago [31,32]. Nulliparous ALHIV had the lowest rates of contraception and dual protection use. Instead of advising ALHIV to refrain from sex, relationships or related risk-taking [33], providers should listen to the aspirations and life circumstances of young women to effectively support them to attain positive SRH outcomes – for themselves, their partners and their children [13].

Second, the timing of these pregnancies is critical. With nearly 95% reporting unintended first pregnancies, adolescent girls and young mothers – particularly ALHIV – must be supported to time their pregnancies for when they are wanted,

**Table 2. Multivariate regression models testing the effect of HIV and motherhood on reproductive aspirations, contraception and dual protection (n = 1712)**

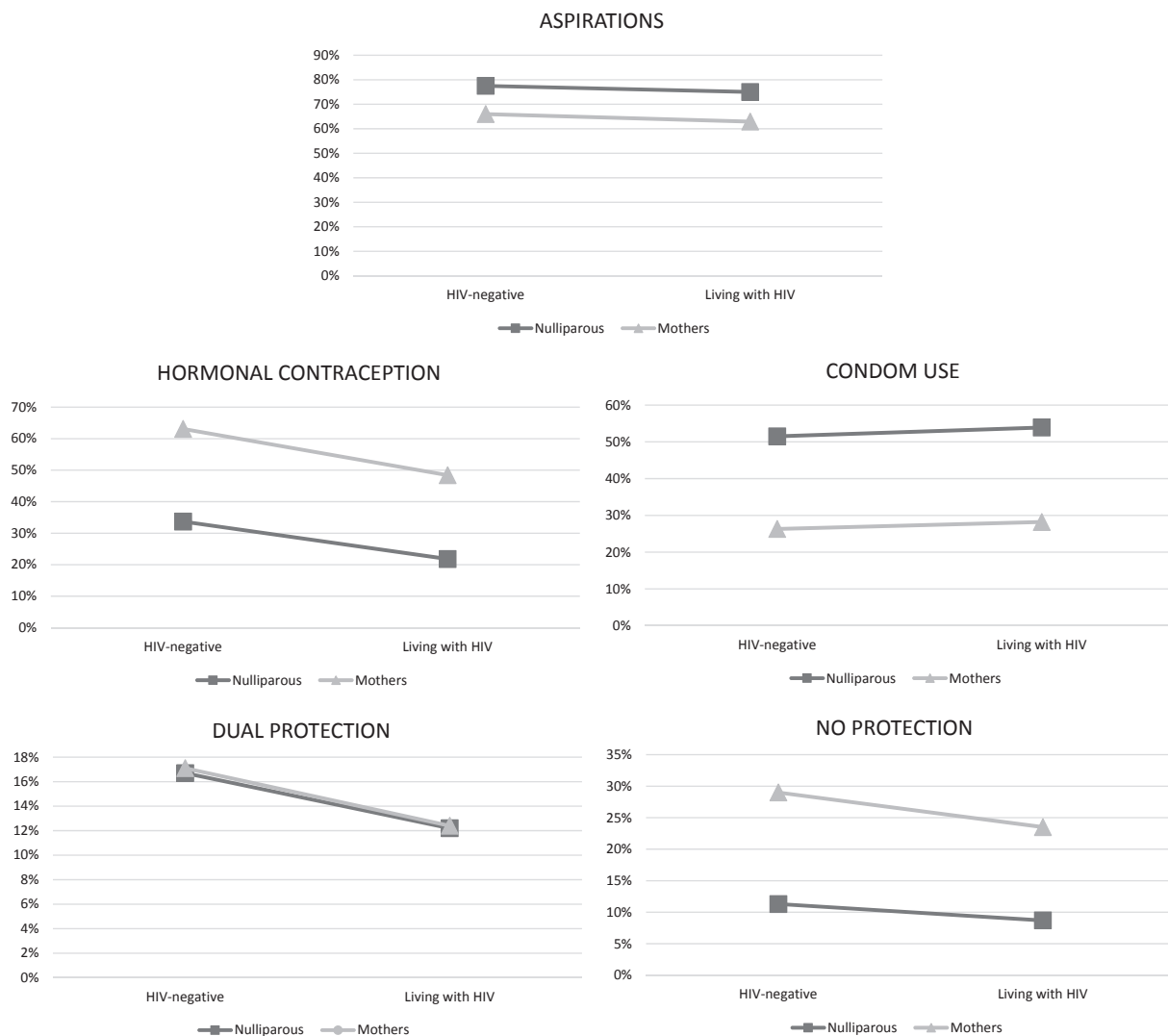
Variables included in each model	Outcome 1: reproductive aspirations (n = 1712)		Outcome 2: hormonal contraception (n = 1712)		Outcome 3: condom use at last sex (n = 1198)	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Age	<b>1.13 (1.08 to 1.18)</b>	<b>≤0.001*</b>	<b>1.30 (1.24 to 1.37)</b>	<b>≤0.001*</b>	1.11 (1.03 to 1.19)	0.006
Housing (informal)	1.56 (1.17 to 2.07)	0.002	1.23 (0.93 to 1.63)	0.147	1.57 (1.15 to 2.15)	0.004
Poverty (missing at least one basic necessity)	1.13 (0.89 to 1.44)	0.319	0.85 (0.66 to 1.11)	0.231	<b>0.50 (0.37 to 0.68)</b>	<b>≤0.001*</b>
HIV-positive status	0.87 (0.69 to 1.11)	0.261	<b>0.55 (0.43 to 0.70)</b>	<b>≤0.001*</b>	1.10 (0.82 to 1.49)	0.515
Motherhood	<b>0.56 (0.42 to 0.75)</b>	<b>≤0.001*</b>	<b>3.37 (2.58 to 4.40)</b>	<b>≤0.001*</b>	<b>0.34 (0.29 to 0.47)</b>	<b>≤0.001*</b>

Variables included in each model	Outcome 4: dual protection at last sex (n = 1712)		Outcome 5: no protection at last sex (n = 1712)	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Age	<b>1.28 (1.20 to 1.36)</b>	<b>≤0.001*</b>	1.07 (1.00 to 1.13)	0.037
Housing (informal)	1.53 (1.11 to 2.10)	0.009	0.68 (0.50 to 0.94)	0.021
Poverty (missing at least one basic necessity)	<b>0.55 (0.41 to 0.74)</b>	<b>≤0.001*</b>	1.73 (1.25 to 2.38)	0.001
HIV-positive status	0.69 (0.51 to 0.93)	0.015	0.75 (0.57 to 1.00)	0.047
Motherhood	1.02 (0.74 to 1.43)	0.886	<b>3.21 (2.25 to 4.58)</b>	<b>≤0.001<sup>§</sup></b>

\*Significant at 0.001 level, when adjusted using the Benjamini–Hochberg correction for multiple outcome testing.

<sup>§</sup>Significant at 0.05 level, when adjusted using the Benjamini–Hochberg correction for multiple outcome testing.



**Figure 1. Predicted probabilities of reporting outcomes among adolescent girls and young women by HIV status (n = 1712).**

ideally when women are healthy and well-supported emotionally, socially and financially [34]. Improving adolescent maternal outcomes and fostering child development also relies on preventing rapid repeat pregnancies. Moreover, given high rates of intimate partner violence and power-inequitable relationships reported by adolescent girls and young women, additional analyses integrating these complex considerations are needed [35]. Further research is needed on the experiences of AMLHIV across HIV, SRH and contraception and maternal and child health services, to better integrate and adapt them to the unique needs of this age group.

Third, access to and use of contraception, including consistent condom use, was low among participants. Motherhood provides an opportunity to support young women to initiate contraception, however, we found increased hormonal contraception seemed to occur in parallel with reduced condom use. Adolescent girls and young mothers – regardless of HIV status – must access a contraceptive methods mix that is consistent, accessible and appropriate for their life stage and the precarious environments they live in [13].

Fourth, the contraceptive and HIV prevention gap reported in this study is extremely time-sensitive: the risk of new HIV infections among adolescent girls increases once they have had their first child in adolescence [36]. Existing research confirms the urgent need for combination prevention to reduce HIV and STI incidence among adolescent girls and young women, including dual protection [37,38]. Low rates of initiation and retention on ART, especially in the postpartum period, combined with high rates of repeated pregnancies in this age group [11], make AMLHIV highly vulnerable to passing HIV on to their children.

Finally, this analyses does not include data on ART access and use alongside conventional dual protection methods. Attaining and maintaining viral suppression – alongside an age and life-stage appropriate contraceptive mix – is central to reducing onward HIV transmission rates. While timely viral load information is not readily available in low resource settings, future analyses on this topic is critical.

This study has several limitations. First, all outcomes are self-reported, and may underestimate actual experiences of



adolescent girls and young women. Data on ART access and viral suppression were not yet available for these analyses. Differential reporting by age and HIV status may have affected results, given potential increased stigma attached to younger motherhood and living with HIV. Second, the data are from South Africa and may not be generalizable. Nonetheless, we conducted the study in a resource-constrained setting, comparable to others in Southern Africa, which may allow for cross-cutting lessons. Third, cross-sectional data limits our ability to draw causal inferences. More complex analyses to investigate potential interactions between HIV status, motherhood and relationship/partner factors, including longitudinal follow-up, are needed to understand factors shaping the SRH practices of adolescent girls and young women. Fourth, as the sample was young (average age 16.2 years), the study most likely underestimates rates of adolescent pregnancy. Finally, this short report includes limited information on the sexual partners of adolescent girls and young women, which is not yet available in this data. Future research on partners will be important in understanding the dynamics of early pregnancy, reproductive aspirations and practices for these girls and young women.

Despite the above limitations, this study has several strengths. First, it is the first and largest quantitative analyses of reproductive aspirations and practices of adolescent girls and young mothers living in HIV-endemic communities. Second, given the high levels of stigmatization reported by ALHIV [39,40] and adolescent mothers [30], conventional recruitment techniques for this sample would have resulted in a biased sample. The research team designed a systematic sampling approach prioritizing non-stigmatization and use of community and peer networks to increase reach and uptake among this group.

## 4 | CONCLUSIONS

As new infections among adolescents persist, and as more ALHIV reach childbearing age [5], we need to better understand how to engage adolescent mothers in comprehensive, tailored health services to effectively reduce HIV-related morbidity and mortality [17]. Safe conception considerations – planned pregnancies that coincide with viral suppression, but also socio-emotional readiness – must be integrated in HIV and SRH service provision for adolescent girls and young women living with HIV. It is also critical to shift away from a risk-centred narrative, promoting more nuanced evidence on young women's sexual and reproductive health needs and practices, especially among ALHIV [15,30,41]. Additional research is needed to understand which factors support adolescent girls and young women to use dual protection and have well-timed, supported pregnancies, particularly in the context of HIV. Our preliminary results echo calls for the integration of HIV and SRH services made at recent academic, policy and donor forums – the time for saving future generations is now!

## COMPETING INTERESTS

Study sponsors were not involved in study design, data collection, analyses nor interpretation, the writing of this manuscript, nor the decision to submission of

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## AUTHOR'S CONTRIBUTIONS

ET, LC, LS and CW designed and implemented the overall study. ET and LC conceptualized the analyses. ET led the analyses, with support from LC, NL and SZ. ET, LC and CL wrote the manuscript's first draft. ET and CL led on the revisions following peer reviews. All authors provided edits and feedback on manuscript content and have approved the final draft.

## ABBREVIATIONS

AIDS, acquired immunodeficiency syndrome; ALHIV, adolescent girls living with HIV; AMLHIV, adolescent mothers living with HIV; ART, antiretroviral therapy; HIV, human immunodeficiency virus; SRH, sexual and reproductive health; STIs, sexually transmitted infections.

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## COMMENTARY

# Directed and target focused multi-sectoral adolescent HIV prevention: insights from implementation of the 'DREAMS Partnership' in rural South Africa

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### Abstract

**Introduction:** The "DREAMS Partnership" promotes a multi-sectoral approach to reduce adolescent girls and young women's (AGYW) vulnerability to HIV in sub-Saharan Africa. Despite widespread calls to combine structural, behavioural and biomedical HIV prevention interventions, this has not been delivered at scale. In this commentary, we reflect on the two-year rollout of DREAMS in a high HIV incidence, rural and poor community in northern KwaZulu-Natal, South Africa to critically appraise the capacity for a centrally co-ordinated and AGYW-focused approach to combination HIV prevention to support sustainable development for adolescents.

