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Paediatric and Adolescent HIV and the Sustainable Development Goals: the road ahead to 2030

Guest Editors: Douglas Webb, Chewe Luo, Lucie Cluver
Supplement Editor: Marlène Bras

Volume 21, Supplement 1, February 2018

WILEY

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This special issue was organized by Marissa Vicari (Manager, CIPHER) and Diddie Schaaf (Project Manager, CIPHER).

Acknowledgements

CIPHER would like to thank the Guest Editors Lucie Cluver, Douglas Webb and Chewe Luo, and the contributing authors for making this Special Issue possible.

Support

The publication of this special issue was supported by CIPHER, with continued support from Founding Sponsor ViiV Healthcare and with support from Janssen.

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Volume 21, Supplement 1
February 2018

JIAS
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http://onlinelibrary.wiley.com/doi/10.1002/jia2.25071/full | https://doi.org/10.1002/jia2.25071

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JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

EDITORIAL

Evolution or extinction? Paediatric and adolescent HIV responses in the Agenda 2030 era

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Keywords: Sustainable Development Goals; HIV; children; paediatric; adolescents

Received 28 December 2017; **Accepted** 18 January 2018; **Published** 27 February 2018

For the past 30 years, HIV has united the international community in an unprecedented fashion. Grassroot groups have mobilized in both the north and the south; policy-makers and donors have worked with civil society, researchers and the private sector, and the epidemic response has inspired new thinking and medical innovation. The Millennium Development Goal (MDG) era was epitomized by the HIV response. For example, the remarkable progress on antiretroviral therapy has put the world closer to reaching the global target on reducing AIDS-related deaths. Since 2000, two million HIV infections have been averted in children as a result of pregnant women living with HIV being able to access antiretroviral medicines [1]. This progress has motivated the global HIV community to commit to fast track the response to end AIDS by 2030, a target in the new development era [2].

During this time, much of the advocacy for the importance of paediatric and adolescent HIV has been within the HIV/AIDS constituency itself, ensuring that children are not forgotten or discriminated against in the global HIV response [3]. Advocacy has focused on prevention of mother to child transmission (PMTCT), meeting the specific needs and conditions of children living with HIV and advancing the complex interventions related to preventing infection in adolescents. Despite this, progress in ensuring access to antiretroviral treatment for children and adolescents has been slower than for pregnant women and adults [4], and we continue to witness the slow progress in preventing new infections in adolescents [5].

The Agenda 2030 and associated Sustainable Development Goals (SDGs) now bring a fundamental change. Instead of having a Millennium Development Goal focused on combating the major infectious diseases of HIV, TB and malaria, HIV is subsumed within one of 169 targets and 17 goals that comprise the SDGs [6]. This could be construed as a dilution of attention to HIV, or conversely a redressing of the balance, given the evolution of the global burden of disease and the plurality of major disease threats, especially the rise of non-communicable diseases (NCDs). The shift from exceptionalism to active integration of HIV across health, education, violence prevention, poverty and the lived environment is the new imperative.

Should the SDGs be framed as a major "threat" to HIV funding, support and response capacity? The SDGs are here, and the HIV community, both epistemic and activist, needs to resituate itself within this new dominant development framework. UNAIDS and the International AIDS Society have spearheaded a conversation and strategic thinking on this reconfigured relationship, capitalizing on the growing sub-discipline that aims to articulate the "learning from AIDS" to inform and promote solutions to address other public health challenges. These are characterized by complex causal networks, "combination" structures, and the need for advanced investment and governance models which coordinate a spectrum of responding actors across systems and society as a whole [7].

SDG Target 3.3 urges the global community to "By 2030, end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases." The indicator 3.3.1 is one of five for this target, tracking the "Number of new HIV infections per 1000 uninfected population, by sex, age and key populations." The scale of intention has also shifted from "halt and reverse" HIV in relation to the previous MDG 6, to the more substantial "end the epidemic" by 2030. While the development scope has broadened, the level of HIV response required has actually intensified.

The complexity of Agenda 2030 entails the need to prioritize and inevitably embark on a series of trade-offs at country level. The UN Development Group, led by UNDP, is undertaking a series of inter-agency missions to countries to help develop SDG roadmaps at national and where appropriate, sub-national level [8]. Furthermore, a recent Global Review of the UNAIDS Operational Model recommended introduction of

country resource envelopes to domesticate and enhance the joint UN response in priority high HIV burden countries, so called fast-track countries. This domestication and prioritization of SDGs aims to seek the most cost-effective combination of investments across the targets, bespoke to the situation and prioritizing interventions that at scale will deliver against multiple targets and goals simultaneously, the "accelerators" of sustainable development. Addressing the causes and consequences of HIV is arguably one of these accelerators.

HIV/AIDS experience has major value in informing the SDG core approaches, over and above being a component response in its own right. UNAIDS argues that "…lessons learned from the multisectoral, multistakeholder AIDS response, including engagement of civil society are key to progress across the SDGs. The AIDS response has advanced such issues as the right to health, gender equality, health information systems, service delivery platforms, commodity access and security and social protection. The response has garnered substantial experience in addressing entrenched social norms, social exclusion and legal barriers that undermine health and development outcomes, and its investment approach is increasingly being adopted to accelerate gains across global health and development. The AIDS response can be a leader in leveraging strategic intersections with the SDGs, while disseminating lessons learned from three decades of unprecedented progress." [9]

The implication is that the HIV response has not only intrinsic value in its efforts to end AIDS by 2030 (as a component of target 3.3), but also has extrinsic value in leveraging other associated and potentially connected development objectives. This framing of the HIV "dividend" relates to both the synergies between HIV response and other objectives, as well as the understanding that the HIV response infrastructure, with its inbuilt experience and precedents, is a significant asset on which to build comprehensive health and social service provision. HIV responses are a driver of universal health coverage, for both integrated service delivery and through deliberate exposure and overcoming of barriers to accessing quality health services. All the while, the human rights of HIV-affected communities have permeated the advocacy, programme design, monitoring and impact assessment. Action on HIV has deliberately targeted "those left behind", the core group of obligation in the 2030 Agenda.

HIV-focused or invested institutions cannot be seen as the sole claimant of this positive scenario. A conversation is ongoing across a broad range of themes regarding their valued contribution, given the synergistic nature of the SDGs and the need to view targets and their associated themes as integral to a larger whole, interdependent on shared successes across targets. We stress, however, that the claim of HIV responses to a central SDG role is a strong one. For example in the field of global health, HIV has innovated through the building and use of evidence, and normalized this research evidence as fundamental to the validity and expansion of the response infrastructure. Understanding this value of the HIV response for children and adolescents within and for the development agenda is the purpose of commissioning this Special Issue, led by the Collaborative Initiative for Paediatric HIV Education and Research at the International AIDS Society.

These papers identify a set of opportunities for addressing paediatric and adolescent HIV that are offered by the SDGs. They highlight the areas of common interest and specific connections with targets and indicators beyond HIV and health alone. They illustrate how HIV and AIDS responses have the latent potential to be a driver across the development arena. Extraordinary knowledge, skills and expertise have been built, new ways of working, of implementation and of embedding evidence-based practice. Over the past 30 years, the evolution and multiple reinvention of programming has been in response to positive and negative changes such as advances in prevention technology, new treatment regimens and the threat of viral resistance, all with their own intended and unintended consequences. So this is the new challenge, to evolve in a way that capitalizes on the opportunities of the SDGs and that ensures that children and adolescents both vulnerable to and affected by HIV are themselves not left behind.

The papers in this Special Issue address this challenge from a range of perspectives. Several retain the core focus on SDG 3 (healthy lives and wellbeing) and examine new challenges and solutions in the SDG era. All seek synergies at various levels with other SDGs and targets.

Cluver and colleagues demonstrate the impressive effects of combined service provision, as a proxy of SDG interaction, on HIV mortality in adolescents in South Africa. Longevity and survival is associated not only with ART but with food security, social protection and access to non-HIV health services [10]. Chaudhury and colleagues delve deeper into questions of equity of access to treatments and care for children in Tanzania across age groups. Compared to paediatric cases, adolescence is associated with risk of late presentation, delayed treatment initiation and loss of continuity of care. Improving health and wellbeing for all, "at all ages" as required by Goal 3, entails particular attention to the adolescents living with HIV [11]. Fatti and colleagues examine treatment adherence and outcomes (notably the degree of viral suppression) for adolescents living with HIV in South Africa, and their findings suggest that community-based support could be the crucial link between clinical support and progress toward several health, economic and equity-related SDG targets [12]. Slogrove and colleagues assess treatment outcomes in adolescents living with perinatally acquired HIV across 25 countries. They conclude that at the macro-level and irrespective of ART access, measurable differences in mortality relate to the income status of the country, with poorest outcomes in the lower income countries, highlighting the relevance of promoting equality within and between nations [13].

Kilburn and colleagues generate further evidence that poverty alleviation and reduction of HIV risks are highly connected. In South Africa, conditional cash transfers work in part through delaying sexual debut or reducing the number of sexual partners of adolescent girls and young women. Intimate partner violence is reduced and proves a critical mediator in reducing HIV risks [14]. Grosso et al. draw the link between HIV-related risk behaviours in female sex workers in Lesotho that are directly influenced by experience of sexual abuse as children. The complex causal pathways between child sexual abuse, sex work and HIV risk are mapped out and demand our attention with regard to intervention design and impact mitigation, again with the life course and range of SDGs in full view [15].

Leaving no one behind means full accountability of the state to those who are in need of quality and accessible HIV services. Gleeson and colleagues highlight the need for adolescents and young people to be meaningfully engaged as leaders of HIV within the SDG response [16]. Hodes and colleagues examine what happens when this is enacted through participatory engagement. Adolescents in South Africa identified strong needs and linkages between SDGs 2 (end hunger), 3 (healthy lives and wellbeing) and 6 (clean water and sanitation) in material, not abstract policy terms [17].

The SDGs demand policy coherence across development policy domains and innovative partnerships to advance them. Penazzato and colleagues describe how capacity-building and South-North collaborations have the potential to accelerate availability of optimized treatment options not only for infectious diseases including HIV, but also for tuberculosis and viral hepatitis, which affect children in low- and middle-income countries [18]. Tinasti assesses the criminalization of drug use and punitive policy environments and their impact on adolescents' health and HIV transmission risks [19]. Similarly, Chamla and colleagues explore the connections between HIV and humanitarian setting engagement. With 9 of the 21 countries in Africa deemed by UNAIDS as being "high priority" for HIV, being fragile, conflict-affected, or impacted by climate-related hazards, to what extent is HIV and crisis prevention and recovery integrated? While clearly work in progress, the drug policy-HIV service synergies, and the humanitarian-development nexus provide important frameworks that could bridge divides between these all-too-often disparate areas of concern [20].

We are privileged to have been guest editors for this Special Issue and emerge convinced that while HIV responses were advanced prior to the SDG agenda, ending AIDS will only be possible as one of its core components.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

DW, LC and CW reviewed all articles in the special issue, and formulated, drafted and developed the editorial. All authors have read and approved the final version.

ACKNOWLEDGEMENTS

We thank Marlene Bras, Biljana Samopjan Radovic, Douglas Fraser, Marissa Vicari and Martina Penazzato, as well as all the authors and peer reviewers for the articles in this Special Issue.

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Cluver L et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25056
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25056/full | https://doi.org/10.1002/jia2.25056

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RESEARCH ARTICLE

Sustainable Survival for adolescents living with HIV: do SDG-aligned provisions reduce potential mortality risk?

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Abstract

Introduction: The Sustainable Development Goals (SDGs) present a groundbreaking global development agenda to protect the most vulnerable. Adolescents living with HIV in Sub-Saharan Africa continue to experience extreme health vulnerabilities, but we know little about the impacts of SDG-aligned provisions on their health. This study tests associations of provisions aligned with five SDGs with potential mortality risks.

Methods: Clinical and interview data were gathered from N = 1060 adolescents living with HIV in rural and urban South Africa in 2014 to 2015. All ART-initiated adolescents from 53 government health facilities were identified, and traced in their communities to include those defaulting and lost-to-follow-up. Potential mortality risk was assessed as either: viral suppression failure (1000+ copies/ml) using patient file records, or adolescent self-report of diagnosed but untreated tuberculosis or symptomatic pulmonary tuberculosis. SDG-aligned provisions were measured through adolescent interviews. Provisions aligned with SDGs 1&2 (no poverty and zero hunger) were operationalized as access to basic necessities, social protection and food security; An SDG 3-aligned provision (*ensure healthy lives*) was having a healthy primary caregiver; An SDG 8-aligned provision (*employment for all*) was employment of a household member; An SDG 16-aligned provision (*protection from violence*) was protection from physical, sexual or emotional abuse. Research partners included the South African national government, UNICEF and Pediatric and Adolescent Treatment for Africa.

Results: 20.8% of adolescents living with HIV had potential mortality risk – i.e. viral suppression failure, symptomatic untreated TB, or both. All SDG-aligned provisions were significantly associated with reduced potential mortality risk: SDG 1&2 (OR 0.599 CI 0.361 to 0.994); SDG 3 (OR 0.577 CI 0.411 to 0.808); SDG 8 (OR 0.602 CI 0.440 to 0.823) and SDG 16 (OR 0.686 CI 0.505 to 0.933). Access to multiple SDG-aligned provisions showed a strongly graded reduction in potential mortality risk: Among adolescents living with HIV, potential mortality risk was 38.5% with access to no SDG-aligned provisions, and 9.3% with access to all four.

Conclusions: SDG-aligned provisions across a range of SDGs were associated with reduced potential mortality risk among adolescents living with HIV. Access to multiple provisions has the potential to substantially improve survival, suggesting the value of connecting and combining SDGs in our response to paediatric and adolescent HIV.

Keywords: HIV/AIDS; SDGs; adolescents; viral load; tuberculosis; South Africa; social protection

Received 9 May 2017; **Accepted** 20 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

The Sustainable Development Goals (SDGs) signal a radical change for the paediatric and adolescent HIV sector. We have moved from an HIV-focused Millennium Development Goal to a new agenda that incorporates wider health needs within a multifaceted set of human capital targets - ranging from education to gender equality to violence prevention. Importantly, the SDGs also prioritize integration and partnership between the goals and their targets [1].

In sub-Saharan Africa, where 60% of adolescents living with HIV reside [2], survival remains a major concern. Adolescent rates of adherence and retention in care remain low [2-5], and viral suppression failure [6] and TB are common [7]. AIDS is the leading cause of death among adolescents in Africa, and adolescent AIDS-related mortality rates are not decreasing [8]. Systematic reviews show few effective interventions for adolescents living with HIV [9,10], and a primary focus on healthcare provision [11]. But qualitative data suggests that adolescents living with HIV do not see health as their only concern, and instead regard themselves as multifaceted individuals with holistic needs [12]. In line with this, new WHO guidelines see adolescent health outcomes as a result of intertwined experiences in multiple spheres of their lives [13]. Could then a shift to the wider-ranging focus of the SDGs benefit adolescent HIV care and potential for long-term

survival? And does integration across goals and targets bring risks or opportunities for this exceptionally vulnerable group?

We do not yet have data on adolescents living with HIV that is specifically designed to assess impacts of attainment of SDG targets. However, an existing large-scale community study of adolescents living with HIV in South Africa [14,15] provides an opportunity to examine existing services that directly correlate to the contribution of achieving SDG targets, and whether they are associated with reductions in potential mortality risks. Of course, it will be important that future studies specifically measure whether SDG targets are met among adolescents living with HIV at national and international levels, but this study aims to provide valuable input as the world moves towards operationalization of the SDGs. We use adolescents living with HIV as the unit of analysis, examining whether and how individual-level access to SDG-aligned provisions affects potential mortality risk (operationalized as viral failure or symptomatic untreated TB).

2 | METHODS

The study was designed in partnership with the South African National Departments of Health, Social Development and Basic Education and National AIDS Council, UNICEF, PEPFAR-USAID, and Pediatric Adolescent Treatment for Africa (PATA). We conducted a total population sampling survey of adolescents living with HIV in a health district of South Africa's Eastern Cape, a province characterized by poor infrastructure and limited service access. The study included ART-initiated adolescents, irrespective of whether they were engaged in care at the time of the survey. In order to do this we targeted one urban/peri-urban/rural health district and visited all health facilities providing HIV services (hospitals, community health centres, and primary care clinics). Of these, all 53 health facilities that provided ART for adolescents were sampled. In each health facility, we went through paper and computerized records to identify all adolescents aged 10 to 19 that had ever initiated ART.

From March 2014 to September 2015, adolescents were traced to their communities and invited to participate in a study of young people, health and social services in South Africa. Of 1202 eligible adolescents, 90.1% (n = 1060) were interviewed. 3.7% of adolescents were untraceable, primarily due to inaccurate names and addresses in clinic files. 0.9% were unable to be interviewed due to very severe developmental disability, and 4.1% refused to participate (either adolescent or primary caregiver), 1.2% were excluded for other reasons. In order to prevent stigma, HIV was not mentioned in recruitment, and neighbouring adolescents were also interviewed (n = 467, not included in analyses). Community-based tracing resulted in a sample that included high proportions of ART-initiated adolescents who do not regularly attend facilities, default from treatment, or missed recent appointments (44% of the sample).

Ethical approval was given by the Universities of Cape Town (CSSR 2013/4) and Oxford (SSD/CUREC2/12-21), the Provincial Departments of Health and Education and ethical review committees of participating facilities. Full voluntary informed consent was obtained from both adolescents and their primary caregivers, and included interviews and access to clinical records. Given low levels of literacy, consent procedures were additionally read aloud. The study did not use financial incentives for participation, but all adolescents received a small gift pack, refreshments and a certificate of participation. Participants were informed that all responses were confidential except in the case of risk of harm to the adolescent or someone else. Where participants or caregivers reported abuse, recent attempted suicide, active untreated TB or other serious risks, immediate referrals and follow-up were made to health, police and social services, including taking the participant to a health facility when health or abuse-related cases were reported. 69 high-risk referrals were made. These included 38 for severe food insecurity, 22 for psychosocial or family issues, 6 for sexual abuse, 5 for suicide attempts, 5 for physical abuse, 4 for extreme illness and 2 for drug use.

Clinical records identified most recent viral load measures, diagnoses and treatment of tuberculosis. With the support of interviewers, adolescents participated in a tablet-based questionnaire lasting approximately 90 minutes. Standardized measures were translated into Xhosa, back-translated and provided in both Xhosa and English according to participant choice. The questionnaire was designed in collaboration with our Teen Advisory Group of 20 adolescents to be engaging and adolescent-friendly, and was pre-piloted with a further 25 adolescents living with HIV in the Eastern Cape. Interviewers were trained in working with HIV-affected adolescents and their families.

2.1 | Measures

Potential mortality risk for adolescents living with HIV was assessed using two key predictors: treatment failure and symptomatic pulmonary tuberculosis [16,17]. Antiretroviral treatment failure was operationalized as virologic suppression failure in the past two years (defined as viral load 1000 +/ml [18]). Viral load data were extracted from clinic records, however limited health service capacity in the Eastern Cape meant that viral load tests were not consistently performed or recorded: only 673 adolescents (64.5% of the sample) had any viral load recorded in their patient files. Furthermore, only 412 adolescents (38.6%) had a viral load test in the past two years. Viral load measurements that had been taken more than two years prior to the study were excluded. In the very few cases where adolescents had more than one viral load taken in the past two years, the most recent viral load was selected.

Symptomatic pulmonary TB – the leading cause of death among HIV-infected populations in the region – was unable to be assessed through clinical records as almost none reported any TB testing or results. Consequently, TB was measured as 1) adolescent-reported TB diagnosis without subsequent treatment or 2) self-reported current symptoms of TB using WHO diagnostic criteria, validated among 8979 participants in Zimbabwe against two sputum specimens [19,20]. This study identified that positive predictive value (PPV) was highest for the symptom combination of chronic cough and weight loss (sensitivity 72.9%, specificity 85%, PPV 11.4). Negative predictive value (NPV) was highest for the symptom combination of any cough, drenching night sweats, and weight loss (sensitivity 75%, specificity 82.4%, NPV 99.2). Area under ROC curves was estimated to provide a summary measure of diagnostic

accuracy, with AUC of 0.81 for HIV-positive TB. We required fulfilment of criteria for both positive and negative predictive values to maximize precision for each case identification of TB.

We identified provisions aligned with SDG targets that may have potential to improve adolescent outcomes, using systematic reviews and studies of risk and protective factors for child, adolescent and adult HIV-outcomes [21-23]. First, adult studies suggest that poverty may present a barrier to HIV healthcare access through lack of transport and food [24-26] and that social protection provision may have potential to improve retention in care [27,28]. Given the overlap between ending poverty, food insecurity and social protection, we combined provisions aligned to SDGs 1 and 2 ("End poverty" and "end hunger"). These were operationalized as access to all of the following: eight basic necessities for children as endorsed by over 80% of the population in the nationally representative SA Social Attitudes Survey, including "3 meals per day" and "free school;" and access to a child-focused grant (child support or foster child grant) in the household. These provisions align to SDG targets 1.1 ("end extreme poverty"), 1.2 ("reduce [. . .] poverty in all its dimensions"), 1.3 ("Implement nationally appropriate social protection") and 2.1 ("end hunger").

Second, studies of HIV-affected families find improved outcomes for children with healthy and surviving caregivers [29,30]. Consequently, we identified a surviving and healthy caregiver as a provision aligned with SDG 3 ("Ensure healthy lives"). This was measured through adolescent self-report of having a surviving parent or caregiver taking care of them at home, who was not suffering from chronic illness. This provision is aligned with SDG targets 3.1 ("reduce maternal mortality") and 3.2 ("end the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases"). Adolescent health was not included as a potential provision due to high risk of confounding with the study outcomes of viral failure and TB.

Third, studies suggest that caregiver capacity to provide sustained household income can lead to improved child outcomes in the context of HIV [31]. Consequently, we included the potential provision of household employment, as aligned with SDG 8 ("Employment. . . for all"). This was operationalized as adolescent report of at least one employed person in their household.

Fourth, there is now substantial evidence demonstrating that violence has negative health impacts [32], and that protection from abuse may improve adolescents' psychological and physical capacity to engage with healthcare. Thus, we included a provision aligned with SDG 16 ("Peace and justice," specifically "end abuse. . . and all forms of violence against. . . children"). Never having been physically, emotionally or sexually abused was aligned with targets 16.1 ("significantly reduce all forms of violence") and 16.2 ("end abuse, exploitation, trafficking and all forms of violence against. . .children"), and measured through adolescent self-report using the UNICEF Measures for National-level Monitoring of Orphans and Other Vulnerable Children and the Juvenile Victimization Questionnaire (JVQ), both used previously in South Africa [33].

2.1.1 | Covariates

Age (10 to 14 versus 15 to 19), *gender, and urban/rural location* were measured using items based on South Africa's Census [34]. *Mode of HIV-infection* was measured using clinical algorithms, with adolescents coded as vertically infected if they had initiated ART prior to age 12 or if they had been on ART for more than 5 years, based on the year of widely available ART access in the study area [35,36]. *Time on ART* was measured via self-report. Based on evidence of higher defaulting risk in the first year of treatment [37], a dummy variable was computed to differentiate between 1: "more than one year on treatment" and 0: "one year or less."

2.2 | Analysis

Analyses were conducted in six stages in SPSS 22 and STATA 14. First, eligible participants included in the study (90.1%) were compared to those excluded (not found or refused participation) on known socio-demographic characteristics (age, gender and urban/rural household location) using χ^2 tests. Second, frequency distributions for high mortality risk among adolescents living with HIV, each of the hypothesized SDG-aligned provisions, socio-demographic and HIV-related covariates were reported. Third, to test initial associations of each SDG-aligned provision against potential mortality risk among adolescents living with HIV, bivariate logistic regressions were run. Fourth, a multivariate logistic regression was run, including all SDG-aligned provisions simultaneously and controlling for all potential covariates. All potential two-way and three-way interactions were tested in logistic regressions.

Fifth, to compute combined effects of multiple SDG-aligned provisions the following steps were taken, using provisions found to be significantly associated with reduced mortality risk in Stage 3. First, categorical principal components analysis established that all provisions loaded onto a first component (eigenvalue 1.2, 24.4% of total variance). Loadings for each provision were >0.35. To assess combined effects of multiple SDG-aligned provisions, a summative index was computed, weighted by the respective component loadings. This weighted summative index was highly correlated with a simple summation of the unweighted dichotomies (Spearman's *rho*, 0.961; $p < 0.001$), and therefore, for ease of interpretation, the unweighted scale was used. Sixth, a marginal effects model was run to assess predicted probabilities of high mortality risk by combined effects of multiple SDG-aligned provisions, holding all socio-demographic and HIV-related co-factors at mean values. This was plotted with 95% confidence intervals.

3 | RESULTS

No differences were found between included and excluded participants on age, gender or rural/urban location (Table 1). Table 2 shows socio-demographic and HIV-related

Table 1. Comparisons between reached and unreached adolescents

	HIV+ (n = 1060)	Excluded (n = 116)	Comparison tests*
Age (mean, SD)	13.8, 2.834	14.8, 2.91	$p = 0.671$
Female (n, %)	587, 55.2%	66, 56.9%	$p = 0.769$
Rural (n, %)	228, 21.4%	26, 22.4%	$p = 0.813$

*p values associated with z score and χ^2 tests.

Table 2. Socio-demographic covariates, mortality risk and access to SDG-aligned provisions

	n, %
Under 15	659, 62.2
Female	584, 55.1
Rural household location	228, 21.5
> 1 year on treatment	753, 70.9
Vertically infected	708, 66.8
Potential mortality risk	221, 20.8
Viral load failure	93, 8.8
TB	145, 13.7
SDG-aligned provisions	
SDG1 + 2 (basic necessities, food security and social protection)	161, 15.2
SDG3 (caregiver alive and healthy)	810, 76.4
SDG8 (household access to work)	706, 66.6
SDG16 (no child abuse victimization)	551, 52.0
Combined effects of multiple SDG-aligned provisions	
No SDG-aligned provisions	53, 5.0
One SDG-aligned provision	217, 20.5
Two SDG-aligned provisions	425, 40.1
Three SDG-aligned provisions	299, 28.2
All four SDG-aligned provisions	66, 6.2

characteristics, potential mortality risk and access to SDG-aligned provisions. Adolescents had a mean age of 13.8 (SD 2.8), were 55% female and 67% vertically infected. 70.9% had been on treatment for >1 year. 20.8% of adolescents had potential mortality risk – either viral failure (8.8% of the full sample), or symptomatic untreated tuberculosis (13.7%). Only 38.6% of the adolescents had results of a viral load test recorded in their clinic files within the past two years. Access to SDG-aligned provisions varied: 15.2% accessed basic necessities, food security and social protection (SDGs 1 and 2), 76.4% had a healthy and surviving caregiver (SDG 3), 66.6% had someone working within their household (SDG 8) and 52% reported no exposure to physical, emotional or sexual abuse (SDG 16).

Bivariate associations between SDG-aligned provisions and potential mortality risk are presented in Table 3. Multivariate logistic regression (Table 4) showed that all SDG-aligned provisions remained significantly associated with lower mortality risk for adolescents living with HIV. This was independent of each of the other SDG-aligned provisions, as well as all socio-demographic and HIV-related covariates. Effect sizes were similar across SDGs, ranging from the highest effect OR = 0.57 (SDG 3) to the lowest OR = 0.68 (SDG 16). No covariates were significant in the multivariate model. The Hosmer-Lemeshow Test indicated good model fit (χ^2 (df) = 10.425 [8], p = 0.236). No interaction terms showed significant effects.

Potential combined effects of access to multiple provisions were tested in a marginal effects model (Figure 1). Independent of all socio-demographic and HIV-related covariates, access to a greater number of SDG-aligned provisions was associated with reduced mortality risk among adolescents living with HIV. There was a clearly graded relationship: with access to none of the provisions, 38.5% of adolescents living with HIV were at potential mortality risk. With access to all four SDG-aligned provisions, 9.3% of adolescents living with HIV were at potential mortality risk.

Table 3. Model 1: Bivariate regressions between SDG-aligned provisions and potential mortality risk

SDG-aligned provisions	Unadjusted OR	Lower CI	Upper CI
SDG 1 + 2 basic necessities & social protection	0.546**	0.367	0.814
SDG 3 healthy caregiver	0.510***	0.380	0.683
SDG 8 household access to work	0.655**	0.500	0.857
SDG 16 no emotional, physical or sexual abuse	0.650***	0.501	0.843

**Indicates significance at $p < 0.005$; ***indicates significance at $p < 0.001$.

Table 4. Model 2: Multivariate regression predicting mortality risk with all hypothesized covariates and SDG-aligned provisions included

	AOR	Lower CI	Upper CI
Socio-demographic covariates			
Younger than 15	0.742	0.523	1.05
Female	0.750	0.548	1.02
Rural location	1.28	0.896	1.83
HIV-related covariates			
Vertical HIV infection	1.25	0.749	2.10
> 1 year on treatment	0.875	0.533	1.43
SDG-aligned provisions			
SDG 1 + 2 basic necessities & social protection	0.599*	0.361	0.994
SDG 3 healthy caregiver	0.577***	0.411	0.808
SDG 8 household access to work	0.602***	0.440	0.823
SDG 16 no emotional, physical or sexual abuse	0.686**	0.505	0.933

*Indicates significance at $p < 0.05$; **indicates significance at $p < 0.005$; ***indicates significance at $p < 0.001$.

4 | DISCUSSION

This study asks: does an agenda triggered by the SDGs hold out hope for adolescents living with HIV in Southern Africa? First, findings show strong associations of reduced mortality risk with provisions aligned to socio-economic, family and violence prevention SDGs. These suggest that, whilst treatment access and health system responses are essential, the broader vision of the SDGs may support the long-term survival of adolescents living with HIV. Second, findings show high rates of severe health deficiency among a large sample of ART-

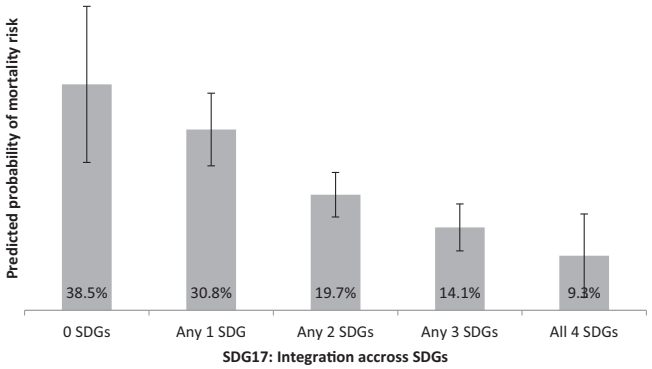

Figure 1. Predicted probabilities of adolescent potential mortality risk by combined SDG-aligned provisions, controlling for socio-demographic and HIV-related co-factors (n = 1060).

initiated adolescents recruited from over 50 health facilities in South Africa. With substantial global populations of adolescents living with HIV [38] and a youth explosion within Africa reaching 435 million adolescents by 2050 [39], addressing adolescent HIV will be essential if we are to protect the most vulnerable in the region. Third, findings show that access to key SDG-aligned provisions – social protection, caregiver health, household employment and protection from violence – has the potential to improve critical aspects of health among adolescents living with HIV. The SDG agenda provides a pathway of hope and provision for this group and this study indicates that some of the interventions are to hand and can be incorporated into services to good effect. Moreover, exposure to multiple provisions is associated with greater health benefits for adolescents living with HIV. This suggests potential added value to policymakers, via synergies between SDG objectives and efficiency gains from services that have multiple impacts including and beyond health. How this is done – through integrated services or through multiple avenue provision – needs to be understood in greater depth. Recent research finds economic "development synergies" that may assist in operationalizing such multisectoral service delivery [40]. Our data suggest the imperative for such combined provision as a standard of care.

It is important to note a number of study limitations. First, clinic files showed extremely low rates of viral load testing, with only a third of adolescents having any viral load record in the two years prior to recruitment. Rates of viral suppression failure among adolescents who had not been tested are unknown. This may have led to an underestimate of virological suppression failure in the present sample. Second, the viral load data was recorded in clinic files within two years prior to our data collection, which introduces problems of temporality. Third, rates of TB-testing recorded in clinic files were also exceptionally low – consequently we used self-reported TB diagnosis without treatment, and self-reported symptom-based screening, shown in Zimbabwe to have diagnostic value comparable to sputum testing among a large sample of people living with HIV. It would be of value for future studies to conduct independent TB-testing of adolescents. These limitations reflect some of the challenges of conducting research in real-world health services in Africa, outside high-quality teaching hospitals and donor-funded clinics. Fourth, provisions aligned with two of the SDGs (end poverty and end hunger) were combined due to conceptual overlap. Whilst there are plausibly separate pathways to mortality risk through food insecurity and socio-economic status, combining these was desirable for two reasons: (i) most poverty scales (including the one applied in this study) include food security items; and (ii) the two scales were correlated (Pearson's $r = 0.166$, $p < 0.0001$). Fifth, the study was cross-sectional and thus causal relationships cannot be determined, with the potential risk that some covariates may be on the causal pathway between exposure and outcome (although none of the covariates were significantly associated with the outcome in multivariate models). Future research should examine these associations using longitudinal data. Sixth, the study took place in only one country and generalizability to other countries and regions is unknown. Last, we only tested a limited selection of SDG-aligned provisions for which we had data in this existing study, and it will be of great value for future SDG-focused studies to examine associations of additional provisions with adolescent HIV outcomes.

The study also has notable strengths. This is the largest known study of adolescents living with HIV to include social, economic and clinical outcomes. It is the only known study that traces ART-initiated adolescents into their communities, and in doing so includes those who have defaulted on treatment or no longer attend healthcare. Total population sampling was employed within more than 50 healthcare facilities, including hospitals and rural and urban primary health clinics – reflecting a typical range of facilities providing care to adolescents living with HIV within a resource-limited area of South Africa.