**Discussion:** DREAMS employed a directed target-focused approach in which local implementing partners were resourced to deliver defined packages to AGYW in selected geographical areas over two years. We argue that this approach, with high-level oversight by government and funders, enabled the rapid roll-out of ambitious multi-sectoral HIV prevention for AGYW. It was most successful at delivering multiple interventions for AGYW when it built on existing infrastructure and competencies, and/or allocated resources to address existing youth development concerns of the community. The approach would have been strengthened if it had included a mechanism to solicit and then respond to the concerns of young women, for example gender-related norms and how young women experience their sexuality, and if this listening was supported by versatility to adapt to the social context. In a context of high HIV vulnerability across all adolescents and youth, an over-emphasis on targeting specific groups, whether geographically or by risk profile, may have hampered acceptability and reach of the intervention. Absence of meaningful engagement of AGYW in the development, delivery and leadership of the intervention was a lost opportunity to achieve sustainable development goals among young people and shift gender-norms.

**Conclusions:** Centrally directed and target-focused scale-up of defined packages of HIV prevention across sectors was largely successful in reaching AGYW in this rural South African setting rapidly. However, to achieve sustainable and successful long-term youth development and transformation of gender-norms there is a need for greater adaptability, economic empowerment and meaningful engagement of AGYW in the development and delivery of interventions. Achieving this will require sustained commitment from government and funders.

**Keywords:** adolescent girls and young women; HIV; holistic; interventions; layering; implementation

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## 1 | INTRODUCTION

In South Africa HIV incidence remains high, especially among adolescents and youth (10 to 25 years old) [1]. Although there is evidence of a decline in HIV incidence of 44% among the general population from 2012, incidence was still higher in adolescent girls and young women (AGYW) [15-24] than their male counterparts [2]. This indicates there is still need for greater efforts to reduce the impact of the HIV epidemic in young people, in particular AGYW [1].

There have long been calls to scale-up evidence-based combination structural, behavioural and biomedical HIV prevention interventions [3-7]. This has been reinvigorated by evidence that "layering," that is providing multiple interventions or services can accelerate progress to sustainable development goals in adolescents living with HIV [8]. In response, the US Presidents' Emergency Plan for AIDS Relief (PEPFAR) with others, supported the 'DREAMS Partnership', a multi-sectoral package of interventions targeting multiple sources of HIV risk and vulnerability for AGYW [9,10]. The aim of DREAMS was

to reduce HIV incidence through strengthening existing interventions and the introduction of new packages for gender-based violence, family and caregiving, social asset building, economic empowerment/cash transfers and pre-exposure prophylaxis (PrEP) (Figure 1) [9,11,12].

DREAMS in South Africa was implemented with high-level oversight by government and funders, through local implementing partners who were resourced to deliver defined and target-focused packages of interventions to AGYW in selected geographic areas over two years. Implementing multi-sectoral programmes is complex [3]; it requires maintaining fidelity to the Theory of Change, coordination across multiple sectors and monitoring coverage of those in need [11,13]. Recognizing these challenges, between 2016 and 2018 we evaluated DREAMS rollout in a poor rural district in northern KwaZulu-Natal (KZN), South Africa, with a high burden of HIV through extensive engagement with implementing partners, community stakeholders and representative surveys of potential beneficiaries of DREAMS [13].

In this commentary we, a multidisciplinary team of researchers, reflect on our experience to appraise the capacity for a co-ordinated and AGYW focused approach to combination HIV prevention to support sustainable development for adolescents. We argue that this approach rapidly scaled-up a

multi-sectoral HIV prevention intervention for AGYW. It was most successful when it strengthened existing infrastructure and/or when tackled youth development that coincided with community concerns. We interrogate and draw lessons from the lost opportunity to support longer term sustainable development goals and transform gender norms for adolescents [14-16].

## 2 | DISCUSSION

### 2.1 | Prescribed and target-driven scale-up of multi-sectoral HIV prevention for AGYW

Prior to DREAMS, there was limited co-ordination of HIV interventions for adolescents and young people in the study area in northern KZN. Health promotion and preventive services were mostly provided through the Department of Health in fixed clinics; life orientation was provided in schools by the Department of Education, and social protection by the Department of Social Development [17]. Prior to 2015, HIV incidence had been persistently high in this area [18] with low uptake of sexual and reproductive health services; in 2015 <50% of sexually active AGYW used condoms at last sex; and <50% were currently using contraception [18].

Package level		Package category	Target group(s)	Description of activities & examples from KZN, South Africa
Individual level	<b>Empower AGYW and reduce their risk</b>	HIV Testing Services	AGYW & male partners	HIV testing; linkage to care & ART if positive, or linkage to other DREAMS prevention if negative
		Social asset building	AGYW	Build social skills and networks; connect AGYW with peers & adults, for information, emotional & material support eg <i>Safe Spaces</i> , <i>Vhutshilo 1&amp;2</i> , <i>Mentorship</i> , <i>Financial Capabilities</i>
		Expand contraceptive mix	AGYW	Promote use of modern contraception, dual methods alongside condoms, to reduce unplanned pregnancy and school drop-out eg <i>Adolescent-friendly services like happy hour</i> , <i>priority queues</i>
		Condom promotion & provision	AGYW & male partners	Increasing consistent use & availability, e.g. through condom distribution, adolescent-friendly SRH services
		Post-violence care	AGYW experienced/ at risk for violence	Youth-friendly screening & care for intimate partner violence/ violence against children, PEP
		PrEP <i>*selected countries</i>	AGYW at highest risk of acquiring HIV	Targeted provision of PrEP, linkage to support services; <i>provided only for female sex workers</i>
Contextual level	<b>Strengthen families</b>	Social protection	AGYW & parents/guardians	Cash transfers, educational subsidies, combination socio-economic approaches e.g. <i>savings groups</i> ; <i>financial literacy training</i> eg. <i>ASPIRES</i> , <i>Vhutshilo</i> , <i>Financial Capabilities</i> , <i>Vocational skills training</i> , <i>Business/entrepreneurial training</i> , <i>Microfinance program</i>
		Parenting/caregiver programmes	AGYW & parents / caregivers of AGYW	Parenting programmes on adolescent sexual/risk behaviours & protection from violence eg <i>Teenagers and Adults Learning to Communicate (TALC)</i>
	<b>Mobilise community for change</b>	School-based HIV prevention	AGYW & boys in schools	HIV & sex education, violence prevention education in schools
		Community mobilisation & norms change	AGYW, boys & men, broader communities	Community-based HIV and violence prevention programmes, social/gender norms change & gender-related messaging eg <i>Stepping Stones</i>
	<b>Reduce risk in male sex partners</b>	Characterisation of male sex partners to target interventions	Sexual partners of AGYW	Target highly effective HIV prevention, care and treatment interventions. Develop services men are more likely to use. Research & characterise 'typical' partners of AGYW.

Figure 1. Framework for DREAMS core package of interventions. Adapted with permission [12].

In order to catalyse multi-sectoral collaborations and strengthen existing resources and policies, such as government cash transfer mechanisms to support AGYW [6] and adolescent and youth friendly services [19], the DREAMS Partnership engaged with the Departments of Health, Social Development and Education [11,20]. However, the rollout of DREAMS was very rapid [20], and these sectors had not previously been co-ordinated by a disease-specific agency such as the AIDS Council. The AIDS council was involved at provincial level as the co-ordinating body and at district level as part of the project team responsible for co-ordinating DREAMS and ensuring the alignment of DREAMS activities with existing programmes [20]. Moreover, some of the interventions were new to the setting, such as community-based interventions for gender-based violence, family and caregiving and HIV PrEP. Five implementing partners were commissioned, each to deliver different interventions of the package based on their expertise. While some implementing partners subcontracted community-based organizations (CBOs) who were embedded in the community, others introduced new organizations to the area [20].

The consequence was that at the height of implementation in 2017, 11 organizations were receiving DREAMS funding to deliver 28 different interventions, grouped into categories (e.g. social protection), which in turn were organized by levels (e.g. “strengthen families”) (Figure 1) [12] that were expected to be layered in order to accelerate benefits in AGYW. Layering also included contextual interventions that were not delivered directly to the individual, but benefitted the AGYW [11-12,21]. In the absence of an existing co-ordinating mechanism, several donor-led steering committee meetings were organized to bring all the players on-board, mapping out geographical working boundaries and ensuring the “layering” approach was understood [21]. Implementing partners were given targets (number of AGYW to reach with specific interventions), which were monitored through the DREAMS Integrated Monitoring and Evaluation System (DIMES) [22]. Quarterly provincial meetings (and monthly at district-level) were held by the co-ordinating partner and AIDS council with implementing partners to measure progress and performance.

In the next section, we appraise the strengths and weaknesses of this prescribed and target-driven approach to combination HIV prevention for AGYW in supporting sustainable development goals among youth in a rural community.

## 2.2 | Lessons learned

### 2.2.1 | *Effective scale-up strengthens existing infrastructure and builds on intervention norms*

Interventions that built on pre-existing interventions with organizations that were already embedded in the setting could be scaled-up rapidly, for example school-based interventions, HIV testing, condom distribution and promotion through existing CBOs, since the infrastructure already existed and little training and adaptation were needed.

CBOs who were already embedded in the communities were able to adapt delivery (but not content) of the DREAMS package to the local context. For example they offered HIV testing during outreach activities at community gatherings (grants pay-out days, sport days, etc), distributed condoms in

shops in the rural settings and formed partnerships with private doctors, police and other implementing partners to support identification and management of post-violence care and improved onward referrals. As a result we found an increased visibility of these CBOs and their activities, such as condoms in bars, shops and remote rural areas.

Some novel interventions such as voluntary medical male circumcision (delivered outside of DREAMS, but escalated during DREAMS) that responded to and resonated with the existing HIV prevention and gendered norms, such as traditional male circumcision, were acceptable and uptake increased [23]. However, while more young people reported being aware of newer biomedical technologies such as PrEP by the second year of scale-up, they and healthcare workers expressed ambiguous feelings around this novel biomedical approach to HIV prevention [23,24]. Young people were concerned about side effects related to the use of PrEP and the potential HIV-related stigma and discrimination they could experience if as young women they accessed PrEP from healthcare facilities [23,25].

### 2.2.2 | *Youth development was embraced by the community; transforming gender-norms less so*

Unemployment, poverty and violence are recognized as youth development issues of importance in the area, and therefore community members welcomed the broader multi-sectoral approach that underpinned DREAMS. This was particularly the case when delivered through CBOs with a history in the area, which were trusted and embraced the benefits of “layering” interventions. Consequently, there was a rapid increase in the proportion of AGYW who received all three “layers” of DREAMS interventions, that is interventions at community, family and individual levels (Figure 1). More than half of AGYW were invited to participate in DREAMS, with over 80% of those accessing  $\geq 3$  interventions [12].

Community leaders saw DREAMS multi-sectoral approach as a lost opportunity to include young men who faced similar youth development challenges [26]. While young men have sexual reproductive health (SRH) needs and are partners of AGYW [26] in our community this ambivalence mirrored the well-described barriers to shifting gender-norms in South Africa [27-29]. DREAMS implemented a package that addressed gender-based violence explicitly and gender dynamics implicitly (contraception education and access, stepping stones and cash transfers). However, the prescribed nature of the packages and limited opportunities for meaningful engagement of young women and men in implementation, constrained the transformative potential to radically challenge social constructs of gender that continue to drive the disproportionate burden of HIV on adolescents and young women [30-32].

### 2.2.3 | *Youth centred adaptation to social context is an important ingredient*

DREAMS implementing partners were required to deliver interventions listed in the DREAMS package as per their contractual agreement and area of expertise and were monitored with respect to centrally designed standards of delivery. Organizations delivering these interventions felt that they could be



more successful if they were able to adapt to their social context and respond to unmet youth development needs. However, they felt a tension between this and being seen to deliver interventions with fidelity to the central design standards. The overall effect was a limited scope for iterative adaptation or innovation.