5 | CONCLUSIONS

We are at a point of both crisis and potential. On the most basic measure of survival, adolescents living with HIV are among the global populations "furthest behind." Sustainable Development Goal 3 includes the ending of the epidemics of AIDS and tuberculosis (SDG 3.3) – a crucial target to ensure the health and well-being of millions in Southern Africa. This study's findings demonstrate that this aim cannot be conceptualized within the goal of health alone [41]. Instead, findings suggest that service provisions aligned with a range of SDGs are strongly associated with reduced potential mortality risk, and that combinations of protective provisions are more effective than any single factor alone. As the SDGs progress from aspirations into policies and programmes, it is essential that we develop a strong evidence-base of SDG-aligned services, as well as national planning and fiscal environments that support access to these services for adolescents living with HIV.

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COMPETING INTERESTS

The authors declare no competing interests.

AUTHORS' CONTRIBUTIONS

LC, MP and ET had responsibility for the overall study design and management. LC, MP, MO and LS had responsibility for conceptualizing the paper. MO, LC and MP conducted the analyses for the paper. LC, LS, SM, MP and ET wrote the paper. All authors reviewed and approved the final version.

ACKNOWLEDGEMENTS

Funding: The study was supported by the Nuffield Foundation under Grant CPF/41513, Janssen Pharmaceutica N.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson, Evidence for HIV Prevention in Southern Africa, a UKAID programme managed by Mott MacDonald (MM/EHPSA/UCT/05150014), the International AIDS Society through the CIPHER grant (155-Hod), the Clarendon-Green Templeton College Scholarship (MP/ET), the Economic and Social Research Council (IAA-MT13- 003). Additional support for LC was provided by the European Research Council (ERC) under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no 313421 and the Philip Leverhulme Trust (PLP-2014-095).

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JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Equity of child and adolescent treatment, continuity of care and mortality, according to age and gender among enrollees in a large HIV programme in Tanzania

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Abstract

Introduction: Global scale up of anti-retroviral therapy (ART) has led to expansion of HIV treatment and prevention across sub-Saharan Africa. However, age and gender-specific disparities persist leading to failures in fulfillment of Sustainability Development Goals, including SDG3 (achieving healthy lives and wellbeing for all, at all ages) and SDG5 (gender equality). We assessed ART initiation and adherence, loss to follow-up, all-cause death and early death, according to SDG3 and SDG5 indicators among a cohort of HIV-infected children and adolescents enrolled in care in Dar-es-Salaam, Tanzania

Methods: SDG3 indicators included young (<5 years) and older paediatric children (5 to <10 years), early adolescent (10 to <15 years) and late adolescent (15 to <20 years) age group divisions and the SDG5 indicator was gender. Associations of age group and gender with ART initiation, loss to follow-up and all-cause death, were analysed using Cox proportional hazards regression and with adherence, using generalized estimating equations (GEE) with the Poisson distribution. Associations of age group and gender with early death were analysed, using log-Poisson regression with empirical variance.

Results: A total of 18,315 enrollees with at least one clinic visit were included in this cohort study. Of these 7238 (40%) were young paediatric , 4169 (23%) older paediatric, 2922 (16%) early adolescent and 3986 (22%) late adolescent patients at enrolment. Just over half of paediatric and early adolescents and around four fifths of the late adolescents were female. Young paediatric patients were at greater risk of early death, being almost twice as likely to die within 90 days. Males were at greater risk of early death once initiated on ART (HR 1.35, 95% CI 1.09, 1.66)), while females in late adolescence were at greatest risk of late death (HR 2.44 [1.60, 3.74] <0.01). Late adolescents demonstrated greater non-engagement in care (RR 1.21 (95% CI 1.16, 1.26)). Among both males and females, early paediatric and late adolescent groups experienced significantly greater loss to follow-up.

Conclusion: These findings highlight equity concerns critical to the fulfillment of SDG3 and SDG5 within services for children and adolescents living with HIV in sub-Saharan Africa. Young paediatric and late adolescent age groups were at increased risk of late diagnosis, early death, delayed treatment initiation and loss of continuity of care. Males were more likely to die earlier. Special attention to SDG3 and SDG5 disparities for children and adolescents living with HIV will be critical for fulfillment of the 2030 SDG agenda.

Keywords: gender; SDGs; equity; antiretrovirals; HIV-infected; children; adolescents

Additional Supporting Information may be found online in the Supporting information tab for this article.

Received 12 June 2017; **Accepted** 18 January 2018; **Published** 27 February 2018

1 | INTRODUCTION

Global expansion of anti-retroviral therapy (ART) has led to the marked success of prevention of mother-to-child transmission (PMTCT) programmes and increased enrolment into HIV care programmes across sub-Saharan Africa [1]. Despite significant strides in PMTCT globally, significant age and gender disparities exist in outcomes of efforts to prevent, diagnose, treat and manage HIV among children and adolescents, with significant implications for the fulfillment of SDG3 (achieving healthy lives and wellbeing for all, at all ages) and SDG5 (gender equality). Children are particularly vulnerable, experiencing a wide array of challenges, ranging from barriers to testing and treatment, to failures in continuity of care [1]. Not all

mothers receive antiretroviral medicines (ARVs), and delays in newborn testing and treatment persist with effects on perinatal transmission and disease management [2,3]. Global disparities in HIV-related child mortality continue to disproportionately burden sub-Saharan Africa [4]. While global reductions in HIV-related mortality have largely been driven by successful treatment of infections across other age groups, HIV-related deaths among adolescents, particularly among girls, have risen during the same period [5,6]. Within the sub-Saharan African HIV epidemic, adolescent girls are known to experience higher incidence of infections and barriers to care in late adolescence [7], while males experience relatively higher mortality [8,9]. Failure to address the age and gender-specific needs of children and adolescents infected with HIV in sub-Saharan Africa leads to failure to fulfill SDG3 and SDG5, with further interdependent failings in several Sustainability Development Goals (SDGs) [10].

The SDGs provide scope for the unification of development efforts across different sectors in the fulfillment of a single agenda for health [11]. Arguably health is central to the fulfillment of the SDGs, being both as essential precursor and consequence of sustainable development [12]. Integrating framework approaches can incorporate multiple SDG targets and provide opportunity for intersectoral and coordinated action for health [12]. To achieve health for all children living with HIV in sub-Saharan Africa, an integrated approach may strengthen links between targets within SDG3, such as SDG 3.3 (to end the AIDS and TB epidemics), 3.7 (sexual and reproductive health) and 3.8 (universal health coverage) and also strengthen links across different sectors. For instance, links between SDG3 and SD4 (education) targets, such as SDG 4.1 to 4.7, may emphasize relationships between child and adolescent sexual health and primary and secondary education. Links with SDG8 (economic productivity) targets 8.1 to 8.6 may facilitate measurement of the impacts of child and adolescent HIV on varying dimensions of the economic growth within the nation. An integrating framework approach can map differences in progress across all of the implicated sectors according to gender (to highlight progress towards SDG5) and according to international standards (to highlight progress towards SDG10 (reducing inequality within and among countries)) [8-16]. Through mapping and measuring progress across the multiple sectors implicated by the HIV epidemic among children and adolescents, greater progress towards SDG17 may also be achieved, driving improvements in data required for greater accountability. Failure to achieve gender and age equity within the control of the African HIV epidemic, would lead to the failure of multiple interrelated SDG targets and objectives.

Shortfalls in approaches to HIV treatment and care and attendant age and gender-specific disparities in treatment, health outcomes, and continuity of care within the health services of sub-Saharan African countries have been increasingly well described over the past several years [8,9,13-19]. This establishes a precedent for greater measurement of the impacts of these deficits on fulfillment of the SDGs as we move towards 2030. Tracking progress within an integrating SDG framework would allow for better capture of the interlinked impacts of child and adolescent health on varying aspects of sustainable development. Better monitoring and evaluation of progress towards 2030 goals additionally highlight novel intersectoral opportunities for intervention. Current efforts to track progress in delivering health for children and adolescents living with HIV largely rely on the UNAIDS 90-90-90 targets [20]. Integrating UNAIDS 90-90-90 targets within an SDG framework would also shed light on opportunities to improve the health of children and adolescents living with HIV through intersectoral approaches [20].

Continued engagement with existing services is critical to the care of children living with HIV. Non-engagement and loss to follow-up are important indicators of failure in continuity of care [18,19,21]. Although there is no singular gold standard measure to describe the varying forms of non-engagement in care, non-attendance has been described as a useful indicator of non-engagement within this setting [19]. Non-engagement in care is associated with worse health outcomes among HIV-infected patients [21]. It is important to further understand the varying failures in the continuity of care of HIV-positive children and adolescents enroled in services in high disease prevalence and impoverished settings [21]. This prospective cohort study assesses early death and late all-cause death, ART initiation, non-attendance as a form of non-engagement in care and loss to follow-up. Utilizing SDG3 and SDG5 age and gender-specific indicators, we sought to assess disparities in access to treatment, continuity of care and outcomes, among children and adolescents enrolled in a large sub-Saharan African HIV care service in Tanzania.

2 | METHODS

2.1 | Study population

The cohort included all HIV-infected patients who were under 20 years of age at enrolment in services, between October 2004 and September 2014, within the urban HIV care and treatment clinics of Dar-es-Salaam, Tanzania (supported by Management and Development for Health (MDH) and the US President's Emergency Plan for AIDS relief (PEPFAR)). At the beginning of the study period the study catchment area included 28 clinics, which grew to 48 clinics by the end of the study period. Patients under the age of 15 years were considered paediatric for treatment purposes. The year of MDH enrolment was categorized, to reflect changes in Tanzanian National AIDS Control Program treatment guidelines, as 2004 to 2007, 2008 to 2011, and 2012 to 2014. Verbal consent for inclusion within research activities within the clinical programme was obtained from parents of children or from those patients over the age of 16 years, at enrolment, as appropriate. The Harvard TH Chan School of Public Health and Muhimbili University of Health and Allied Sciences Institutional Review Boards gave ethical clearance for this study (IRB 17-1998).

2.2 | Patient assessments, ART and follow-up visits plan

All participants received free routine care and treatment for HIV according to Tanzanian National AIDS Control Program (NACP) Ministry of Health and Social Welfare guidelines, approved by the World Health Organization (WHO). Patients eligible for ART received free ART provision, subsidized by the Tanzanian government. Patients on ART were followed every

28 days for repeat physician assessment, refill of ART medication and counseling to discuss adherence, dosing and drug side effects. Late adolescent patients, who did not receive ART received supportive care and regular assessment of their eligibility for ART initiation every 6 months. Pediatric patients on care were reviewed monthly if under 5 years of age, or were reviewed every 3 months if above 5 years of age. ART initiation criteria differed by CD4 count percentage, age and period of enrolment. Before 2008, ART was initiated regardless of CD4 count percentage for children who were at WHO disease stage III/IV; for children with WHO stage I/II disease, ART was initiated if CD4 was below age-adjusted thresholds (for those who were 12 to 18 months of age when CD4+ % was less than 25; between 19 and 59 months of age when CD4+ % was below 20; and for children 5 years of age and above when CD4+ % was below 15 (or CD4+ cell count <200 cells/ml)). For those <12 months of age, criteria changed in 2008. After 2008, ART was initiated if CD4+ % was <25 for those at WHO stage I/II and for all children who were <12 months of age, regardless of CD4+ % or WHO stage. Patients age 15 or older were treated by adult criteria. Weight and height were recorded at each visit. Data on ART and TB treatment, pregnancy and next appointment date were collected at each visit and laboratory measurements, and CD4 counts were performed and recorded every 6 months.

2.3 | Definition of outcomes

Person-time was divided between time "pre-ART" and time "on ART". Patients whose time of follow-up coincided with their time to ART initiation were considered pre-ART, as they had no follow-up on ART. For both types of person-time we considered 3 outcomes: "early death" (all cause death within 90 days of the beginning of that type of person-time), 'late death' (all-cause death more than 90 days after the beginning of that type of person-time), "loss to follow-up" (for pre-ART patients, this means that the time to death or the study cutoff date was more than 180 days later than the scheduled appointment at their last recorded visit, or if there was no scheduled appointment recorded, more than 240 days later than their last visit). Patients on ART were considered lost to follow-up, if time to death or the study cutoff date was more than 190 days after the scheduled appointment at their last recorded visit, or if there was no scheduled appointment recorded, more than 120 days later than their last visit. In addition, among patients on care, we considered the outcome of "ART initiation". Among patients on ART, we considered the outcome of "non-engagement in care", defined as being 20% of the interval between visits later than the date of the scheduled appointment.

2.4 | Data collection

Standardized forms were completed at each visit to detail clinical information. Standardized procedures for the measurement of height and weight were in place to record these at each clinic visit. Blood samples were taken at registration and every 6 months thereafter for hematologic, biochemical and immunologic profiling. Data assurance processes were in place at the point of entry including review checks, double data entry and supervisory checks for inconsistencies identified on second entry. Furthermore, weekly quality assurance checks of data were in place.

2.5 | Statistical analysis

Primary determinants in the analysis included SDG3 and SDG5 indicators, generated through categorizing patients into five-year age groups (0 to <5 young paediatric patients, 5 to <10 older paediatric patients, 10 to <15 early adolescent, 15 to <20 late adolescent) and according to gender, to compare intragroup differences in outcomes to assess equity. All analyses were undertaken separately among pre-ART and on ART patients. Baseline characteristics were examined for the young and older paediatric, early and late adolescent age group, as well as gender groups. Means and standard deviations or medians with interquartile ranges were used to describe the centrality and distribution of continuous measurements and proportions to describe categorical measurements of baseline characteristics. Baseline covariates including WHO stage and immunodeficiency for age, HIV wasting syndrome (defined as at least 10% weight loss if the patient had diarrhoea and chronic weight loss and documented fever for at least 30 days not attributable to any concurrent condition), TB treatment, year of first clinic visit, district of clinic and marital and pregnancy status (for older adolescents). Immunodeficiency for age categories were constructed (with CD4 percent intervals cut at 25%, 30% and 35% for children <11 months of age, at 20%, 25% and 30% for children aged between 12 and 35 months and at 15%, 20% and 25% for children aged between 36 and 59 months with CD4 count intervals cut at 15% or 200, 350 and 500 cells/mm^3 for children older than 5 years of age) in keeping with 2007 WHO guidelines [19]. Age-specific weight-for-length and BMI z-scores were categorized at z-scores of −3 and −2, categorized as severely malnourished (z-score <−3), malnourished (z-score ≥−3 by <−2), and not malnourished (z-score ≥−2) (using weight-for-length z-scores for children under 5 years of age and BMI z-score for patients 5 years of age and over). The year of MDH enrolment was categorized, roughly coinciding with changes in the treatment guidelines of the Tanzanian National AIDS Control Program, as 2004 to 2007, 2008 to 2011, and 2012 to 2014. Missing indicators were created as necessary. For continuous variables the median value was imputed.

Crude rates and their 95% confidence intervals were determined using Poisson regression. Relative risks (RR) and 95% confidence intervals (CI) for early death were determined using generalized estimating equations (GEE) with the log link and the Poisson distribution to approximate log-binomial regression [18]. Associations of age group and gender with late death, ART initiation and loss-to-follow-up were analysed, using Cox proportional hazards regression. Age group and gender associations with non-attendance were examined with generalized estimating equations (GEE) with the log link and Poisson distribution for repeated measures of patient visits, using a compound symmetry working correlation and the robust variance.

Hazard ratios (HR) for receiving a prescription for ART were determined using proportional hazards models, adjusted for death and loss to follow-up, using inverse probability weighting. Relative risks (RR) and 95% confidence intervals (CI) for non-engagement in care were determined using GEE models with the log link, the Poisson distribution, and the

exchangeable working covariance structure [22]. For analyses using the subset of patients on ART, we also controlled for 4-knot splines of time to ART initiation.

Given that the central exposures of interest in this study were baseline values (to include gender and age group at enrolment), we did not adjust for time-varying covariates. We controlled for baseline covariates measured at enrolment to adjust for differences between age and gender groups. Covariates used included immunodeficiency for age and WHO HIV clinical stage based on 2007 WHO guidelines [19], presence of HIV wasting syndrome (as determined by the evaluating clinician), treatment for tuberculosis (TB), weight-for-height z-scores, weight-for-length z-scores for children under 5 and BMI z-score for patients 5 and over), categorized as severely malnourished (z-score <−3), malnourished (z-score ≥−3 by <−2), and not malnourished (z-score ≥−2) and district of Dar es Salaam. Potential confounders were selected, using *a priori* knowledge. Adjusted models included age group, gender, WHO HIV stage, BMI or weight-for-length z-score (<−3, −3 to <−2, ≥−2), HIV wasting syndrome, immunodeficiency for age, TB treatment at enrolment, year of first clinic visit (2004 to 2007, 2008 to 2011, 2012 to 2014) and district of Dar es Salaam (Ilala, Kinondoni, Temeke). In all situations where the analysis used a subset of the data (e.g. late death, on ART), inverse probability weighting was used to adjust for censoring.

Cumulative incidence curves were constructed, using the Breslow estimator for multivariate proportional hazards models and adjusted for the following variables at enrolment: WHO HIV stage, immunodeficiency for age, HIV wasting syndrome, BMI or weight-for-length z-score, pregnancy status, year of enrolment and district. Results were standardized to WHO HIV stage 1, CD4 high (500+ or 25%+), no HIV wasting syndrome, BMI or weight-for-length z-score at least −2, not treated for TB, not pregnant, year 2004 to 2008, Ilala district.

For each outcome, univariate models of age group and gender SDG3 and SDG5 indicators, multivariate adjusted models, and models including interactions of age group with gender, were constructed. For proportional hazards models, *p*-values for interaction were calculated, using the likelihood ratio test. For log-Poisson models, *p*-values for interaction were computed using the robust score test. All statistical tests were two-sided, and *p*-values of 0.05 or less were considered statistically significant. If the interactions were significant at the $p = 0.05$ level, we reported the results for age group within gender and for gender within age group. To test for non-proportionality of hazards over time we divided the follow-up time for each outcome at the mean and introduced two-way interactions with age and gender. We selected backwards on these variables, retaining other model variables. No adjustment was made for multiple comparisons. Statistical analysis was undertaken using SAS 9.3 (Cary, North Carolina, USA).

3 | RESULTS

A total of 18,315 patients who were under 20 at MDH enrolment were included in our data. Of these, 10,790 (59%) were female, and 7325 (41%) were male. Among the paediatric and early adolescent patients there were approximately equal numbers of girls and boys, but among the late adolescents around 80% were young women. Around a third of the females who enrolled in late adolescence were pregnant at enrolment (Table 1).

Median follow-up time (IQR) was 656 (145, 1605) days. Among all patients, 12,299 (67%) received prescriptions for ART, including 658 (4% of those who received ART prescriptions) whose last follow-up was the same as the date of the ART prescription (Table 1). Among pre-ART patients, 331 (2%) had an early death (within 90 days of MDH enrolment), 197 a late death (3% of the 6315 who were followed for more than 90 days on care) and 5346 were lost to follow-up. Among patients on ART, 365 (3%) had an early death), and 483 (5% of the 10,085 who were followed for more than 90 days after ART initiation) had a late death (Table 1 and Table 2). Among those on ART, the median time from MDH enrolment to ART initiation was 28 days (IQR (10, 137) days). Among pre-ART patients, the hazard ratios for receiving a prescription for ART varied jointly by gender and age (gender-age interaction $p < 0.01$), with early adolescents being most likely to receive prescriptions among the girls, but older paediatric patients being most likely to receive prescriptions among the boys (Table 3). Among late adolescents, males were much more likely to receive prescriptions than females (HR 1.32; 95% CI 1.21, 1.45). Among pre-ART patients, follow-up time was related to the effects of both age group and gender on receiving a prescription for ART. For both females and males, all age groups were less or approximately equally likely to receive ART prescriptions than older paediatric patients before the mean time, but much more likely to receive ART prescriptions after the mean time.

SDG3 indicators demonstrated that among pre-ART patients, young paediatric patients were most likely to experience both early and late death. Risk of early death was highest in pre-ART patients but remained comparably high among patients on ART. Follow-up time did not influence the hazard ratios for late death. SDG3 indicator for late adolescents was most strongly associated with loss to follow-up, followed by the young paediatric group. Neither SDG3 nor SDG5 indicators were related to late death. SDG3 was implicated within loss to follow-up, being greater among young paediatric patients, but higher still for both genders in late adolescence (Table 3).

Among patients on ART, both SDG3 and SDG5 indicators were implicated with males, young paediatric and early adolescent patients being more likely to experience early death. Young paediatric patients were the least likely to be lost to follow-up. Follow-up time did not influence the hazard ratios for these outcomes. Among patients on ART, follow-up time affected the hazard ratios for age group for the late death outcome, with a halving of the hazard ratio for young paediatric patients relative to older paediatric patients in both genders after the mean follow-up time. Both before and after the mean follow-up time, hazard ratios for the other age groups relative to the older paediatric group were more extreme among females than among males.

SDG3 indicator for late adolescence was most significantly implicated with regards to poor engagement in care. For both genders late adolescents were more likely to be lost to follow up and non-engaged in care. Among pre-ART patients SDG 3 and SDG5 indicator interactions were significant for loss to follow-up and ART initiation, but not among those patients already on ART for loss to follow up and non-engagement.

Table 1. Basic characteristics of patients by age group and gender SDG3 and SDG5 indicators

		SDG3 indicators				SDG5 indicators	
	Total	Young paediatric	Older paediatric	Early adolescent	Late adolescent	Female	Male
Number of patients (N, (%))	18,315	7238 (40)	4169 (23)	2922 (16)	3986 (22)	10,790 (59)	7525 (41)
Age at enrolment (Mean (SD))	8.3 (6.5)	1.9 (1.5)	7.3 (1.4)	12.3 (1.4)	18.0 (1.4)	9.3 (6.8)	6.8 (5.6)
Follow-up years (Median (IQR))	1.8 (0.4, 4.4)	1.5 (0.6, 3.0)	7.2 (6.1, 8.5)	12.2 (11.1, 13.5)	18.3 (17.0, 19.2)	1.2 (0.2, 3.9)	1.6 (0.2, 4.4)
Female (N, (%))	10,790 (59)	3, 781 (52)	2251 (54)	1614 (55)	3144 (79)	—	—
Married (N, (%))	1142 (6)	0 (0)	0 (0)	0 (0)	1142 (29)	1027 (10)	115 (2)
Pregnant female (N, (%))	1116 (6)	0 (0)	0 (0)	5 (0.2)	1111 (28)	1116 (10)	—
WHO stage (N, (%))							
I	4561 (31)	1925 (34)	669 (20)	437 (18)	1530 (48)	2963 (35)	1598 (25)
II	3556 (24)	1321 (23)	1067 (31)	619 (26)	549 (17)	1980 (23)	1576 (25)
III	5479 (37)	2012 (35)	1470 (43)	1109 (46)	888 (27)	2924 (35)	2555 (41)
IV	1142 (8)	424 (8)	220 (6)	248 (10)	250 (8)	580 (7)	562 (9)
Immune deficiency (N, (%))							
None	1665 (37)	954 (45)	4 (9)	83 (5)	624 (31)	897 (31)	768 (48)
Mild	975 (21)	392 (19)	6 (14)	89 (24)	411 (20)	657 (22)	318 (19)
Advanced	909 (20)	410 (20)	8 (19)	80 (21)	411 (20)	642 (22)	267 (17)
Severe	999 (22)	350 (16)	25 (58)	126 (33)	498 (25)	747 (25)	252 (16)
HIV wasting (N, (%))[a]	222 (1)	102 (2)	36 (1)	46 (2)	38 (1)	108 (1)	114 (2)
Weight for height z-score (N, (%))							
<−3	4149 (23)	1757 (24)	965 (23)	619 (21)	808 (20)	2446 (23)	1703 (23)
−3 to <−2	1811 (10)	736 (10)	389 (9)	264 (9)	422 (11)	1051 (10)	760 (10)
−2+	12,337 (67)	4735 (66)	2811 (68)	2036 (70)	2755 (69)	7284 (59)	5053 (67)
On TB treatment (N, (%))	641 (4)	154 (2)	173 (5)	143 (6)	171 (5)	345 (4)	296 (5)
Only one visit (N, (%))	1854 (10)	794 (11)	337 (8)	213 (7)	510 (13)	1167 (11)	687 (9)
Year of 1st visit (N, (%))							
2004 to 2008	6732 (37)	3291 (45)	1724 (41)	1022 (35)	695 (17)	3674 (34)	3058 (41)
2009 to 2011	6962 (38)	2567 (36)	1593 (38)	1205 (41)	1597 (40)	4078 (38)	2884 (38)
2012 to 2014	4621 (25)	1380 (19)	852 (20)	695 (24)	1694 (43)	3038 (28)	1583 (21)
District of enrolment (N, (%))							
Ilala	7930 (44)	3089 (45)	1926 (46.7)	1332 (46)	1583 (40)	4460 (42)	3470 (47)
Kinondoni	5416 (30)	2015 (29)	1161 (28.2)	851 (29)	1389 (35)	3365 (32)	2051 (28)
Temeke	4544 (25)	1812 (26)	1038 (25.2)	713 (25)	981 (25)	2722 (26)	1822 (25)

[a]HIV wasting syndrome defined as at least 10% weight loss if diarrhoea, chronic weight loss, documented fever for 30 days not attributable to any condition other than HIV.

Table 2. Crude rates[a] of early and late death and loss to follow-up by age group and gender SDG3 and SDG5 indicators

	Early death		Late death		ART initiation		Loss to follow-up	
SDG3 and SDG5 indicators	Years of follow-up	Crude rate [95% CI]/ 100 person years	Years of follow-up	Crude rate [95% CI]/ 100 person years	Years of follow-up	Crude rate [95% CI]/ 100 person years	Years of follow-up	Crude rate [95% CI]/ 100 person years
Patients pre-ART								
Female	1327	12.2 [8.6, 17.4]	6038	1.7 [1.2, 2.6]	7293	96.2 [93.9, 98.4]	7363	47.5 [30.6, 73.7]
Young paediatric	2616	18.6 [11.7, 29.5]	2138	2.1 [1.2, 3.8]	2587	89.8 [86.2, 93.5]	2616	51.8 [26.5, 101.4]
Older paediatric	1673	8.8 [3.4, 22.7]	1391	1.8 [0.7, 4.5]	1658	95.0 [90.3, 99.7]	1673	34.9 [11.0, 110.9]
Early adolescent	954	13.2 [6.5, 26.6]	772	1.8 [0.6, 5.5]	944	130.1 [122.9, 137.4]	954	36.4 [9.6, 138.3]
Late adolescent	2120	6.2 [1.9, 20.1]	1736	1.2 [0.5, 2.7]	2103	89.6 [85.5, 93.6]	2120	57.0 [26.4, 123.4]
Male	4592	19.1 [13.6, 26.7]	3707	2.5 [1.5, 4.1]	4543	116.3 [113.2, 119.5]	4592	24.4 [24.4, 72.9]
Young paediatric	2070	24.2 [15.2, 38.3]	1649	3.0 [1.4, 6.4]	2041	107.3 [102.8, 111.8]	2070	54.5 [26.9, 110.2]
Older paediatric	1445	12.0 [5.3, 27.2]	1211	1.4 [0.6, 6.4]	1438	98.6 [93.5, 103.8]	1444	28.7 [7.9, 104.0]
Early adolescent	777	15.2 [7.6, 30.4]	626	2.6 [0.7, 9.2]	772	134.3 [126.2, 142.5]	777	28.5 [6.0, 135.4]
Late adolescent	300	20.4 [7.1, 58.4]	222	4.5 [2.4, 8.6]	292	218.8 [201.9, 235.8]	300	58.2 [12.3, 276.1]
Patients on ART								
Female	1497	11.6 [8.3, 16.3]	15,343	1.7 [1.0, 2.9]	—	—	16,480	17.3 [15.6 19.2]
Young paediatric	496	16.7 [10.6, 26.4]	5375	1.8 [0.7, 4.6]	—	—	5871	17.2 [14.1, 20.9]
Older paediatric	355	6.5 [2.0, 20.5]	6021	0.9 [0.4, 2.2]	—	—	4659	15.3 [12.4, 18.9]
Early adolescent	278	9.5 [5.6, 25.4]	3189	1.7 [0.4, 7.6]	—	—	3467	16.0 [13.2, 19.3]
Late adolescent	368	8.4 [4.4, 20.7]	2475	2.7 [1.1, 6.6]	—	—	2844	22.6 [18.4, 27.9]
Male	1161	16.4 [11.1, 24.3]	13,358	1.7 [1.0, 2.9]	—	—	14,519	16.6 [14.9, 18.6]
Young paediatric	474	19.4 [10.6, 35.5]	5362	1.5 [0.7, 3.1]	—	—	5836	17.0 [14.2, 20.4]
Older paediatric	322	10.3 [4.7, 22.4]	4033	1.4 [0.4, 4.2]	—	—	4355	15.8 [13.2, 19.0]
Early adolescent	232	15.5 [7.8, 30.8]	2832	2.1 [0.6, 7.4]	—	—	3064	15.7 [12.0, 20.5]
Late adolescent	133	22.5 [7.5, 68.1]	1131	2.7 [0.7, 10.8]	—	—	1264	20.2 [14.2, 28.9]

[a]Crude rates computed by Poisson regression. N.B. Person-years may not add to totals because of rounding errors.

Figure 1 shows the cumulative incidence of death was generally more severe among males than females, with highest cumulative incidence of death being among early adolescent males. Early adolescents generally experienced the highest cumulative incidence of death followed by late adolescents, then paediatric patients (younger, followed by older paediatric patients, among females (see Figure 1a,c)). (Where there was suggestion of non-proportionality and the further test for age-time interaction was significant at the *p*-value results were further disaggregated by time and presented in the supporting information).

Figure 2 shows that the overall hazard ratio for death according to age at enrollment, was highest shortly after birth, decreasing sharply until around age 6, and then increasing into late adolescence, when compared to death at aged 10 years at enrolment. Patients on ART generally experienced more rapid declines in relative risk of death, than patients on care, until around 5 years of age at MDH enrolment (see Figure 2c and 2d)).

4 | DISCUSSION

Current experience of enrollees in HIV care and treatment programmes across sub-Saharan Africa is being increasingly well described [7-16]. Both female [3,5], and male [7-9] children and adolescents living with HIV experience age and gender-specific inequities in access to and continuity of HIV treatment and care with significant implications for the fulfillment of SDG3 and SDG5. Given the centrality of health for all ages and gender equality within the SDG agenda, intersectoral opportunities to protect and promote the health of children and adolescents living with HIV in sub-Saharan Africa must be further examined.

It has been well recognized that young children living with HIV remain vulnerable to shortcomings in testing [2] and linkage to treatment [3], with potential consequence for their survival. Our findings corroborate that young paediatric patients remain particularly vulnerable to early death. Both in terms of SDG3 and SDG5 indicators, this study highlights that the young paediatric age group and male gender children are particularly at risk of early death, even when linked with care. This may be due to delays in testing or linkage to treatment once test results are available. Risk of early death was highest for the pre-ART young children, but remained high among those on ART. But these findings suggest further measures must be taken to improve care during early life for these high-risk groups.