Even after DREAMS rollout, contraception uptake remained low among adolescent girls [13-19] despite many being sexually active [12,33]. We found that strengthening provision of adolescent and youth-friendly SRH services within the primary healthcare clinics in this rural setting during the period of evaluation did not translate to uptake; well-described social, health facility and individual level factors all contributed to poor uptake. At an individual level, persisting myths and misconceptions around conception [23,33] and anticipated stigma associated with being seen entering a clinic, fear of judgement and transport costs were described by AGYW as barriers to use. Data from our team suggested that young people and the organizations working with them felt that more active involvement of young people may have increased demand for services and promoted innovations in healthcare delivery that overcome barriers to uptake; for example the use of peer outreach workers to promote sexual health and delivery of SRH services in youth centres and mobile clinic [31,34,35].

Similarly, there was limited flexibility within DREAMS to respond to other health issues such as mental health and alcohol use, even though they are well-described [36] structural factors that predispose young people to HIV acquisition and poor health. Common mental health disorders increased steadily with age among AGYW in this setting (up to 33% in 22-year olds), and were associated with food insecurity, migration and experiencing violence [36]. Similarly, alcohol was easily available to and perceived as a normative part of adolescence and transition into adulthood. Poor mental health and alcohol were described as barriers to engagement and retention in the prevention, treatment and care services offered by DREAMS. For example young people described engaging in unplanned and unprotected sex under the influence of alcohol or drugs and reported forgetting to take their PrEP or ART pills when drunk [23-24,37].

### **2.2.4 | Target focused delivery may reduce reach to those most in need**

In a setting where there were few prior HIV interventions targeting young people, local implementing partners had to develop new ways to identify vulnerable AGYW to reach. They relied on their organizational databases of orphans and vulnerable children and families and worked with schools for recruiting and targeting AGYW in need of services. This targeting of DREAMS interventions by place or type of person, with goal of "saturating" targeted AGYW may have, particularly under the pressure to rapidly implement, paradoxically hindered reach to those most in-need or vulnerable.

During multiple donor-led meetings and with resources focused on geographical mapping and identifying higher risk AGYW, the challenges local implementers faced became apparent. Vulnerable AGYW were widely dispersed, often mobile and engaging AGYW in the geographical areas where HIV-infection was high, was frequently a challenge. For example we found more than one in ten of sexually active AGYW

reported transactional sex or sex-work activities, but only a handful of them were aware of PrEP and none had taken PrEP, a service that was specifically targeted at this group of young women [24]. AGYW engaging in commercial sex often did not self-identify or report themselves as sex-workers and were thus missed by PrEP outreach programmes [24]. A differentiated approach, investing in universal health and social services for adolescents and young people that could be tailored to individual needs, combined with evidence-based approaches to reaching those who are harder to reach, such as through social networks or venue-based approaches, may result in more effective coverage of vulnerable and at risk AGYW in this type of rural setting [17].

### **2.2.5 | Youth leadership and sustainable development goals**

DREAMS was a lost opportunity to embed sustainable development goals and build the capacity for youth leadership in a deprived rural community. Youth unemployment was high (>80% among 18+ year-olds) [18] and there was a lack of recreation and educational opportunities for young people who had completed school, increasing vulnerability to transactional sex and crime [37]. Migration was high among this group (about 20% among AGYW in 2017 reported ever migrating in the past year) mainly for seeking employment and school purposes, and these AGYW were missed out of interventions [12], yet they are at high risk [38].

While DREAMS did support the delivery of many of the development accelerators such as government cash transfers [39], support to stay in schools, parenting support and safe spaces, there was limited investment in long-term interventions to strengthen employability and income generation, such as skill building or microfinance initiatives [6,30]. Furthermore, there was little done to build youth capacity to deliver these or actively engage in the local DREAMS co-ordination mechanism [31]. The transition out of the DREAMS Partnership in the study area, after two years, happened shortly after the implementing partners had gained traction and started to implement this complex intervention. The absence of local leadership and in particular youth leadership left a void in co-ordinating the multiple sectors with no-one to actively advocate for sustaining activities post-DREAMS funding, and ensure the capacity and skills gained during DREAMS could be useful for the CBOs activities post-DREAMS [16,40,41].

## **3 | CONCLUSIONS**

Centrally directed, prescribed and target-focused scale-up of multi-sectoral HIV prevention interventions for AGYW in a poor rural South African setting was largely successful in rapidly reaching AGYW and layering development accelerators such as government cash transfers, parenting support, violence interventions, safe spaces and friendly health services for AGYW. The approach was most successful when it built on the capacity of existing infrastructure and brought resources to tackle youth development of concern to the community. However, to protect young people better and achieve sustainable and successful long term youth development, we need greater adaptability and meaningful engagement of AGYW in



the development and delivery of the intervention [14–16]. Expanding holistic HIV prevention interventions such as the DREAMS partnership to support youth development, including economic empowerment, and mobilizing youth to transform gender norms, and build social capital may provide the foundation for a sustained impact on the HIV epidemic and improvements in the wellbeing of young people in sub-Saharan Africa. Achieving this will require sustained commitment from government and funders.

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## COMPETING INTERESTS

The authors declare they have no conflict of interest.

## AUTHORS' CONTRIBUTIONS

Natsayi Chimbindi, Maryam Shahmanesh and Isolde Birdthistle involved in conceptualization. Natsayi Chimbindi and Maryam Shahmanesh also involved in writing the original draft of the manuscript. Maryam Shahmanesh, Natsayi Chimbindi, Isolde Birdthistle, Guy Harling, James Hargreaves, Nondumiso Mthiyane, Sian Floyd, Thembelihle Zuma, Janet Seeley and Sian Floyd contributed to reviewing and editing of the manuscript. All authors reviewed drafts and read and approved the final manuscript.

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## DISCLAIMER

None declared.

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## COMMENTARY

# The HIV drug optimization agenda: promoting standards for earlier investigation and approvals of antiretroviral drugs for use in adolescents living with HIV

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### Abstract

**Introduction:** Most clinical trials for new antiretroviral (ARV) agents are conducted among narrowly defined adult populations. Only after safety and efficacy have been clearly demonstrated among adults living with HIV are trials including adolescents, children and infants conducted. This approach contributes to significant delays in the availability of optimal new ARV regimens for infants, children and adolescents. This commentary discusses issues related to the inclusion of adolescents aged 12 to 18 years in initial HIV clinical phase 3 trials of novel antiretrovirals (ARVs) or conducting parallel phase 3 clinical trials among adolescents.

**Discussion:** The absorption, metabolic and excretion or elimination pathways for drugs do not significantly differ between adolescents and adults. In fact, dosing recommendations for ARVs are the same for adults and adolescents who meet the age and weight criteria. Although conducting clinical trials among adolescents present special challenges (e.g. consenting minors and concerns about trial completion and contraception), these challenges can be addressed to obtain high-quality trial results. Importantly, new agents and optimized combinations have more favourable dosing schedules and side-effect profiles and are more effective ARV agents with higher HIV drug resistance thresholds, which would be extremely beneficial to improve outcomes among HIV-positive adolescents.

**Conclusions:** Adolescents may not present with significantly different pharmacokinetic characteristics from those in adults. Including HIV-positive adolescents in phase 3 ARV clinical trials, either with adults or in specific adolescent studies conducted in parallel, would allow adolescents to access promising, more effective treatment for HIV years earlier than with the current stepwise approach.

**Keywords:** HIV; adolescents; drug optimization; ARV

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## 1 | INTRODUCTION

Most clinical trials for new antiretroviral drugs (ARVs) are conducted among narrowly defined adult populations. Only after safety and efficacy have been clearly shown in adults do trials move to include HIV-positive children and adolescents, significantly delaying the availability of ARVs and/or optimized combinations for use among these groups (see Table 1). This stepwise approach also is applied to pregnant or breast-feeding women and to women of reproductive age who are not receiving contraception. Historical rationale for this approach mostly includes; focus on the differences between adults and children/adolescents as they relate to drugs, developmental variability, complexities of parental involvement and adaptations required in research procedures [35].

The Paediatric Antiretroviral Working Group led by the World Health Organization (WHO), has proposed optimizing research approaches for children and adolescents to speed-up

the availability of ARVs and formulations for these groups [1]. Recently, the United States Food and Drug Administration (US FDA) recommended that ARV drug trials include adolescents (aged 12 to <18 years) in phase 3 clinical trials along with adults, or that a separate phase 3 clinical trial among adolescents be conducted in parallel [2]. Adult trials for tuberculosis [3] and cancer treatment [4] as well as ADVANCE, a recent clinical trial that enrolled HIV-positive participants aged ≥12 years, have shown the feasibility of including adolescents in adult clinical trials [5].

Adolescence is a period of rapid growth and change. Physical, mental and emotional maturation changes occur as a person transitions into adulthood and begins to take their own care and decision making [6]. Adolescents are a heterogeneous population that includes individuals in various stages of emotional, physical, intellectual and sexual development. Gender differences, and environmental factors such as geographical location, socioeconomic and sociodemographic differences,

**Table 1. Examples of antiretroviral approvals by the United States Food and Drug Administration and dosing recommendations in adults and adolescents<sup>a</sup>**

Drug	Year approved, adults	Dose, adults	Year approved, adolescents	Dose, adolescents
Tenofovir disoproxil fumarate (Viread)	2001	300 mg OD	2010	300 mg OD for $\geq 12$ years and $\geq 35$ kg
Darunavir (Prezista)	2006	600 mg BID	2008	600 mg BID, for $\geq 40$ kg
Bictegravir, only available in a fixed-dose combination tablet (Biktarvy) Bictegravir 50 mg/emtricitabine 200 mg/tenofovir alafenamide 25 mg	2018	50 mg OD	2019	50 mg OD, for $\geq 25$ kg

<sup>a</sup>United States Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV. Available at <http://aidsinfo.nih.gov/contentfiles/lvguidelines/AdultandAdolescentGL.pdf>. OD, once a day; BID, twice a day.

home environment, cultural and social support, play a mayor role in influencing adolescents' behaviour. Adolescence has been widely associated with risk-taking behaviour [7]; however, it is also a period for reflection, for generating great ideals and building one's personality. In this commentary, we defined adolescents as individuals age 12 to 18 years, thus aligning with the US FDA clinical trials recommendation.

UNAIDS 2018 estimates that 1.6 million adolescents aged 10 to 19 years are living with HIV globally. Adolescents also remain vulnerable to acquiring new HIV infection and to have sub-optimal clinical outcomes [8]. There is a paucity of HIV treatment coverage data for adolescents living with HIV (ALHIV) and where there is data, access and uptake of antiretroviral treatment (ART) is often reported to be lower than among HIV-positive adults [9]. Better-tolerated ARVs and ART regimens are needed for ALHIV, to reduce acute and late-onset side effects, to improve adherence and to ensure long-term viral suppression. Expanding treatment options for adolescents is a priority, requiring clinical trial generated evidence on new ARVs formulations, dosing options and combination regimens to optimize treatment for this vulnerable population. Not including adolescents in new drug development trials, simplification trials or HIV treatment failure studies will continue to widen the existing ART knowledge gap and further disadvantage this population. This commentary discusses benefits and challenges of including adolescents in clinical phase 3 trials of ARVs or the performance of parallel adolescents' phase 3 clinical trials irrespective of the mode of HIV acquisition, that is perinatally and sexually acquired.

## 2 | DISCUSSION

This section provides the rationale and justification for including adolescents in initial adult clinical phase 3 trials of novel ARVs and combinations or conducting parallel phase 3 clinical trials among adolescents.

### 2.1 | No major pharmacokinetic differences

Absorption, hepatic metabolism and renal elimination of drugs in infants and young children are significantly different than in

adults, but there are no major pharmacokinetic differences between adolescents and adults [10,11]. However, bone mineralization, which is associated with bone metabolism and growth may be a physiological difference between adolescents and adults. Bone, which is a metabolic tissue, undergoes rapid changes during adolescence and approximately 80% of adolescents achieve peak bone mass by age 18 years [12]. Tenofovir disoproxil fumarate (TDF) is the ARV most clearly related to decreased bone mineral density in HIV-positive adults. Data on children and youth are conflicting. Results of a 10-year follow-up study in Italy indicate that a TDF-containing regimen does not decrease the bone mineral density of HIV-positive youths [13]. However, a longitudinal study in Brazil showed that TDF contributes to decreased bone mineral density among adolescents [14]. Both the US Department of Health and Human Services (DHHS) guidelines and the WHO guidelines recommend the use of TDF at the adult dose in adolescents weighing  $>35$  kg. WHO guidelines also recommend Zidovudine and Abacavir as alternatives to TDF under special circumstances [15-17].

### 2.2 | Similar dosing recommendations for adolescents and adults

Dosing recommendations for ARVs have consistently been the same for adults and adolescents. The DHHS guidelines recommend "adult tablets" for both adults and post-pubertal adolescents [11,15]. The DHHS guidelines also recommend using most adult tablets for adolescents with a few exceptions based on weight: for example all adult ARV tablets are allowed for adolescents weighing  $\geq 40$  kg, some adult ARV tablets are allowed for adolescents weighing  $>35$  kg, and in some cases,  $>25$  kg [15]. The annex to the updated WHO recommendations on ARV regimens suggests the same dosing for adults and adolescents [16].

Furthermore, the ODYSSEY trial evaluated the use of the adult dolutegravir (DTG) tablet (50 mg) not only in adolescents, but also in children weighing 20 to  $<40$  kg. The results showed that the adult tablets achieved appropriate pharmacokinetic profiles with no safety signal, allowing practical dosing and rapid access to DTG [19].

The DHHS guidelines recommend taking the patient's sexual maturation rating (SMR) into consideration to select the dosing for ARVs, but neither the WHO 2016 ARV guidelines [17] or the Penta 2019 guidelines [18] even mention SMR. SMR is only mentioned three times in the DHHS Paediatric Guidelines Dosing Annex: dosing for efavirenz (400 mg) has not been evaluated in patients with an SMR 3 or less; for cobicistat/elvitegravir/emtricitabine/tenofovir (brand name, Stribild) which is recommended for adolescents who weigh >35 kg and have SMR 4 to 5; and TDF is recommended for adolescents who weigh >35 kg and have SMR 1 to 2. However, the guidelines do not provide different dosing recommendations based on SMR. Practically, healthcare providers consider age and/or weight (vs. SMR) to select the dosing and to initiate ARVs per WHO or DHHS recommendations which have already factored in SMR [15,17,34].

### 2.3 | Supply chain benefits

Using the same ARV formulations and dosing for adolescents and adults can synergize programme-level supply chain management. For example new drugs approved for both adolescents and adults can use an existing supply chain system, thereby minimizing inefficiencies caused by setting up a new supply chain system for adolescents only. Using the same dosing, formulations and combinations enhance the effectiveness and efficiency of the supply chain by minimizing the different types of ARVs that a supply chain specialist, a healthcare provider and clients have to manage. Having different types of ARVs for adults and adolescents can overwhelm the healthcare system and providers leading to an overloaded/inefficient supply chain system.

Moreover, using same dosing and formulations for both adolescents and adults streamlines ARVs treatment across populations, facilitating the implementation of treatment guidelines.

### 2.4 | Possible challenges to participation of adolescents in clinical trials

Challenges to allowing adolescents to participate in adult clinical trials include recruiting adolescents, lack of treatment adherence and sub-optimal retention [3,21]. Obtaining informed consent from adolescents also can be difficult because adolescents typically are required to obtain the approval of an adult caregiver. Adolescents also need specific clinical trial materials that explain the trial using age-appropriate language. Some clinical trials require female participants to use contraception which may be challenging to assess and to address possibly due to fear of disclosure [36].

### 2.5 | Recruiting adolescents into clinical trials

Other types of clinical trials have had challenges recruiting adolescents. For example the participation rate of 15 to 19 year olds in a national clinical trial of cancer drugs in the United States (1997 to 2003) was approximately half of the corresponding rate in children aged <15 years [20]. The study suggested that one of the reasons for low enrolment numbers could be that adolescents exist in a "no-man's land" between the worlds of paediatric and adult medical oncology [21].

Enhanced collaboration between paediatric and adult specialists involved in caring for adolescents may improve participation in clinical trials.

Adolescent participation in HIV clinical trials is variable. The recent ADVANCE trial enrolled participants aged  $\geq 12$  years in South Africa; after 2 years 1053 patients had undergone randomization, but only 14 patients were <19 years, despite extensive efforts to recruit adolescents [5]. However, in the ODYSSEY trial (PENTA 20), a randomized trial of DTG-based ART versus the standard of care for children aged <18 years starting first-line ART or switching to second-line ART, the targeted number of adolescents was achieved quickly due to higher than expected numbers of adolescent willing to participate. To increase the numbers of younger children in this trial, the researchers had to cap the recruitment of ART-naïve children who weighed  $\geq 35$  kg. Of 708 enrolled participants, 52% were aged >12 years at trial initiation [22].

Collaboration among paediatric, adolescent and adult HIV clinics is crucial. Protocols that not only allow adolescents to be recruited but also identify specific adolescent HIV clinics, could facilitate recruiting adolescents. FDA guidance advises doing these studies in parallel or in the same protocol for adults [2].

### 2.6 | Adherence to treatment and follow-up retention in clinical trials

There are concerns that adolescents have difficulty adhering to medication regimens, which might hinder adherence to study drugs and attendance at follow-up visits after enrolment [23]. The advanced FDA Paediatric HIV guidance for Industry suggests that adolescents have lower adherence rates than adults [2]. Nevertheless, similar treatment adherence estimates have been reported both overall and by region in a meta-analysis of adult adherence [24] and in a meta-analysis of adolescent adherence [25]. Researchers could consider providing additional adherence support to young adolescents participating in trials with adults since young adolescents may have limited ability to self-care.

Some trials have shown excellent retention of children and adolescents, for example in the BREATHER (PENTA 16) trial, an open-label, non-inferiority trial of Efavirenz-based regimen. The study included 199 participants from 11 countries with a median age of 14 years (interquartile range, 12 to 18 years). Follow-up in the trial was outstanding, with over 98% of the clinic visits attended up to week 48 [26]. This result demonstrates that excellent follow-up of ALHIV can be achieved. Researchers are often concerned that including adolescents will skew the results if included in the adult trial. To address these concerns, researchers may analyse the adolescent and the adult population data separately to evaluate the consequences of possible differences. Stratification methods may also be used.

### 2.7 | Informed consent

Various ethical and legal complexities may arise when including children and adolescents in clinical trials, especially when obtaining informed consent. Clinical trials must obtain consent from a participant with legal capacity, or from a person with the authority to consent on the participant's behalf. This means that in most countries, adolescents aged <18 years



(except emancipated minors) would need to obtain permission from their caregivers [27] to participate in a study.

Not uncommonly, especially in low-income countries, adolescents' caregivers are grandparents or other relatives who are not officially recognized. For example in the ARROW clinical trial in Zimbabwe, a substantial number of potential research participants were orphans (120/400; [30%]), and only 1/120 (0.08%) had a court-appointed guardian. The Zimbabwean ARROW research team informed the Ethical Committee of this challenges and how this legal requirement could potentially disadvantage this group of children. The Ethical Committee waived the legal guardianship requirement but requested that caregivers sign an informed consent document for the children's participation [28].

Apart from caregiver consent, adolescents younger than the legal age of consent are required to provide an informed assent to participate in a trial. In addition, if adolescents turn 18 years old during the trial, they have to re-consent by signing the informed consent document. For adult trial teams this might be an additional hurdle. However, as anecdotally shown in paediatric trials, well-trained trial teams can successfully carry out the consent and assent processes.

Depending on country policy, some structural level adjustments would be beneficial to make inclusion of adolescents into clinical trials possible. For example in South Africa, a 12-year-old can consent to medical treatment without caregiver consent but cannot consent to participate in research. A stage 3 trial would benefit from including younger children for medical treatment, but other countries may not have this policy, which makes it difficult to manage the participants of the same age in other countries. Discussing this difficulty with key stakeholders could help determine specific country considerations and solutions.

Lastly, there are family and social-cultural considerations for protecting adolescents from harm, especially in trials involving highly sensitive topics for families and their communities (sexual behaviour, gender identity, disclosure, etc.) [35]. Educating Institutional Review Boards and investigators about special regulatory protection can facilitate including adolescents in adult phase 3 clinical trials. Institutional Review Board committees play a critical role in advancing research for all populations and discussing these issues can overcome barriers to including adolescents in phase 3 adult clinical trials for adults.

## 2.8 | Designing specific clinical trial materials for adolescents

In a discussion about conducting HIV preventive vaccine trials with adolescents Mc-Clure *et al* [29] recommend designing protocols in close consultation with local community leaders and adolescent consultants. Using recruitment materials and clinic sites that are friendly, attractive and accessible to adolescents also can help improve participation.

Penta Foundation has supported the creation of Youth Trial Boards in Uganda, Zimbabwe, South Africa and UK to develop a youth-centred approach for meaningful involvement of young patients in clinical trials and studies. ODYSSEY (PENTA 20) was the first trial that used a Youth Trial Board [30]. This model has been used in a few new trials (e.g. D3, BREATHER-plus, LATA) in children, adolescents and young people led by Penta and/or the Clinical Trials Unit at the University College of London [33].

## 2.9 | Contraception in adolescence

Contraception, especially for women, is usually an inclusion criterion particularly in clinical trials for new drugs or vaccines. Adolescents' reluctance to disclose whether they are sexually active, is one of the many barriers which hinders their access to contraception [36]. Also, there is a lack of training among paediatricians and adult physicians on age-appropriate sexual and reproductive health counselling [36].

In most settings, contraceptive use is governed by specific country policies. Therefore, enrolment of adolescent girls also depends on the country policy that dictates the age when adolescent girls can use contraceptives. Especially in resource-limited settings key issues pertaining to the use of contraceptives in adolescent girls such as cultural norms, religious beliefs, community perspectives and stigma (for HIV and contraceptive use), might pose major enrolment concerns and could be addressed during the trial planning phase [31]. Raising community awareness and education is also crucial [32].

## 3 | CONCLUSIONS

HIV-positive adolescents remain at a disadvantage in terms of access to new drugs. Adolescents do not differ significantly from adults in weight, physiology, pharmacokinetics or adherence to treatment. Therefore, including ALHIV in initial phase 3 clinical trials with adults or in separate parallel studies could allow adolescents to benefit earlier from optimized ART. Coordinating research efforts with key stakeholders and sharing experiences on how to overcome perceived and real difficulties could help promote clinical trials among adolescents.

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The idea started at a WHO Paediatric Drug Optimization meeting (PADO 4) led by MP. PR and MP outlined the article. PR and DC wrote the first draft, which was reviewed by AT, MP and FV. The final draft was reviewed and approved by all authors.

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COMMENTARY

# Preventing mental health conditions in adolescents living with HIV: an urgent need for evidence

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## Abstract

**Introduction:** As adolescents transition from childhood to adulthood, they experience major physical, social and psychological changes, and are at heightened risk for developing mental health conditions and engaging in health-related risk behaviours. For adolescents living with HIV (ALHIV), these risks may be even more pronounced. Research shows that this population may face additional mental health challenges related to the biological impact of the disease and its treatment, the psychosocial burdens of living with HIV and HIV-related social and environmental stressors.

**Discussion:** Psychosocial interventions delivered to adolescents can promote positive mental health, prevent mental health problems and strengthen young people's capacity to navigate challenges and protect themselves from risk. It is likely that these interventions can also benefit at-risk populations, such as ALHIV, yet there is little research on this. There is an urgent need for more research evaluating the effects of interventions designed to improve the mental health of ALHIV. We highlight four priorities moving forward. These include: generating more evidence about preventive mental health interventions for ALHIV; including mental health outcomes in research on psychosocial interventions for ALHIV; conducting intervention research that is sensitive to differences among ALHIV populations; and involving adolescents in intervention design and testing.

**Conclusions:** More robust research on promotive and preventive mental health interventions is needed for ALHIV. Programmes should be informed by adolescent priorities and preferences and responsive to the specific needs of these groups.

**Keywords:** adolescents; interventions; public health; social support; mental health; psychosocial interventions

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## 1 | INTRODUCTION

As adolescents transition from childhood to adulthood, they undergo major physical, social and psychological changes [1]. Physical changes, which include puberty and rapid brain development, take place in the context of newly developing autonomy, responsibility and decision-making abilities. This transition is also influenced by a complex set of socio-economic factors, including family and cultural environments, which interact with each other and shape adolescents' health trajectories and vulnerabilities [2]. During this dynamic yet precarious life stage, adolescents are at heightened risk for developing mental health conditions (such as depression and anxiety) and engaging in health-related risk behaviours. As many as 10% to 20% of people will develop mental health conditions during adolescence, and it is estimated that up to 50% of all mental health conditions start before the age of 14 [3]. Self-harm, which includes suicidal behaviours, is among the top three causes of death for 15- to 19-year-old boys and girls globally [4].