Recent evidence also suggests that adolescents remain vulnerable to poor adherence and loss of retention within HIV

Table 3. Adjusted relative risks of early and late death, loss to follow-up, ART initiation and late attendance among patients pre-ART or on ART

Patients pre-ART	SDG3 and SDG5 indicators	Early death RR [95% CI] *p*-value	Late death HR [95% CI] *p*-value	Loss to follow-up HR [95% CI] *p*-value	ART-initiation RR [95% CI] *p*-value
[a]Non-proportionality test (*p*-value)		—	0.25	0.63	<0.01
	Female	REF	REF	—	—
	Male	1.24 [0.99, 1.54] 0.06	1.01 [0.71, 1.42] 0.98		
	Young paediatric	2.33 [1.71, 3.18] <0.01	1.45 [0.93, 2.27] 0.10	—	—
	Older paediatric	REF	REF		
	Early adolescent	1.19 [0.80, 1.76] 0.39	0.92 [0.52, 1.64] 0.79		
	Late adolescent	1.13 [0.72, 1.77] 0.60	0.78 [0.40, 1.50] 0.45		
Gender–age interaction (*p*-value)		0.91	0.30	<0.01	<0.01
Young paediatric	Female	—	—	REF	REF
	Male			0.94 [0.87, 1.02] 0.16	1.06 [1.00, 1.13] 0.04
Older paediatric	Female	—	—	REF	REF
	Male			0.79 [0.70, 0.80] <0.01	1.14 [1.06, 1.23] <0.01
Early adolescent	Female	—	—	REF	REF
	Male			0.76 [0.64, 0.89] <0.01	1.01 [0.93, 1.10] 0.29
Late adolescent	Female	—	—	REF	REF
	Male			0.62 [0.53, 0.73] <0.01	1.32 [1.21, 1.45] <0.01
Female	Young paediatric	—	—	1.35 [1.22, 1.49] <0.01	1.01 [0.95, 1.08] 0.68
	Older paediatric			REF	REF
	Early adolescent			0.89 [0.78, 1.01] 0.08	1.19 [1.10, 1.28] <0.01
	Late adolescent			1.99 [1.79, 2.22] <0.01	0.83 [0.77, 0.90] <0.01
Male	Young paediatric	—	—	1.27 [1.15, 1.41] <0.01	1.08 [1.01, 1.15] 0.03
	Older paediatric			REF	REF
	Early adolescent			0.85 [0.72, 1.00] 0.05	1.06 [0.97, 1.14]
	Late adolescent			1.56 [1.30, 1.87] <0.01	0.97 [0.88, 1.07] 0.49
Patients on ART	**SDG3 and SDG5 indicators**	**Early death RR [95% CI]; *p***	**Late death HR [95% CI]; *p***	**Loss to follow-up HR [95% CI]; *p***	**Non-engagement in care RR [95% CI]; *p***
[a]Non-proportionality test (*p*-value)		—	0.02	<0.01	—
	Female	REF	—	REF	REF
	Male	1.35 [1.09, 1.66] <0.01		1.01 [0.96, 1.07] 0.76	1.01 [0.98, 1.03] 0.66
	Young paediatric	1.96 [1.44, 2.68] <0.01	—	0.93 [0.87, 1.00] 0.05	1.06 [1.02, 1.09] <0.01
	Older paediatric	REF		REF	REF
	Early adolescent	1.47 [1.04, 2.09] 0.03		0.95 [0.87, 1.03] 0.21	1.12 [1.08, 1.16] <0.01
	Late adolescent	1.27 [0.87, 1.85] 0.22		1.05 [0.95, 1.16] 0.31	1.21 [1.16, 1.26] <0.01
Patients on ART	**SDG3 and SDG5 indicators**	**Early death HR [95% CI]; *p***	**Late death RR [95% CI]; *p***	**Loss to follow-up HR [95% CI]; *p***	**Non-engagement in care RR [95% CI]; *p***
Gender–age interaction (*p*-value)		0.38	0.05	0.90	0.75

Chaudhury S et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25070
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25070/full | https://doi.org/10.1002/jia2.25070

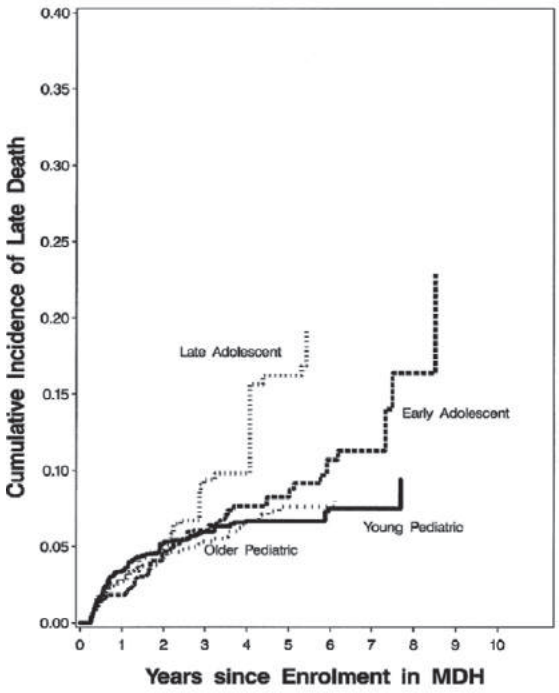
Table 3. (*Continued*)

Patients pre-ART	SDG3 and SDG5 indicators	Early death RR [95% CI] *p*-value	Late death HR [95% CI] *p*-value	Loss to follow-up HR [95% CI] *p*-value	ART-initiation RR [95% CI] *p*-value
Young paediatric	Female	—	REF	—	—
	Male		0.86 [0.66, 1.13] 0.28		
Older paediatric	Female	—	REF	—	—
	Male		1.61 [1.11, 2.36] 0.01		
Early adolescent	Female	—	REF	—	—
	Male		1.29 [0.90, 1.83] 0.17		
Late adolescent	Female	—	REF	—	—
	Male		0.86 [0.59, 1.26] 0.55		
Female	Young paediatric	—	1.96 [1.33, 2.89] <0.01	—	—
	Older paediatric		REF		
	Early adolescent		1.87 [1.23, 2.86] <0.01		
	Late adolescent		2.44 [1.60, 3.74] <0.01		
Male	Young paediatric	—	1.67 [1.12, 2.48] <0.01	—	—
	Older paediatric		REF		
	Early adolescent		1.43 [0.98, 2.09] 0.06		
	Late adolescent		1.30 [0.82, 2.08] 0.27		

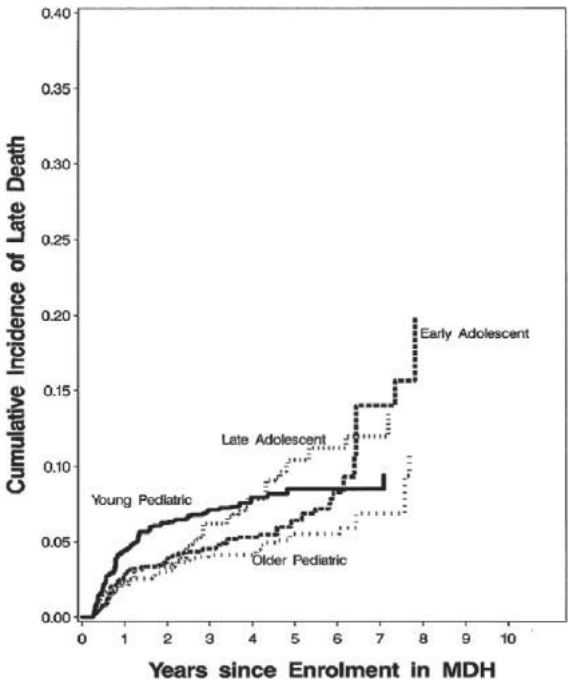
HR, Hazard ratio RR, Relative risk CI, confidence interval. For early death pre-ART: Based on generalized estimating equations (GEE) models with the log link and the Poisson distribution, controlling for controlling for the year of MDH enrolment, presence of HIV wasting syndrome, immunodeficiency for age, WHO clinical HIV stage, TB treatment, weight-for-height category, district of Dar es Salaam, all at MDH enrolment. *p*-value for interaction based on the robust score test. For early death on art: Based on generalized estimating equations (GEE) models with the log link and the Poisson distribution, controlling for controlling for the year of MDH enrolment, presence of HIV wasting syndrome, immunodeficiency for age, WHO clinical HIV stage, TB treatment, weight-for-height category, district of Dar es Salaam all at MDH enrolment; 4 knot splines of time to ART; weighted by the inverse probability of having follow-up after ART initiation. *p*-value for interaction based on the robust score test. For late death pre-ART: Based on proportional hazards models controlling for the year of MDH enrolment, presence of HIV wasting syndrome, immunodeficiency for age, WHO clinical HIV stage, TB treatment, weight-for-height category, district of Dar es Salaam, all at MDH enrolment, weighted by the inverse probability of having more than 90 days of follow-up. *p*-value for interaction based on the likelihood ratio test. For late death on art: Based on proportional hazards models controlling for the year of MDH enrolment, presence of HIV wasting syndrome, immunodeficiency for age, WHO clinical HIV stage, TB treatment, weight-for-height category, district of Dar es Salaam, all at MDH enrolment; 4 knot splines of time to ART; weighted by the inverse probability of having more than 90 days of follow-up on ART. *p*-value for interaction based on the likelihood ratio test. For LTF pre-ART: Based on proportional hazards models controlling for the year of MDH enrolment, presence of HIV wasting syndrome, immunodeficiency for age, WHO clinical HIV stage, TB treatment, weight-for-height category, district of Dar es Salaam, all at MDH enrolment. *p*-value for interaction based on the likelihood ratio test. For LTF on ART: Based on proportional hazards models controlling for the year of MDH enrolment, presence of HIV wasting syndrome, immunodeficiency for age, WHO clinical HIV stage, TB treatment, weight-for-height category, district of Dar es Salaam, all at MDH enrolment; 4 knot splines of time to ART; weighted for inverse probability of ART initiation. *p*-value for interaction based on the LRT. For ART initiation: Based on proportional hazards models controlling for the year of MDH enrolment, presence of HIV wasting syndrome, immunodeficiency for age, WHO clinical HIV stage, TB treatment, weight-for-height category, district of Dar es Salaam, all at MDH enrolment. The *p*-value for interaction based on the likelihood ratio test. For poor engagement in care on ART: Based on generalized estimating equations (GEE) models with the log link and the Poisson distribution, controlling for controlling for the year of MDH enrolment, presence of HIV wasting syndrome, immunodeficiency for age, WHO clinical HIV stage, TB treatment, weight-for-height category, district of Dar es Salaam; 4 knot splines of time to ART; weighted by the inverse probability of having follow-up after ART initiation. *p*-value for interaction based on the robust score test.

[a]Non-proportionality test based on age-gender interaction over time (where the interaction was statistically significant at $p < 0.05$ level further segregation of results by time presented within supporting information).

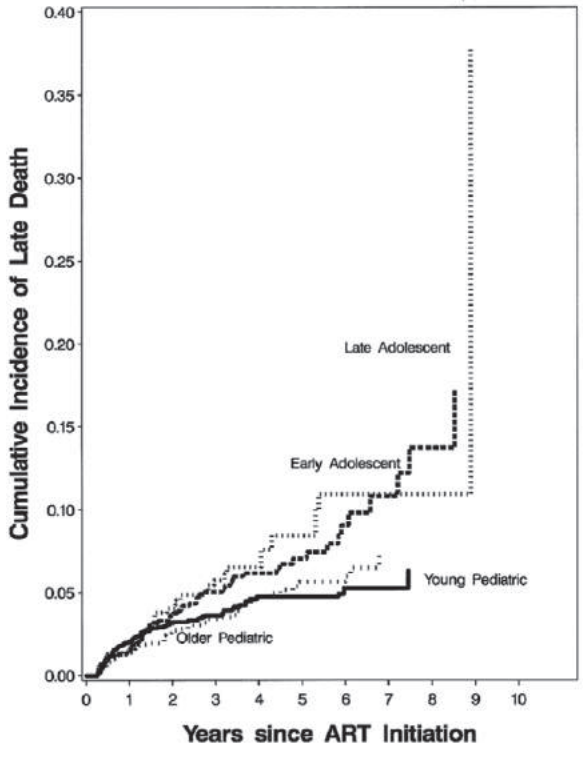
Chaudhury S et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25070
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25070/full | https://doi.org/10.1002/jia2.25070



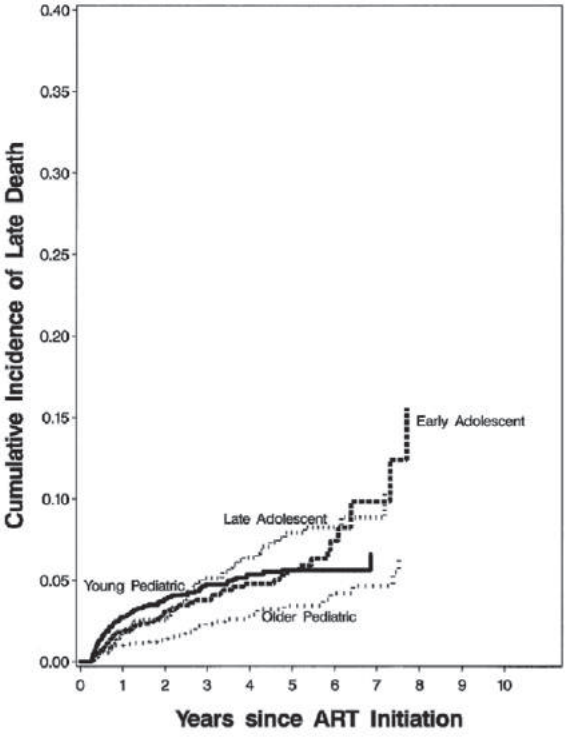
a. Cumulative Incidence of Late Death Among Females pre-ART



b. Cumulative Incidence of Late Death Among Males pre-ART

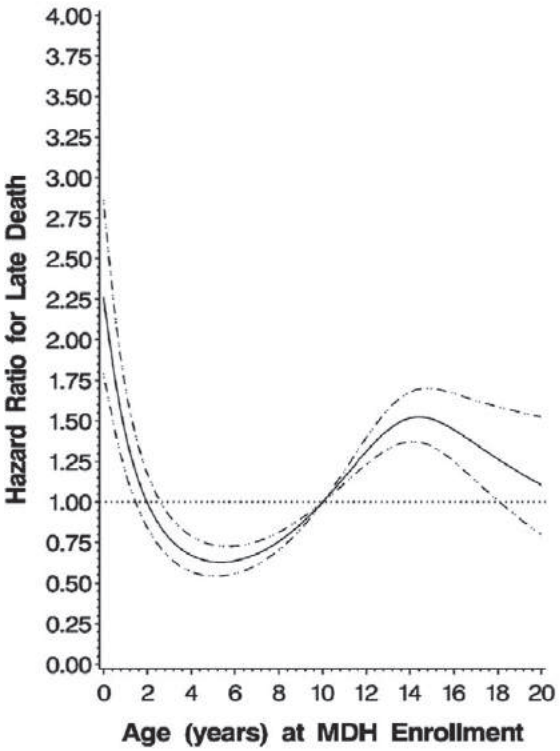


c. Cumulative Incidence of Late Death Among Females on ART

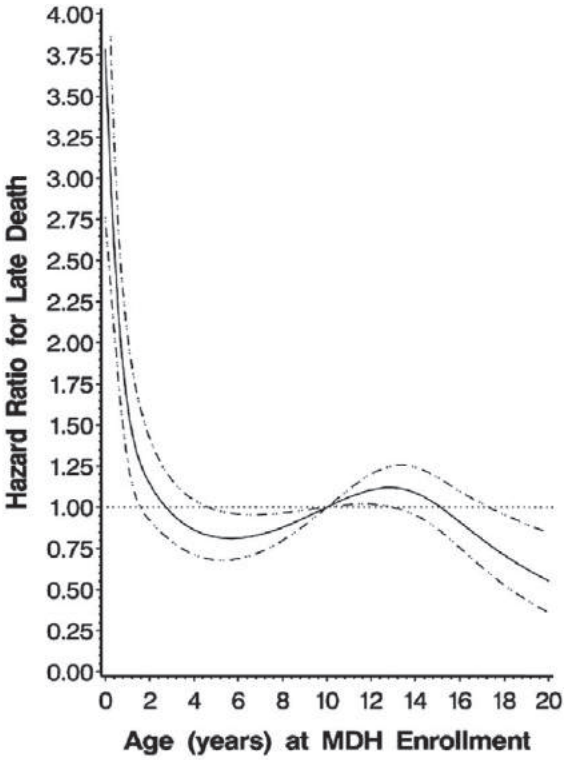


d. Cumulative Incidence of Late Death Among Males on ART

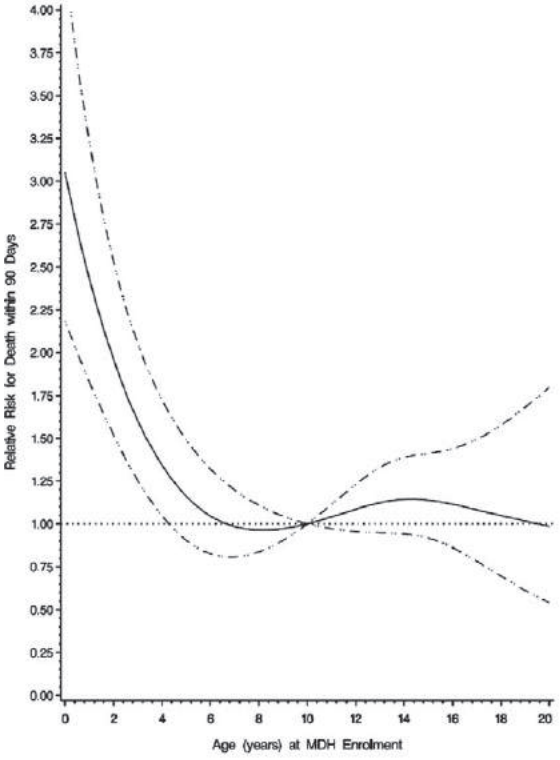
Figure 1. Adjusted cumulative incidence of death by Age Group and Gender SDG3 and SDG5 indicators. (a) Cumulative incidence of late death among females pre-ART. (b) Cumulative incidence of late death among males pre-ART. (c) Cumulative incidence of late death among females on ART. (d) Cumulative incidence of late death among males on ART



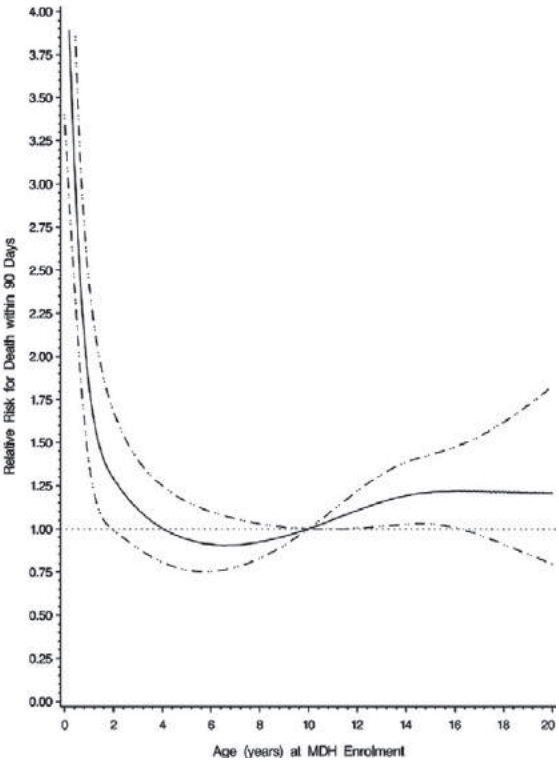
2a. Hazard Ratios with 95%CI for Late Death pre-ART



2b. Hazard Ratios with 95%CI for Late Death on ART



2c. Relative Risks with 95%CI for Early Death pre-ART



2d. Relative Risks with 95%CI for Early Death on ART

Figure 2. Hazard ratio for death according to age in years at enrolment (relative to rate at Age 10). (a) Hazard ratios with 95% CI for late death pre-ART. (b) Hazard ratios with 95%CI for late death on ART. (c) Relative risks with 95% CI for early death pre-ART. (d) Relative risks with 95%CI for early death on ART

care programmes [14-16]. Our findings further confirm that the SDG3 indicator of late adolescence was particularly implicated in loss to follow up and poor engagement with care. SDG3 and SDG5 interactions being significant among the pre-ART children and adolescents, implies significant age and gender differences in patterns of engagement with care, particularly prior to ART initiation. This further supports the assertion that fulfillment of SDG3 and SDG5 for children living with HIV prior to ART initiation depends on age and gender specific strategies to address engagement with care.

SDG 5 indicators were implicated significantly for early death in our findings. Additionally, crude death rates were the highest among males, being worst among the younger paediatric patients, reducing among the older paediatric patients, before worsening with increasing age category into late adolescence. Higher death rates among males may be explained by later presentation and greater non-enegagement with care among [14,23,24]. Adolescent males are known to access HIV services less frequently than females in sub-Saharan Africa [9,13]. The greater majority of our adolescent patients were female with many engaging in care during pregnancy. This has been thought to be partially due to the successful expansion of national PMTCT programs, with adolescent females being supported and encouraged to access services and be tested for HIV during pregnancy; hence presenting at an earlier stage of disease. However, there may be more generalized barriers to access and adherence that specifically affect males, such as community stigmatization of health-seeking behavior, reputational damage for those seeking HIV testing and treatment, social norms surrounding HIV status disclosure and clinic opening hours conflicting with hours of employment are reported by males in qualitative investigation [25-28]. Higher mortality among males who have never sought care has been more recently highlighted [9]. Delays to presentation to services may significantly impact survival among males once treatment is started. Expansion of national programming to specifically address the intersection of SDG5 and SDG3 concerns, may seek to remove barriers for adolescent male attendance and retention within HIV care and treatment programmes and assist in altering community perception to achieve cultural normalization of male health-seeking behavior among adolescents living with HIV [27].

Within the context of an integrating framework of SDGs, leveraging the educational sector could facilitate changes within primary and secondary education to improve adolescent male knowledge and attitudes towards health (SDG4.1-4.7). Demonstrating links between the health of males of sexually active ages and consequent economic productivity, both through the education sector (SDG4.1-4.7) and employment sector (SDG8.1-8.6) could further highlight opportunities for intervention. Integrating SDG approaches may ultimately allow for greater alignment of intersectoral efforts in achieving the unifying objective of improved control of and response to the HIV epidemic for children and adolescents living with HIV.

Overall SDG3 and SDG5 indicator findings point to a number of key stages of life during which more rigorous attention to age- and gender-specific needs may render significant benefits. Adolescents living with HIV remain particularly vulnerable to health inequity within HIV services, experiencing greater non-adherence, loss to follow-up and higher cumulative risk of death, than across other age categories. Those who enroled in care in early adolescence within our cohort had the highest cumulative mortality overall, across the age groups, with males having higher cumulative risk of death across every age group. Paediatric and early adolescent patients within our cohort may have been the most likely to have been perinatally infected, representing particularly high-risk groups (although age at enrolment can offer only a crude indicator of timing of infection). Higher cumulative risk of death among those enrolled during early adolescence, may point to longer duration of perinatally acquired HIV infection and shortcomings in management of earlier infection. More rigorous attention to testing and linkage to care for children affected by HIV in early life, or loss of retention within care, during earlier childhood may reduce the impacts on mortality in early life [2,3,15,16]. Those enrolling in early adolescence may have experienced a lack of sustained management of their disease, or a repeated number of enrolments across different HIV services. Strengthening linkages for testing and treatment of infants once mothers are enrolled in PMTCT, and continued engagement with children once born within PMTCT programmes may diminish losses in continuity of care, that may be worsening the survival of perinatally infected children. The second highest cumulative risk of death, according to age group, was found among late adolescents, who may have been more likely to be sexually infected. Hence, later ART initiation, loss to follow-up and worse non-adherence in late adolescence, may lead to greater cumulative risk of death with age during adolescence. Hence, interventions supporting focused engagement, adherence and retention, within care, could save many years of life for adolescents living with HIV in sub-Saharan Africa [15,16]. Strategies for improving services for adolescents have been described [27]. Tanzania has made significant progress in incorporating evidence within national strategies for mapping HIV service delivery strategies for adolescents [27,28]. National efforts may be additionally better substantiated by incorporation of integrating SDG frameworks in the future.

SDG5 was implicated in our findings with females in late adolescence being more likely to experience delayed ART initiation. Many of the adolescent girls in our cohort were pregnant at enrolment, representing an important time during which adolescent girls access services. Adolescent females may generally present at an earlier disease stage during a high-risk period of sexual reproductive life. However, a lack of integration of sexual and reproductive health services within HIV services (SDG 3.7) may lead to discrimination against women and girls in sub-Saharan Africa [30,31]. Adolescent girls are vulnerable to sexually transmitted infections and require access to effective sexual, reproductive and HIV health services. High quality sexual and reproductive health services may mitigate incident HIV infections and unwanted pregnancies among adolescents (SDGs 3.3, 3.7, 3.8) [7]. Failings in services for both adolescent males and females have important consequences for the fulfillment of SDG 3.8, limiting the achievement of effective universal health coverage, financial risk protection and access to quality essential health care services and medicines.

SDG3 indicators utilized in this analysis may have formed proxy indication of most likely mode of transmission, given that paediatric and early adolescent infections were more likely to have been perinatally transmitted and late adolescent

infections were more likely to have been sexually transmitted. These limitations are usual to data from clinical cohorts, as engagement with clinical services relies on prevailing social and cultural norms concerning health-seeking behaviors. Further measures for appraising SDG3, SDG5 and related SDG targets may be incorporated into future studies. Gains in health from application of integrating SDG framework approach to programme management, monitoring and evaluation could also be demonstrated in future research work. While studies from enrollees within HIV treatment services in sub-Saharan African countries are becoming increasingly available, population-based sampling is ideally needed for a more accurate estimation of population health [8, 9]. Sampling only from sites of clinical care may lead to misclassification and measurement error [9, 31]. For instance, those who die in childhood following maternal transmission of infection and those who are lost to follow-up are unlikely to be reported or confirmed as dead. Limits to national systems of health-related data collection limit the potential for fulfillment of SDG 17.18 (data monitoring and accountability) to track progress made in expanding treatment for HIV [15].

Despite the widespread expansion of ART treatment, further action is required to improve access to care and retention within health services [13-17]. Additionally, emphasis is required on community and structural factors, which lead to poor health outcomes for this population, such as gender power inequity, stigma, poverty and lack of other resources needed to access care [32-35]. A holistic approach to the well-being of children and adolescents affected by HIV in sub-Saharan Africa is needed to prevent failure of efforts to achieve the SDGs. Failings in fulfillment of SDG3 for HIV-infected children and adolescents in sub-Saharan Africa have implications for the fulfillment of several further SDGs, including SD4 (the commitment to inclusive and equitable quality education for all) and multiple aspects of SDG8 (sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all). HIV-infected adolescent males are experiencing higher cumulative risk of death and reductions in life expectancy [8,9], preventing their primary and secondary education (impacting SDGs 4.1-4.7) and contribution to the sustained economic growth of the nation (impacting SDGs 8.1.1, 8.2.1, 8.3.1, 8.5 and 8.6) [29]. Well-developed national commitments to the fulfillment of SDG 8b (to develop and operationalize a global strategy for youth employment) must recognize the impact of the HIV epidemic on adolescent lives. Strategies to improve adolescent engagement with and adherence and retention within HIV-treatment programmes are necessary to mitigate the inter-related failure of SDGs 3, 4 and 8 and the subsequent failure of SDG 10 (the reduction in inequality within and among countries).

Our data highlight important equity concerns for children and adolescents seeking HIV treatment and care services in sub-Saharan Africa. Threats to the fulfillment of Sustainability Development Goals (SDGs) concerning health for all ages (SDG3), gender equality (SDG5), education (SDG4) and economic growth (SDG8) are highlighted by this study. Further downstream consequences of failed attempts to effectively treat and care for HIV-infected children and adolescents within sub-Saharan African health services would additionally undermine efforts to reduce inequalities within and among countries (SDG10). Efforts to improve national systems of data monitoring and accountability (SDG17) need to incorporate the measurement of the health of children and adolescents living with HIV, within integrating SDG frameworks in the future, to realize maximum benefits for population governance.

5 | CONCLUSION

Strengthening health services for HIV-infected children and adolescents in sub-Saharan Africa will require special attention to age and gender inequities for fulfillment of the SDGs by 2030.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

SC, EH, DS and WF designed the study. AM, DS, NU and LM contributed significantly to data collection. SC and EH performed the analysis. SC wrote the first draft.

All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS AND FUNDING

The authors received no financial support for the research, authorship, and/or publication of this article. This research has been supported by the U.S. Presidents' Emergency Plan for AIDS Relief (PEPFAR, grant number U51HA02522) through Centers for Disease Control and Prevention under the terms of grant 5U2GPS001966.

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SUPPORTING INFORMATION

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

Table S1. Disaggregation of hazard ratios by age-gender interactions over time for outcomes according to non proportionality tests

Fatti G et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25041
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25041/full | https://doi.org/10.1002/jia2.25041

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

The effectiveness and cost-effectiveness of community-based support for adolescents receiving antiretroviral treatment: an operational research study in South Africa

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Abstract

Introduction: Adolescents and youth receiving antiretroviral treatment (ART) in sub-Saharan Africa have high attrition and inadequate ART outcomes, and evaluations of interventions improving ART outcomes amongst adolescents are very limited. Sustainable Development Goal (SDG) target 3c is to substantially increase the health workforce in developing countries. We measured the effectiveness and cost-effectiveness of community-based support (CBS) provided by lay health workers for adolescents and youth receiving ART in South Africa.

Methods: A retrospective cohort study including adolescents and youth who initiated ART at 47 facilities. Previously unemployed CBS-workers provided home-based ART-related education, psychosocial support, symptom screening for opportunistic infections and support to access government grants. Outcomes were compared between participants who received CBS plus standard clinic-based care versus participants who received standard care only. Cumulative incidences of all-cause mortality and loss to follow-up (LTFU), adherence measured using medication possession ratios (MPRs), CD4 count slope, and virological suppression were analysed using multivariable Cox, competing-risks regression, generalized estimating equations and mixed-effects models over five years of ART. An expenditure approach was used to determine the incremental cost of CBS to usual care from a provider perspective. Incremental cost-effectiveness ratios were calculated as annual cost per patient-loss (through death or LTFU) averted.

Results: Amongst 6706 participants included, 2100 (31.3%) received CBS. Participants who received CBS had reduced mortality, adjusted hazard ratio (aHR) = 0.52 (95% CI: 0.37 to 0.73; $p < 0.0001$). Cumulative LTFU was 40% lower amongst participants receiving CBS (29.9%) compared to participants without CBS (38.9%), aHR = 0.60 (95% CI: 0.51 to 0.71); $p < 0.0001$). The effectiveness of CBS in reducing attrition ranged from 42.2% after one year to 35.9% after five years. Virological suppression was similar after three years, but after five years 18.8% CBS participants versus 37.2% non-CBS participants failed to achieve viral suppression, adjusted odds ratio = 0.24 (95% CI: 0.06 to 1.03). There were no significant differences in MPR or CD4 slope. The cost of CBS was US$49.5/patient/year. The incremental cost per patient-loss averted was US$600 and US$776 after one and two years, respectively.

Conclusions: CBS for adolescents and youth receiving ART was associated with substantially reduced patient attrition, and is a low-cost intervention with reasonable cost-effectiveness that can aid progress towards several health, economic and equality-related SDG targets.

Keywords: HIV; antiretroviral treatment; adolescents; United Nations Sustainable Development Goals; community-based support; cost-effectiveness

Received 8 May 2017; **Accepted** 11 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

The UN Sustainable Development Goals (SDGs) are 17 universal, ambitious and interrelated goals established to guide the development policy and agenda of member states till 2030 [1]. UNAIDS has also set ambitious HIV treatment targets to help end the AIDS epidemic by 2030 (SDG 3.3) [2]. For the SDGs to be achievable, evidence-based interventions need to be implemented [3], and to reach the UNAIDS treatment goals, innovative and efficient healthcare service delivery models are required [4].

Amongst adolescents in sub-Saharan Africa (SSA), progress towards the SDGs and HIV prevention and care goals are particularly lagging [5,6]. Adolescents in SSA have the highest HIV incidence globally [7,8], and adolescents are the only demographic group in whom AIDS-related mortality is

increasing, having tripled since 2000 [9,10]. Adolescents and youth receiving antiretroviral treatment (ART) have poorer patient retention and treatment outcomes than adults [11-15]. Ensuring high retention is a crucial aspect of the ART programme to maximize treatment outcomes [16], as well as to reduce community viral load to prevent horizontal transmission [17,18]. ART programmes retention in SSA is poor, being only 56% after five years [19]. The barriers to retention amongst adolescents and youth are numerous and diverse, and include the burden of multiple vulnerabilities, barriers to healthcare access, mental health needs, a lack of psychosocial support, a lack of trained healthcare workers focusing on adolescent-specific care, and lack of support during the transition from paediatric to adult care [20-23]. Appropriate, individualized, holistic and durable interventions that support adolescent's clinical, psychosocial and nutritional care have been suggested [20,21,23].

In SSA, adolescents and youth form the greatest proportion of the population (over 33%), and SSA is the only region in which this group continues to grow substantially [24]. The health of adolescents is crucial that they may meaningfully contribute to the economy [25,26]. Their economic potential will support progress towards SDGs 1, 2, 8 and 9 to reduce poverty and hunger, promote economic growth and build industry. As SSA has very high HIV prevalence amongst adolescents and youth [27], promoting the health of adolescents and youth living with HIV is essential for the region to make meaningful progress towards the SDGs over and beyond health-related SDGs.

HIV-infected adolescents are a neglected group [28]. Recent systematic reviews indicate that the evidence base for adherence and retention-enhancing interventions amongst HIV-infected adolescents and youth is very sparse, and that most studies focussed on high-income countries and had low participant numbers [23,28,29]. These reviews conclude that identifying effective interventions that improve ART outcomes amongst adolescents is overdue. Evidence of the longer-term effectiveness and cost-effectiveness of adherence and retention-enhancing interventions are particularly lacking [30]. The limited evidence that exists suggests that interventions that include individualized psychosocial support, counselling and education, and the provision of specific adolescent-tailored services are promising and require further investigation [23,28,29].

SSA also has critical shortages of professional healthcare workers–particularly aggravated due to the HIV/AIDS epidemic–and needs to substantially increase its health workforce to attain its development goals [31,32]. SDG target 3c is to substantially increase the recruitment, development and training of the health workforce in developing countries [1]. Community-based support (CBS) programmes are task-shifting healthcare interventions involving lay healthcare workers that have been developed to increase the health workforce at limited cost in developing countries [33,34]. Amongst others, CBS programmes have aimed to support HIV-infected adults receiving ART [35]. The effectiveness of CBS for adolescents receiving ART requires evaluation, and cost-effectiveness evaluations of CBS are lacking [36].

South Africa has the greatest number of people living with HIV globally, and is showing poor performance regarding its HIV-related SDG target [3,37]. South Africa also has one of the most unequal societies worldwide [38]. South Africa's unemployment rate (27%) is amongst the ten highest national unemployment rates globally, [39,40] with youth unemployment being approximately 50% [41]. Almost two-thirds of young South African children live in poverty, and 20% of the population live in extreme poverty [38,42].

This study aimed to evaluate the effectiveness and cost-effectiveness of a large CBS programme for HIV-infected adolescents and youth receiving ART (with five years of patient outcomes) in four South African provinces.

2 | METHODS

A retrospective cohort study was performed at 47 public ART facilities, using routinely collected clinical data. The facilities were located in KwaZulu-Natal, Western Cape, Eastern Cape and Mpumalanga provinces, in both urban (33 facilities) and rural areas (14 facilities). Included facilities were all facilities supported by Kheth'Impilo, a non-profit organization, which had a CBS programme for adolescents and youth. Kheth'Impilo supports the South African Department of Health with public health systems strengthening. The majority were primary healthcare facilities, and six were secondary-level hospitals. Antenatal HIV prevalence in these provinces varied between 18.2% and 37.4% [43]. Co-infection with tuberculosis amongst adolescents and youth starting ART in South Africa is high (9% to 13%) [13].