Furthermore, mental health conditions during this period are associated with a range of risk behaviours, including tobacco and alcohol use, drug misuse, risky sexual behaviours and violence [5,6], the effects of which may persist throughout the life course.

Adolescents living with HIV (ALHIV) are at an even greater risk of developing mental health conditions and risk behaviours [7]. Worldwide, an estimated two million adolescents are living with HIV, with over 80% of them residing in sub-Saharan Africa [8]. Depression, anxiety, hopelessness and fear for the future are common in this population, which makes mental health a vital area of concern for ALHIV [9]. Research shows that these risks are manifold, related to the biological impact of the disease and its treatment, the psychosocial burden of living with HIV and HIV-related social and environmental stressors. From a biological perspective, for adolescents who acquired HIV perinatally, the effects of the virus on brain development persist into adolescence [10], and there is mixed evidence on whether highly active antiretroviral therapy can

slow or reverse damage to the developing brain [11,12]. ALHIV also face numerous psychosocial challenges. Many young people with perinatally acquired HIV first learn they are living with HIV during adolescence, which can be highly stressful and create familial tensions if they blame their parents for their condition [13]. Relatedly, ALHIV may also experience grief from losing one or both parents, or other caregivers, contributing to their own expectations and fears of illness and death [9,14]. Social and environmental stressors include experiencing heightened stigma and isolation; adolescents may also be increasingly required to manage their own treatment adherence [15,16]. ALHIV engaging in romantic and sexual relationships for the first time need to grapple with how to disclose their status to partners and protect against potential fears of rejection [17]. Additionally, adolescents living in vulnerable households with others who are also living with HIV may have additional mental health needs that intersect with experiences of poverty and illness [18].

There is additional evidence that the mental health of ALHIV affects other domains of their health and wellbeing. In general, clinical outcomes for adolescents tend to be worse than those of adults, and adolescents have poorer levels of adherence to antiretroviral therapy (ART) and thus higher viral loads [19,20]. Evidence from adult populations reveals a complex relationship between mental health and HIV, including poor physiological and psychological outcomes related to factors such as disease progression, medication side effects, social isolation and the financial burden of being ill [21]. The same mechanisms that can contribute to poor health in adults living with HIV are likely to affect ALHIV; however, improving mental health can also foster better HIV outcomes such as adherence and retention in care [22], especially for adolescents [23].

## 2 | DISCUSSION

Adolescence is thus a critical time to intervene with this vulnerable group – to prevent mental conditions, to promote positive mental health and to strengthen young people's capacity to navigate challenges and protect themselves from risk. Psychosocial interventions have been identified as beneficial when delivered to universal, or general, adolescent populations: these interventions adopt a psychological, behavioural, and/or social approach to improve psychosocial wellbeing and reduce the risk of poor mental health outcomes [24]. Our meta-analysis found that psychosocial interventions that included specific components (emotional regulation, interpersonal skills, mindfulness, assertiveness training, problem solving, stress management, and alcohol and drug education) were associated with more successful programme outcomes for adolescent mental health [24].

However, there is less research about the impact of these types of interventions among targeted groups, such as ALHIV, who are likely to have specific, additional psychosocial support needs. From an equity perspective, it is critical to consider if and how psychosocial interventions might benefit special populations, including ALHIV. The same skills taught and practiced in a psychosocial intervention for a universal population of adolescents – for example, navigating changing peer dynamics or setting goals – may take on new significance as they help ALHIV disclose their status to a trusted peer, or conceptualise a healthy, fulfilling adult life. With a growing number of adolescents globally – including the largest

number of children born with HIV to survive into adolescence – this imperative is even greater.

*Helping Adolescents Thrive* (HAT), a joint initiative between the World Health Organization and UNICEF, represents one such attempt to provide more evidence for both universal and targeted interventions for adolescent mental health. A 2019 evidence review linked with HAT, conducted in preparation for the development of the WHO Guidelines on Mental Health Promotive and Preventive Interventions for Adolescents, found only three randomised controlled trials targeting mental health outcomes for ALHIV ages 10 to 19 [25–27], shown in Table 1. As the burden of HIV and mental health continues to persist among this population, there is an urgent need for research evaluating the effects of interventions designed to improve the mental health of ALHIV. Drawing primarily on this review, we have distilled four recommendations to guide future research in this area.

### 2.1 | Invest in high-quality research to test the effectiveness of interventions to prevent mental health conditions and promote positive mental health for ALHIV

There is a clear need to invest in more research about the mental health of ALHIV. Increased HIV-related research on adolescents regarding new strategies for biomedical treatment and adherence, given their unique risk profile and susceptibility to worse HIV outcomes, is promising [28]. However, there are glaring omissions in the evidence on mental health for ALHIV. Mental health, as a critical foundation for overall wellbeing and quality of life, must be prioritised in research and interventions with ALHIV. We argue that there should be an equally robust approach to generating evidence about how best to promote positive mental health, and prevent mental conditions and risk behaviours, in this population. Integrating services that consider and address mental health into existing HIV services that adolescents routinely access is one way to bridge this gap. Recent reviews have identified the need for integrating mental health services into HIV care in high-burden settings [29], especially for adolescents [7]. Integrated models, which might consist of multidisciplinary teams coordinating care in a “one-stop shop”, or service providers managing two-way referrals between HIV and mental health care, have been found to be both feasible and acceptable in high-burden, low-resource settings [30,31].

There is also a need to build process data into studies evaluating effectiveness, to give stakeholders and funders a multi-dimensional understanding of the complexity of programming with ALHIV. Process measures might include attendance, dosage and coverage of sessions; delivery characteristics; delivery and participation costs; content relevance; contextual barriers and enablers; implementer competence; and implementer soft skills. For adolescents who are more difficult to reach, more innovative engagement methods may be necessary. These include adolescents who do not access clinical care or HIV treatment consistently, those in age-disparate relationships, those living in vulnerable family circumstances and those who are involved in sex work or transactional relationships [32,33]. Research using process data holds important lessons for understanding why certain interventions may be easier to implement in given populations, or why some interventions may show limited evidence of effectiveness.

Table 1. Summary of studies included in review

Author and year	Article name	Country	Programme Intent	Total sample (N), % girls	Age (mean, sd)	Study population description	Mental health outcomes measured <sup>a</sup>	Summary of findings as reported by authors
Bhana et al. (2014)	The VUKA family programme: piloting a family-based psychosocial intervention to promote health and mental health among HIV infected early adolescents in South Africa	South Africa	RCT to prevent depression and anxiety; promote communication and mental wellbeing	65, 49.2%	11.57, n/s	Recruited children between 10 and 14 years old enrolled in HIV care at the hospital and aware of their HIV status at two clinical sites in KwaZulu-Natal	<ul style="list-style-type: none"> <li>Positive mental health (mental wellbeing and mental functioning)</li> <li>Mental disorders (depression and anxiety)</li> </ul>	At 3 months post-intervention, intervention participants showed a significant improvement in positive mental health (youth/caregiver communication comfort, $\beta = 0.796$ , $p = 0.002$ and communication frequency, $\beta = 0.478$ , $p = 0.09$ ). Mental disorders showed a non-significant reduction in symptoms (depression, $\beta = 0.736$ , $p = 0.417$ ).
Webb et al. (2018)	Mindfulness instruction for HIV-infected youth: A randomized controlled trial	United States	RCT to prevent stress, aggression and lower CD4 count; promote mindfulness, mental functioning, life satisfaction and adherence	72, 45.8%	18.71, 2.31	Adolescent participants were eligible if they received their medical care at one of the clinics, did not have any significant cognitive, behavioural, or psychiatric disorders and had a current CD4 count above 200	<ul style="list-style-type: none"> <li>Mental disorders (depression and anxiety)</li> <li>Positive mental health (mental wellbeing and mental functioning)</li> <li>Adherence to antiretroviral treatment</li> <li>Aggressive, disruptive and oppositional behaviours</li> </ul>	At three months post-intervention, intervention participants showed significant improvements in positive mental health (mindfulness, $\beta = 0.65$ , 95%CI [0.06, 1.24], $p = 0.03$ , problem-solving coping $\beta = 0.49$ , 95%CI [0.05, 0.92], $p = 0.03$ , and life satisfaction, $\beta = 0.57$ , 95%CI [0.01, 1.13], $p = 0.05$ ) and aggressive, disruptive and oppositional behaviours (aggression, $\beta = -0.89$ , 95%CI [-1.41, to 0.37], $p = 0.002$ ).



**Table 1.** (Continued)

Author and year	Article name	Country	Programme Intent	Total sample (N), % girls	Age (mean, sd)	Study population description	Mental health outcomes measured <sup>a</sup>	Summary of findings as reported by authors
Willis et al. (2019)	Effectiveness of community adolescent treatment supporters (CATS) interventions in improving linkage and retention in care, adherence to ART and psychosocial wellbeing: a randomized trial among adolescents living with HIV in rural Zimbabwe	Zimbabwe	RCT to promote adherence, self-esteem and quality of life	94, 59.6%	10 to 15, n/s	Adolescents living with HIV, receiving ART at three selected clinic sites	<ul style="list-style-type: none"> <li>Positive mental health (mental wellbeing)</li> <li>Adherence to antiretroviral treatment</li> </ul>	At 12-month follow-up, intervention participants reported significant increases in positive mental health (confidence, self-esteem and self-worth, point difference = 0.49, 95%CI [0.313, 0.667], $p < 0.001$ ) and adherence to ART (OR = 3.934, 95%CI [1.404, 11.02], $p = 0.0087$ ). Significant increases in quality of life were reported for both intervention participants (point difference = 0.29, 95%CI [0.031, 0.549], $p = 0.028$ ) and control participants (point difference = 0.26, 95%CI [0.061, 0.459], $p = 0.011$ ).

<sup>a</sup>These measures are worded accordingly to the outcome specifications in the review.  
 RCT = randomised controlled trial

## 2.2 | Include mental health outcomes in studies of the effectiveness of psychosocial interventions to promote HIV treatment adherence and reduce risk behaviours

There is a large body of evidence relating to behavioural and psychosocial interventions for ALHIV; however, these studies rarely report on mental health outcomes specifically, often focusing on treatment adherence and sexual and reproductive health outcomes [34–37]. Existing interventions tend to be specifically designed to promote adherence to ART and prevent risky sexual behaviours such as unprotected intercourse [38], which are seen as essential to supporting adolescent health and preventing onward transmission. At the same time, these interventions tend to employ content and delivery mechanisms that are also likely to benefit mental health, such as decision-making skills, self-esteem, coping skills, support networking, psychoeducation and peer support [35,39,40].

As such, it is critical that measures that capture self-reported or parent-reported mental health are included in these types of studies as primary or secondary outcomes. In the absence of these measures and accompanying data, it is impossible to know whether psychosocial interventions have positive, null, or potentially negative effects on participants' mental health. Similarly, the effectiveness of adherence and risk behaviour interventions may be mitigated by underlying mental health outcomes that are not being accurately considered or incorporated into analysis: for example, the impact of self-harm or suicidal ideation on non-adherence. Embedded within this recommendation is a note of caution about context. As psychosocial interventions for ALHIV are increasingly implemented in sub-Saharan African settings, selecting the appropriate mental health measures and ensuring their validity among the research population is essential to gathering high-quality data [41].

## 2.3 | Conduct intervention research that is sensitive to individual differences and specific needs among heterogeneous populations of ALHIV

While many ALHIV share a common set of vulnerabilities, acknowledging the diversity and complexity of this group is critical when considering how to design and implement programmes. Differences in mode of infection, age group (younger versus older) and gender, as well as additional adolescent comorbidities, may affect how adolescents engage with an intervention. Evidence shows that as children born with HIV transition into adolescence, the way that they relate to their HIV status and engage in treatment behaviours may change, as they gain autonomy, come to terms with their illness and take control of their own health care-seeking [42,43]. Adolescents who acquire HIV later in their teens may experience a different set of challenges that complicate their ability to initiate care, with underlying mental health problems contributing to poorer health and adherence outcomes [44]. Depending on mode of infection – and on the duration of their illness, access to social support networks and other intersecting life stressors and risk behaviours – ALHIV may have ways of relating to their illness that are diverse. Research that is attuned to differences by mode of HIV infection could provide a more nuanced approach to improving mental health and could identify means of engaging and retaining adolescents in these interventions.