Antiretroviral-naive adolescents and youth aged 10 to 24 years who initiated ART between 01 January 2004 and 30 September 2010 were included. Follow-up was until mortality, loss to follow-up (LTFU), documented transfer-out to other sites, 30 September 2011 (database closure) or five years on ART (whichever occurred first). To evaluate the effectiveness of CBS, ART outcomes were compared between adolescents and youth who received CBS plus standard clinic-based care versus adolescents and youth who received standard care only. During the pre-ART preparation period, patients initiating ART were evaluated by a facility-based community co-ordinator (named a "site-facilitator"), who assigned patients in a non-randomized manner to receive CBS in addition to usual care if the following criteria were fulfilled: CBS-workers were active in the area of the patient's home, CBS-worker capacity was available, and patient consent was obtained. As the development of the CBS programme was progressive, few patients initially received CBS but this increased as the programme expanded. Clinical and socioeconomic factors were not criteria in the allocation of patients to receive CBS. For analyses, patients were assigned to the CBS group if they were allocated to and received support from a named CBS-worker from ART initiation.

2.1 | CBS intervention

CBS-workers are clinic-linked, lay community health workers who provided ART patient support by undertaking home visits to ascertain and address household challenges impacting on clinic attendance and adherence. CBS-workers resided in low socioeconomic, high HIV-prevalence areas. Preference was given to employing previously unemployed people as CBS-workers. They were trained regarding HIV and tuberculosis

(TB) infection and treatment, including addressing psychosocial issues impacting adherence. Support started from the time of pre-ART preparation and continued throughout long-term care. Patient, family and household issues assessed by CBS-workers included nutrition security, substance abuse, mental health including depression, domestic violence, non-disclosure, and HIV-related stigma and discrimination. Issues were discussed at clinic multidisciplinary team meetings and interventions agreed by the team were implemented by the CBS-worker as appropriate. CBS included providing one-on-one counselling regarding adherence, and support and referral for psychosocial problems and nutrition security. Participants were provided with information and education regarding sexual and reproductive health and family planning. Adolescents' carers were offered educational sessions regarding HIV/TB information, medication adherence, and nutrition. Adolescents and youth who defaulted clinic visits were traced by CBS-workers. Eligibility for government social assistance grants (for poverty relief) was assessed and support provided to obtain these where eligible.

Participants were scheduled for weekly visits during the first months following ART initiation, then monthly for at least six months. Once stable, home visits were performed at least quarterly, but if clinic visits were delayed, home visit frequency increased. Health promotion education and symptom screening for TB, opportunistic infections and sexually transmitted infections (STIs) were performed, with referral to clinics for further management if indicated.

CBS-workers had a specific geographic area which they supported and were assigned 80 to 120 patients each. Career development of CBS-workers was encouraged, with certain CBS-workers subsequently employed as social auxiliary workers or home-based care co-ordinators [44].

2.2 | Outcomes and definitions

The primary outcomes were as follows: time to all-cause mortality after starting ART, and time till LTFU after starting ART. Attrition was defined as a combined endpoint due to patient losses due to either mortality or LTFU. The secondary outcomes were as follows: (i) Adherence to ART measured using Medication Possession Ratios (MPRs)–an adherence measure derived from pharmacy refill data (number of days of dispensed medication divided by the number of days between the first and last pharmacy refill during the study period) [45,46]; (ii) CD4 cell count increases between months 0 and 36 after starting ART; (iii) CD4 count slope (mean change in CD4 count per month) between months 0 to 6 and 6 to 60; and (iv) the proportion of patients not achieving virological suppression after three years and during the fifth year of ART. We were primarily interested in longer-term immunological reconstitution and virological outcomes and not the initial rapid rise in CD4 count following ART initiation [47].

Deaths were recorded as reported by professional healthcare workers or family members. Patients were defined as LTFU if they were not known to have died or to have transferred out (as documented in site databases), and had no visit to the site for six months or more prior to database closure [48,49]. Patients who returned to care after treatment interruptions were considered remaining in care. The date of last contact was assigned for the outcome of mortality or LTFU in time-to event analyses, with one day of follow-up added for patients who did not return after initiating ART to include them in analyses. Patients documented as transferring to other facilities were censored on the last clinic visit date. Patients who did not receive CBS who missed appointments were traced by telephone or a district tracing team would visit the home where available. All patients visited the clinic at a frequency determined by clinic professional staff (generally monthly). Virological suppression was defined as viral load <400 copies/ml. Laboratory measurements were performed by the South African National Health Laboratory Service.

Individual-level patient data were collected prospectively for programme monitoring purposes by designated site-based data capturers at each visit using standardized custom-designed databases, which were regularly pooled to a data warehouse, using standardized operating procedures. Site databases were designed in Microsoft Access®, and were used for clinical data collection and patient and clinic management. Regular data cleaning and quality control procedures were implemented.

Participant baseline characteristics were compared with medians, interquartile ranges and percentages, and binary variables were compared with risk ratios and 95% confidence intervals. Outcomes were by intention-to-treat ignoring changes in exposure status after ART initiation. Cumulative incidence functions were used to calculate time till mortality or LTFU, using a competing-risks approach. Multivariable Cox regression and Fine and Grey competing-risks regression were used to compare mortality and LTFU between patients who received and did not receive CBS, controlling for demographic, clinical and site-related confounding. To account for clustering of observations within sites, stratified Cox regression was conducted allowing the baseline hazard for each site to vary [50], and for the competing-risks models site was included as a fixed effect. Incidence rate ratios of attrition were calculated stratified by site, with the combined estimate calculated using Mantel–Haenszel weights.

Mean MPR was analysed using generalized estimating equations specifying for clustering within sites and using Huber–White (robust) variance estimates. MPR was also analysed as a binary variable with mixed-effects logistic regression including site as a random intercept, using a threshold MPR of ≥95% to indicate high adherence. CD4 count increases were analysed with linear regression, and CD4 cell slopes were analysed with multilevel mixed-effects linear regression including site and patient as random effects to account for the longitudinal nature of the data and clustering within sites. Models were adjusted for ART duration and baseline variables were included as fixed effects. Proportions of patients not achieving viral suppression were analysed using mixed-effects logistic regression.

To impute missing baseline covariate data, multiple imputations by chained equations were conducted using 20 imputed datasets, under the assumption that missing data were likely missing at random. Multivariable analyses were run on each data set that included the imputed values and the results combined, using Rubin rules [51].

All available plausible demographic, clinical and site-related variables were considered as potential confounders and were included in multivariable models when their inclusion altered

the association between CBS and the outcomes or were significantly associated with the outcomes with $p < 0.05$. Modification of the effect of CBS on outcomes was assessed by stratifying effect measures by plausible modifiers. The number needed to treat (NNT) to prevent a case of death or LTFU were calculated as appropriate for time-to-event outcomes [52].

2.3 | Cost-effectiveness analyses

A top-down expenditure approach was used to determine the incremental cost of CBS to usual ART care from a provider perspective. Expenditure of the CBS programme according to the financial records of the programme were collected, which included costs of human resources, training, management and administration, infrastructure and equipment, and monitoring and evaluation over a two-year period between 01 April 2011 and 31 March 2013. The cost of usual ART patient care was not considered and was assumed to be equal between patients with and without CBS. The number of patient-years of CBS during this period was calculated from programme monitoring data.

The cost outcomes were: (i) average cost of CBS per patient-year of support, and (ii) cost-effectiveness defined as cost per patient-loss (through death or LTFU) averted. The effectiveness of CBS in preventing patient attrition at annual intervals after starting ART (compared to usual care) was calculated as the difference in patient attrition between patients who did and who did not receive CBS (estimated from a stratified Cox model) divided by attrition amongst patients who did not receive CBS [53]. Incremental cost-effectiveness ratios (ICERs) were calculated from one through five years of treatment. For cost calculations, patients lost to care were considered lost at the mid-point of each year. Costs were converted to United States dollars at the average exchange rate of ZAR 1 = US$0.1219 in 2012 [54]. For ICERs, costs and patient losses averted were discounted at 3% per annum [55]. Analyses were conducted with Stata® version 13.1 (College Station, TX, USA), and Microsoft Excel®. The University of Cape Town Human Research Ethics Committee provided the studies ethical approval, and the study conformed to the Declaration of Helsinki ethical principles.

3 | RESULTS

Database records of 85,997 patients who initiated ART were screened for inclusion, with the following excluded: 3756 patients aged <10 years when starting ART; 74,123 aged ≥25 years; and 1412 who started ART after the study enrolment period. Thus 6706 participants were included, of whom 2100 (31.3%) received CBS and 4606 (68.7%) who received standard care only. Most (82.4%) participants were female and 1810 (27.0%) were aged 10 to 19 years. At ART initiation, participants who received CBS had: a higher proportion with advanced clinical stage disease (World Health Organization (WHO) stages III/IV), a slightly higher median CD4 count, a higher proportion who received concomitant TB treatment, a higher proportion who were pregnant, a higher proportion who attended rural facilities and a higher proportion who attended primary healthcare clinics (Table 1). The proportion of patients who received CBS increased from 19.3% to 33.5% during the study period.

During 9215 person-years of follow-up, 87 (4.1%) and 256 (5.6%) of participants who received and did not receive CBS were reported as having died, respectively ($p = 0.015$). A further 286 (13.6%) and 885 (19.2%) became LTFU amongst those who received and did not receive CBS, respectively ($p < 0.0001$). 375 (8.5%) participants transferred out. After five years of ART, the cumulative incidence of mortality amongst adolescents and youth who received and did not receive CBS was 8.3% and 10.8%, respectively ($p = 0.027$), and the cumulative incidence of LTFU was 29.9% and 38.9%, respectively ($p < 0.0001$) (Figure 1).

For multivariable analyses, the proportions of imputed baseline values were: TB treatment status-5.6%; pregnancy status-5.3%; CD4 count-17.1%; initial regimen-15.6%; WHO stage-34.0%. After controlling for confounding using multivariable Cox regression, participants who received CBS had a significantly reduced probability of mortality, adjusted hazard ratio (aHR) = 0.52 (95% CI: 0.37 to 0.73; $p < 0.0001$) (Table 2). Estimates from the competing-risks regression models were similar. Adolescents and youth who received CBS had a 40% reduced probability of becoming LTFU, aHR = 0.60 (95% CI: 0.51 to 0.71; $p < 0.0001$). The effect of CBS on LTFU was more pronounced at rural facilities, aHR = 0.43 (95% CI: 0.30 to 0.62) and slightly more pronounced amongst pregnant women, aHR = 0.53 (95% CI: 0.31 to 0.92).

The NNT to prevent one case of mortality after one and three years was 6.4 (95% CI: 3.6 to 16.7) and 5.3 (3.2 to 13.0), respectively, and the NNT to prevent one case of LTFU after one and three years was 6.0 (95% CI: 4.4 to 9.4) and 5.4 (4.2 to 8.0), respectively.

Considering the combined endpoint of attrition, the incidence rate of attrition was 12.9 cases/100 person-years (95% CI: 11.7 to 14.3) amongst adolescents and youth who received CBS, and 18.0 cases/100 person-years (95% CI: 17.0 to 19.1) amongst adolescents and youth without CBS, incidence rate ratio (stratified by site) = 0.55 (95% CI: 0.48 to 0.64; $p < 0.0001$).

Mean MPR was similar between patients with and without CBS; 82.5% and 83.0%, respectively, adjusted mean difference = −1.0 % (95% CI: −2.6% to 0.5%), $p = 0.20$ (Table 3). There was no difference in the proportion of patients who achieved high adherence (MPR ≥95%), viz. 35.4% and 35.8% amongst patients with and without CBS, respectively, adjusted odds ratio (aOR) = 1.00 (95% CI: 0.86 to 1.19; $p = 0.92$).

CD4 count increases were 384.5 cells/μl and 366 cells/μl amongst adolescents and youth with and without CBS, respectively, after 36 months. CD4 count slope between months 6 to 60 in adolescents and youth with and without CBS was 6.7 cells/μl/month and 7.1 cells/μl/month, respectively, with no difference in multivariable analyses; coefficient = 1.28 cells/μl/month (95% CI: −1.12 to 3.68; $p = 0.30$).

The proportions of adolescents with and without CBS who failed to achieve virological suppression after three years were similar, aOR = 0.96 (95% CI: 0.41 to 2.28), $p = 0.93$. During the fifth year of ART, the proportions with and without CBS who failed to achieve virological suppression were 18.8% and 37.2%, respectively, with the adjusted effect measure approaching a significant difference in favour of CBS, aOR = 0.24 (95% CI: 0.06 to 1.03), $p = 0.055$.

Table 1. Characteristics of adolescents and youth at antiretroviral treatment initiation who received and did not receive CBS in South Africa

	Total (n = 6706)	Did not received CBS (n = 4606)	Received CBS (n = 2100)	Risk ratio (CBS vs. no CBS) (95% CI)[a]
Female, n (%) (n = 6706)	5523 (82.4)	3752 (81.5)	1771 (84.3)	1.04 (1.01 to 1.06)
Median age, years, (IQR) (n = 6706)	22.4 (19.6 to 23.9)	22.4 (19.5 to 23.9)	22.5 (19.9 to 23.9)	
Age categories, n (%) (n = 6706)				
Ages 10 to 19 years	1810 (27.0)	1268 (27.5)	542 (25.8)	0.93 (0.86 to 1.02)
Ages 20 to 24 years	4896 (73.0)	3338 (72.5)	1558 (74.2)	
WHO clinical stage, n (%) (n = 4424)				
I/II	1564 (35.4)	1171 (37.5)	393 (30.1)	
III/IV	2860 (64.7)	1949 (62.5)	911 (69.9)	1.12 (1.06 to 1.17)
CD4 cell count, cells/μl, median (IQR) (n = 5560)	136 (70 to 187)	131 (65 to 182)	145 (82 to 195)	
Pregnancy amongst females, n (%) (n = 5166)				
Not pregnant	4512 (87.3)	3031 (88.4)	1481 (85.3)	
Pregnant	654 (12.7)	399 (11.6)	255 (14.7)	1.26 (1.09 to 1.46)
Received tuberculosis treatment, n (%) (n = 6332)				
No	5623 (88.8)	3831 (89.6)	1792 (87.1)	
Yes	709 (11.2)	443 (10.4)	266 (12.9)	1.25 (1.08 to 1.44)
Initial regimen, n (%) (n = 5657)				
d4T-3TC-EFV	2792 (49.4)	1961 (52.5)	831 (43.2)	
d4T-3TC-NVP	2006 (1342)	1342 (36.0)	664 (34.5)	
ZDV-3TC-EFV	38 (0.7)	19 (0.5)	19 (1.0)	
ZDV-3TC-NVP	106 (1.9)	37 (1.0)	69 (3.6)	
TDF-3TC-EFV	339 (6.0)	163 (4.4)	176 (9.2)	
TDF-3TC-NVP	322 (5.7)	184 (4.9)	138 (7.2)	
Other	54 (1.0)	27 (0.7)	27 (1.4)	
Year of starting ART, n (%)(n = 6706)				
2004 to 2005	218 (3.3)	176 (3.8)	42 (2.0)	
2006 to 2007	1384 (20.6)	1038 (22.5)	346 (16.5)	
2008 to 2010	5104 (76.1)	3392 (73.6)	1712 (81.5)	
Location of site attended, n (%) (n = 6706)				
Urban	5238 (78.1)	3784 (82.2)	1454 (69.2)	
Rural	1468 (21.9)	822 (17.9)	646 (30.8)	1.72 (1.58 to 1.88)
Hospital-based clinic/primary healthcare clinic attended, n (%) (n = 6706)				
Hospital	1612 (24.0)	1407 (30.6)	205 (9.8)	
Primary healthcare clinic	5094 (76.0)	3199 (69.5)	1895 (90.2)	1.30 (1.27 to 1.33)
Province, n (%) (n = 6706)				
Western Cape	803 (12.0)	523 (11.4)	280 (13.3)	
Eastern Cape	1259 (18.8)	587 (12.7)	672 (32.0)	
KwaZulu-Natal	4035 (60.2)	3243 (70.4)	792 (37.7)	
Mpumalanga	609 (9.1)	253 (5.5)	356 (17.0)	

ART, antiretroviral treatment; CBS; community-based support; WHO, World Health Organization; IQR, interquartile range; CI, confidence interval; d4T, stavudine; 3TC, lamivudine; EFV, efavirenz; NVP, nevirapine; ZDV, zidovudine; TDF, tenofovir.
[a]For binary variables.

3.1 | Cost-effectiveness results

The average cost of CBS was US$49.5/patient/year, with 84% spent on human resources (Table 4). The entire programme employed 576 CBS-workers. The effectiveness of CBS in reducing patient attrition ranged from 42.2% after one year to 35.9% after five years. The incremental cost of CBS per patient-loss averted after one, two and five years was US $600, US$776 and US$1149, respectively (Table 5).

4 | DISCUSSION

The SDGs are opportune to improve the health and wellbeing of disadvantaged groups globally. Government commitment to the SDGs needs to be translated into programmes that can deliver on the wide-ranging goals and accompanying targets. The SDG targets are interrelated and overlap; notably 28 targets across 11 goals are health-related [3,26]. To reach the SDGs for adolescents by 2030, the importance of innovations

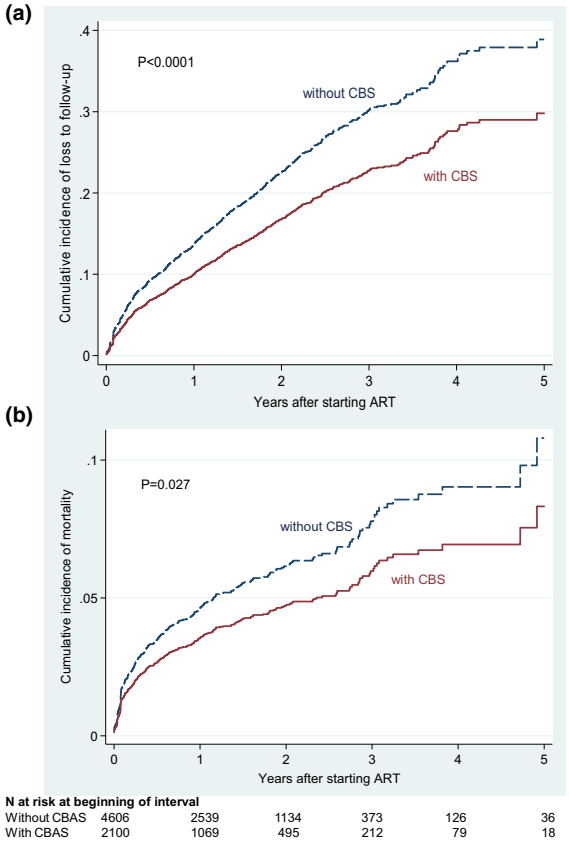

Figure 1. Cumulative incidence of (A) Loss to follow-up and (B) mortality amongst adolescents and youth starting antiretroviral treatment in South Africa.

in adolescent health involving biomedical and behavioural interventions delivered together has recently been highlighted [56].

Adolescents are a key group for targeting of the UNAIDS 90-90-90 HIV treatment goals [57]. In view of their poorer ART outcomes, there have previously been calls for adolescents and youth to receive specific additional support [11-13,15]. This study has found that CBS was associated with substantially improved retention in adolescents and youth receiving ART, and is a low-cost intervention with reasonable cost-effectiveness. Cost-effectiveness of CBS was greatest during the first two years of treatment.

Improved programme retention increases the number of HIV-infected adolescents and youth receiving ART, which would lead to greater numbers potentially being able to achieve viral suppression due to ART use. In turn, this can potentially decrease sexual transmission due to ART [58,59] and aid progress towards SDG target 3.3 to reduce HIV incidence.

Community support has previously been found to reduce ART programme attrition amongst adults and children [35,60]. Mechanisms underlying these improvements include defaulter tracing, psychosocial support offered by CBS workers, improved patient links with clinics, decreased treatment fatigue, improved self-management skills regarding HIV/AIDS, greater disclosure, greater social capital and a widened community safety net [35,61,62]. The primary driver of decreased attrition associated with CBS in this study was reduced LTFU, with reduced mortality accounting for a small component only. Except for a trend towards improved viral suppression at five years amongst those who received CBS, significant differences in immunological restitution or the adherence measure utilized were not observed. In the absence of these, the reasons for the difference in mortality observed are unclear and require further research. It is plausible that CBS was associated with health aspects not measured in this study, such as earlier referral and treatment for incident opportunistic infections, improvements in nutritional status or mental health, or improved socioeconomic status through access to grants. Future research should also incorporate more accurate measures of adherence.

In adults, the cost-effectiveness of strategies to reduce ART patient attrition have been evaluated in two previous studies. A hypothetical study found that interventions costing up to US$120/person/annum with effectiveness ≥40% in reducing attrition would be cost-effective with high degrees of regional ART coverage [63]. A Cote d'Ivoire study found that interventions preventing LTFU would result in a substantial saving of life-years, and an intervention costing US$53 per person/annum would be cost-effective by international criteria (<3 times gross domestic product per capita) if ≥28% effective [53]. Although we did not model cost-effectiveness based on disability-adjusted life years averted, CBS was found to cost US $50/person/annum and have effectiveness between 42% to

Table 2. Univariable and multivariable models of factors associated with loss to follow-up and mortality amongst adolescents initiating ART in South Africa

Predictor (baseline)	Loss to follow-up						Mortality					
	Univariable Cox		Multivariable Cox		Multivariable competing risks		Univariable Cox		Multivariable Cox		Multivariable competing risks	
	HR (95% CI)	*p*-value	aHR (95% CI)	*p*-value	asHR (95% CI)	*p*-value	HR (95% CI)	*p*-value	aHR (95% CI)	*p*-value	asHR (95% CI)	*p*-value
Received CBS												
Yes	0.59 (0.50 to 0.70)	<0.0001	0.60 (0.51 to 0.71)	<0.0001	0.61 (0.52 to 0.73)	<0.0001	0.45 (0.32 to 0.63)	<0.0001	0.52 (0.37 to 0.73)	<0.0001	0.56 (0.41 to 0.76)	<0.0001
No	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Age (years)	1.03 (1.02 to 1.05)	<0.0001	1.03 (1.02 to 1.05)	<0.0001	1.04 (1.02 to 1.05)	<0.0001	1.00 (0.98 to 1.03)	0.88	0.99 (0.96 to 1.01)	0.29	0.98 (0.96 to 1.01)	0.28
Gender												
Female	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Male	0.86 (0.73 to 1.00)	0.048	0.97 (0.82 to 1.15)	0.71	0.97 (0.82 to 1.15)	0.70	1.02 (0.78 to 1.35)	0.84	0.91 (0.67 to 1.22)	0.52	0.90 (0.33 to 1.21)	0.48
WHO stage												
I/II	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
III	1.10 (0.94 to 1.29)	0.22	1.18 (1.00 to 1.39)	0.049	1.18 (1.02 to 1.37)	0.028	2.19 (1.54 to 3.11)	<0.0001	1.84 (1.29 to 2.64)	0.001	1.86 (1.30 to 2.66)	0.001
IV	1.12 (0.86 to 1.48)	0.38	1.20 (0.91 to 1.60)	0.19	1.21 (0.93 to 1.57)	0.16	4.5 (2.79 to 7.27)	<0.0001	3.48 (2.15 to 5.62)	<0.0001	3.4 (2.12 to 5.51)	<0.0001
CD4 count, cells/μl												
0 to 99	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
100 to 199	1.06 (0.92 to 1.22)	0.40	1.04 (0.90 to 1.20)	0.63	1.09 (0.94 to 1.27)	0.25	0.36 (0.28 to 0.47)	<0.0001	0.42 (0.31 to 0.54)	<0.0001	0.42 (0.32 to 0.55)	<0.0001
200 to 349	1.11 (0.91 to 1.36)	0.30	1.11 (0.90 to 1.37)	0.32	1.17 (0.94 to 1.45)	0.17	0.27 (0.17 to 0.42)	<0.0001	0.36 (0.22 to 0.58)	<0.0001	0.35 (0.21 to 0.56)	<0.0001
≥350	1.03 (0.86 to 1.23)	0.72	1.33 (0.93 to 1.92)	0.12	1.47 (1.02 to 2.10)	0.036	0.16 (0.05 to 0.51)	0.002	0.18 (0.05 to 0.57)	0.004	0.18 (0.05 to 0.60)	0.005
Pregnancy												
Yes	1.42 (1.17 to 1.72)	<0.0001	1.43 (1.17 to 1.74)	<0.0001	1.45 (1.19 to 1.77)	<0.0001	0.25 (0.12 to 0.52)	<0.0001	0.38 (0.19 to 0.79)	0.010	0.38 (0.19 to 0.79)	0.009
No	Reference	-	Reference	-			Reference	-	Reference	-	Reference	-
TB treatment												
Yes	0.95 (0.79 to 1.15)	0.61	0.98 (0.80 to 1.19)	0.82	0.98 (0.81 to 1.19)	0.87	1.10 (0.77 to 1.55)	0.61	0.88 (0.61 to 1.29)	0.48	0.90 (0.63 to 1.30)	0.57
No	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Year of starting ART (continuous)	1.12 (1.05 to 1.19)	<0.0001	1.17 (1.10 to 1.25)	<0.0001	1.15 (1.08 to 1.22)	<0.0001	0.71 (0.64 to 0.79)	<0.0001	0.77 (0.69 to 0.86)	<0.0001	0.74 (0.67 to 0.82)	<0.0001
Site location												
Urban	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-
Rural	1.01 (0.27 to 3.75)	0.98	1.15 (0.31 to 4.27)	0.83	0.65 (0.17 to 2.50)	0.54	1.46 (0.16 to 12.60)	0.73	1.19 (0.13 to 11.03)	0.88	1.31 (0.15 to 11.7)	0.81
PHC clinic /hospital												
Hospital	0.68 (0.51 to 0.90)	0.007	0.71 (0.53 to 0.96)	0.025	0.57 (0.25 to 1.30)	0.19	1.35 (0.77 to 2.37)	0.30	0.88 (0.47 to 1.64)	0.69	3.42 (0.40 to 28.9)	0.26
PHC clinic	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-	Reference	-

Regression results using models with multiple imputation of missing covariate data, using 20 imputed datasets. To account for clustering within sites, Cox models were stratified by site, and a fixed-effects approach was used for the competing risks models. Multivariable models were also adjusted for initial antiretroviral regimen. HR, hazard ratio; aHR, adjusted hazard ratio; asHR, adjusted subhazard ratio; CBS, community-based support; ART, antiretroviral treatment; TB, tuberculosis; WHO, World Health Organization; PHC, primary healthcare; CI, confidence interval.

Table 3. Secondary outcomes of CBS for adolescents and youth receiving antiretroviral treatment in South Africa

Outcome	Received CBS	Did not receive CBS	Crude effect measure (95% CI) (CBS vs. no CBS)	Crude *p*-value	Adjusted effect measure (95% CI)[a]	Adjusted *p*-value
Mean MPR, % (95% CI)	82.5% (81.6% to 83.4%)	83.0% (82.3% to 83.7%)	−0.6% (−1.7% to 0.6%)[b]	0.33	−1.0% (−2.6% to 0.5%)[c]	0.20
Proportion with MPR ≥95%, % (95% CI)	35.4% (33.2% to 37.6%)	35.8% (34.1% to 37.5%)	0.99 (0.92 to 1.07)[d]	0.79	1.00 (0.86 to 1.19)[e]	0.92
CD4 count increases after three years of ART, cells/μl (IQR)	384.5 (152 to 521)	366 (208 to 485)	11.9 (−67.6 to 91.6)[f]	0.76	21.8 (−60.2 to 103.9)[f]	0.60
CD4 cell slope between months 0 and 6 after ART initiation, cells/μl/month, median (IQR)	27.0 (12.9 to 43.4)	25.6 (11.9 to 42.0)	1.31 (−1.92 to 4.55)[g]	0.43	2.10 (−1.21 to 5.39)[g]	0.22
CD4 cell slope between months 6 and 60 after ART initiation, cells/μl/month, median (IQR)	6.7 (−2.0 to 16.4)	7.1 (−0.6 to 16.1)	1.09 (−1.34 to 3.51)[g]	0.38	1.28 (−1.12 to 3.68)[g]	0.30
Proportions not achieving viral suppression after three years of ART, % (95% CI)	28.2% (19.7% to 37.9%)	32.7% (26.1% to 39.7%)	0.81 (0.48 to 1.36)[e]	0.43	0.96 (0.41 to 2.28)[e]	0.93
Proportions not achieving viral suppression during fifth year of ART, % (95% CI)	18.8% (7.2% to 36.4%)	37.2% (24.1% to 51.9%)	0.39 (0.14 to 1.11)[e]	0.079	0.24 (0.06 to 1.03)[e]	0.055

[a]Adjusted for baseline confounding using 20 multiple imputed datasets.
[b]Mean absolute difference.
[c]Coefficient from generalized estimating equation specifying for clustering within sites.
[d]Risk ratio.
[e]Odds ratios using mixed-effects logistic regression including site as a random intercept.
[f]Coefficient from linear regression.
[g]Coefficient from mixed-effects linear regression (cells/μl/month) including site and individual as random effects, and adjusted for duration of ART.
CBS, community-based support; MPR, medication possession ratios; IQR, interquartile range.

Table 4. Costs of CBS for antiretroviral treatment patients in South Africa

Total patient-years supported	126,485
No. community workers employed	576
Item	**Average costs per patient year supported, US$ (%)[a]**
Human resources	41.83 (84.4)
Training	5.97 (12.1)
Infrastructure and equipment	0.02 (0.05)
Clothing for CBS-workers	0.15 (0.3)
Management and administration	0.48 (1.0)
Monitoring and evaluation	0.10 (0.2)
Overhead costs	0.99 (2.0)
Total cost per patient supported/year	49.5 (100.0)

[a]Values in parentheses are percentages of the total cost.

36%, and would thus be expected to cost-effectively reduce high attrition amongst SSA adolescents and youth.

The health workforce underpins every aspect of the health system, and is the rate-limiting step in achieving universal health coverage by 2030 [64]. There is pronounced inequity in the distribution of health workers globally, with Africa carrying 25% of the world's disease burden but only 1.3% of the world's health workers, with little progress being evident in this regard [65,66]. To achieve health-related SDGs, task-shifting to maximize the use of available funds and health workers in the region will be essential. Efficiency and value for money will be important priorities. Amongst children, UNICEF is promoting task-shifting from professional to community health workers to improve access to health interventions, in order to achieve SDG target 3.2 to prevent common causes of child mortality [67]. The CBS programme evaluated in this study extends this model for the care of HIV-infected adolescents and youth.

Community health workers can play a key role in attaining a number of SDGs, including health, ending poverty and hunger, equality, clean water and sanitation, and partnerships for global health (SDG 17), as highlighted in the recent Kampala statement [68,69]. Important actions to support the role of community health workers in this regard include financial and political support, partnerships with a range of healthcare providers, and disseminating cross-country learnings. Rigorous research to expand the evidence base for policy and practice to maximize the contribution and potential of community health workers in progress towards these SDGs is vital [70]. Research priorities include the roles of cross-cutting enabling factors such as education and accreditation of community health workers, management, effective linkage with other professional staff cadres, remuneration, and motivation and performance [64,68]. Translating evidence to investment decisions will also be required to enable sustainable health solutions in pursuit of the SDGs. Including community engagement as an additional aspect of the SDG health targets has also been suggested [26].

Innovations in health worker training will be important in attaining the SDGs. CBS involves training previously unemployed persons living in impoverished areas and employing them as lay health workers, and assisting their further career development [44]. As CBS is labour-intensive, large CBS programmes will aid progress towards SDG targets 4.4, 8.5 and 8.6 (provision of skills to facilitate employment and job creation). Job-creation further impacts other health-related targets, as access to gainful employment improves the mental and physical well-being of families and young people [26]. Provision of jobs for CBS-workers also increases income to the lowest 40% income group (SDG target 10.1) which can support the targets to reduce poverty and food insecurity amongst CBS-workers and their families (SDG targets 1.1, 1.2 and 2.1).

HIV-related interventions that have cross-sectoral benefits produce development synergies and will accelerate progress across development goals [71]. CBS-workers provided counselling regarding mental health, sexual and reproductive health (particularly for adolescent girls), nutrition counselling, and support to access social grants. These interventions can aid progress towards SDG target 3.4 (promotion of mental health and wellbeing), SDG target 3.7 (universal access to sexual and reproductive healthcare services), as well as reduce poverty

Table 5. Cost-effectiveness of CBS for ART patients in South Africa

Duration of ART (years)	Proportion of patients retained in care (%)[a]		Effectiveness of intervention in reducing patient attrition (%)[b]	No. patient losses averted due to CBS (per 100 patients initiating ART)[c]	Cumulative cost of CBS (per 100 patients initiating ART), US$[c,d]	Cost-effectiveness ratio (US$/patient-loss averted)
	With CBS	Without CBS				
1	89.3	81.5	42.2	7.6	4549	600.7
2	82.7	71.0	40.3	11.0	8561	776.3
3	76.4	61.5	38.7	13.6	12,165	892.1
4	70.7	53.5	37	15.3	15,400	1007.7
5	66.9	48.4	35.9	16.0	18,337	1149.1

[a]Estimated from the survivor function of a stratified Cox model.
[b]The effectiveness of the CBS programme in preventing attrition (through death or loss to follow-up) was calculated as the difference in patient attrition between patients who did and who did not receive CBS divided by attrition amongst patients who did not receive CBS.
[c]Costs and no. of patient losses averted were discounted at 3% per annum.
[d]Patients lost to the programme were considered lost at the mid-point of each year.
CBS, community-based support; ART, antiretroviral treatment.

and hunger. As almost 85% of CBS-supported participants were female, gender-equality progress (SDG target 5.6) is also supported. The impact of these services was not assessed in this evaluation; however, future economic analyses may incorporate the potential cross-sectoral benefits of CBS.