## 2.4 | Involve and empower adolescents in intervention development and testing

Actively involving and engaging adolescents throughout the conceptualisation and implementation stages of interventions is important for ensuring interventions are acceptable and relevant – and ultimately effective. Special considerations should be made to develop adolescent-friendly interventions that actively include adolescents at all stages, and not to retrofit interventions used with adult populations. Co-production strategies, such as adolescent advisory boards, allow adolescents to drive how content is delivered and what messages are emphasised [45,46]. As this field develops, adolescents should take a lead role in crafting interventions that speak to their distinct needs and are also informed by cutting-edge evidence.

## 3 | CONCLUSIONS

ALHIV are faced with many potential risks to their mental health, yet there are few evaluations of promotive and preventive mental health interventions for this group. This group is a critical population to engage further through more frequent, robust research that can inform the development of new interventions. We call for more high-quality research into interventions for ALHIV that is informed by adolescent priorities and preferences and responsive to the specific needs of this group.

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The authors declare no competing interests.

### AUTHORS' CONTRIBUTIONS

CAL conceptualized and drafted the manuscript, and coordinated further writing and editing among the co-authors. SS led the team that conducted the systematic reviews in collaboration with the WHO. SG, OAO, NA, MB, AB, SD and GJMT, along with CAL, all worked on the systematic review team and made important contributions to identifying eligible articles, extracting data, assessing risk of bias, analysing data, and conducting literature reviews to contextualise findings. MT, CS, TD and DAR provided leadership and input to the review team throughout the duration of the project and supported in conceptualising the manuscript. All authors reviewed the manuscript and provided feedback at various stages, and read and approved the final manuscript.

### ABBREVIATIONS

ALHIV, adolescents living with HIV; ART, antiretroviral therapy; HIV, human immunodeficiency virus; WHO, World Health Organization.

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COMMENTARY

# Is HIV index testing and partner notification safe for adolescent girls and young women in low- and middle-income countries?

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## Abstract

**Introduction:** While HIV index testing and partner notification (PN) services have the potential to reach adolescent girls and young women (AGYW) aged 15 to 24 and their sexual partners in need of HIV testing services, the potential social harms have not yet been studied. This commentary highlights the risks of this approach, including intimate partner violence (IPV), stigma and discrimination, and outlines an urgent research agenda to fully understand the potential harms of PN for AGYW, calling for the development of mitigation strategies.

**Discussion:** A substantial evidence base exists demonstrating the feasibility, acceptability and effectiveness of index testing and partner notification for adults aged 18 years and older in low- and middle-income countries (LMICs), particularly for men, and for adults who are married/cohabiting and referring a current sexual partner. AGYW who are most vulnerable to HIV infection in LMICs do not reflect these demographics. Instead, they are often in age-disparate partnerships, have limited negotiating power within relationships, experience high rates of violence and face economic challenges that necessitate transactional sex. PN services may be particularly difficult for adolescent girls under 18 who face restrictions on their decision making and are at increased risk of rape. Adolescent girls may also face coercion to notify partners due to unequal power dynamics in the provider–adolescent client relationship, as well as judgemental attitudes towards adolescent sexual activity among providers.

**Conclusions:** As index testing and PN with AGYW is already being rolled out in some LMICs, research is urgently needed to assess its feasibility and acceptability. Implementation science studies should assess the availability, accessibility, acceptability and quality of HIV PN services for AGYW. Qualitative studies and routine monitoring with age-disaggregated data are critical to capture potential social harms, PN preferences and support needs for AGYW aged 15 to 17, 18 to 20 and 21 to 24. To mitigate potential harms, PN methods should prioritize confidentiality and avoidance of adverse outcomes. Healthcare providers should be trained to conduct routine enquiry for IPV and provide first-line support. Support services for AGYW living with HIV and survivors of violence should be implemented alongside HIV PN.

**Keywords:** adolescent girls and young women; HIV; testing; stigma; violence; gender; LMIC

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## 1 | INTRODUCTION

Adolescent girls and young women (AGYW) are a priority population that may benefit from HIV index testing to ensure early linkage to care and treatment services [1]. Recently, partner notification (PN) linked with HIV index testing has also been recommended for AGYW in low- and middle-income countries (LMICs) to support global efforts to reach UNAIDS' 95-95-95 goals and achieve epidemic control by 2030 [2]. HIV PN for AGYW is also seen as an entry point for engaging adolescent boys and young men, populations that are harder to reach, in HIV services [3]. However, little is known about the safety of this approach or the potential social harms that AGYW may experience due to HIV PN in LMICs.

Based on the strong evidence of feasibility and acceptability of HIV PN among adults 18 years of age and older, the World

Health Organization (WHO) published guidelines for HIV self-testing and partner notification in 2016 [3]. While HIV PN for adolescents is recommended by WHO, only three studies with adolescents, two qualitative and one observational, were referenced in the guidelines, all of which focused on sexually transmitted infection (STI) PN in high-income countries [4-6]. The dearth of evidence continues; there are still no published data on the feasibility and acceptability of this approach in LMICs, especially with adolescent girls aged 15 to 17.

A technical report by YouthPower Learning [7] written by the current authors identified only one additional qualitative study, which examined concerns about and potential barriers to PN among adolescent girls and boys in the United States (U.S.) if diagnosed with a STI not including HIV [8]. More recently, a study examined factors associated with successful PN among adolescents aged 13 to 24 living with HIV in 14

U.S. cities. However, the study population was predominantly black men who have sex with men (MSM) whose average age was 21 [9].

Given the paucity of feasibility and acceptability data in LMICs, especially among adolescent girls less than 18, the safety and potential harms of this approach must be considered. This commentary highlights the potential risks, including intimate partner violence (IPV) and stigma, and outlines an urgent research agenda to fully understand the potential harms of PN for AGYW, calling for the development of mitigation strategies.

## 2 | DISCUSSION

### 2.1 | Types and preferences of partner notification services

HIV PN can be passive, in which clients living with HIV are encouraged to contact their sexual partners directly and inform them that they should be tested, or assisted, where a provider supports the index client to notify their sexual partners [10]. Among adults, assisted referral appears to be the preferred method of notification, and the most effective [7]. A meta-analysis of three randomized controlled trials (RCTs) conducted by Dalal et al. [10] found that assisted partner notification services led to a 1.5-fold increase in uptake of HIV testing services (HTS) among partners compared to passive referral. Conversely, studies with adult women and men in Tanzania [11] and youth in the U.S. [9] have reported preferences for passive referral. No studies have examined potential gender or age differences in HIV PN preferences.

Studies on STI PN among youth in high-income countries have indicated that youth may prefer technology-facilitated PN, including SMS or text messages, both for convenience and to enhance privacy [4,6]. However, anonymous provider referral has also been suggested given adolescents' concerns about their safety and reputation when discussing STI exposures with partners [8]. While we know that different methods of HTS are broadly acceptable to adolescents, including home-based testing, provider-initiated testing and, more recently, self-testing [12], PN is new for this population, so assessing PN preferences, as well as acceptability of PN, is important. In settings where HIV index testing and PN has not yet been rolled out, formative research on PN preferences for AGYW should be conducted to determine the safest methods, which may vary by age and context. Youth engagement is key for implementation science research on adolescent HTS and linkage to care in LMICs [13]. In addition to being study participants, research should actively involve AGYW in the design, implementation and evaluation of the studies to ensure that the insights of adolescents themselves are incorporated into index testing and PN programmes and implementation strategies in order to increase comfort and reduce potential harms.

### 2.2 | Is HIV index testing and partner notification safe for AGYW?

In short, we do not yet know if index testing and partner notification will be safe for AGYW in LMICs. While a substantial evidence base exists demonstrating the feasibility, acceptability and effectiveness of index testing and partner notification for

adults aged 18 years and older [10], no studies have included girls between the ages of 15 and 17. We also did not find evidence on HIV PN services with transgender women under the age of 18. The average age of participants in eight feasibility studies included in a recent meta-analysis [10] ranged from 26 [14] to 33 years [11]. Evidence suggests that successful notification and referral are more likely when index clients are male, married or cohabitating, or are referring a current sexual partner [11]. Partner type and quality of the relationship are also predictors of successful PN [9].

However, the AGYW who are most vulnerable to HIV infection in LMICs do not reflect these demographics. Instead, they are often in age-disparate or short-term partnerships, have limited negotiating power within relationships, experience high rates of violence and face economic challenges that necessitate transactional sex [15,16]. PN services may be particularly difficult for adolescent girls under 18, who face restrictions on their decision making and are at increased risk of rape [15,16] as well as family rejection and social stigma if their HIV status is known. Adolescent girls may also face coercion to notify partners due to unequal power dynamics in the provider–adolescent client relationship, as well as judgemental attitudes towards adolescent sexual activity among providers [17].

As index testing and PN with AGYW is already being rolled out in some LMICs, research is urgently needed to assess its feasibility and acceptability. Implementation science studies with youth engagement [18] should assess the availability, accessibility, acceptability and quality of HIV PN services for AGYW. They should also acknowledge the transience and frequent change in adolescent relationships. Qualitative studies, including participatory methods such as Photovoice [19], and routine monitoring with age-disaggregated data are critical to capture potential social harms, PN preferences and support needs for AGYW aged 15 to 17, 18 to 20 and 21 to 24. These age cohorts are in different developmental stages, which may translate into different types of partnerships, with different motivations and different social harms related to partner notification.

Structural barriers related to ethical and legal challenges, it should be noted, often stand in the way of rigorous research with adolescents, especially on sensitive topics such as sexual and reproductive health [20]. Given this, the lack of evidence on HIV PN services among AGYW is not surprising. The WHO recently published practical guidance for researchers and reviewers on the most pressing ethical questions [21]. This is an important step in overcoming these barriers and expanding research on sexual and reproductive health with adolescents.

### 2.3 | Potential social harms of partner notification

Implementing HIV index testing for AGYW in LMICs could cause undue social harm and impede a healthy transition to adulthood. A range of harms are considered, including anticipated stigma, lack of confidentiality, coercion, risk of IPV and economic ramifications.

#### 2.3.1 | Anticipated stigma

Disclosure of HIV serostatus is a key concern of AGYW living with HIV [22,23]. The anticipation of stigma from peers, family



and community members can be severe, and AGYW are often encouraged by parents or guardians not to share their HIV status with anyone outside of their family to protect them from social harms [24,25]. Access to sexual and reproductive health (SRH) services is often limited, and many AGYW may face additional social and family stigma and consequences if it becomes known that they have begun sexual activity, regardless of whether that sexual activity was consensual [26-28]. Support services for AGYW living with HIV in LMICs are limited, especially as girls age out of pediatric services and enter adult care and treatment services [29]. Given the dual threat of stigmatization for both sexuality and HIV status, disclosure, even to trusted friends and family, is limited for AGYW living with HIV [30,31].

Concerns of judgemental attitudes by healthcare providers and a lack of trust in providers have been cited as potential barriers to HIV PN in previous research [32]. Fear of embarrassment, social stigma and shame have also been noted as potential barriers to HIV and STI PN among adults in Barbados and adolescents in the U.S. [8,32]. In South Africa, one study found that anticipated stigma was the most common stigma-related barrier to HIV PN [33].

### 2.3.2 | Confidentiality and coercion

The ability to maintain confidentiality in HTS and PN for AGYW is a particular concern. According to UNAIDS, parental consent is required for young people under certain ages before accessing one or more SRH services in 72 countries [34]. Given the varied consent policies in place for adolescents and young people aged 15 to 24 in LMICs, implementing HIV PN with AGYW in this age group may prove challenging [35]. Indeed, recent research suggests that lowering the age of consent for HIV testing may have more of an impact on achieving the UNAIDS 95-95-95 targets than any new testing modality [36]. A critical first step in scaling-up HIV PN for AGYW will be for countries to develop consent policies and practices to facilitate access to and uptake of HTS for adolescents.