South Africa has recently introduced and is scaling-up implementation of new national adherence guidelines [72]. In line with this, CBS workers currently provide home and clinic-based support for the initial 12 months after starting ART and for patients who are unstable. This study's results provide evidence of the effectiveness of an individualized approach to support adolescents and youth, and encourage scale-up of implementation of these guidelines. Individual and group counselling and education for adolescents have shown promise in previous smaller studies conducted mostly in developed countries [28,29]. The role of CBS workers is currently expanding to include facilitation of community and clinic-based adherence clubs for stable, virologically suppressed adults from 12 months of ART and beyond.

Challenges faced by the CBS programme include the rural context of many patients' homes with long travel distances and inadequate transport, and inconsistent availability of some adolescents for follow-up counselling sessions. CBS is not a panacea, and other important facets of comprehensive care include youth-friendly clinical management, peer-support groups, and integrated management of the transition from child to adult care services [20,21].

The strengths of this study include the large sample size drawn from many sites situated in low-income, high HIV prevalence areas, with results thus likely being generalizable to other SSA areas. Prospectively collected individual-level data were collected with up to five years of patient follow-up. Additionally, clinical as well as cost outcomes were analysed.

The study limitations include the non-random allocation of patients to groups, with the potential for selection bias and unmeasured or residual confounding. Effect measures were, however, adjusted for site-related and individual-level confounding using multiple imputation of missing covariate values. Differences in measured baseline characteristics were observed between CBS and non-CBS patients; however, most confounders associated with increased attrition were more prevalent amongst CBS patients (advanced clinical stage disease [73], concurrent TB [74], pregnancy [75], more recent year of starting ART [14,76], and attending rural facilities [77]). Residual confounding is thus unlikely to have confounded effect measures in favour of CBS. The routine nature of the data may have produced information bias. Mortality was likely underestimated in both CBS and non-CBS patients, as misclassification of patients who have died as being LTFU is common in SSA routine ART data [78]. Patients who were classified as LTFU may have been undocumented transfers to other treatment sites outside the study facilities.

5 | CONCLUSIONS

The SDG process reinforces the central importance of health in sustainable development. Greater attention to adolescent health, particular regarding HIV/AIDS, will be critical to achieve universal and sustainable development [56]. This study found CBS to be a low-cost intervention associated with substantially improved retention in adolescents and youth receiving ART, which had reasonable cost-effectiveness. CBS for adolescents and youth can potentially aid progress towards twelve targets from eight health, economic, equality and education-related SDGs. Future qualitative research may shed greater light on mechanisms that may improve outcomes and how community-support may be further tailored specifically for adolescents.

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COMPETING INTERESTS

The authors all declare that they have no conflicts of interests.

AUTHORS' CONTRIBUTIONS

GF and AG conceived the study. GF designed the study. GF contributed to data collection and managed the data. GF analysed the data. GF drafted the manuscript. All authors interpreted the data and contributed to writing the manuscript. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS AND FUNDING

The authors gratefully acknowledge the Global Fund to Fight AIDS, Tuberculosis and Malaria, and the Departments of Health of KwaZulu-Natal, Eastern Cape, Western Cape and Mpumalanga. Funding for the study was provided by the US President's Emergency Plan for AIDS Relief, USAID. This research has been supported by the U.S. Presidents' Emergency Plan for AIDS Relief (PEPFAR, grant number U51HA02522) through Centers for Disease Control and Prevention under the terms of grant 5U2GPS001966.

DISCLAIMER

The content is solely the responsibility of the authors and does not necessarily represent the official views of the United States Agency for International Development or the President's Emergency Plan for AIDS Relief. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

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Slogrove AL *Journal of the International AIDS Society* 2018, **21**(S1):e25044
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25044/full | https://doi.org/10.1002/jia2.25044

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Inequality in outcomes for adolescents living with perinatally acquired HIV in sub-Saharan Africa: a Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Cohort Collaboration analysis

CIPHER Global Cohort Collaboration[§]

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Abstract

Introduction: Eighty percent of adolescents living with perinatally and behaviourally acquired HIV live in sub-Saharan Africa (SSA), a continent with marked economic inequality. As part of our global project describing adolescents living with perinatally acquired HIV (APH), we aimed to assess whether inequality in outcomes exists by country income group (CIG) for APH within SSA.

Methods: Through the CIPHER cohort collaboration, individual retrospective data from 7 networks and 25 countries in SSA were included. APH were included if they entered care at age <10 years (as a proxy for perinatally acquired HIV) and had follow-up at age >10 years. World Bank CIG classification for median year of first visit was used. Cumulative incidence of mortality, transfer-out and loss-to-follow-up was calculated by competing risks analysis. Mortality was compared across CIG by Cox proportional hazards models.

Results: A total of 30,296 APH were included; 50.9% were female and 75.7% were resident in low-income countries (LIC). Median [interquartile range (IQR)] age at antiretroviral therapy (ART) start was 8.1 [6.3; 9.5], 7.8 [6.2; 9.3] and 7.3 [5.2; 8.9] years in LIC, lower-middle income countries (LMIC) and upper-middle income countries (UMIC) respectively. Median age at last follow-up was 12.1 [10.9; 13.8] years, with no difference between CIG. Cumulative incidence (95% CI) for mortality between age 10 and 15 years was lowest in UMIC (1.1% (0.8; 1.4)) compared to LIC (3.5% (3.1; 3.8)) and LMIC (3.9% (2.7; 5.4)). Loss-to-follow-up was highest in UMIC (14.0% (12.9; 15.3)) compared to LIC (13.1% (12.4; 13.8)) and LMIC (8.3% (6.3; 10.6)). Adjusted mortality hazard ratios (95% CI) for APH in LIC and LMIC in reference to UMIC were 2.50 (1.85; 3.37) and 2.96 (1.90; 4.61) respectively, with little difference when restricted only to APH who ever received ART. In adjusted analyses mortality was similar for male and female APH.

Conclusions: Results highlight probable inequality in mortality according to CIG in SSA even when ART was received. These findings highlight that without attention towards SDG 10 (to reduce inequality within and among countries), progress towards ensuring healthy lives and promoting wellbeing for all at all ages (SDG 3) will be hampered for APH in LIC and LMIC.

Keywords: adolescent; HIV; perinatally acquired; sub-Saharan Africa; Sustainable Development Goals

Additional Supporting Information may be found online in the Supporting information tab for this article.

Received 6 June 2017; **Accepted** 11 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

Sub-Saharan Africa (SSA) is a complex region marked by diversity and inequality. Across the continent gross national income per capita varies almost thirty fold from <USD300 to more than USD7,500, national adult literacy rates are as low as 25% in some countries and as high as 96% in others and national under-5 mortality rates range from <40/1000 to >160/1000 [1]. Sub-Saharan Africa is also home to 80% of the 1.8 million adolescents age 10 to 19 years (as defined by the World Health Organisation) living with perinatally or horizontally acquired HIV and 14 of the 15 countries with the highest burden of adolescent HIV [2–4]. Where adolescent-specific estimates of HIV-prevalence are available, this ranges in younger adolescents, age 10 to 14 years, from 0.6% in Kenya to almost 3% in Zimbabwe and for older adolescents, age 15 to 19 years from 0.5% in Côte d'Ivoire to 5% in Mozambique [2].

With increasing availability in SSA of early infant diagnosis and antiretroviral therapy (ART), there is now a burgeoning population of adolescents living with perinatally acquired

HIV (APH) [5, 6]. However, progress in scaling up HIV diagnostic and treatment interventions has not been uniform across the continent. By modelled estimates, coverage of ART in children age 0 to 14 years is only 20% (uncertainty bound (UB) 16%–25%) in West and Central Africa compared to 63% (UB 56%–71%) in East and Southern Africa [3]. Furthermore, although AIDS-related deaths in younger adolescents have started to decline in a number of high-burden countries, they continue to rise in others [2, 3]. Inequality in health and wellbeing for adolescents compared to children and adults living with HIV is evident, with adolescents experiencing greater challenges remaining in care, lower rates of virological suppression and higher rates of mortality [7–11].

The Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Cohort Collaboration, previously conducted a global analysis of the epidemiology of APH comparing characteristics and outcomes across multiple regions of the world [12]. In this analysis we observed that the hazard for mortality was two to four times higher for APH residing in SSA than for APH in Europe [12]. However, as the global community pursues attainment of the United Nations Sustainable Development Goals (SDGs) by 2030, a more precise understanding of how the APH experience differs across SSA and where the inequalities or inequities lie within the region is required. This will aid informing the appropriate global and regional policy response for APH needed to achieve the SDG targets related to ensuring healthy lives and promoting wellbeing for all at all ages (Goal 3), gender equality (Goal 5) and reducing inequality within and between countries (Goal 10) [13].

As such, the primary objective of this CIPHER analysis was to compare the patient and treatment characteristics of APH in SSA by country income groups (CIG), sex and birth cohort. Our secondary objective was to compare the outcomes of mortality, transfer and loss to follow-up between 10 and 15 years of age across CIG, sex and birth cohort.

2 | METHODS

2.1 | Study methods

The CIPHER Cohort Collaboration is a global network of observational paediatric HIV cohorts or cohort networks convened by CIPHER of the International AIDS Society, contributed to by 12 cohort networks described elsewhere [12]. In this sub-Saharan Africa-specific analysis, individual patient-level data from seven networks was included: Baylor International Pediatric AIDS Initiative at *Texas Children's Hospital* (BIPAI); International Epidemiology Database to Evaluate AIDS (IeDEA) – Central Africa; IeDEA – East Africa; IeDEA – Southern Africa; IeDEA – West Africa; Médecins Sans Frontières Pediatric Cohorts; Identifying Optimal Models for Care in Africa (Optimal Models-ICAP). The data contributed by the networks were drawn from a range of care settings including routine care cohorts and programmatic services. Twenty two of 56 included cohorts were ART-only cohorts in which ≥95% of APH received ART; 12/40 cohorts in low-income countries (LIC), 1/5 cohorts in lower-middle income countries (LMIC) and 9/11 cohorts in upper-middle income countries (UMIC).

2.2 | Analytical methods

This cohort analysis was restricted to APH resident in sub-Saharan Africa. APH were defined as HIV-infected children with at least one recorded HIV care visit prior to age 10 years, as a proxy for perinatal HIV infection, and at least one additional HIV care visit after 10 years of age. Children with known non-vertical routes of HIV infection were excluded.

Our primary analysis described patient characteristics (age, height, weight, CD4 T-lymphocyte counts and percentages) of APH at key time points including first ever HIV-associated clinic visit, ART start, age 10 years and last visit (for surviving APH only). These characteristics were compared by CIG, sex and birth cohort. Individual country level characteristics were described for countries with at least 50 APH included (see Supplementary Tables S3 and S4). Observation time was censored at 19 years of age in adolescents with follow-up beyond this age. World Health Organization (WHO) weight-for-age (WAZ) and height-for-age Z-scores (HAZ) were calculated from the measured weights and heights for APH in all regions using the WHO "igrowup_restricted" Stata macro for measurements up to 5 years of age [14] and the "who2007" Stata macro for measurements from age 5–10 years for WAZ and age 5–19 years for HAZ [15]. Stunting was defined as HAZ <−2. CIG were assigned according to World Bank country income group classification for the median year of first visit for each country [16]. Birth cohorts were classified as born prior to 2000 or born in the year 2000 or later.

Our secondary analysis focused on patient outcomes classified as mortality, transferred out, lost to follow-up (LTFU) or alive and retained in care. Mortality included all-cause mortality as reported in the database. Transfer out included documented transfer to a different HIV care site for any reason. LTFU was defined as no observed visit for more than 365 days before the last recorded visit for the cohort. APH classified as LTFU were censored 365 days after their last observed visit. APH considered to be alive and in care at database closure were those not known to have died or transferred and with an observed visit within 365 days prior to the last visit for the cohort. Cumulative incidence functions for the outcomes mortality, transfer out and LTFU at 15 years of age were calculated using competing risks analysis for the whole cohort as well as by CIG, sex and birth period. Transfer out and LTFU were both considered to be competing risks for mortality rather than censoring events. This approach was chosen as the survival distribution of adolescents transferred out or LTFU is likely to be different to those retained in care, with better survival in stable transferred patients and poorer survival in patients LTFU and possibly no longer on ART [17].

Mortality across CIG was further compared by hazard ratios and 95% confidence intervals (CI) using Cox proportional hazard models with delayed entry at age 10 years. Proportionality assumptions were evaluated using the Schoenfeld test. Adjusted hazard ratios were calculated controlling for baseline differences between CIG. Missing CD4, weight and height measurements were imputed for the multivariable models using multiple imputation by chained equations with five iterations of 20 cycles each [18]. The imputation model contained all measured variables and used predictive mean matching for anthropometric and CD4 measures. All analyses were conducted using Stata version 13.0

(StataCorp, College Station, Texas, USA) and the "stcompet" package was used to calculate the cumulative incidence functions from the competing risks analysis. Figures were plotted using the ggplot2 package in R version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria).

Primary data collection by all participating networks was approved by their respective research ethics boards of authority. The pooling of data and analysis at the University of Cape Town (UCT) data centre was approved by the UCT Health Research Ethics Committee [HREC Ref 264/2014].

3 | RESULTS

This analysis includes 30,296 APH from 25 countries in SSA, 20 countries designated as low income countries (LIC; Table 1). Seventy five percent of APH resided in LIC, compared to 4.6% in LMIC and 19.8% in UMIC. A total of 78,619 years of adolescent follow-up between age 10 and 19 years were observed.

For the total cohort, birth year ranged from 1994 to 2005 with the earliest documented HIV-associated visit occurring in 1996 and follow-up continuing until at least 2014 in all CIGs.

Table 1. Country income group classification of countries represented in sub-Saharan African CIPHER adolescent cohort

Low income N = 22,925	Lower-middle income N = 1,386	Upper-middle income N = 5,985
Benin (N = 44)	Cameroon (N = 38)	Botswana (N = 540)
Burkina Faso (N = 122)	Lesotho (N = 793)	South Africa (N = 5,445)
Burundi (N = 66)	Swaziland (N = 555)	
Central African Republic (N = 2)		
Democratic Republic of Congo (N = 402)		
Cote d'Ivoire (N = 635)		
Ethiopia (N = 1,761)		
Ghana (N = 148)		
Guinea (N = 75)		
Kenya (N = 5,913)		
Malawi (N = 1,753)		
Mali (N = 208)		
Mozambique (N = 1,523)		
Rwanda (N = 1,244)		
Senegal (N = 88)		
Tanzania (N = 1,521)		
Togo (N = 31)		
Uganda (N = 2,313)		
Zambia (N = 4,224)		
Zimbabwe (N = 952)		

Countries classified according to World Bank country income group for median year of first visit per country. N represents number of APH included in analysis.

The majority of APH in this cohort were born in the year 2000 or later, 65.4% in LIC, 69.5% in LMIC and 56.9% in UMIC. The median [interquartile range (IQR)] age at first visit was younger in UMIC (6.6 [4.3; 8.4] years) than in LIC (7.3 [5.5; 8.7] years) and LMIC (7.8 [6.2; 8.6] years) as was age at ART start (Table 2, Figure 1). Median [IQR] age at last follow-up was 12.1 [10.9; 13.8] years with little difference between CIGs. Median [IQR] CD4 count at ART start was 310 [165; 520] cells/mm^3, with APH in all CIG experiencing a substantial improvement in CD4 count and CD4 percent between ART start and last visit, the largest increase occurring in APH in LMIC (Table 2, Figure 1). Height growth was severely impaired at ART start, with the median HAZ <−2 in all CIGs. APH in LIC and UMIC experienced an improvement in HAZ by last visit, but not APH in LMIC. APH in UMIC experienced the largest improvement in HAZ. In the total cohort, of which 21.5% of APH were in ART-only cohorts, 88% received ART at some stage. In the 78.5% of APH in cohorts including pre-ART children 82.8% of APH received ART at some stage. Among APH that did receive ART, 14.3% in LIC only started ART after age 10 years compared to 11.7% in LMIC and 6.6% in UMIC ($p < 0.0001$).

There were few differences between male and female APH (Table 3, Figure 2). Male APH had a lower CD4 count at first visit and lower absolute CD4 count change than female APH, but equivalent improvement in CD4 percent between ART start and last visit. Male APH experienced less of an improvement than female APH in HAZ between ART start and last visit. A greater proportion of female than male APH started ART after 10 years of age (13.5% vs. 11.6%, $p < 0.0001$).

Compared to APH born prior to 2000, age at first visit and ART start was younger for APH in the most recent birth cohort born in 2000 or later (Supplementary Table S1, Supplementary Figure S1). CD4 count at ART start, last visit and CD4 count change between ART start and last visit were all higher in the most recent birth cohort than the birth cohort born prior to 2000. HAZ was severely impaired at first visit and ART start in both birth cohorts, with similar improvements in HAZ by last visit. Similar proportions of APH started ART in both birth cohorts, however a greater proportion started after age 10 years amongst APH born prior to 2000 compared to APH born in 2000 or later (19.8% vs. 8.4%, $p < 0.0001$).

Documented mortality occurred in a total of 576 (1.9%) APH, 3,941 (13.0%) APH were known to have been transferred out for any reason and 2,363 (7.8%) were LTFU. The cumulative incidence [95% CI] in the total cohort for observed mortality between 10 and 15 years of age before any other competing event was 2.92% [2.67; 3.21], ranging from 1.05% [0.75; 1.44] in UMIC to 3.85% [2.67; 5.36] in LMIC and 3.45% [3.12; 3.80] in LIC (Table 4). The cumulative incidence for transfer out between 10 and 15 years of age ranged from 17.54% [16.82; 18.26] in LIC to 27.53% [24.16; 30.99] in LMIC. The cumulative incidence of LTFU was highest in UMIC (14.08% [12.89; 15.33]) and lowest in LMIC (8.27% [6.28; 10.61]). Restricting to only APH that did ever receive ART marginally reduced the cumulative incidence estimates for mortality in all CIG. Stratified by birth cohort, the cumulative incidence for mortality was lower in the most recent birth cohort in all CIG, however LTFU was higher in LIC and UMIC in the most recent birth cohort (Table 4). Stratified by sex,

Table 2. Adolescent characteristics at first visit, ART start, age 10 years and last visit compared by country income group

	Total	Low income	Lower-middle income	Upper-middle income
Total N (row %)	30,296 (100.0)	22,925 (75.7)	1,386 (4.6)	5,985 (19.8)
Male – N (%)	15,007 (49.5)	11,258 (49.1)	697 (50.3)	3,052 (51.0)
Birth Cohort				
Born 2000–2005 – N (%)	19,352 (63.9)	14,982 (65.4)	963 (69.5)	3,407 (56.9)
Year of birth – median (IQR)	2000 (1999; 2002)	2000 (1999; 2002)	2001 (1999; 2002)	2000 (1998; 2002)
Age in years – median (IQR)				
First visit	7.1 (5.3; 8.6)	7.3 (5.5; 8.7)	7.2 (5.7; 8.6)	6.6 (4.3; 8.4)
ART start	7.9 (6.0; 9.3)	8.1 (6.3; 9.5)	7.8 (6.2; 9.3)	7.3 (5.2; 8.9)
Last visit	12.1 (10.9; 13.8)	12.0 (10.9; 13.7)	12.1 (10.9; 13.8)	12.4 (11.1; 14.3)
CD4 count in cells/mm^3 – median (IQR)				
First visit all ages (N = 15,582)	405 (201; 699)	418 (211; 721)	391 (221; 616)	361 (172; 662)
First visit if age ≥ 5 years (N = 12,591)	370 (180; 646)	388 (191; 678)	370 (208; 592)	296 (134; 521)
ART start all ages (N = 15254)	310 (165; 520)	310 (165; 520)	292 (174; 417)	318 (162; 558)
ART start if age ≥ 5 years (N = 13,635)	301 (158; 500)	309 (163; 526)	285 (168; 380)	281 (139; 474)
Age 10 years (N = 19,829)	671 (430; 964)	652 (414; 947)	707 (479; 973)	719 (475; 1006)
Last visit (N = 24,223)	689 (460; 953)	668 (434; 945)	735 (532; 985)	729 (513; 971)
Mean CD4 count change[a] (95% CI; N = 15,784)	318 (312; 326)	295 (286; 303)	463 (440; 486)	353 (338; 367)
CD4% – median (IQR)				
First visit (N = 10,201)	15 (9; 23)	16 (10; 25)	14 (9; 21)	14 (8; 20)
ART start (N = 10,386)	13 (8; 18)	13 (8; 19)	12 (7; 17)	13 (8; 18)
Age 10 years (N = 12,089)	27 (20; 34)	27 (19; 34)	28 (21; 35)	28 (20; 34)
Last visit (N = 16,652)	28 (20; 35)	28 (20; 35)	30 (23; 36)	29 (21; 35)
Mean CD4% change[a] (95% CI; N = 10,483)	14 (13; 14)	13 (12; 13)	18 (17; 19)	14 (14; 15)
WAZ – median (IQR)				
First visit (N = 22,073)	−1.76 (−2.74; −0.90)	−1.81 (−2.80; −0.94)	−1.85 (−2.82; −1.03)	−1.45 (−2.37; −0.64)
ART start (N = 19,658)	−1.75 (−2.70; −0.92)	−1.81 (−2.76; −0.98)	−1.94 (−2.83; −1.10)	−1.46 (−2.36; −0.64)
Age 10 years (N = 24,794)	−1.46 (−2.24; −0.75)	−1.49 (−2.35; −0.80)	−1.54 (−2.27; −0.87)	−1.12 (−1.81; −0.42)
HAZ – median (IQR)				
First visit (N = 16,525)	−1.97 (−2.94; −1.04)	−1.98 (−2.96; −1.03)	−1.91 (−2.72; −1.08)	−1.97 (−2.88; −1.10)
ART start (N = 16,181)	−2.02 (−2.95; −1.11)	−2.01 (−2.97; −1.08)	−2.08 (−2.95; −1.33)	−2.02 (−2.86; −1.17)
Age 10 years (N = 20,584)	−1.66 (−2.45; −0.91)	−1.66 (−2.46; −0.90)	−2.03 (−2.77; −1.30)	−1.55 (−2.29; −0.87)
Last visit (N = 25,333)	−1.75 (−2.57; −0.94)	−1.77 (−2.60; −0.95)	−2.02 (−2.77; −1.30)	−1.54 (−2.31; −0.77)
Mean HAZ change[a] (95% CI; N = 16,512)	0.20 (0.18; 0.22)	0.16 (0.14; 0.18)	0.04 (−0.02; 0.10)	0.44 (0.40; 0.49)
ART – N (%)				
Ever received	26,727 (88.2)	19,768 (86.3)	1,209 (87.2)	5,750 (96.1)
Started > age 10 years	3,352 (12.9)	2,829 (14.3)	141 (11.7)	382 (6.6)
On ART at age 10 years	19,729 (65.1)	13,919 (60.7)	1,015 (73.2)	4,795 (80.1)
On ART at last visit	23,321 (78.5)	16,744 (74.6)	1,127 (83.4)	5,450 (91.8)

ART, antiretroviral therapy; HAZ, height-for-age *z*-score; IQR, interquartile range; WAZ, weight-for-age *z*-score.
[a]Change between antiretroviral therapy start and last visit.

the estimated cumulative incidence for mortality, transfer out and LTFU for the total cohort was similar in males and females. However, in LMIC the cumulative incidence for mortality was higher in males than in females and in UMIC the opposite was observed (Table 4).

The hazard of observed mortality was substantially higher in APH in LIC (adjusted hazard ratio (aHR) 3.05 [95% CI 2.27; 4.09]) and LMIC (aHR 3.57 [2.30; 5.54]) compared to UMIC (Table 5, Supplementary Table S2, model 1). Adjusting for differences in baseline characteristics across CIG including sex, birth cohort, ever on ART and first visit-age, -CD4 count, -WAZ and -HAZ, marginally increased the aHR for mortality in APH in LIC and LMIC relative to UMIC in a model including complete cases only (Table 5 and Supplementary Table S2,

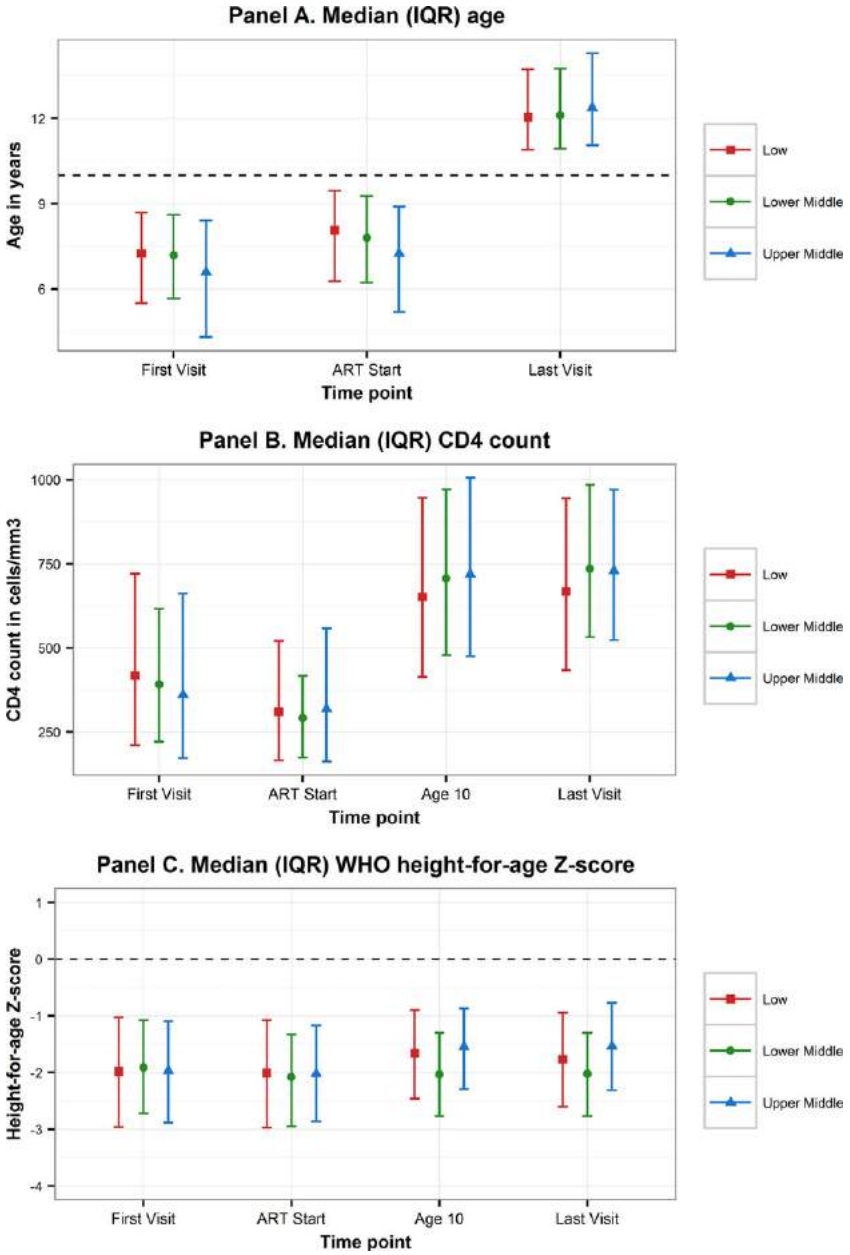

Figure 1. Graphic comparison by country income group of characteristics at first visit, ART start, age 10 years and last visit of adolescents living with perinatally acquired HIV.

model 2) and somewhat reduced the aHR in a model including all cases with imputed missing values (Table 5 and Supplementary Table S2, model 3). In a model restricted only to APH that did ever receive ART, observed mortality remained substantially elevated for APH in LIC (aHR 2.67 [1.94; 3.67]) and LMIC (aHR 3.07 [1.91; 4.95]), relative to APH in UMIC (Table 5 and Supplementary Table S2, model 4). After controlling for baseline differences there was no significant effect of sex on mortality nor was there a significant interaction between sex and CIG or sex and age at first visit or ART start.

Individual country level description is presented for key characteristics and mortality hazard ratios in Supplementary Tables S3 and S4.

4 | DISCUSSION

This large cohort describes the characteristics and outcomes of more than 30,000 APH in SSA with almost 80,000 years of combined adolescent follow-up, three quarters of whom were residing in countries classified as low income. Although this is largely a young adolescent cohort with almost two-thirds born in 2000 or later, the majority of these APH started ART well into childhood at a median age of almost 8 years and were stunted by the time ART was initiated. Despite this, overall APH experienced improvements following ART start in CD4 measures as well as height. These improvements did differ by CIG though. APH in LMIC experienced the largest

Table 3. Adolescent characteristics at first visit, ART start, age 10 years and last visit compared by sex

	Total	Female	Male
Total N (row %)	30,296 (100.0)	15,289 (50.5)	15,007 (49.5)
Birth cohort – N (%)			
2000–2005	19,352 (63.9)	9,711 (63.5)	9,641 (64.2)
Age in years – median (IQR)			
First visit	7.1 (5.3; 8.6)	7.2 (5.4; 8.7)	7.0 (5.2; 8.6)
ART start	7.9 (6.0; 9.3)	8.0 (6.2; 9.4)	7.8 (5.9; 9.2)
Last visit	12.1 (10.9; 13.8)	12.1 (10.9; 13.9)	12.1 (10.91; 13.8)
CD4 count in cells/mm^3 – median (IQR)			
First visit all ages (N = 15,582)	405 (201; 699)	427 (217; 726)	382 (186; 672)
First visit if age ≥ 5 years (N = 12,591)	370 (180; 646)	393 (198; 676)	348 (161; 614)
ART start all ages (N = 15,254)	310 (165; 520)	314 (174; 524)	305 (155; 516)
ART start if age ≥ 5 years (N = 13,635)	301 (158; 500)	308 (170; 509)	292 (146; 491)
Age 10 years (N = 19,829)	671 (430; 964)	689 (444; 989)	655 (416; 938)
Last visit (N = 24,223)	689 (460; 953)	696 (466; 979)	681 (453; 931)
Mean CD4 count change[a] (95% CI; N = 15,784)	318 (312; 326)	329 (319; 339)	308 (299; 318)
CD4% – median (IQR)			
First visit (N = 10,201)	15 (9; 23)	16 (10; 24)	14 (8; 22)
ART start (N = 10,386)	13 (8; 18)	13 (8; 19)	12 (7; 18)
Age 10 years (N = 12,089)	27 (20; 34)	28 (20; 35)	26 (19; 33)
Last visit (N = 16,652)	28 (20; 35)	29 (21; 36)	28 (20; 34)
Mean CD4% change[a] (95% CI; N = 10,483)	14 (13; 14)	14 (13; 14)	14 (13; 14)
WAZ – median (IQR)			
First visit (N = 22,073)	−1.76 (−2.74; −0.90)	−1.69 (−2.66; −0.85)	−1.82 (−2.84; −0.96)
ART start (N = 19,658)	−1.75 (−2.70; −0.92)	−1.72 (−2.66; −0.90)	−1.78 (−2.75; −0.93)
Age 10 years (N = 24,794)	−1.46 (−2.24; −0.75)	−1.51 (−2.29; −0.78)	−1.44 (−2.17; −0.68)
HAZ – median (IQR)			
First visit (N = 16,525)	−1.97 (−2.94; −1.04)	−1.92 (−2.85; −0.98)	−2.03 (−3.01; −1.12)
ART start (N = 16,181)	−2.02 (−2.95; −1.11)	−1.99 (−2.90; −1.06)	−2.04 (−2.99; −1.16)
Age 10 years (N = 20,584)	−1.66 (−2.45; −0.91)	−1.72 (−2.52; −0.95)	−1.60 (−2.35; −0.89)
Last visit (N = 25,333)	−1.75 (−2.57; −0.94)	−1.67 (−2.51; −0.81)	−1.84 (−2.62; −1.06)
Mean HAZ change[a] (95% CI; N = 16,512)	0.20 (0.18; 0.22)	0.25 (0.22; 0.28)	0.15 (0.12; 0.18)
ART – N (%)			
Ever received	26,727 (88.2)	13,338 (87.2)	13,389 (89.2)
Started > age 10 years	3,352 (12.9)	1,794 (13.5)	1,558 (11.6)
On ART at age 10 years	19,729 (65.1)	9,690 (63.4)	10,039 (66.9)
On ART at last visit	23,321 (78.5)	11,638 (77.6)	11,683 (79.4)

ART, antiretroviral therapy; HAZ, height-for-age *z*-score; IQR, interquartile range; WAZ, weight-for-age *z*-score.
[a]Change between antiretroviral therapy start and last visit.

improvement in CD4 count and percent, but no improvement in height, whereas APH in UMIC experienced a substantially larger improvement in height growth following ART start than APH in LIC and LMIC. Furthermore, APH in LIC and LMIC experienced at least a three times greater hazard of observed mortality compared to APH in UMIC with this inequality persisting after controlling for baseline differences and when comparing only APH that did ever receive ART.

Considering that the median year of birth for this cohort was the year 2000, at least 5 years before extensive scale-up of paediatric ART services commenced in SSA [19], and that the median age at first visit was 7 years, this cohort of APH likely represents the best-case scenario for the current generation of APH in SSA. A much larger cohort of children in SSA would have died prior to being diagnosed, linked to HIV care or reaching 10 years of age [20]. In this context, amongst APH that did receive ART, even though age and CD4 measures at ART start did not differ markedly between CIG, improvement in height growth was substantially better and mortality substantially lower in APH from UMIC than LIC and LMIC. Impaired length growth during childhood, specifically stunting, is associated with numerous detrimental consequences that can impact on social and economic functioning during adolescence and adulthood including poorer educational grade attainment, lower adult income and reduced likelihood of gaining formal adult employment [21–23]. In light of this, neurocognitive outcomes and other morbidities, not measured in this cohort, could also be expected to be worse in

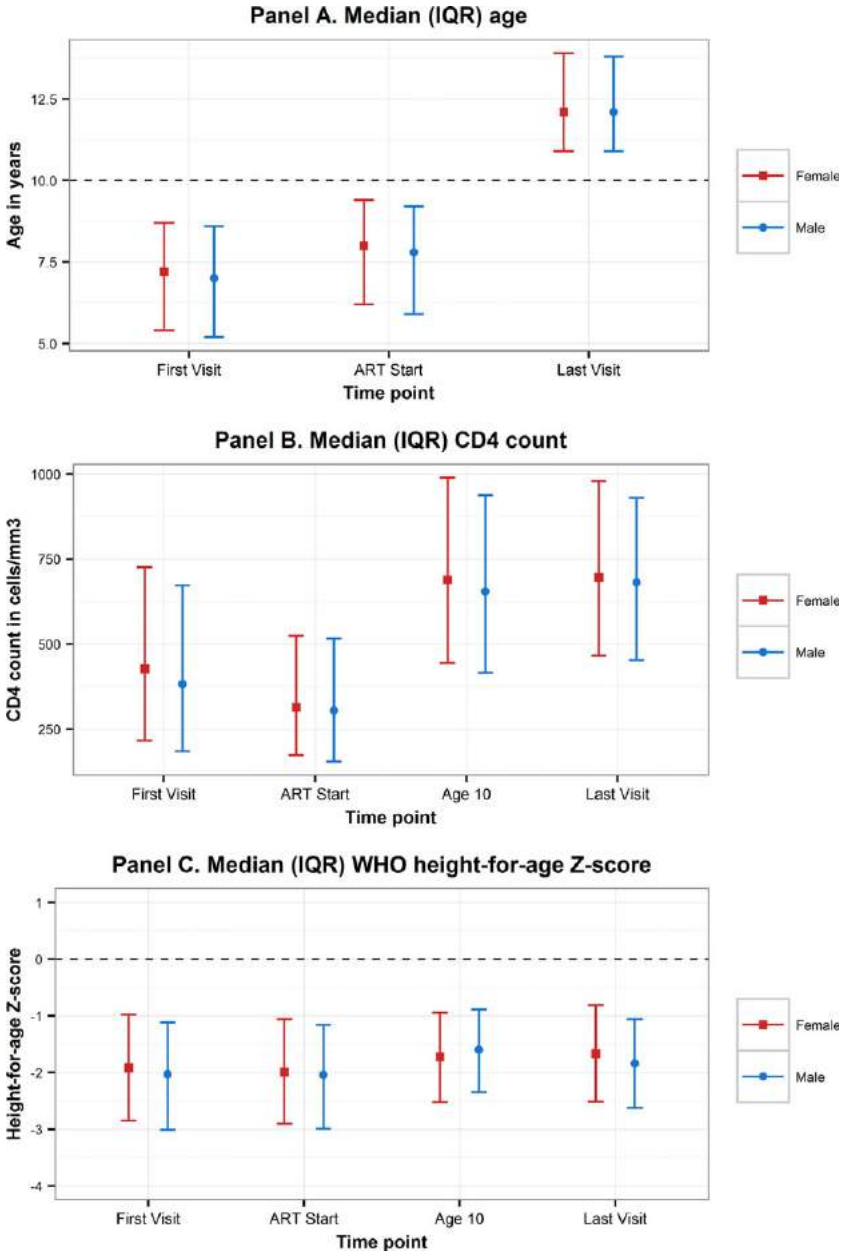

Figure 2. Graphic comparison by sex of characteristics at first visit, ART start, age 10 years and last visit of adolescents living with perinatally acquired HIV.

APH in lower income settings [9]. Thus, despite receiving HIV care and treatment, inequality remains in survival, health and wellbeing of APH in LIC and LMIC compared to UMIC. These inequalities in growth and survival indicate how progress towards SDG 3, specifically reducing HIV-associated mortality during adolescence, is intertwined with SDG 10 to reduce inequality within and between countries.

In male APH a smaller improvement in height growth was observed after starting ART than in female APH. This is consistent with previous studies in HIV-infected as well as HIV-uninfected children that have observed greater impairments in length growth in male than female children [24, 25]. In this cohort of adolescents with median follow-up to 12 years of age, the timing of the pubertal growth spurt may account for some of this difference. Puberty is known to be delayed in HIV-infected children and females experience accelerated pubertal growth earlier than males with the potential for males to recover this growth deficit later in adolescence [26, 27]. Although in the descriptive and unadjusted analysis there appeared to be differences in mortality between male and female APH, these did not remain in the adjusted analyses. In this cohort male and female APH had a similar hazard of mortality with no evidence for gender inequality in mortality up to age 15 years.

Until recently, national and global HIV monitoring systems have largely ignored the adolescent age group with the only age-disaggregation of indicators being above (adult) and below (children) 15 years of age. UNAIDS now reports adolescent

Table 4. Cumulative incidence of outcomes (mortality, transfer out and lost to follow-up) between 10 and 15 years of age compared by country income group

	Total	Low income	Lower-middle income	Upper-middle income
All adolescents				
N	30,296	22,925	1,386	5,985
Mortality %	2.92 (2.67; 3.21)	3.45 (3.12; 3.80)	3.85 (2.67; 5.36)	1.05 (0.75; 1.44)
Transfer out %	19.34 (18.71; 19.98)	17.54 (16.82; 18.26)	27.53 (24.16; 30.99)	23.72 (22.35; 25.12)
Lost to follow-up %	13.15 (12.58; 13.73)	13.07 (12.41; 13.75)	8.27 (6.28; 10.61)	14.08 (12.89; 15.33)
Restricted to adolescents ever receiving antiretroviral therapy				
N	26,018	19,114	1,207	5,697
Mortality %	2.86 (2.58; 3.16)	3.43 (3.07; 3.83)	3.91 (2.62; 5.58)	1.02 (0.71; 1.42)
Transfer out %	18.57 (17.90; 19.24)	16.32 (15.56; 17.11)	26.67 (23.07; 30.39)	23.76 (22.36; 25.20)
Lost to follow-up %	10.39 (9.84; 10.96)	9.98 (9.34; 10.64)	2.94 (1.72; 4.69)	12.62 (11.45; 13.85)
Stratified by birth cohort				
Born < year 2000				
N	10,944	7,943	423	2,578
Mortality %	3.53 (3.17; 3.90)	4.15 (3.71: 4.63)	5.01 (3.20; 7.39)	1.39 (0.97; 1.95)
Transfer out %	16.98 (16.24; 17.74)	15.16 (14.32; 16.02)	22.09 (18.16; 26.27)	21.83 (20.15; 23.56)
Lost to follow-up %	11.57 (10.93; 12.22)	12.17 (11.41; 12.96)	8.74 (6.22; 11.78)	10.17 (8.93; 11.50)
Born ≥ year 2000				
N	19,352	14,982	963	3,407
Mortality %	2.01 (1.65; 2.44)	2.44 (1.92; 3.06)	4.07 (1.50; 8.69)	0.39 (0.19; 0.74)
Transfer out %	24.53 (22.58; 26.51)	22.41 (20.18; 24.73)	89.43 (84.05; 93.08)	25.34 (22.72; 28.02)
Lost to follow-up %	23.03 (19.70; 26.53)	21.31 (17.13; 25.81)	6.50 (4.10; 9.64)	25.11 (21.30; 29.08)
Stratified by sex				
Female				
N	15,289	11,667	689	2,933
Mortality %	2.90 (2.54; 3.30)	3.35 (2.90; 3.84)	2.07 (1.08; 3.61)	1.34 (0.87; 2.00)
Transfer out %	18.68 (17.82; 19.55)	16.94 (15.97; 17.94)	24.70 (20.49; 29.13)	23.51 (21.57; 25.49)
Lost to follow-up %	13.32 (12.52; 14.15)	13.28 (12.35; 14.24)	8.45 (5.72; 11.90)	14.06 (12.37; 15.85)
Male				
N	15,007	11,258	697	3,052
Mortality %	2.93 (2.57; 3.32)	3.51 (3.04; 4.03)	4.86 (3.04; 7.30)	0.60 (0.34; 0.99)
Transfer out %	20.04 (19.11; 20.98)	18.14 (17.08; 19.23)	29.63 (24.61; 34.81)	23.83 (21.90; 25.82)
Lost to follow-up %	12.97 (12.18; 13.79)	12.80 (11.8; 13.76)	7.47 (4.99; 10.60)	14.01 (12.36; 15.76)

Table 5. Mortality hazard ratios (95% confidence intervals) by country income group with reference to upper-middle income countries

Low income	Lower-middle income	Upper-middle income
1. Unadjusted HR (N = 30,296)		
3.05 (2.27; 4.09)	3.57 (2.30; 5.54)	Reference
2. Adjusted[a] HR – complete cases only (N = 13,985)		
3.75 (2.02; 6.95)	3.74 (1.80; 7.78)	Reference
3. Adjusted[a] HR – multiple imputation for missing CD4, WAZ, HAZ (N = 30,296)		
2.50 (1.85; 3.37)	2.96 (1.90; 4.61)	Reference
4. Adjusted HR[b] – multiple imputation for missing CD4, WAZ, HAZ & restricted to those ever on ART (N = 26,018)		
2.67 (1.94; 3.67)	3.07 (1.91; 4.95)	Reference

ART, antiretroviral therapy; HAZ, height-for-age Z-score; HR, hazard ratio; WAZ, weight-for-age *z*-score.
[a]Adjusted for – on ART ever; sex; age; birth cohort; first visit -CD4 count, -WAZ, -HAZ.
[b]Adjusted for – sex; age; birth cohort; first visit -CD4 count, -WAZ, -HAZ.

specific HIV indicators where possible and in 2015 the World Health Organization issued Consolidated Strategic Information Guidelines that strongly recommend age disaggregation in 5 year age bands [3, 28, 29]. With expanding electronic monitoring systems in SSA such age disaggregation is becoming feasible [30], however challenges remain for countries even with electronic monitoring systems to provide appropriately age-disaggregated data [31]. Particularly in SSA with high rates of maternal and child mortality, national health information systems have not been oriented towards monitoring the general adolescent population, who with lower all-cause mortality rates than other age groups, receive little attention from healthcare systems [32, 33]. Efforts towards SDG 17.18, to increase significantly the availability of high-quality, timely and reliable data disaggregated by income, sex and age among other parameters, have the potential to greatly improve monitoring of health outcomes for all adolescents and specifically adolescents living with HIV.

We recognize that classifying countries according to income groups at a single point in time represents a unidimensional, static assessment of their capacity and that achievements in accelerating health and development are influenced by governmental, legal, societal and numerous other structures not represented by the CIG classification [11]. Furthermore, the CIG of the country may not correspond with individual household level income, the effect of which we are not able to address with this dataset and in this analysis. However, comparing outcomes by CIG is a first step to more broadly understanding how outcomes for APH in SSA may be influenced by factors beyond the healthcare system and provision of ART. This analysis is not able to interrogate what the socio-economic and structural drivers of mortality in APH are, however it does highlight the need for studies that can inform socio-economic and structural interventions to improve health and survival of APH across SSA. Moreover, with indications that international funding for HIV is likely to plateau, and evidence that most low income HIV high-burden countries are unlikely to have the domestic capacity to finance the needs of their HIV-epidemic, it is appropriate to consider the real possibility that inequalities in outcomes may widen further for APH living in LIC and LMIC compared to UMIC [34].

Our analysis was restricted to adolescents most likely to have perinatally acquired HIV who survived into adolescence and does not apply to the larger population acquiring HIV during adolescence in whom important gender inequalities and additional vulnerabilities exist [35]. Due to generally poor recording of mode of transmission, we utilized a pragmatic definition of perinatally acquired HIV according to entry into care before age 10 years, that excluded the important group of APH that are only identified and diagnosed after age 10 years [6]. Although our analysis includes representation from 14 of the 15 countries with the highest adolescent HIV burden, it does not include Nigeria, the country with the second largest population of adolescents living with HIV and the only country in which mortality in younger adolescents is still estimated to be increasing [3]. This analysis likely overestimates the proportion of APH ever receiving ART, particularly in UMIC where more than 80% of cohorts were ART-only cohorts compared to <30% of cohorts in LIC and LMIC. With the high rates of LTFU in this cohort, mortality is likely underestimated with a proportion of LTFU due to unascertained mortality. This limits comparison of mortality estimates across CIG. Methods in adult HIV cohort research have been advanced through tracing studies of patients LTFU or linkage to mortality registries to be able to informatively adjust estimates of mortality based on the proportion lost to follow-up and the size of the ART programme [36, 37]. Such methods are yet to be developed for children and adolescents living with HIV, highlighting further inequality in research investment for children and adolescents compared to adults.

5 | CONCLUSIONS

Irrespective of CIG, this cohort of APH entered care and started ART well into childhood, with consequent marked growth impairment likely to impact on social and economic capacity as this generation of adolescents enter adulthood. Even when receiving ART, inferior growth improvement and higher mortality was observed in APH from LIC and LMIC compared to UMIC signalling the role of factors beyond the ART programme in determining the health and wellbeing of APH. Without broader national capacity development in LIC and LMIC in SSA, and measurable progress towards reducing inequality within and among countries (SDG 10), outcomes for APH in LIC and LMIC in SSA will continue to lag behind those of their peers in UMIC. Without concerted efforts in relation to SDG 17.18 to monitor APH within national health information systems, the needs of this diverse and complex population will continue to go unnoticed.

COMPETING INTERESTS

MVs work at CIPHER is funded through Unrestricted Educational grants received from ViiV Healthcare and Janssen to the International AIDS Society. CS has received personal payment for preparation of educational materials for Gilead Sciences and ViiV Healthcare. JW's institution has received academic grants from the INSERM-ANRS, for cohorts of JW's responsibility involved in the study. SW receives a fee from Baylor International Pediatric AIDS Initiative for consultancy services related to research. All remaining authors declare no conflicts of interest.

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ACKNOWLEDGEMENTS

The following sites, their personnel and patients are acknowledged for their contribution to the participating networks that made the CIPHER Cohort Collaboration Adolescent Project possible:

BIPAI: Baylor Botswana, Gabriel Anabwani; Baylor Lesotho, Edith Mohapi; Baylor Malawi, Peter N. Kazembe; Baylor Swaziland, Makhosazana Hlatshwayo; Baylor Tanzania, Mwita Lumumba; Baylor Uganda, Adeodata Kekitiinwa-Rukyalekere. Baylor International Pediatric AIDS Initiative *at Texas Chidlren's Hospital* Founder, Mark Kline.

IeDEA Central Africa: Burundi, Christelle Twizere – Association Nationale de Soutien aux Séropositifs; HIV-clinic (CPAMP-CHUK), Bujumbura University Hospital; Hôpital Prince Régent Charles; Democratic Republic of Congo, Marcel Yotebieng – Bomoi Health Center; Kalembe Lembe Pediatric Hospital; Rwanda, Jean D'amour Sinayobye - Bethsaid Hospital; Busanza Health Center; Gahanga Health Center; Gikondo Health Center; Kabuga Health Center; Kanombe Hospital/Rwanda Military Hospital; Kicukuri Health Center; Masaka Hospital; Nyarugunga Hospital; Women's Equity in Access to Care & Treatment.

IeDEA East Africa: Academic Model Providing Access to Healthcare, Kenya, Samuel Ayaya; National Institute for Medical Research, Family AIDS Care and Education Services, Kenya, Elizabeth Bukusi; National AIDS Control Program, Tanzania, Geoffrey Somi; Morogoro Regional Hospital, Tanzania, Rita Lyumuya; Tumbi Regional Hospital, Tanzania, Ngonyani Kapella; National Institute for Medical Research, Kisesa Clinic, Tanzania, Mark Urassa; Masaka Regional Referral Hospital, Ugana, Mark Ssali; Rakai Health Science Program, Uganda, Fred Nalugoda. IeDEA East Africa also acknowledges senior data manager Beverly Musick, Indiana University, USA.

IeDEA Southern Africa: Aid for AIDS, South Africa, Gary Maartens; Aurum Institute for Health Research, South Africa, Christopher J. Hoffmann; Centre for Infectious Disease Research in Zambia, Zambia, Michael Vinikoor; Centro de Investigacao em Saude de Manhica, Mozambique, Eusebio Maceta; Dignitas, Malawi, Monique van Lettow; Gugulethu Cohort (Desmond Tutu HIV Centre),

South Africa, Robin Wood; Harriet Shezi Clinic, Chris Hani Baragwanath Hospital (Wits Paediatric HIV Clinics), South Africa, Shobna Sawry; Hlabisa (Africa Centre for Health & Population Studies), South Africa, Frank Tanser; Khayelitsha ART Programme, South Africa, Andrew Boulle; Kheth 'Impilo, South Africa, Geoffrey Fatti; Lighthouse Truse clinic, Malawi, Sam Phiri; McCord Hospital, South Africa, Janet Giddy; Newlands Clinic, Zimbabwe, Cleophas Chimbetete; Queen Elizabeth Hospital, Malawi, Kennedy Malisita; Rahima Moosa Mother & Child Hospital (Wits Paediatric HIV Clinics), South Africa, Karl Technau; Red Cross War Memorial Children's Hospital and School of Child & Adolescent Health, University of Cape Town, South Africa, Brian Eley; SolidarMed SMART Programme Lesotho, Lesotho, Christiane Fritz; SolidarMed SMART Programme Mozambique, Mozambique, Michael Hobbins; SolidarMed SMART Programme Zimbabwe, Zimbabwe, Kamelia Kamenova; Themba Lethu Clinic, Helen Joseph Hospital, South Africa, Matthew P. Fox; Tygerberg Academic Hospital, South Africa, Hans Prozesky.

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Médecins Sans Frontières: The following sites contributed to the MSF Pediatric Cohorts : *Cameroon* – Douala Nylon, Douala Soboum; *Central African Republic* – Boguila, Carnot, Zemio; *Democratic Republic of Congo* – Bukavu Baraka, Katanga Dubie, Katanga Kilwa, Kimbi Lulenge, Kinshasa, Mweso, Shamwana; *Ethiopia* – Abdurafi; *India* – Manipur, Moreh, Mumbai; Malawi – Chiradzulu; Mozambique – Alto Mae, Chamanculo; *Myanmar* – Dawei, Insein, Kachin Bhamo, Kachin Moegaung, Kachin Myitkyina 1, Kachin Myitkyina 1, Kachin Phakant, Kachin Waimaw, Rakhine Maugdaw, Rachine Sittwe, Shan Laiza, Shan Lashio, Shan Muse, Yangon B, Yangon C, Yangon I, Yangon T, Yangon TIB, Yangon TIC; South Sudan – Leer, Nasir; Guinea – Conakry; *Uganada* – Arua.

Optimal Models-ICAP: The following people and sites contributed to Optimal Models: *Ethiopia* -Mohamed Ahmed, Harari Regional Health Bureau; Zelalem Habtamu, Oromia Regional Health Bureau; Kassahun Hailegiorgis, Dire Dawa Regional Health Bureau; Zenebe Melaku, ICAP Ethiopia. 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Avega Clinic, Bethsaida Health Center, Bigogwe Health Center, Busasamana Health Center, Butare Hospital, Carrefour Polyclinic, Central Hospital-Kigali, Congo Nil Health Center, Gisenyi District Hospital, Gisenyi Prison, Gisovu Health Center, Kabaya District Hospital, Kabusunzu Health Center, Kayove Health Center, Kibuye District Hospital, Kicukiro Health Center, Kigali Central Prison, Kigufi Health Center, Kinunu Health Center, Kirambo Health Center, Kirinda District Hospital, Kivumu Health Center, Mugonero District Hospital, Muhima District Hospital, Muhororo District Hospital, Mukungu Health Center, Munzanga Health Center, Murunda District Hospital, Mushubati Health Center, Mwendo Health Center, Ndera Neuropsychiatric Hospital, Nyabirasi Health Center, Nyakiriba Health Center, Nyange A health Center, Nyange B Health Center, Ramba Health Center, Rambura Health Center, Rubengera Health Center, Rugarama Health Center, Rususa health Center, Shyira District Hospital; *Tanzania* - Gretchen Antelman, ICAP Tanzania; Redempta Mbatia, ICAP Tanzania; Geoffrey Somi, National AIDS Control Program. 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Individual networks contributing to the CIPHER Cohort Collaboration have received the following financial support: IeDEA Central Africa receives funding from the United States (US) National Institutes of Health (NIH; https://www.nih.gov; U01AI096299-07); IeDEA East Africa receives funding from the US NIH (U01-A1069911); IeDEA Southern Africa receives funding from the US NIH (U01-AI069924); IeDEA West Africa receives funding from the US NIH (U01AI069919); The Optimal Models project was supported by the President's Emergency Plan for AIDS Relief (PEPFAR) through the Centers for Disease Control and Prevention (https://www.pepfar.gov) under the terms of Cooperative Agreement Number 5U62PS223540 and 5U2GPS001537. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

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SUPPORTING INFORMATION

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

Figure S1 Graphic comparison by birth cohort of characteristics at first visit, ART start, age 10 years and last visit of adolescents living with perinatally acquired HIV.

Table S1 Adolescent characteristics at first visit, ART start, age 10 years and last visit compared by birth cohort.

Table S2 Complete multivariable models: mortality hazard ratios and 95% confidence intervals.

Table S3 Individual country descriptive characteristics.

Table S4 Individual country mortality hazard ratios.

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

Conditional cash transfers and the reduction in partner violence for young women: an investigation of causal pathways using evidence from a randomized experiment in South Africa (HPTN 068)

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This study is registered at ClinicalTrials.gov (NCT01233531).

Abstract

Introduction: Evidence has shown that the experience of violence by a partner has important influences on women's risk of HIV acquisition. Using a randomized experiment in northeast South Africa, we found that a conditional cash transfer (CCT) targeted to poor girls in high school reduced the risk of physical intimate partner violence (IPV) in the past 12 months by 34%. The purpose of this analysis is to understand the pathways through which the CCT affects IPV.

Methods: HPTN 068 was a phase 3, randomized controlled trial in rural Mpumalanga province, South Africa. Eligible young women (aged 13–20) and their parents or guardians were randomly assigned (1:1) to either receive a monthly cash transfer conditional on monthly high school attendance or no cash transfer. Between 2011 and 2015, participants (N = 2,448) were interviewed at baseline, then at annual follow-up visits at 12, 24 and 36 months. The total effect of the CCT on IPV was estimated using a GEE log-binomial regression model. We then estimated controlled direct effects to examine mediation of direct effects through intermediate pathways. Mediators include sexual partnership measures, the sexual relationship power scale, and household consumption measures.

Results: We found evidence that the CCT works in part through delaying sexual debut or reducing the number of sexual partners. The intervention interacts with these mediators leading to larger reductions in IPV risk compared to the total effect of the CCT on any physical IPV [RR 0.66, CI(95%):0.59–0.74]. The largest reductions are seen when we estimate the controlled direct effect under no sexual debut [RR 0.57, CI(95%):0.48–0.65] or under no sexual partner in the last 12 months [RR 0.53, CI(95%):0.46–0.60].

Conclusions: Results indicate that a CCT for high school girls has protective effects on their experience of IPV and that the effect is due in part to girls choosing not to engage in sexual partnerships, thereby reducing the opportunity for IPV. As a lower exposure to IPV and safer sexual behaviours also protect against HIV acquisition, this study adds to the growing body of evidence on how cash transfers may reduce young women's HIV risk.

Keywords: intimate partner violence; cash transfers; gender; South Africa; HIV prevention

Additional Supporting Information may be found online in the Supporting information tab for this article.

Received 9 May 2017; **Accepted** 12 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

Violence against women, and specifically intimate partner violence (IPV), is a major global public health problem, causing significant morbidity and mortality worldwide [1]. Around a third of women globally have experienced IPV [2] and South Africa, the location of this study, is no exception [3, 4]. Partner violence in South Africa is particularly a problem for young women, putting them at risk for sexual and reproductive health issues including HIV infection [5]. IPV can be a direct cause of HIV transmission through forced or coercive sex with a HIV-positive male but can also indirectly lead to HIV transmission by limiting young women's ability to negotiate and practice safe sexual behaviours such as using condoms [5–7]. Moreover, poverty can exacerbate young women's risk for both IPV and HIV as it often heightens this gendered power

imbalance by pressuring young women to engage in transactional sex [7–9]. Given the critical intersections of HIV and IPV, the success of HIV prevention interventions may be conditional upon changes in gendered power inequalities.

The importance of addressing these interconnections—those among health, gender inequalities and poverty—has even been articulated in the United Nations Sustainable Development Goals (SDGs) in order to advance the global development agenda. In context of HIV prevention for female adolescents in South Africa, a focus on combination interventions which work towards reducing national poverty (SDG 1.2) and gender inequality (SDG 5), particularly intimate partner violence (SDG 5.2.1), may be the most imperative to reduce new HIV infections (SDG 3.3.1). Social protection programmes have become an explicit part of the development agenda (SDG 1.3) to reduce national poverty and lately, these programmes—particularly cash transfers—have also been promoted for HIV prevention. The theory is that cash transfers may reduce women's HIV risk as they can address poverty as structural driver of risk and because cash transfers may be an effective vehicle for empowering women and lead to safer sexual behaviours [10–13]. Moreover, cash transfers often increase children's educational attendance (SDG 4.1) with even stronger effects when the money is tied to an explicit condition [13]. As education can also be empowering for girls, providing the cash conditional on school attendance may be an important mechanism for reducing young women's vulnerability to HIV and IPV [14–16].

In this analysis, we examine how a conditional cash transfer (CCT), HIV Prevention Trial Network (HPTN) 068 study, helped address these intersecting issues in poor, rural South Africa. HPTN 068 was an experimental intervention for HIV prevention that provided monthly cash transfers to young women and their households conditional high school attendance by the young woman. The main findings of HPTN 068 (published in the Lancet) revealed that the CCT had no significant effect on HIV incidence but did reduce young women's risk of IPV by 34 percent [17]. While similar evidence has been found in other studies of cash transfers [18–21], most evidence comes from Latin America and focuses on older women. Moreover, little is known about how these programmes work to prevent IPV [21]. In this paper, we build upon the Lancet findings to investigate the causal pathways through which a CCT intervention targeted to young women in South Africa works to reduce IPV; concentrating on perceived sexual relationship power, sexual behaviours and economic wellbeing.

2 | METHODS

2.1 | Study site and design

The HPTN 068 study site is in the Mpumalanga province in northeast South Africa. Villages in our study are located within the Agincourt Health and Socio-Demographic Surveillance Systems (AHDSS) catchment area—a rural but densely populated and characterized by high poverty and high HIV prevalence [22, 23]. A 2010 population-based HIV prevalence survey undertaken in Agincourt found HIV prevalence rises significantly among young women of similar age to our study sample—from 5.5% among 15–19 year olds to 27% among 20–24 year olds [23]. Incidence among young women from the HPTN 068 study was <2% (per person-year) [17], which was low considering a 4.5% incidence rate among black African females aged 20–34 from a recent national survey in South Africa [24].

The study was designed as a phase III randomized control trial to test the effectiveness of CCTs for HIV prevention among young women (aged 13–20) attending high school. Enrolled participants were randomly assigned to the treatment arm, and participants and their parents or guardians received monthly cash transfers of 100 and 200 Rand (R) respectively (or roughly US$ 10 and US$ 20 using 2012 the conversion rates). At baseline, monthly per capita household expenditure was R295 so transfer amounts made up a significant proportion of pre-programme consumption. For both the young woman and the parent or guardian, transfer funds were deposited directly into respective bank accounts. Cash transfers were conditional on the young woman attending at least 80% of school days during the month. As long as the young woman was eligible to be in school and met the attendance criteria, she could receive the transfer for up to 3 years.

2.2 | Eligibility and randomization

To be eligible for the study, young women had to be aged 13–20 years and enrolled in a participating high school (grades 8, 9, 10, or 11) in the study location. They also had to be unmarried, not pregnant, able to read, living with at least one parent or guardian, willing to take an HIV and herpes simplex virus (HSV)-2 test, and have or be able to open a bank account (or post office account). Between March 2011 and December 2012, a total of 10,134 young women were screened from the ADHSS population, and 2,537 were found eligible and enrolled [25]. After young women were recruited to the study, participants completed an Audio Computer-Assisted Self-Interview (ACASI) and HIV and HSV-2 testing, which included pre and post-test HIV counselling. After baseline assessments, young women (and their parent or guardian) were individually randomized (1:1) to either the treatment group (monthly cash transfer conditional on school attendance) or control group (no cash). All participants were then reassessed annually at 12, 24, and 36 months until they graduated from high school or the study ended, whichever came first. Each visit included the ACASI, HIV and HSV-2 testing (if negative at the previous visit), and pre and post-test HIV counselling. A household survey was also completed with parents or guardians at baseline and each follow-up visit. Consent for study participation was obtained at the home visits with written informed consent from both young women and her parent or guardian. Written assent was obtained for female participants under 18 years old. Institutional Review Board approval for this study was obtained from the University of North Carolina at Chapel Hill and the University of the Witwatersrand Human Research Ethics Committee as well as the Provincial Department of Health's Research Ethics Committee.

2.3 | Measures

The ACASI asked respondents about sexual and physical IPV experiences regardless of whether they reported having a sexual partner. "Forced sex" is an indicator any experience of

forced sex by a partner in the previous 12 months. "Any physical IPV" is an indicator for any experience of physical intimate partner violence in the previous 12 months as defined by the WHO [2];

Has a partner (responses are yes or no):

1 Slapped you or thrown something at you that could hurt you?
2 Pushed you or shoved you?
3 Hit you with a fist or with something else that could hurt?
4 Kicked you, dragged you, or beaten you up?
5 Choked or burnt you on purpose?
6 Threatened to use or actually used a gun, knife, or other weapon against you?

We also created indicators for moderate and severe IPV as defined by the WHO, where moderate IPV indicates any experience of violence from items 1 or 2 and severe IPV indicates any experience of violence from items 3–6. Variables are not mutually exclusive; young women could experience both moderate and severe IPV.

Mediation pathways we examined included sexual behaviours, perceived sexual relationship power and household economic wellbeing. We chose to explore these variables based on hypothesized conceptual pathways through which the cash transfer might reduce IPV [21, 26]. For one, sexual behaviours that increase the risk of IPV (e.g. transactional sex) may be driven in part by poverty, including relative poverty. Individual transfers to young women may reduce these behaviours if the money improves outcomes such as food security or consumption for "symbolic purposes" [27]. In addition, young women are more susceptible to violence if they are economically dependent on their male partners. But, with their own source of money, relationship power dynamics may change or women may feel more empowered to leave abusive relationships. Finally, income transfers at the household level have been shown to reduce economic insecurity, which in turn may further lower young women's risk of IPV by changing household time-use decisions. For young women, this may include more time spent in school and at home vs. high-risk settings such as unsafe work environments.

Sexual behaviour measures included an indicator for sexual debut (vaginal or anal) after baseline, an indicator for whether the girl had any sexual partners in the past 12 months, and the number of sexual partners in the last 12 months. Sexual relationship power was defined only for young women that reported ever having had sex and operationalized with the Sexual Relationship Power Scale (SRPS), which measures constructs of relationship control and decision-making dominance [28,29]. We looked at the continuous scale (higher scores indicate greater perceived empowerment) and similar to other studies that use the SRPS, we split the scale into terciles based on scores from all waves. Economic measures included per capita household expenditure (in logarithms) and an indicator for being in the top quartile of per capita household expenditure.

2.4 | Analysis methods

We began with an intention-to-treat (ITT) analysis of the total effect of the CCT on IPV measures and on potential mediators for all participants with an HIV-negative status at baseline. Intervention effects were modelled using generalized estimating equation (GEE) models with robust variance to account for repeated observations on study participants. We estimated risk ratios using log-binomial regressions for binary (and count) mediators. For continuous mediators (SRPS and log per capita expenditure), coefficients are calculated using a Gaussian distribution. All models control for participant's age at baseline. In addition, sexual debut was modelled using a discrete time survival analysis and includes dummy variables for study visits.

To explore mediation of the effect of the CCT on IPV, we used the counterfactual approach to causal mediation [30–32] where we estimate the risk of IPV, Y, for everyone under each possible exposure; treatment, Y(1), and control, Y(0). Only mediators that were significantly impacted by treatment were considered for mediation analysis. We estimated the controlled direct effect (CDE) of the CCT, which expresses the effect of keeping the mediator controlled at level M for everyone but switching exposure from control, Y(0), to treatment, Y(1).

$$\mathrm{CDE}(M) = E[Y(1,M)]/E[Y(0,M)]$$

In general, CDEs are used to estimate what the difference in the effect of the exposure would be if you could impose a mediator intervention. In our study, CDEs represent the hypothetical risk reduction if we were able to set our mediators at a more protective level (e.g. reducing sexual partners).

We estimated the CDE using the parametric g-formula [33]. In the first step, we fit log-binomial models for the effect of CCT on IPV at each time point, including terms for each mediator, treatment-mediator interactions, and baseline levels of confounders (see Appendix S1 for details). We then used the coefficients from this model to estimate the predicted probabilities of the outcome under each hypothetical intervention on the exposure (treatment or control) and mediator. We report risk ratios for each contrast of interest as the ratio of the average predicted outcome probability under each hypothetical intervention compared. Standard errors of the risk ratios were estimated as the standard deviation of the point estimate from 5,000 bootstrap samples of the observed data [34].