Partner notification requires an individual to report details of a partner name and contact information, so it will only be possible if AGYW know the name and contact details of their sexual partner/s. However, unequal power dynamics between healthcare providers and clients, particularly AGYW, and judgemental attitudes towards adolescent sexual activity among providers, may lead to partner notification that is unwanted or unsafe [37]. Women living with HIV are at particular risk of stigma or coercion in the health setting [38,39], and this same potential exists for AGYW. To limit such harms, providers must receive training on how to offer stigma-free, gender-sensitive, youth-friendly services in a non-judgemental and supportive manner [40-43] that reduces coercion.

### 2.3.3 | Risk of intimate partner violence

AGYW are particularly vulnerable to HIV during their early sexual life, in part due to high prevalence of gender-based violence (GBV) and IPV. A recent study in Kenya found that four in 10 AGYW experienced coerced first sex, and one in nine reported forced first sex [44]. GBV-associated HIV transmission may be compounded over the sexual life course of AGYW

[45] as repeated acts of violence perpetrated by more than one partner are commonly reported [46,47]. While cases of IPV linked directly to HIV PN have not been reported following HIV PN among adult women in the literature [48-51], the risk of IPV following HIV PN may be greater for AGYW and must be monitored.

To minimize the potential for IPV among AGYW following PN, healthcare providers must be trained on how to conduct routine enquiry for IPV. Providers should also be trained on the provision of first-line support for AGYW who disclose experiences or fear of violence. This training should include information on how to utilize new PN tools for screening AGYW for risk of GBV, IPV or other social harms that may result from HIV PN [52]. A list of resources and support services for AGYW living with HIV and their sexual partner/s, as well as survivors of violence, should also be available to providers to facilitate referral.

### 2.3.4 | Economic ramifications

Partnership dissolution, particularly for women fearing loss of economic support, was identified as a key barrier to HIV PN among women in LMICs [32,53,54,55]. Among adolescents, loss of a relationship was also identified as a concern and cited as a key deterrent to notifying a partner about exposure to an STI [8]. The economic ramifications of partnership dissolution for AGYW in LMICs, especially adolescent girls aged 15 to 17, may be especially severe, as they may rely on transactional sex with older men to pay for school fees and daily necessities, such as food and clothing. Given this, AGYW may be hesitant to accept PN. Successfully adapting HIV PN services for AGYW in LMICs may require linkages to structural interventions and social programmes that support girls' continuation in school (e.g. subsidies for uniforms, cash transfer programmes, etc.) and provide nutritional and housing support to remove the need for transactional sex [16,56].

## 2.4 | Considerations for adapting PN for AGYW

Paramount among considerations regarding the roll-out of HIV PN for AGYW is ensuring "voluntarism, with informed consent and the explicit right to decline," as expressly stated in the HIV Self-Testing and Partner Notification guidance document published by WHO [3]. A range of policy, programmatic and research considerations are recommended prior to or alongside scale-up of HIV index testing and PN with this vulnerable population (Box 1).

To tailor HIV PN for AGYW, services should ideally be part of a comprehensive package of HIV prevention, care and treatment services that are youth-friendly [57]. HTS can be an entry point for youth to access other services, such as reproductive health education; peer counselling; life skills development; family planning; diagnosis and treatment of STIs; prevention of vertical transmission of HIV; and mental health and psychosocial support services. Integrating positive youth development (PYD) features into comprehensive HIV services can help support healthy adolescent development, reduce HIV risk behaviours, and address potential barriers and challenges to HIV PN. These features include access to age-appropriate and youth-friendly services, life skills-building, creating safe spaces and building healthy relationships [58].

# Box 1. Key recommendations for ensuring the safety of HIV index testing and partner notification for adolescent girls and young women in low- and middle-income countries.

## Recommendations<sup>a</sup> for researchers

1. Conduct feasibility and acceptability studies of HIV PN<sup>b</sup> with AGYW<sup>c</sup> in LMICs<sup>d</sup> where implementation is being planned before scaling up HIV PN with this vulnerable population. Where research is underway, encourage age-disaggregation of data to learn more about young cohorts from ages 15 to 17, 18 to 20 and 21 to 24 years old.
2. Prior to implementing HIV PN for AGYW, countries should conduct rapid situational assessments to understand what PN methods will be safest and most acceptable to AGYW and what resources are available to support AGYW who suffer social harms such as IPV or stigma due to PN.
3. In countries where HIV PN is already being implemented for AGYW, implementation science research to assess the availability, accessibility, acceptability and quality of HIV PN services for AGYW should be conducted and programmes adjusted as needed based on the findings.

## Recommendations<sup>a</sup> for programme implementers

1. Conduct routine programme monitoring of HIV PN services for AGYW once implemented to identify and correct any procedures or processes that may facilitate social harms.
2. Ensure that resources, like gender-based violence (GBV) support services and social support services for adults and adolescents living with HIV, are in place and prepared to support all adolescents referred from HIV PN services.
3. Alongside the implementation of HIV PN for AGYW, targeted efforts should be made to introduce adolescent boys and young men to HIV testing and increase their engagement in partner referral.
4. Healthcare providers should be trained on:
  - a. how to conduct routine enquiry for intimate partner violence (IPV), including how to ask about experience or fear of IPV and sexual violence and the provision of first-line support for AGYW who do disclose experience or fear of violence, including information on how to utilize new tools<sup>e</sup> to screen AGYW for risk of GBV, IPV or other social harms that may result from HIV PN; and
  - b. provision of stigma-free, gender-sensitive, adolescent- and youth-friendly services in a non-judgemental and supportive manner.
5. Ensure that HIV PN services are embedded into comprehensive HIV services that are youth-friendly and integrate positive youth development<sup>f</sup> features.
6. Implement community mobilization strategies to increase awareness of UNAIDS 95-95-95 goals and generate enthusiasm for participating in HIV testing services, including HIV PN.
7. Ensure that adolescent girls and boys have access to information through schools and local community centres and are given the opportunity to build skills on reproductive health to enhance both their knowledge and ability to communicate about reproductive health topics with both healthcare providers and partners.

## Recommendation<sup>a</sup> for policy makers

1. Paramount to the successful implementation of HIV PN for AGYW is the need for countries to develop consent policies and practices to facilitate access to and uptake of HIV testing services among adolescents and ensure confidentiality.

<sup>a</sup>These recommendations were adapted and reprinted with permission from: Stangl A, Seban M, Kapungu C, *et al.* Technical and Programmatic Considerations for Index Testing and Partner Notification for Adolescent Girls and Young Women: Technical Report. Washington, DC: Youth Power Learning, Making Cents International; 2019. <sup>b</sup>PN: partner notification; <sup>c</sup>AGYW: adolescent girls and young women; <sup>d</sup>LMICs: low- and middle-income countries; <sup>e</sup>Ricker, C, Stangl, A, Seban, M, *et al.* (2019) Planning and Conducting Index Testing and Partner Notification for AGYW: Implementation and Clinical Guidance for Health Services; <sup>f</sup>Positive Youth Development (PYD) features include: access to age-appropriate and youth-friendly services, life skills-building, creating safe spaces and building healthy relationships.

For AGYW, age differentials of sexual partners and unequal power dynamics make disclosure of HIV status particularly challenging. Self-efficacy is an important predictor of client initiated STI PN for adults and adolescents [59-62]. Peer support groups and safe spaces can help youth share experiences, address stigma and discrimination and build skills to support partner disclosure. Peer counsellors can serve as trusted and credible sources of support [62]. Integrated youth-friendly services provide the opportunity for youth-centred prevention,

care and treatment for the multitude of issues affecting youth living with HIV [63].

Strategies for involving adolescent boys and young men in HTS, including index testing and PN, will be critical for minimizing harm for AGYW, who risk being blamed for “spreading HIV” if PN is focused solely on them. Such strategies could include targeted efforts to introduce adolescent boys and young men to HIV testing and increase their engagement in partner referral. Sensitizing the public through mass media campaigns and

community mobilization strategies is also recommended to increase awareness of 95-95-95 targets and generate broad enthusiasm for participating in HTS, including HIV PN.

Other HIV PN options for AGYW, besides provider-initiated PN, should be considered for casual partners, including anonymous technology-facilitated PN (e.g. SMS) or provider referral. HIV PN may not be recommended for unmarried AGYW with few or single partners, as there are real risks of loss of confidentiality due to limited sexual networks. In all cases, HIV PN should only be carried out if preferred by the AGYW and should include follow-up counselling for all parties.

### 3 | CONCLUSIONS

While PN services have the potential to reach AGYW and their sexual partners in need of HIV testing services, the implementation of PN needs careful consideration to minimize potential social harms, particularly for girls under age 18 who may be experiencing violence or stigma, fear violence or stigma, or who may have acquired HIV as a result of violence. PN services for AGYW should also be designed to ensure that AGYW who know their status are linked to appropriate HIV services, such as pre-exposure prophylaxis (PrEP) to prevent HIV infection, antiretroviral therapy (ART) to suppress HIV viral load, and adherence and social support services for adolescents or partners living with HIV. Such strategies should be incorporated into HIV and SRH services and complemented with the scale-up of outreach, HIV testing services and PN for adolescent boys, as well as young and adult men.

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#### COMPETING INTERESTS

None declared.

#### AUTHORS' CONTRIBUTIONS

AS, CJ and CK conceptualized the manuscript. MS and CR conducted the literature review. AS led the manuscript writing. MS, CK, CJ, CR and EC were involved in drafting the manuscript and provided critical feedback on the full manuscript. All authors read and approved the final manuscript.

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COMMENTARY

# Fostering successful and sustainable collaborations to advance implementation science: the adolescent HIV prevention and treatment implementation science alliance

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## Abstract

**Introduction:** HIV continues to devastate the adolescent population in sub-Saharan Africa (SSA). The complex array of interpersonal, social, structural and system-level obstacles specific to adolescents have slowed progress in prevention and treatment of HIV in this population. The field of implementation science holds promise for addressing these challenges.

**Discussion:** There is growing consensus that enhanced interactions between researchers and users of scientific evidence are important and necessary to tackle enduring barriers to implementation. In 2017, the Fogarty International Center launched the Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA) to promote communication and catalyse collaboration among implementation scientists and implementers to enhance the cross-fertilization of insights as research advances and the implementation environment evolves. This network has identified key implementation science questions for adolescent HIV, assessed how members' research is addressing them, and is currently conducting a concept mapping exercise to more systematically identify implementation research priorities. In addition, AHISA pinpointed common challenges to addressing these questions and discussed their collective capacity to conduct implementation science using the shared learning approach of the network. Specifically, AHISA addresses challenges related to capacity building, developing mentorship, engaging stakeholders, and involving adolescents through support for training efforts and funding region-/country-specific networks that respond to local issues and increase implementation science capacity across SSA.

**Conclusions:** Innovative platforms, like AHISA, that foster collaborations between implementation science researchers, policy-makers and community participants to prioritize research needs and identify and address implementation challenges can speed the translation of effective HIV interventions to benefit adolescent health.

**Keywords:** implementation science; adolescent; HIV; alliance; Africa

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## 1 | INTRODUCTION

While HIV continues to be one of the leading causes of death for adolescents in sub-Saharan Africa (SSA) [1], interventions to address HIV prevention and treatment in this population have had limited effectiveness especially in low-resource settings like SSA [2]. In these settings, the benefits of proven interventions have not been fully realized because of enduring barriers to uptake, replication and scale-up including a complex array of interpersonal, social, structural and systems-level obstacles that often ignore developmental stages of and the many needs particular to adolescents [3].

The field of implementation science holds promise for addressing these challenges. However, critical research capacity in implementation science and deliberate and strategic efforts to facilitate collaboration, communication and

relationship building among researchers and the users of research evidence are needed to make substantial advancements. Given this critical link in the context of implementation science and representing a collective commitment to the goal of reducing adolescent HIV infections, the Center for Global Health Studies at the United States (US) National Institutes of Health's (NIH) Fogarty International Center launched the Adolescent HIV Prevention and Treatment Implementation Science Alliance (AHISA). This innovative platform was established to identify gaps and provide opportunities for enhanced communication and collaboration between implementation scientists and programme implementers and policymakers to facilitate better utilization of scientific evidence in adolescent HIV programming while simultaneously helping to ensure that research is country driven and responsive to the adolescent context. Through this approach AHISA thereby promotes



scalable, empowering, and sustainable interventions. This commentary identifies both key implementation science questions and common implementation challenges related to adolescent HIV prevention and treatment research and outlines how AHISA is collectively addressing them.