3 | RESULTS

3.1 | Baseline data

Baseline descriptive statistics for study participants (total and by study arm) are provided in Table 1. We exclude baseline HIV positive or unknown cases (N = 85) from our analysis leaving a baseline sample of 2,448 HIV-negative young women. All young women participating in the study were South African and of black race/ethnicity. Young women had a median age of 15 years (IQR 14–17) and were distributed equally across all school grades (8–11). All demographic and outcome variables in Table 1 were tested for baseline balance and we found no significant differences in means between study arms at the 10 percent significance level. In addition, the study arms were also balanced on other key behavioural outcomes, including the main outcomes of HIV and HSV-2 infection status [17].

Table 1. Baseline demographics and outcomes for young women study participants by treatment arm

	Total (n = 2,448)	Treatment group (n = 1,225)	Control group (n = 1,223)
		N (%) or Median (IQR)	
Age (years)	15 (14 to 17)	15 (14 to 17)	15 (14 to 16)
School grade enrolment			
Grade 8	614 (25)	310 (25)	304 (25)
Grade 9	669 (27)	321 (26)	348 (28)
Grade 10	677 (28)	347 (28)	330 (27)
Grade 11	488 (20)	247 (20)	241 (20)
Ever physical IPV	415 (17)	219 (18)	196 (16)
Ever forced sex	73 (3.0)	33 (2.7)	40 (3.3)
Any physical IPV in past 12 months	254 (11)	136 (11)	118 (10)
Ever vaginal or anal sex	649 (27)	324 (26)	325 (27)
Any sexual partner in past 12 months	645 (27)	316 (26)	329 (27)
Number of sexual partners in past 12 months			
0 partners	1,773 (73)	893 (74)	880 (73)
1 partner	504 (21)	247 (20)	257 (21)
≥2 partners	141 (6)	69 (6)	72 (6)
Sexual relationship power scale (SRPS)[a]	28 (23 to 32)	28 (23 to 32)	29 (24 to 32)
Highest tercile SRPS (34–36)	132/653 (20)	70/324 (22)	62/329 (19)
Log PC Expenditure (2.9–9.7)	5.7 (5.2 to 6.2)	5.7 (5.2 to 6.2)	5.7 (5.2 to 6.2)

No significant differences ($p < 0.1$) found between treatment and control outcomes at baseline.
[a]SRPS is only reported for girls who had been sexually active (n = 697), scale range is from 1 to 36 with higher scores representing greater empowerment.

At baseline, 17 percent of all young women in the study reported ever having experienced physical IPV by a partner and 11 percent had experienced some form of physical IPV in the past 12 months. The majority of study participants were not sexually active at baseline, only 27 percent reported ever having had sex (vaginal or anal). In addition, only around 3 percent had ever experienced forced sex.

Table 2 shows ITT programme impacts on all IPV outcomes including the main effects of whether a participant experienced forced sex by a partner (row 1) and physical IPV (row 2) in the past 12 months. We found no effect on forced sex, but, as reported in the Lancet [17], the programme resulted in a significant reduction in physical IPV. Young women in the treatment group have a 34 percent lower risk of IPV (RR 0.66), significant at the 99.9% CI level.

Below the main treatment effects, we break down any physical IPV into its component parts and find that treatment effect is robust across each of these different specifications. For the six separate acts of physical violence, risk ratios for each measure are similar to the overall impact (ranging from 0.59–0.65) and significant at the 99.9% CI level. In addition, results are just as robust to categorization of IPV into moderate and severe categories (p-values < 0.001).

Earlier we described the potential pathways we examined related to sexual partnerships, relationship power and economic wellbeing to explain the effect of the CCT on reducing risk of IPV. Table 3 shows the treatment impacts on these pathways. As a necessary condition for mediation, we should find that the CCT directly impacts these pathways.

Using a discrete time-survival analysis, we find that there is a reduced risk of sexual debut (RR 0.83), significant at the 95% CI level. In other words, the CCT has a cumulative, protective effect of first sex at each study visit. It is important to note that in the main trial findings, no significant difference was found in sexual debut between study arms using a cox proportional hazards model to measure risk of debut over the entire study period [17]. We chose to examine the cumulative risk of debut for this analysis because we are interested in the pathways that affect incident IPV by visit. Another difference is that we excluded cases of debut if women reported an age of first sex that was younger than their age at baseline. However, sensitivity analysis confirms that results are robust to model choice and not dependent on the inclusion or exclusion of these cases.

In addition, the programme had a positive effect of reducing sexual partnerships during the study. Since partner number is a count variable and most sexually active girls had only one partner we estimated the incident rate ratio and find that being in the intervention resulted in a significantly lower risk of having an additional partner (IRR 0.86). Similarly, participants in the treatment arm had a 9% lower risk of having any sexual partner in the last 12 months (p-value < 0.05).

In addition, we examined the effect of CCT on young women' perceived relationship power using the SRPS. As only young women that reported having sexual partnerships have SRPS scores, the sample is reduced considerably (Table 3). We found no significant effect of the CCT intervention on either the continuous SRPS scale or the likelihood of scoring in the top tercile (a score of 34 or greater). Lastly, we found no effect of the CCT on logged per capita household expenditure or on the likelihood of being in the top quartile of per capita expenditure.

Table 2. Intent to Treat Impacts of the CCT on IPV among young women enrolled in HPTN 068

	Treatment	Obs.[a]	Control	Obs.[a]	Risk ratio (95% CI)
Forced sex	58 (2.5%)	2,282	46 (2.2%)	2,062	1.13 (0.75–1.70)
Any physical IPV	473 (18.5%)	2,559	636 (27.8%)	2,290	0.66*** (0.59–0.74)
Individual items					
Slapped or threw something	377 (14.7%)	2,564	519 (22.6%)	2,295	0.65*** (0.57–0.74)
Pushed or shoved	282 (11.0%)	2,564	391 (17.1%)	2,292	0.64*** (0.56–0.74)
Hit with fist/another item	203 (7.9%)	2,563	309 (13.5%)	2,294	0.59*** (0.50–0.69)
Kicked, dragged, or beaten up	198 (7.7%)	2,562	272 (11.9%)	2,293	0.65*** (0.54–0.78)
Choked or burnt	148 (5.8%)	2,561	222 (9.7%)	2,293	0.60*** (0.48–0.73)
Threatened or used gun/another weapon	140 (5.5%)	2,563	205 (8.9%)	2,293	0.61*** (0.49–0.75)
Severity					
Moderate	445 (17.4%)	2,559	591 (25.8%)	2,290	0.67*** (0.60–0.75)
Severe	260 (10.2%)	2,559	367 (16.0%)	2,290	0.63*** (0.54–0.74)

Data are n (%) unless otherwise stated. RRs from GEE log-binomial model adjusted for age.
$^{+}p < 0.10$, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.
[a]Observations over the three follow-up study visits, out of total N of 2,302 study participants (1,209 treatment and 1,093 control) followed up for at least one visit after baseline.

Table 3. Intent to Treat Impacts of the CCT on Hypothesized Mediators among young women enrolled in HPTN 068

	Treatment	Obs.[a]	Control	Obs.[a]	RR, IRR, or Coef. (95% CI)
Sexual debut[b,c]	245 (13.9%)	1,762	250 (16.6%)	1,510	RR 0.83* (0.71–0.98)
Number of sexual partners in the last 12 months (Mean, SD)	0.41 (0.7)	2,574	0.46 (0.8)	2,292	IRR 0.86** (0.78–0.96)
Any sexual partner in last 12 months	841 (33%)	2,574	824 (36%)	2,292	RR 0.90* (0.83–0.99)
Over one sexual partner in last 12 months	147 (5.7%)	2,574	149 (6.3%)	2,292	RR 0.88 (0.68–1.09)
SRPS[d,e] (Mean, SD)	28.6 (7.0)	936	28.6 (6.7)	916	Coef. 0.06 (−0.63–0.75)
High SRPS[e,f]	296 (31.6%)	936	264 (28.8%)	916	RR 1.12 (0.96–1.30)
Log per capita expenditure (Mean, SD)	6.0 (0.7)	2,583	6.0 (0.7)	2,290	Coef. 0.03 (−0.02–0.08)
Top quartile per capita expenditure	670 (26.9%)	2,583	552 (24.1%)	2,290	RR 1.09 (0.97–1.22)

Data are n (%) unless otherwise stated. Estimates from GEE models adjusted for age (sexual debut also adjusts for time dummies).
RR, risk ratio; IRR, incident rate ratio; Coef, coefficient.
$^{+}p < 0.10$, $*p < 0.05$, $**p < 0.01$, $***p < 0.001$.
[a]Observations over the three follow-up study visits, out of total N of 2,302 study participants (1,209 treatment and 1,093 control) followed up for at least one visit after baseline.
[b]Among those who had not debuted before baseline.
[c]Per person-visit.
[d]Sexual Relationship Power Scale, scores ranges from 1 to 36.
[e]Only girls that reported having sex either at some point at that visit or before, or if she reported having a partner after being asked IPV questions.
[f]High SRPS is top tercile (≥34) and compared to low or moderate SRPS score.

To examine causal mediation of the CCT on IPV, we used the three partnership measures that were significantly affected by treatment (sexual debut, any sexual partner and number of sexual partners). Since treatment effects in Table 2 are robust to different specifications of IPV, we used any IPV as our key outcome to analyse mediation. We estimated CDEs for each mediator-outcome pair using the G-computation formula for mediation (Table 4). For each mediator intervention defined in the left column, we show the CDE broken into the absolute risk of IPV (for each arm) and the risk ratio.

Compared to total effect of RR 0.66 (shown in the last column), we find that each mediator intervention additionally lowered the risk of IPV for young women in treatment. The first mediator intervention sets all young women to no sexual debut after baseline resulting in a risk ratio of 0.57, approximately 9 percentage points lower than the total effect. The second row shows the effect of setting all young women in the study to having no sexual partner. This intervention results in the smallest risk ratio (0.53), which is more than 10 percentage points lower than the original total effect. In the last row, we tested a less restrictive mediation scenario by reducing sexual partnerships by 1 (for all those with 1 or more partners). This also reduced the risk of IPV by 7 percentage points (RR 0.59) from total effect. Moreover, for each mediator intervention, we see that the absolute risk of IPV is lower for young women in the treatment group compared to the

Table 4. Controlled direct effects of mediator interventions on physical intimate partner violence using parametric G-computation formula

Mediator intervention	Risk (%) (T = treatment C = control)	Risk ratio (95% CI)	No mediator intervention
No sexual debut	T = 14.8	0.57 (0.48–0.65)	Risk (%)
	C = 26.2		T = 18.5
No sexual partner (past 12 months)	T = 14.8	0.53 (0.46–0.60)	C = 27.8
	C = 27.9		(RR 0.66)
Reduce sexual partners by one (past 12 months)	T = 16.2	0.59 (0.53–0.66)	
	C = 27.4		

Adjusted for age and baseline level of mediator. Binary outcomes estimated using a GEE log-linear model and robust variance. Number of sexual partners estimated using a linear regression model with standard errors clustered at the individual level. Effects estimated from Monte Carlo sample (N = 5,000) with 95% CIs calculated from standard deviations of point estimates.

original risk in the right-hand column (18.5 percent). For young women in the control group, however, the risk is about the same as the original (27.8 percent). Therefore, the interaction of the mediator and treatment is driving the result—intervening on the mediator works to reduce risk of IPV only in combination with the CCT.

4 | DISCUSSION

This study explored how a cash transfer intervention given to young women in South Africa conditional on school attendance reduced the risk of intimate partner violence. We first showed treatment effects were significant for all types of physical violence, but that there was no coinciding effect on sexual violence. The CCT also had significant impact on sexual partnerships including sexual debut by visit, any partner in the last 12 months, and number of partners in the last 12 months. We then used the G-formula for mediation analysis to estimate CDEs for each of these sexual partnership mediators. Our findings indicate that while the intervention had a strong direct effect on physical IPV, it also had a significant interactive effect with sexual partnership behaviours, leading to even lower risks of IPV. While CDE estimates are hypothetical effects, they provide insight into how mediators work and they have the potential to inform policy about how complementary interventions might work using observed effects [35].

This evidence adds to the growing body of literature showing that CCTs can reduce the risk of IPV [18–21]. However, whereas the current evidence focuses on older women who are married or cohabiting with their intimate partner, our study provides new evidence on the effect for adolescent girls and young women still living at home and attending school. Developmentally, this may be important for adolescents' successful transition into adulthood since for most of these young women this is their first relationship, thus setting patterns for experiencing IPV in future relationships. In addition, our results are important because there was concern that the cash could lead to more conflict within relationships and increase risk of IPV [18, 21]. Instead, we provide evidence for the supporting role that economic interventions can have on young women's risk of IPV and potential effect on HIV transmission given the critical intersections of the two.

Despite our finding that the CCT reduced risky sexual behaviours and the link between IPV and HIV in South Africa [5], the CCT intervention did not lead to a parallel reduction in new HIV infections [17]. A likely reason is that the intervention did not lead to differential rates of school attendance between treatment and control groups—it was very high for both groups—and that schooling itself has a protective effect on HIV. Indeed, the study found school attendance itself had a significant effect on HIV incidence [17]. It is also possible that the reductions in sexual debut and partner number were not enough to affect HIV incidence (or to enable discernible differences in incidence) given fairly low rates in both arms during the trial. This is also true for forced sex—sexual violence was much less prevalent compared to physical violence at baseline, which could help explain the null findings.

Besides the inability to link impacts on IPV to HIV incidence, our analysis of mediation pathways could be improved with better measures. For one, the SRPS is only available for women who reported ever having sex. Unlike evidence from other studies linking reductions in IPV to relationship power dynamic changes [20], the CCT does not have an impact on sexual relationship power within current relationships. This may again speak to the point that young women are choosing to not engage in any sexual relationships (which itself could be the ultimate form of sexual relationship power). However, since most young women were still in school and living at home as opposed to cohabiting with partners, potential impacts in an older, married or largely cohabiting population may be different. In addition, despite the fact there was no treatment effect on household expenditures, economic wellbeing likely plays a role since the direct effect on IPV is so robust. Qualitative evidence indicates that the cash had positive effects on young women's feelings of independence and financial empowerment [36]. Therefore, a more universal measure of empowerment could improve our understanding of how the intervention affects young women' attitudes and decision-making.

Despite these limitations, there are noteworthy strengths of the study including the randomized study design and longitudinal data that not only allows for causal estimation of treatment effects but provides stronger causal assumptions for estimation of mediation effects. In addition, we believe our findings have broader generalizability across poor, rural settings in South Africa given the high coverage of other social protection programmes.

5 | CONCLUSIONS

This study is the first to investigate the causal pathways through which a cash transfer programme reduced IPV among young women. In contrast to other studies with older women, we do not find that the cash works through changing power dynamics within existing partnerships but rather the effect was boosted through young women choosing not to engage in sexual partnerships. Furthermore, there is a remaining direct effect of the CCT on physical IPV. In terms of the global development agenda, these results show improved SDG outcomes for gender equality, specifically the reduction in physical violence against women (SDG 5.2.1). But, since there was no effect on HIV incidence (SDG 3.3.1) or sexual violence (also SDG 5.2.1), is not clear that CCTs alone are an effective strategy for HIV prevention for young women in South Africa.

Nonetheless, given the critical intersections of HIV and IPV in high-poverty contexts, this study adds to the growing evidence on the role of social protection in reducing poor young women's risk of HIV [12,13,37]. In the context of South Africa, social protection already reaches many vulnerable groups, including poor adolescents under 18 covered under the Child Support Grant (CSG). Recent evidence has shown that the CSG is similarly protective of HIV risk behaviours in adolescents 18 and under [37,38]. In view of our findings, continued cash payments for young women older than 18 could extend this protective effect, especially considering youth between 18 and 24 in South Africa are regularly still in school or unemployed and this is the age when HIV incidence starts to take off [23]. Extending or expanding existing programmes is clearly not an insignificant policy decision, but greater inclusion of vulnerable young people into social protection schemes could have important implications for HIV prevention and the health of the next generation.

Although our findings come from an experimental intervention, cash transfers play a major role in many SSA governments' social protection schemes [39]. Consequently, these findings illustrate the potential for current social protection programmes in the SSA region to achieve important progress in SDGs, which builds on other recent findings demonstrating how social protection in South Africa is benefiting adolescent across many SDGs [40]. In particular, our results highlight the benefits of combining age and gender-sensitive targeting with structural interventions to achieve the SDG agenda as it relates to adolescent HIV prevention. In this regard, policy-makers across social development and public health ministries would do well to work together to integrate targeted public health interventions for young women into social protection programmes in order to harness the synergistic power of the two and improve SDGs related to poverty, health and gender equality.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

KNK and JKE contributed to data analysis, data interpretation and writing of this manuscript. AP and AS contributed to study design, development of data collection instruments and the protocol, study oversight and implementation, data interpretation, data analysis and writing of this manuscript.CM and KK contributed to study design, development of data collection instruments and the protocol, study oversight and implementation, and editing of this manuscript. RT contributed to the protocol development, study implementation and oversight, and editing of the manuscript. JPH contributed to study design, development of the protocol, data interpretation and editing of this manuscript. JW contributed to data analysis, data interpretation and editing of the manuscript. RW contributed to study implementation and oversight, and editing of the manuscript.

ACKNOWLEDGEMENTS

The authors acknowledge and thank all of the young women and their families who participated in HIV Prevention Trials Network (HPTN) 068 and made the study possible.

FUNDING

The HPTN was provided by the National Institute of Allergy and Infectious Diseases (NIAID), the National Institute of Mental Health (NIMH), and the National Institute on Drug Abuse (NIDA) of the National Institutes of Health (NIH; award numbers UM1AI068619 [HPTN Leadership and Operations Center], UM1AI068617 [HPTN Statistical and Data Management Center], and UM1AI068613 [HPTN Laboratory Center]. The study was also funded under R01MH110186, R01MH087118, and R24 HD050924 to the Carolina Population Center. Research reported in this publication was also supported by the NIAID of the NIH [Award Number T32AI007001]. Additional funding was provided by the Division of Intramural Research, NIAID, and NIH. The Agincourt Health and Socio-Demographic Surveillance System is supported by the School of Public Health University of the Witwatersrand and Medical Research Council, South Africa, and the UK Wellcome Trust (grants 058893/Z/99/A; 069683/Z/02/Z; 085477/Z/08/Z; and 085477/B/08/Z). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

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SUPPORTING INFORMATION

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

Appendix S1 Models used to estimate controlled direct effects.

Grosso A et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25042
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25042/full | https://doi.org/10.1002/jia2.25042

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

HIV risks and needs related to the Sustainable Development Goals among female sex workers who were commercially sexually exploited as children in Lesotho

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Abstract

Introduction: Sustainable Development Goals (SDGs) about gender equality; decent work; and peace, justice, and strong institutions include a focus on eradicating trafficking and sexual exploitation of and violence against women and children. In Lesotho, 86% of women have experienced gender-based violence. In addition, overall HIV prevalence is among the highest globally, and higher among adolescent girls than boys. Moreover, nearly three quarters of female sex workers (FSW) are estimated to be living with HIV in Lesotho. In this context, sexually exploited children may be particularly vulnerable to violence and HIV acquisition risks. This study's objective is to examine the prevalence and correlates of experiencing sexual exploitation as a child among FSW in Lesotho.

Methods: FSW (≥18 years) recruited through respondent-driven sampling in Maseru and Maputsoe from February to September 2014 completed HIV and syphilis testing and an interviewer-administered survey, including a question about the age at which they started providing sex for money. This study examined correlates of experiencing sexual exploitation as a child (<18 years) through multivariable logistic regression analyses for each city, controlling for current age.

Results: Across both cities, 20.0% (142/710) of participants were sexually exploited as children. Among them, 65.5% (93/142) tested positive for HIV and 31.0% (44/142) for syphilis, which was similar to those who started selling sex as adults, after adjusting for current age. Participants who experienced child sexual exploitation were more likely to have been forced to have sex before age 18 than those who started selling sex as adults (Maseru-adjusted odds ratio (aOR): 3.52, 95% Confidence Interval (CI): 1.61 to 7.66, $p = 0.002$; Maputsoe-aOR: 4.39, 95% CI: 1.22 to 15.75, $p = 0.023$). In Maseru, participants who were sexually exploited as children were more likely to avoid carrying condoms to prevent trouble with police (aOR: 3.18, 95% CI: 1.50 to 6.75, $p = 0.003$).

Conclusions: Risk determinants for HIV and violence among sexually exploited children can be studied retrospectively through research with adult FSW. Further research working directly with sexually exploited children will improve understanding of their needs. Preventing commercial sexual exploitation of children and addressing the social and healthcare needs of those who are exploited are necessary to fully achieve SDGs 5, 8 and 16 and an AIDS-Free Generation.

Keywords: AIDS; sex trafficking; human trafficking; sexual violence; physical violence; adolescents

Received 5 October 2017; **Accepted** 11 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

Much of the research on the sexual exploitation of children has been conducted in Asia and the Americas, [1] but studies have increasingly explored this topic in sub-Saharan Africa [2]. For example, studies with adult female sex workers (FSW) in Namibia [3] and Ghana [4] have included questions about the age at which the participant started selling sex, with some women reporting experiencing this before age 18. The sexual exploitation of children in the region has been shown to be associated with socio-demographic factors, violence, positive and negative interactions with police, and risks for HIV and other sexually transmitted infections.

The death of one or both parents has been reported as a reason for selling sex before the age of 18 in qualitative research in Tanzania and Nigeria [5,6]. Limited education may be the cause of or consequence of experiencing sexual exploitation as a child. In a study in West Africa, the majority of sexually exploited children in Niger had completed primary school or less, and in Benin the majority were uneducated or had dropped out of school [7]. Leaving school and inability to afford school fees were also common themes in interviews

with women who were sexually exploited as children in Zimbabwe [8] and Ethiopia [9].

Sexually exploited children are also at risk for experiencing physical and sexual violence. In a multi-country study, compared to FSW who started selling sex as adults, FSW who were sexually exploited as children were more likely to report they had been beaten up in Swaziland and tortured in the Gambia [10]. In Uganda, youth who were sexually exploited had five times higher odds of experiencing any rape than youth who were not exploited [11].

Despite being at risk for experiencing violence, sexually exploited children may be unwilling or unable to report these experiences of violence to the police because they may be arrested for selling sex; however many countries in the region have supportive policies, such as in Cameroon where children do not have to be accompanied by a parent or guardian to press charges [12].

Sexually exploited children are often at elevated risk for sexually transmitted infection (STI) and HIV acquisition, particularly in sub-Saharan Africa due to the high HIV prevalence overall. In Cote d'Ivoire, FSW who were commercially sexually exploited as children were more likely to test positive for HIV than those were not [13]. In Mozambique, a higher percentage of sexually exploited youth had recent STI symptoms than adult FSW [14]. One reason for this elevated risk may be challenges in using condoms. In Kenya, FSW who were sexually exploited as children had lower condom use self-efficacy and were less likely to use condoms consistently with clients [15]. In Burkina Faso, reporting that clients removed condoms or paid more not to use condoms was more common among FSW who were sexually exploited as children than FSW who were not [16].

Ending sexual exploitation and human trafficking is included in the targets of three Sustainable Development Goals (SDGs) [17]: Goal 5, Gender Equality; Goal 8, Decent Work; and Goal 16, Peace, Justice and Strong Institutions. Several SDG indicators are relevant to sexually exploited children and their risks and vulnerabilities. These include the proportion of victims of human trafficking by age and form of exploitation, rape before age 18, intimate partner violence, sexual violence by other types of perpetrators, and reporting violence to the authorities. Table 1 provides more details about these goals, targets and indicators.

The majority of new HIV infections among young people aged 15 to 24 occur in sub-Saharan Africa [22]. In Lesotho, overall HIV prevalence is among the highest globally [23], and four times higher among adolescent girls than boys [24]. Moreover, nearly three quarters of FSW are estimated to be living with HIV in Lesotho [25]. Concurrent with this high HIV prevalence is widespread violence against women; 86% of women have experienced gender-based violence [26], and studies have called for more rigorous evidence on abuse and the exploitation of children. In this context, sexually exploited children may be particularly vulnerable to gender-based violence and HIV acquisition risks. Given the difficulties of obtaining parental consent for research with sexually exploited children, some studies have asked adult FSW about the age at which they started exchanging sex for money [27,28]. The purpose of this study is to examine the prevalence of experiencing commercial sexual exploitation as a child among adult FSW in two cities in Lesotho and its associations with variables related to the SDG indicators.

2 | METHODS

2.1 | Sampling

FSW aged 18 years and older were recruited through respondent-driven sampling (RDS) in Maseru and Maputsoe from February to September 2014 to participate in a survey and biological testing to estimate the prevalence and correlates of HIV infection. The study team chose RDS, a chain-referral peer-driven sampling method, because it can generate representative data for hidden populations [29,30]. Eligibility criteria included being assigned female sex at birth, selling sex within the past six months as a principal source of revenue, providing verbal informed consent in Sesotho or English, having a valid recruitment coupon, and living in Lesotho for at least the past three months. Seven and 12 "seeds" (initial participants) in Maseru and Maputsoe respectively, were each given up to three coupons to recruit other FSW into the study, who were then given up to three coupons after participation until the study ended. The sample size was calculated using the assumption that HIV prevalence among FSW in Lesotho would be similar to levels observed in Swaziland, where the HIV prevalence was 61.0% (95% CI: 52.1 to 69.0) among FSW [31]. The formula used for this study to calculate the sample size was:

$$n = \text{deff}.\frac{P_A(1-P_A)}{\left(se(\hat{P}_A)\right)^2}$$

where n = sample size, deff = design effect and P = assumed prevalence [32]. Assuming HIV prevalence in Lesotho FSW could have been as low as 52%, the lower limit of the 95% confidence interval (CI) of the Swaziland FSW HIV prevalence estimate, design effect of 2, and a standard error no greater than 0.035, it was estimated that a sample size of 408, rounded off to 410, FSW per site was needed. Homophily, the tendency for participants to recruit others like them, was low (under ±0.25). Convergence was achieved for the variable on child sexual exploitation, defined using the criteria that the required number of recruitment waves estimated to reach equilibrium was smaller than the number of waves in the RDS sample.

2.2 | Survey administration and biological testing

The study took place in Maseru in rooms leased at a sexual health clinic, while in Maputsoe space was rented at a hotel connected to a bar where FSW work. Whole blood samples were drawn from participants by trained nurse counsellors for HIV testing using Determine Rapid Test (Alere Waltham, Massachusetts, USA) and syphilis testing using Unigold Rapid Test (Trinity, Ireland), consistent with national guidelines. Participants who tested positive for active syphilis were offered free treatment. Participants who tested positive for HIV were referred to treatment and care services during post-test counselling. Prior to biological testing, participants completed an interviewer-administered survey in a private room. Participants who completed the survey and biological testing were given 20 LSL (approximately 2 USD) as reimbursement for their time, 26 LSL (approximately 2.60 USD) as

Table 1. Definitions and Sustainable Development Goals related to trafficking and sexual exploitation and relevant study variables

Human trafficking includes using force, coercion or payments to a control another person for exploitation, including prostitution and sexual exploitation [18]. Exploitation of a child under 18 years old is considered trafficking even if it does not involve force or coercion.

Child sex trafficking is sometimes defined as recruiting or transporting a child for the purposes of commercial sex, but is also used more generally to refer to the sale of sex with a child under the age of 18 for remuneration to the child or a third person [19].

The sexual exploitation of children, which is sometimes equated with child sex trafficking, includes sale of sex with a child and can also encompass child pornography, child sex tourism, and child marriages [20].

In this paper, the term "sexual exploitation of children" is used to refer only to the sale of sex for money with a child under 18 years old [21].

Goals	Targets	Indicators	Related Survey Questions
5. Achieve gender equality and empower all women and girls	5.2. Eliminate all forms of violence against all women and girls in the public and private spheres, including trafficking and sexual and other types of exploitation	5.2.1. Proportion of ever-partnered women and girls aged 15 years and older subjected to physical, sexual or psychological violence by a current or former intimate partner in the previous 12 months, by form of violence and by age	"Has someone ever physically hurt you (pushed, shoved, slapped, hit, kicked, choked, or otherwise physically hurt you)?" "Who was the person who physically hurt you? I will read you the following options, and please tell me for each one whether this type of person ever beat you up or physically hurt you." • Husband, boyfriend or any current or past non-paying sexual partner
		5.2.2. Proportion of women and girls aged 15 years and older subjected to sexual violence by persons other than an intimate partner in the previous 12 months, by age and place of occurrence	"Has someone ever forced you to have sex when you did not want to? (By forced I mean physically forced, coerced to have sex or penetrated with an object, when you did not want to)." "When was the last time someone forced you to have sex?"
8. Promote sustained, inclusive and sustainable economic growth, full and productive employment and decent work for all	8.7. Take immediate and effective measures to eradicate forced labour, end modern slavery and human trafficking and secure the prohibition and elimination of the worst forms of child labour, including recruitment and use of child soldiers, and by 2025 end child labour in all its forms	8.7.1. Proportion and number of children aged 5 to 17 years engaged in child labour, by sex and age	"Approximately how old were you the first time you provided sexual acts in exchange for money?"
16. Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels	16.1. Significantly reduce all forms of violence and related death rates everywhere	16.1.3 Proportion of population subjected to physical, psychological or sexual violence in the previous 12 months	"Has someone ever physically hurt you (pushed, shoved, slapped, hit, kicked, choked, or otherwise physically hurt you)?" "Approximately how many times has someone physically hurt you in any way in the past 12 months?" "Has someone ever forced you to have sex when you did not want to? (By forced I mean physically forced, coerced to have sex or penetrated with an object, when you did not want to)." "When was the last time someone forced you to have sex?"

Table 1. (*Continued*)

16.2. End abuse, exploitation, trafficking and all forms of violence against and torture of children	16.2.2. Number of victims of human trafficking per 100,000 population, by sex, age and form of exploitation	"What were the reasons you started selling sex? I will read you several possible reasons. For each, please tell me if it was a reason you started selling sex." • I was forced against my will (By forced, I mean physically forced or coerced into selling sex) • Someone talked me into it or pressured me (defined as social pressure. For example, a participant was considering it and someone else heavily encouraged or pushed her into selling sex). "Why do you currently sell sex?" • I am being coerced or forced • Someone is pressuring me to continue selling sex
	16.2.3. Proportion of young women and men aged 18 to 29 years who experienced sexual violence by age 18	"Has someone ever forced you to have sex when you did not want to? (By forced I mean physically forced, coerced to have sex or penetrated with an object, when you did not want to)." "Approximately how old were you the first time someone forced you to have sex? (age in years)"
16.3. Promote the rule of law at the national and international levels and ensure equal access to justice for all	16.3.1. Proportion of victims of violence in the previous 12 months who reported their victimization to competent authorities or other officially recognized conflict resolution mechanisms	"After someone forced you to have sex, who did you tell about this experience? I will read you the following options, and please tell me for each one whether you told this person about the experience(s)." • Uniformed officer (police, military, security officer) "How would you describe your relationship, in general, with police?" (bad, neutral or good) "Have you ever avoided carrying condoms because you were afraid that they might get you in trouble with the police?"

reimbursement for transport, male and/or female condoms, and HIV information materials. Participants also received 20 LSL (about 2 USD) for each eligible participant they recruited and another 26 LSL for transport if they returned to collect their recruiter reimbursement and complete a post-recruitment questionnaire. The Population Services International Research Ethics Board and the National Health Research Ethics Committee of Lesotho approved the study.

The survey was adapted from studies with FSW across sub-Saharan Africa [16,33-37] and pre-tested with FSW community members to ensure that questions were understood in English and Sesotho. Topics included socio-demographic characteristics, human rights violations, sexual behaviour, health service access, mental health, social capital, and reproductive health. Survey data were double-entered using EpiData (Odense, Denmark).

2.3 | Analytical methods

To measure child sexual exploitation, the dependent variable was dichotomized such that those who reported that they exchanged sex for money at any age less than 18 years old were coded as 1 and those who answered any age greater than or equal to 18 years old were coded as 0.

Potential independent variables were considered based on associations with child sexual exploitation in prior studies and guided by the five levels of the modified social ecological model for characterizing HIV risk among key populations [38]: individual, network, community, policy, and stage of the HIV epidemic. The independent variables were also chosen based on their relevance to the SDG indicators. Additional variables in the datasets that were not significantly related to sexual exploitation as a child in bivariate models or in models

adjusting for current age for both cities were considered not to be potential confounders and were excluded as beyond the scope of this paper. For the multivariable models, variables were selected that were applicable to all FSW in the study (rather than, for example, only those who had non-paying partners).

The survey questions from which independent variables related to the SDGs were derived are included in Table 1. In addition, demographic variables included orphanhood (whether at least one of the participant's parents died before she was 18 years old) and education (completed primary school or less). As a structural determinant of HIV risk, a variable indicating whether the participant usually buys all her condoms, gets them for free, both, or neither was included. HIV and syphilis prevalence among participants who were sexually exploited as children and those who were not is also reported.

Correlates of experiencing sexual exploitation as a child were analysed using Stata/SE 14.1 (College Station, TX, USA). Each city's dataset was analysed separately because participants were recruited through separate networks, and the distribution of responses varied substantially by city for the variables of interest. Because missing data were less than six percent, listwise deletion was used. Missing data are indicated in the tables, with denominators adjusted. Participants with missing data on whether they were sexually exploited as children were excluded from the analyses. Factors significantly associated with experiencing child sexual exploitation in bivariate models were entered into multivariable logistic regression models. Due to collinearity, the only physical violence variable included was ever experiencing violence. Because of its relevance to experiencing commercial sexual exploitation before age 18, and due to collinearity, being forced to have sex before age 18 was the only sexual violence variable included. After adjusting for age, HIV status and being orphaned before age 18 were no longer statistically significantly related to experiencing sexual exploitation as a child and were excluded from further multivariable models. The Akaike Information Criterion was used to select the most parsimonious models. All multivariable analyses controlled for age at the time of the survey. Analyses were not adjusted for respondent driven sampling weighting. The variance inflation factor (VIF) was calculated to test multicollinearity. The final model had a mean VIF of 1.37 in Maseru and 2.05 in Maputsoe. The overall multivariable models were significant at the 0.05 level according to the likelihood ratio chi-square statistic. The model predicted 81.8% of the responses correctly in Maseru and 83.8% in Maputsoe. The Pseudo R^2 was 0.20 in Maseru and 0.19 in Maputsoe.