## 2 | DISCUSSION: ADOLESCENT HIV IMPLEMENTATION SCIENCE ALLIANCE

Eliminating HIV as a public health threat among adolescents depends heavily on successful implementation of efficacious interventions that address the context in which adolescents live. Across the HIV continuum of care, adolescents are less likely to be tested [4] and linked to care [5], have higher loss to follow-up [6], and worse adherence [7] and viral suppression rates [8] than their adult counterparts despite evidence for appropriate treatment and care [9]. A number of factors, including youth-friendly health services, gender-based violence, harmful cultural and social norms, limit the uptake of health services within this population. Furthermore, many of the effective adolescent service delivery approaches and models have not been taken to scale and implemented widely.

Implementation science offers a scientific strategy that takes a holistic approach to address these barriers and is defined as the study of methods to promote the integration of research findings and evidence into health care policy and practice to achieve their potential public health impact [10]. The intent of implementation science is to investigate and address major social, behavioural, economic and management bottlenecks that impede effective implementation, test novel approaches to improve health programming and determine the effect of implementation strategies on the causal relationship between the intervention and its impact in order to enable proven intervention to be taken to scale.

Premised on the idea that support for implementation science alone will have limited impact unless coupled with concerted efforts to bring researchers together with policymakers and programme implementers, AHISA teams are made up of researchers with funding from across the NIH and their in-country, implementing partners. AHISA, which is funded by the US Office of the Global AIDS Coordinator (OGAC) and the NIH's Office of AIDS Research, was developed as an innovative platform to enhance communication and catalyse collaboration among the funded implementation science researchers and users of research evidence to promote a cross-fertilization of ideas, insights and experiences in real time as the research progresses and the implementation environment evolves. This innovative platform also helps to seed significant and sustainable implementation science collaborations aimed at addressing critical barriers to implementing proven health interventions among adolescents. Because collaboration between researchers and those who utilize research evidence is an implicit necessity for the field of implementation science, this opportunity to develop formal and informal networks is of particular importance to moving the implementation science agenda for adolescent HIV forward. Building multidisciplinary and multi-sector implementation science collaborations will inform global initiatives (e.g. PEPFAR DREAMS, the Global Fund's Strategic Investment in Adolescent Girls and Young Women, World Health Organization's Global Accelerated Action for the Health of Adolescents

and UNAIDS Start Free, Stay Free, AIDS Free) and help identify and overcome the intractable barriers that drive high rates of HIV among adolescents in SSA.

AHISA is made up of 26 teams of NIH-funded researchers, programme implementers and policymakers working in 11 countries in SSA and includes over 75 members [11]. The alliance is guided by a steering committee of experts from the NIH, OGAC, US Agency for International Development, the US Centers for Disease Control and Prevention, the Elizabeth Glaser Pediatric AIDS Foundation, World Health Organization, UNICEF, and the Desmond Tutu Foundation. In addition to annual in-person meetings, webinars and online discussion, AHISA has also funded several small collaborative awards with the goal of catalysing long-term and sustainable region-/country-specific collaborations that respond to local issues and increase implementation science capacity across SSA. These small investments allow AHISA members to leverage their current research and engage a local audience that the larger alliance may not otherwise reach.

Pulling from the collective experience of its members, AHISA has identified critical implementation research questions that are imperative to moving the field of adolescent HIV prevention and treatment forward (Table 1). While researchers across the field including AHISA teams are addressing these priority areas such as transitions to adult care, predictors to uptake of and adherence to pre-exposure prophylaxis (PrEP), integrating mental health services in clinical care of adolescents with HIV, additional implementation research is needed for effective prevention, screening and treatment of HIV among adolescents [12-23]. Based on priority research questions identified by AHISA, the Eunice Kennedy Shriver National Institute of Child Health and Human Development established a consortium entitled the "Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings (PATC<sup>3</sup>H)," which funds eight research teams to conduct clinical research and evaluation of a variety of combination interventions aimed at the individual, family, community, structural and education, and health systems levels, to improve health outcomes among adolescents at risk for or living with HIV [24].

To more systematically identify implementation research priorities for adolescent HIV, AHISA is harnessing the collective expertise and experience of its members and conducting a concept mapping exercise [25]. Specifically, this exercise uses a rigorous methodology to identify factors that impact the implementation of HIV prevention and intervention programmes for adolescents in SSA. Using a multi-step approach, AHISA members generated responses to the focus question: "In your experience, what factors have facilitated or hindered implementation of evidence-based HIV prevention or treatment for adolescents in SSA?" These statements were sorted into thematically relevant groups and rated each statement on importance and changeability. The exercise will result in a set of agreed upon key factors that facilitate or hinder implementation of evidence-based HIV prevention or treatment for adolescents in SSA; factors that could be addressed by implementation science.

In addition to research priorities, AHISA members have identified common challenges to addressing these questions and discussed their collective capacity to conduct implementation

**Table 1. Priority research areas for adolescent HIV**

Transitions to adult care
Predictors of uptake of and adherence to PrEP
Integrating mental health services in clinical care of adolescents with HIV
Implementation/scale up/roll out/experiences with novel treatment options
Scale-up and disseminating of pilot results (e.g. pilot test for young men who have sex with men in Nigeria)
Drawing lessons from implementation science research to reach the most vulnerable and improve prevention outcomes
Acceptability and adaptation of mHealth approaches to prevention and treatment of HIV among adolescents
Understanding cultural barriers to the use of HIV Prevention methods among adolescent girls and young women and their partners
Optimizing youth engagement
Participation to improve HIV care continuum outcomes among young people. Expanding access and reach of youth-friendly sexual and reproductive health services
Engaging men and boys
Increasing uptake and retention into care using differentiated service delivery model
PrEP, pre-exposure prophylaxis.

science using the shared learning approach of the network. AHISA has outlined and addressed a range of challenges related to implementation science and adolescent HIV research:

**2.1 | Building capacity in implementation science**

Lack of capacity to conduct implementation research exists in the region and global health more generally. To help build implementation science capacity, AHISA in collaboration with the University of North Carolina and Wits University hosted a three-day training to provide alliance members with an in-depth overview of the theory, operational and evaluation approaches to implementation science; methods to assess barriers in implementation science and strategies/tools to overcome them; and options for dissemination of results [26,27].

To further develop tools for sustainable implementation science capacity, through the collaborative awards, AHISA is supporting the development of the Adolescents in Research Toolkit which will source and consolidate information pertaining to clinical, research and ethico-legal aspects of HIV prevention and treatment clinical trials in low- and middle-income countries and share this information through an online toolkit aimed at a wide variety of stakeholders working within adolescent health research and who are designing, implementing and disseminating adolescent health research and implementation science projects.

AHISA continues to build the capacity through trainings at each of the annual meetings and through biannual webinars on topics related to implementation science and adolescent HIV with the aim of strengthening learning among members. These activities allow members to both increase their capacity

for conducting implementation science and share relevant work in the field demonstrating the applicability of implementation science within their own research.

**2.2 | Developing mentorship**

Given the lack of capacity in implementation science, there are insufficient mentors for the discipline especially in SSA. These mentors are needed to build a sustainable pipeline of independent implementation scientists. To help address this challenge, AHISA has developed opportunities for mentoring through ongoing engagement with implementation science experts and continued capacity building. For example the AHISA-supported Central and West Africa Implementation Science Alliance (CAWISA), a locally led alliance with membership from Ghana, Nigeria, Cameroon and the Democratic Republic of the Congo, is supporting mentoring relationships by pairing early investigator mentees with both a senior research member of the CAWISA steering committee and a representative from a local institution for between two and five years. In addition, CAWISA aims to develop a mentorship toolkit as the programme progresses.

**2.3 | Engaging stakeholders**

There are important challenges in engaging stakeholders throughout the research process. First, researchers and policymakers ask different questions. Most researchers ask questions rooted in a quest for empirical evidence, whereas policymakers are often looking for programmatic/public health insights to inform policy and programme changes. Second, researchers and decision makers have different stakeholder audiences. While researchers often pursue broad scientific theory and work with a view towards generalizable findings, policymakers need answers to questions that are targeted to their distinct population. Finally, there is an important tension between the long gestation periods and rigorous requirements of research and the short time frames and need for quick information for policymakers and implementers. Strategies to help reconcile these time frames are critical. Recognizing the critical differences between the issues researchers and decision makers prioritize, AHISA has explored strategies for stakeholder engagement and has hosted several discussions with policymaking and programme implementing partners to understand best practices. Overall, successful research and practice partnerships emphasized the need to engage various stakeholders early in the research process to better align each other's interests and motivation and to include these stakeholders in the process to ensure timely dissemination of the results.

In addition, four collaborative AHISA-sponsored small awards support country-specific alliances – in Kenya, South Africa, Uganda and Zambia – that develop collaborative partnerships with other AHISA teams also engage local stakeholders, including policymakers, programme implementers and youth. By encouraging a more local geographic focus, these alliances are able to address specific local policies, such as Kenya's *Fast-Track Plan to End HIV and AIDS among Adolescents and Young People*, tackle areas of particular concern for a country, such as Uganda's HIV service delivery for adolescents, and focus on more granular populations.

## 2.4 | Involving adolescents

Adolescents themselves are important stakeholders often left out of the research process. They are critical to understanding barriers to implementation as well as to designing effective implementation science studies that address challenges in the context of this unique population. Without their engagement, uptake and feasibility of interventions is severely compromised. Indeed, adolescents can play important roles as advocates, participants and advisors to research. To increase the input of adolescents, AHISA has sponsored youth participants at the 2018 International AIDS Society conference, which gathered over 20,000 participants from more than 170 countries. In addition, AHISA supports the African Youth Implementation Science Alliance, which is developing a cadre of young researchers under 30 years old to build their capacity in implementation science. Along with engaging youth, a key component of the Youth Alliance is to provide both training and ongoing mentorship to ensure that young researchers are supported in the appropriate use of the implementation science designs and frameworks thereby ensuring that their results are efficacious and replicable.

While most of these challenges call for long-term investments, AHISA enables its members to share best practices and novel approaches while supporting the development of creative, empowering, and sustainable collaborations and implementation science capacity.

## 3 | CONCLUSIONS

The work of the alliance is well positioned to inform local and national policies and programmes related to adolescent HIV. For example research being conducted in Kenya in collaboration with the National AIDS and STI's Control Programme is developing a novel approach to address the continuum between paediatric to adult HIV care that can be scaled nationally [28]. Similarly, a partnership between researchers and the Rwanda Biomedical Center is primed to increase ART adherence among young people living with HIV [29]. Research focused on the challenges of effective and sustainable implementation of proven interventions in real-world settings is critical to the goal of achieving an AIDS-free generation and ensuring the survival and health of adolescents. Integration of clinical research evidence, programme implementation, and policy is critical to speed the translation of effective HIV prevention and treatment interventions. Implementation science can help close the gap between evidence and programme and policy as well as address stubborn barriers. Innovative platforms, like AHISA, that bring together and foster collaboration of implementation science researchers with implementers, policymakers and community participants prioritize research needs and identify and address implementation challenges that can speed the translation of effective HIV interventions to benefit adolescent health. Indeed, AHISA helps create and enhance partnerships, galvanizes regional and country investment and ownership, builds regional research capacity in implementation science, and can help promote meaningful engagement of adolescents in helping to overcome implementation challenges.

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## COMPETING INTERESTS

There are no competing interests.

## AUTHORS' CONTRIBUTIONS

RS and SV involved in conception of the work and drafting the article. RS, SV, LGB, WA, CL, SA, DW, BK and LG carried out final approval of the version to be published.

## ABBREVIATIONS

AHISA, Adolescent HIV Prevention and Treatment Implementation Science Alliance; CAWISA, Central and West Africa Implementation Science Alliance; NIH, United States National Institutes of Health; OGAC, US Office of the Global AIDS Coordinator; PATC<sup>3</sup>H, Prevention and Treatment through a Comprehensive Care Continuum for HIV-affected Adolescents in Resource Constrained Settings; PrEP, pre-exposure prophylaxis; SSA, sub-Saharan Africa.

## AUTHORS' INFORMATION

All authors are part of the AHISA Steering Committee.

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## DISCLAIMER

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the US government.

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