3 | RESULTS

3.1 | Socio-demographics

Characteristics of participants in Maseru, Maputsoe, and the two cities combined (n = 744) are reported in Table 2. As shown in Tables 3 and 4 respectively, the mean age of participants who were sexually exploited as children was about 22 in Maseru and about 24 in Maputsoe at the time of the survey. This was younger than the mean age of participants who were not exploited (Maseru-mean age: 21.9 vs. 25.7, odds ratio (OR): 0.81, 95% CI: 0.75 to 0.87, adjusted odds ratio (aOR): 0.82, 95% CI 0.76 to 0.89; Maputsoe-mean age: 23.9 vs. 30.0, OR: 0.87, 95% CI: 0.82 to 0.92, aOR: 0.87, 95% CI: 0.82 to 0.93). Most participants completed primary school or less. Over three quarters of participants who were sexually exploited as children in Maseru and over 60% in Maputsoe reported at least one parent had died during the participant's childhood. In Maseru, this was more likely than among participants who were not exploited in the bivariate analysis (Table 3, 77.7% vs. 59.5%, OR: 2.37, 95% CI: 1.35 to 4.15).

3.2 | Entry into and reasons for exchanging sex for money

In Maseru and Maputsoe, 22.5% (89/395) and 16.8% (53/315) of FSW started exchanging sex for money before the age of 18 respectively. None who experienced child sexual exploitation said they were initially or currently forced or coerced into selling sex. None who were exploited were *currently* pressured to sell sex, but 28.1% in Maseru and 9.4% in Maputsoe were talked into or pressured to *start* selling sex. FSW who were sexually exploited as children were more likely to have been talked into or pressured to start selling sex than those who were not exploited (Table 3, 28.1% vs. 12.1%, OR: 2.84, 95% CI: 1.60 to 5.05, aOR: 3.11, 95% CI: 1.60 to 6.04).

3.3 | Violence

Over half of women who were exploited from Maseru had been physically assaulted ever and in the past 12 months, but fewer women from Maputsoe reported this. About 19% in both cities had ever been physically assaulted by a non-paying sexual partner. Compared to participants who were not exploited, FSW in Maputsoe who were sexually exploited as children were more likely to have experienced physical violence ever (Table 4, 41.5% vs. 18.3%, OR: 3.16, 95% CI: 1.69 to 5.94, aOR: 2.78, 95% CI: 1.39 to 5.56), in the past 12 months (32.1% vs. 16.0%, OR: 2.47, 95% CI: 1.27 to 4.81), and from an intimate partner (18.9% vs. 7.3%, OR: 2.97, 95% CI: 1.29 to 6.83).

One fifth of participants who were sexually exploited as children in Maputsoe and over half of participants in Maseru had ever been forced to have sex. In Maseru, this was more common than among those who were not exploited (Table 3, 56.2% vs. 37.9%, OR: 2.07, 95% CI: 1.28 to 3.34). In Maseru 23.6% and in Maputsoe 11.3% of those who were exploited were forced to have sex before the age of 18. This was more common among those who were sexually exploited as children than among those who were not (Maseru-23.6% vs. 5.9%, OR: 4.94, 95% CI: 2.50 to 9.78, aOR: 3.52, 95% CI: 1.61 to 7.66; Maputsoe-11.3% vs. 3.1%, OR: 4.04, 95% CI: 1.34 to 12.17, aOR: 4.39, 95% CI: 1.22 to 15.75). Nine percent of FSW who were exploited in Maseru and none in Maputsoe reported at least one incident of being forced to have sex by a non-paying sexual partner in their lifetime. Twelve percent in Maseru and 36.4% in Maputsoe ever reported being forced to have sex by any perpetrator to the police or authorities.

3.4 | Relationship with authorities

Most participants who were commercially sexually exploited as children in Maseru had a bad relationship with police,

Table 2. Characteristics of female sex workers recruited through respondent-driven sampling in Lesotho, 2014

	Maseru	Maputsoe	Combined
Socio-demographics			
Age at time of survey (mean)	24.8	29.1	26.8
Education			
Completed primary school or less	56.7% (232/409)	63.1% (210/333)	59.6% (442/742)
Orphaned before age 18			
At least one parent died	64.6% (255/395)	52.0% (169/325)	58.9% (424/720)
Entry into and reasons for selling sex			
Started selling sex <18	22.5% (89/395)	16.8% (53/315)	20.0% (142/710)
Was forced or coerced to start selling sex	0.5% (2/410)	0.0% (0/333)	0.3% (2/743)
Was talked into or pressured to start selling sex	16.8% (69/410)	9.3% (31/333)	13.5% (100/743)
Currently forced or coerced to sell sex	0.2% (1/410)	0.0% (0/333)	0.1% (1/743)
Currently talked into or pressured to sell sex	0.2% (1/410)	0.0% (0/333)	0.1% (1/743)
Experiences of violence			
Experienced physical violence ever	58.5% (240/410)	22.5% (75/333)	42.4% (315/743)
Experienced physical violence from an intimate partner ever	18.6% (76/409)	9.0% (30/333)	14.3% (106/742)
Experienced physical violence from a uniformed officer (police, military, security officer) ever	19.1% (78/409)	0.9% (3/333)	10.9% (81/742)
Experienced physical violence in the past 12 months	53.2% (218/410)	18.3% (61/333)	37.6% (279/743)
Was ever forced to have sex	42.0% (172/410)	15.1% (50/332)	29.9% (222/742)
Was forced to have sex before age 18	10.2% (42/410)	4.8% (16/332)	7.8% (58/742)
Was ever forced to have sex by an intimate partner	7.1% (29/410)	3.3% (11/332)	5.4% (40/742)
Was ever forced to have sex by a uniformed officer	7.3% (30/410)	0.3% (1/332)	4.2% (31/742)
Ever told uniformed officer about being raped	12.2% (21/172)	20.0% (10/50)	14.0% (31/222)
Relationship with authorities			
Relationship with police			
Neutral	18.8% (77/409)	16.8% (56/333)	17.9% (133/742)
Bad	48.2% (197/409)	5.7% (19/333)	29.1% (216/742)
Good	33.0% (135/409)	77.5% (258/333)	53.0% (393/742)
Ever avoided carrying condoms out of fear of trouble with police	12.0% (49/410)	1.5% (5/333)	7.3% (54/743)
Sexually transmitted infections and access to prevention			
Condom acquisition			
Buy all	9.8% (40/410)	3.9% (13/333)	7.1% (53/743)
Get all for free	73.9% (303/410)	87.1% (290/333)	79.8% (593/743)
Buy and get for free	15.6% (64/410)	8.1% (27/333)	12.2% (91/743)
Neither	0.7% (3/410)	0.9% (3/333)	0.8% (6/743)
Laboratory results			
Living with HIV	73.1% (299/409)	70.4% (235/334)	71.9% (534/743)
Active syphilis	27.9% (114/409)	26.4% (88/334)	27.2% (202/743)

while most in Maputsoe had a good relationship with police. In Maputsoe, compared to those who were not exploited they were less likely to have a neutral relationship with police (Table 4, 5.7% vs. 20.2%) compared to a bad (OR: 7.36, 95% CI: 1.54 to 35.12, aOR: 9.99, 95% CI: 1.78 to 56.00) or good relationship (OR: 4.04, 95% CI: 1.21 to 13.50, aOR: 6.34, 95% CI: 1.64 to 24.49). One fifth of participants who were exploited in Maseru and less than 2% in Maputsoe avoided carrying condoms due to potential police conflict. In Maseru this was more likely than among those who were not exploited (Table 3, 20.2% vs. 10.1%, OR: 2.25, 95% CI: 1.19 to 4.25, aOR: 3.18, 95% CI: 1.50 to 6.75).

3.5 | HIV and STI risks

Over 60% of FSW in Maseru and over 70% in Maputsoe who were exploited tested positive for HIV. In Maseru this was lower than the HIV prevalence among those who were not exploited (Table 3, 61.8% vs. 77.1%, OR: 0.48, 95% CI: 0.29 to 0.80). However this was no longer statistically significant after adjusting for current age. Nearly one third of those exploited in Maseru and over one quarter in Maputsoe had active syphilis. Most participants received all their condoms for free. In Maseru, FSW who were exploited as children were more likely to have bought all their condoms (Table 3, 20.2% vs. 7.2%) rather than getting them all for free (OR: 0.30, 95%

Table 3. Prevalence and correlates of experiencing sexual exploitation as a child among female sex workers in Maseru, Lesotho

	Started selling sex <18 (22.5%, 89/395)	Started selling sex 18+ (77.5%, 306/395)	OR (95% CI)	*p*	aOR[a] (95% CI)	*p*
Socio-demographics						
Age at time of survey (mean)	21.9	25.7	**0.81 (0.75 to 0.87)**	**<0.001**	**0.81 (0.75 to 0.88)**	**<0.001**
Education						
Completed primary school or less	56.2% (50/89)	56.4% (172/305)	0.99 (0.62 to 1.60)	0.971	-	-
Orphaned before age 18						
At least one parent died	77.7% (66/85)	59.5% (176/296)	**2.37 (1.35 to 4.15)**	**0.003**	-	-
Entry into and reasons for selling sex						
Was forced or coerced to start selling sex	0.0% (0/89)	0.7% (2/306)	-	-	-	-
Was talked into or pressured to start selling sex	28.1% (25/89)	12.1% (37/306)	**2.84 (1.60 to 5.05)**	**<0.001**	**3.11 (1.60 to 6.04)**	**0.001**
Currently forced or coerced to sell sex	0.0% (0/89)	0.3% (1/306)	-	-	-	-
Currently talked into or pressured to sell sex	0.0% (0/89)	0.3% (1/306)	-	-	-	-
Experiences of violence						
Experienced physical violence ever	60.7% (54/89)	58.8% (180/306)	1.08 (0.67 to 1.75)	0.755	-	-
Experienced physical violence from an intimate partner ever	19.1% (17/89)	18.4% (56/305)	1.05 (0.57 to 1.92)	0.874	-	-
Experienced physical violence from a uniformed officer (police, military, security officer) ever	18.0% (16/89)	20.0% (61/305)	0.88 (0.48 to 1.61)	0.672	-	-
Experienced physical violence in the past 12 months	53.9% (48/89)	53.9% (165/306)	1.00 (0.62 to 1.61)	0.999	-	-
Was ever forced to have sex	56.2% (50/89)	38.2% (117/306)	**2.07 (1.28 to 3.34)**	**0.003**	-	-
Was forced to have sex before age 18	23.6% (21/89)	5.9% (18/306)	**4.94 (2.50 to 9.78)**	**<0.001**	**3.52 (1.61 to 7.66)**	**0.002**
Was ever forced to have sex by an intimate partner	9.0% (8/89)	6.5% (20/306)	1.41 (0.60 to 3.33)	0.429	-	-
Was ever forced to have sex by a uniformed officer	6.7% (6/89)	7.8% (24/306)	0.85 (0.34 to 2.15)	0.730	-	-
Ever told uniformed officer about being raped	12.0% (6/50)	12.8% (15/116)	0.93 (0.34 to 2.55)	0.884	-	-
Relationship with authorities						
Relationship with police						
Neutral	19.1% (17/89)	18.4% (56/305)	Ref.	Ref.	Ref.	Ref.
Bad	52.8% (47/89)	47.5% (145/305)	1.07 (0.57 to 2.01)	0.840	-	-
Good	28.1% (25/89)	34.1% (104/305)	0.79 (0.39 to 1.59)	0.511	-	-
Ever avoided carrying condoms out of fear of trouble with police	20.2% (18/89)	10.1% (31/306)	**2.25 (1.19 to 4.25)**	**0.013**	**3.18 (1.50 to 6.75)**	**0.003**
Sexually transmitted infections and access to prevention						
Condom acquisition						
Buy all	20.2% (18/89)	7.2% (22/306)	Ref.	Ref.	Ref.	Ref.
Get all for free	65.2% (58/89)	76.1% (233/306)	**0.30 (0.15 to 0.60)**	**0.001**	**0.35 (0.16 to 0.75)**	**0.007**
Buy and get for free	13.5% (12/89)	16.0% (49/306)	**0.30 (0.12 to 0.73)**	**0.008**	**0.28 (0.10 to 0.76)**	**0.012**
Neither	1.1% (1/89)	0.7% (2/306)	0.61 (0.05 to 7.30)	0.697	0.50 (0.03 to 7.14)	0.608
Laboratory results						
Living with HIV	61.8% (55/89)	77.1% (235/305)	**0.48 (0.29 to 0.80)**	0.005	-	-
Active syphilis	32.6% (29/89)	26.2% (80/305)	1.36 (0.82 to 2.27)	0.239	-	-

[a]Multivariable logistic regression analyses included the following variables: age at the time of the survey, was talked into or pressured to start selling sex, was ever forced to have sex before age 18, ever avoided carrying condoms out of fear of trouble with police, and condom acquisition. aOR, adjusted odds ratio. The bold values are statistically significant ($p<0.05$).

Table 4. Prevalence and correlates of experiencing sexual exploitation as a child among female sex workers in Maputsoe, Lesotho

	Started selling sex <18 (16.8%, 53/315)	Started selling sex 18+ (83.2%, 262/315)	OR (95% CI)	*p*	aOR[a] (95% CI)	*p*
Socio-demographics						
Age at time of survey (mean)	23.9	30.0	**0.87 (0.82 to 0.92)**	**<0.001**	**0.87 (0.82 to 0.93)**	**<0.001**
Education						
Completed primary school or less	62.3% (33/53)	63.7% (167/262)	0.94 (0.51 to 1.73)	0.839	-	-
Orphaned before age 18						
At least one parent died	61.5% (32/52)	48.6% (124/255)	1.69 (0.92 to 3.11)	0.092	-	-
Entry into and reasons for selling sex						
Was forced or coerced to start selling sex	0.0% (0/53)	0.0% (0/262)	-	-	-	-
Was talked into or pressured to start selling sex	9.4% (5/53)	9.5% (25/262)	0.99 (0.36 to 2.71)	0.981	-	-
Currently forced or coerced to sell sex	0.0% (0/53)	0.0% (0/262)	-	-	-	-
Currently talked into or pressured to sell sex	0.0% (0/53)	0.0% (0/262)	-	-	-	-
Experiences of violence						
Experienced physical violence ever	41.5% (22/53)	18.3% (48/262)	**3.16 (1.69 to 5.94)**	**<0.001**	**2.78 (1.39 to 5.56)**	**0.004**
Experienced physical violence from an intimate partner ever	18.9% (10/53)	7.3% (19/262)	**2.97 (1.29 to 6.83)**	**0.010**	-	-
Experienced physical violence from a uniformed officer (police, military, security officer) ever	1.9% (1/53)	0.8% (2/262)	2.50 (0.22 to 28.08)	0.458	-	-
Experienced physical violence in the past 12 months	32.1% (17/53)	16.0% (42/262)	**2.47 (1.27 to 4.81)**	**0.008**	-	-
Was ever forced to have sex	20.8% (11/53)	13.0% (34/261)	1.75 (0.82 to 3.72)	0.147	-	-
Was forced to have sex before age 18	11.3% (6/53)	3.1% (8/261)	**4.04 (1.34 to 12.17)**	**0.013**	**4.39 (1.22 to 15.75)**	**0.023**
Was ever forced to have sex by an intimate partner	0.0% (0/53)	3.5% (9/261)	-	-	-	-
Was ever forced to have sex by a uniformed officer	0.0% (0/53)	0.4% (1/261)	-	-	-	-
Ever told uniformed officer about being raped	36.4% (4/11)	17.7% (6/34)	2.67 (0.59 to 12.10)	0.204	-	-
Relationship with authorities						
Relationship with police						
Neutral	5.7% (3/53)	20.2% (53/262)	Ref.	Ref.	Ref.	Ref.
Bad	9.4% (5/53)	4.6% (12/262)	**7.36 (1.54 to 35.12)**	**0.012**	**9.99 (1.78 to 56.00)**	**0.009**
Good	84.9% (45/53)	75.2% (197/262)	**4.04 (1.21 to 13.50)**	**0.024**	**6.34 (1.64 to 24.49)**	**0.007**
Ever avoided carrying condoms out of fear of trouble with police	1.9% (1/53)	1.5% (4/262)	1.24 (0.14 to 11.32)	0.849	-	-
Sexually transmitted infections and access to prevention						
Condom acquisition						
Buy all	3.8% (2/53)	4.2% (11/262)	Ref.	Ref.	Ref.	Ref.
Get all for free	84.9% (45/53)	87.4% (229/262)	1.08 (0.23 to 5.04)	0.921	-	-
Buy and get for free	11.3% (6/53)	7.3% (19/262)	1.74 (0.30 to 10.14)	0.540	-	-
Neither	0.0% (0/53)	1.2% (3/262)	-	-	-	-

Table 4. (*Continued*)

	Started selling sex <18 (16.8%, 53/315)	Started selling sex 18+ (83.2%, 262/315)	OR (95% CI)	*p*	aOR[a] (95% CI)	*p*
Laboratory results						
Living with HIV	71.7% (38/53)	69.5% (182/262)	1.11 (0.58 to 2.14)	0.747	-	-
Active syphilis	28.3% (15/53)	25.6% (67/262)	1.15 (0.59 to 2.22)	0.680	-	-

[a]Multivariable logistic regression analyses included the following variables: age at time of survey, experienced physical violence ever, was ever forced to have sex before age 18, and relationship with police. aOR, adjusted odds ratio.
The bold values are statistically significant ($p<0.05$).

CI: 0.15 to 0.60, aOR: 0.35, 95% CI: 0.16 to 0.75) or buying some and getting some for free (OR: 0.30, 95% CI: 0.12 to 0.73, aOR: 0.28, 95% CI: 0.10 to 0.76).

4 | DISCUSSION

In this study, 20.0% (142/710) of FSW study participants sampled in Maseru and Maputsoe, Lesotho were sexually exploited as children. This is comparable to estimates from Kenya [15,39], Mozambique [14], and Sudan [40]. HIV prevalence was extraordinarily high among this sample of FSW in Lesotho compared to that reported in other settings.

In this study, many FSW who were exploited as children had ever and recently experienced physical and sexual violence from intimate partners and others, which are outcomes that are related to indicators 5.2.1 and 5.2.2. Violence has been shown to be associated with HIV risk [35,37]. Addressing targets of SDG 5 could potentially reduce sexual exploitation of children, violence and adolescent HIV. Given the increased attention to sex trafficking in the current United States presidential administration, concurrent with proposed reductions in funds through the President's Emergency Plan for AIDS Relief, framing requests for resource allocation for reducing sexual exploitation of children as also addressing HIV or vice versa may be a practical strategy in the current funding environment.

Many women in this study, regardless of whether they experienced sexual exploitation as children, had been orphaned and had low education, which may have contributed to their entry into the sex trade. In Maseru, those who were sexually exploited as children were more likely to say they were talked into or pressured to sell sex than those who started as adults. It has been posited that, despite the higher education levels of girls than boys in Lesotho, girls who are orphaned (including those whose parents died of AIDS) may drop out of school in order to financially support their families, including some through selling sex [41]. Ending the HIV epidemic, which is part of SDG Target 3.3, may have the additional effect of reducing the number of children orphaned due to AIDS, which may in turn reduce the number of sexually exploited children who are vulnerable to HIV. In this way, HIV programming can contribute to and benefit from the SDG agenda in a bi-directional way. Addressing the economic and educational needs of orphans and vulnerable children could contribute toward achieving Target 8.7 (eliminating the worst forms of child labour) and reduce the HIV risks associated with selling sex at a young age. Cash transfers and social support have been found to reduce transactional sex among adolescent girls elsewhere in sub-Saharan Africa and could be considered for preventing the commercial sexual exploitation of girls in Lesotho [42]. To mitigate the effects of child sexual exploitation, other programmes in Zimbabwe have provided health education and services bringing together resources from programmes for FSW and programmes for adolescents [43].

The relatively low percentage of participants in this study who reported to police that they had been raped may be related to the finding that bad relationships with police and fear of trouble with police due to carrying condoms disproportionally affect women who started selling sex as minors. However, women who were experienced child sexual exploitation who reported a good relationship with police may have been viewed by officers as "trafficking victims" rather than "sex workers" and thus perceived as more worthy of support [44]. Increased protection of these women and decreased enforcement of laws prohibiting selling sex represent an important component of a comprehensive response to decrease significant HIV acquisition and transmission risks observed here and may contribute toward improvements in SDG Indicator 16.3.1.

4.1 | Limitations

This study's methods have some limitations. This is a secondary analysis, and sample size calculations were based on HIV prevalence rather than child sexual exploitation or other variables in these models. However using the same formula, the sample size was greater than the minimum required (Maseru = 282, Maputsoe = 226) to detect the prevalence of experiencing child sexual exploitation observed here. The data are cross-sectional, and causal inferences cannot be made. The study data are from 2014, and no follow-up surveys have been conducted (as is the case with other studies of sexual health in Lesotho, including the Demographic and Health Surveys). However since many of this study's measures were of lifetime experiences (e.g. ever experiencing physical violence), and most participants had been selling sex for three years or more, these results are still potentially relevant in 2017. Self-reported data may be subject to inaccurate recall and social desirability bias. Offering money for recruitment may have resulted in oversampling of lower income FSW. This may skew the results, particularly related to buying condoms or receiving them for free. Male sex workers were not included, therefore this research does not reflect sexual exploitation experiences among boys [45,46]. The age at which participants acquired HIV is unknown. Participants were not asked

whether they would describe their experiences as minors selling sex as exploitation or trafficking [5]. The language used to describe this topic is challenging. The term commercially sexually exploited rather than minors who sell sex was chosen for this paper based on feedback from reviewers and international guidelines. The study participants are adults, and their experiences differ from those who were commercially sexually exploited as children and did not continue to sell sex after age 18. Understanding the experiences of sexually exploited children necessitates overcoming restrictions on minors participating in studies without parental consent and using a trauma-informed research approach to reach this hidden and vulnerable population. Despite these limitations, this study provides evidence of the commercial sexual exploitation of children in an understudied region with high HIV prevalence.

5 | CONCLUSIONS

This study's results indicate that the commercial sexual exploitation of children is prevalent in Maseru and Maputsoe, Lesotho. Experiencing child sexual exploitation in this setting is related to experiencing violence and legal and economic barriers to condom use. Funders of HIV prevention services have given increased attention to understanding specific vulnerabilities among adolescent girls [47]. Sexually exploited children are a very vulnerable group whose determinants of risk can be studied retrospectively through research with adult FSW. Further research (where legally and ethically appropriate) with sexually exploited children is needed to overcome limitations of research with adults including inaccurate recall and survival bias. Addressing the issue of commercial sexual exploitation of children is necessary to achieve the targets of the SDGs and an AIDS-free generation.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

SB, TM, JN, NMN, NT and AG collaborated on the design of the study. AG and SB analyzed the data and wrote the paper. All authors provided critical intellectual input into the interpretation of results.

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Gleeson HS et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25061
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25061/full | https://doi.org/10.1002/jia2.25061

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

COMMENTARY

Ending AIDS by 2030: the importance of an interlinked approach and meaningful youth leadership

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Abstract

Introduction: This commentary by authors from the Adolescent HIV Treatment Coalition calls for action to improve advocacy and service delivery for young people by leveraging the interlinkages between HIV and the broader development agenda. The 2030 Agenda for Sustainable Development includes target 3.3 on ending the AIDS epidemic by 2030, and along with the 2016 Political Declaration on HIV and AIDS, this has led to a global renewal of political commitment to the HIV response. However, young people are still being left behind, and to provide an equitable and sustainable response to HIV we must ensure that we are meeting the needs of the 3.9 million young people living with HIV, and the millions more at risk.

Discussion: While HIV has its own target within the 2030 Agenda, efforts to end AIDS are inextricable from other goals and targets, such as on poverty eradication, education, gender equality and peace. To tackle HIV we must work beyond target 3.3 and provide a comprehensive response that addresses the underlying structural inequalities that impact adolescents and young people, ensuring that we enable the meaningful engagement of youth and adolescents as partners and leaders of sustainable development and the HIV response. Finally, it is necessary to collect better disaggregated data and evidence on the HIV epidemic among adolescents, as well as on best practices for supporting them.

Conclusions: Ending the AIDS epidemic among adolescents and young people (aged 10 to 24) by 2030 is possible. However, it requires an integrated, multi-sectoral response to HIV which pays attention to the social determinants that put adolescents at risk and fuel the epidemic. Positioning efforts to end AIDS among young people within the broader 2030 Agenda and building youth leadership will contribute to building a more healthy, equitable and sustainable society for all.

Keywords: youth leadership; SDGs; interlinkages; participation; HIV; adolescents

Received 15 May 2017; **Accepted** 28 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

In 2015, UN Member States adopted the 2030 Agenda for Sustainable Development, a complex and ambitious human rights-based framework with 17 Sustainable Development Goals (SDGs) and 169 corresponding targets which will drive global priorities until 2030 [1]. Target 3.3 calls for the end of the AIDS epidemic, and builds on the significant progress made under the Millennium Development Goals, which reduced new HIV infections by 40 per cent from 2000 to 2013 [2]. However, inequalities remain, and women, young people and key populations are disproportionately affected. In 2015, there were 250,000 new HIV infections among adolescents, two thirds of which were among adolescent girls [3]. Treatment coverage has been one of the HIV response's biggest successes: while just 375,000 people living with HIV were on antiretroviral therapy (ART) in 2003 [2], this had reached 19.5 million by 2016 [4]. However, progress for young people aged 15 to 24 still lags behind, and this group is less likely to be diagnosed or on treatment than adults [5].

There is growing evidence that medical interventions alone are not sufficient to tackle HIV [6]. Efforts to end AIDS must address the structural barriers which restrict access to treatment and care for the 3.9 million young people aged 15 to 24 living with HIV [4], as well to prevention services for the millions more at risk. This especially includes harmful gender norms which systematically disadvantage women and restrict them from exercising their rights. In this commentary, authors from the Adolescent HIV Treatment Coalition argue that progress in the HIV response for young people can be improved by leveraging the links between HIV and other SDG targets on poverty eradication, education, health, gender equality, and peace and justice. Most importantly, we affirm the right of young people to actively participate in decisions that affect their lives, and emphasize the importance of involving young people, especially those living with and most affected by HIV, at all levels of the HIV response and in SDG implementation. Finally, we call for better data and evidence on how the HIV epidemic impacts young people, and on the best

practices to support them, to ensure effective and sustainable programming.

2 | DISCUSSION

Young people do not live single-issue lives, and their access to HIV information and services is intimately connected to social, political and economic factors. The SDGs are "integrated and indivisible" from each other [1], and in our programming we must strive to see HIV and target 3.3 within a broader lens of social, economic and environmental development. Many SDG targets can support progress towards the HIV response and the 2030 Agenda, and interlinked advocacy and programming has the potential to benefit both simultaneously (Table 1).

Eradicating poverty is highlighted in the preamble of the 2030 Agenda as "an indispensable requirement for sustainable development," and is a prerequisite to improving health [1]. Poverty and HIV have a complex and bi-directional relationship; both are influenced by the same systemic inequalities and power dynamics. Healthcare services, schools and sanitation are often inaccessible for people living in poverty, who may be living in remote or conflict areas [7]. Poverty disproportionately affects women, who are less likely than men to participate in the labour market, and shoulder the majority of unpaid care work [8]. Poverty can also be a driver of transactional sex – the exchanging of sex for material goods including

Table 1. Select SDG targets that connect to the HIV response [1]

Goal	Selected target(s)
1: End poverty in all its forms everywhere	1.3: Implement nationally appropriate social protection systems and measures for all
3: Ensure healthy lives and promote wellbeing for all at all ages	3.3: End the epidemics of AIDS, tuberculosis, malaria and neglected tropical diseases and combat hepatitis, water-borne diseases and other communicable diseases
	3.7: Ensure universal access to sexual and reproductive healthcare services, including for family planning, information and education
4: Ensure inclusive and equitable quality education and promote lifelong learning opportunities for all	4.1: Ensure that all girls and boys complete free, equitable and quality primary and secondary education
	4.7: Ensure that all learners acquire the knowledge and skills needed to promote sustainable development, including, among others, through education for sustainable development and sustainable lifestyles, human rights, gender equality, promotion of a culture of peace and non-violence
5: Achieve gender equality and empower all women and girls	5.1: End all forms of discrimination against all women and girls everywhere
	5.3: Eliminate all harmful practices, such as child, early and forced marriage and female genital mutilation
	5.6: Ensure universal access to sexual and reproductive health and reproductive rights
10: Reduce inequality within and among countries	10.2: Empower and promote the social, economic and political inclusion of all, irrespective of age, sex, disability, race, ethnicity, origin, religion or economic or other status
	10.3: Ensure equal opportunity and reduce inequalities of outcome, including by eliminating discriminatory laws, policies and practices and promoting appropriate legislation, policies and action in this regard
16: Promote peaceful and inclusive societies for sustainable development, provide access to justice for all and build effective, accountable and inclusive institutions at all levels	16.6: Develop effective, accountable and transparent institutions at all levels
	16.7: Ensure responsive, inclusive, participatory and representative decision making at all levels
17: Strengthen the means of implementation and revitalize the Global Partnership for Sustainable Development	17.18: Enhance capacity-building support to developing countries to increase significantly the availability of high-quality, timely and reliable data disaggregated by income, gender, age, race, ethnicity, migratory status, disability, geographic location and other characteristics relevant in national contexts

N.B. targets have been paraphrased. SDG, Sustainable Development Goals.

food, gifts and cash – which in turn increases the risk of HIV acquisition [9].

Social protection systems, which attempt to reduce social and economic vulnerability of the most marginalized groups, further progress towards target 1.3, and can reduce HIV risk behaviours [10], as well as improve adherence to ART for adolescents [11]. While cash transfers alone may have some impact on HIV risk, combining cash with "care" interventions – psychosocial support, such as from parents or teachers – more effectively reduce HIV risk for male and female adolescents [12-15]. Social protection systems have been shown to improve adolescent health outcomes across 12 SDG indicators, spanning the goals on hunger, health, education, gender equality and peaceful societies [10]. There is clear potential for organizations working on poverty reduction to use social protection interventions to support the achievement of target 3.3 for adolescents by reducing HIV risk behaviours and increasing treatment adherence.

Links between HIV and sexual and reproductive health and rights (SRHR), covered by targets 3.7 and 5.6, are widely acknowledged. Poor sexual health has many of the same structural drivers as HIV, including gender-based violence, inequality and criminalization of behaviours including same-sex relationships, sex work and drug use [16]. Bi-directional integration of HIV and SRHR programmes can lead to increased uptake of services, increased condom use, better HIV testing outcomes and reduction in HIV-related stigma, as well increasing cost-effectiveness [17]. Integration of HIV services into maternal health and family planning services may also be a useful entry point for women [18,19]. For young people, integrating HIV and SRHR services has been shown to improve health outcomes due to increased uptake of services, the ability to access multiple services at one time, and improved healthcare provider attitudes [20]. Targets 3.3 and 3.7 should be tackled in tandem with one another, understanding that young people's access to SRH and family planning services can be improved by combining these services with HIV prevention, treatment and support.

Strengthening education systems under SDG 4 can have significant impacts on HIV. Pettifor et al. showed that young women who had missed a school grade or who had missed more than 4 days of school in the last month were significantly more likely to be living with HIV than those who had not, indicating that remaining in school can protect young girls against HIV infection [21]. There is also evidence that this effect goes beyond the individual, with a study from Zambia showing that increased educational attainment at neighbourhood level was linked to lower HIV prevalence among young women [22]. Formal education is a key pathway to economic empowerment for young women and girls, contributing to higher self-esteem, increased uptake of SRHR services, and delayed marriage and childbirth [23,24]. However, there are immense economic and social barriers that affect school attendance, especially for young girls who may be forced into early marriage or domestic work. To end the HIV epidemic among adolescents and youth, investments in education, and in addressing the structural barriers that keep young girls out of school, are therefore critical.

Despite the fact that AIDS is a leading cause of death for young people globally, education on HIV is dangerously inadequate. Only 36% of young men and 30% of young women aged 15 to 24 have comprehensive knowledge of HIV and how to prevent it [5]. Comprehensive sexuality education (CSE) is a crucial intervention for the HIV response, which can support progress towards targets 3.3, 3.7 and 4.7. CSE can contribute to reducing sexually transmitted infections (including HIV) and unintended pregnancy, increasing condom use, increasing self-esteem, and promoting gender equality and more equitable social norms, which in turn can improve health outcomes [25]. We must expand access to CSE, in particular for young women and girls, key populations and out-of-school youth, as this is a key pathway to prevent HIV, reduce HIV stigma and link young people to care and support. Engaging young people in the design, implementation and evaluation of CSE programmes can ensure that material is taught in age-appropriate, culturally sensitive ways, which adequately meet the needs of young people.

It will be impossible to end AIDS without addressing Goal 5 on gender inequality, a primary structural driver of the epidemic. Patriarchal gender norms, cultural beliefs and unequal power dynamics leave women with limited economic opportunities, dependent on male partners, and frequently subjected to intimidation and violence [24]. Women are often unable to make decisions related to their SRHR, and in some cases discriminatory spousal consent laws prevent women from independently accessing SRH or HIV care [26]. Almost a third of women worldwide have experienced physical or sexual violence by a partner, and women who have been abused by their partners are more likely to acquire HIV compared to women who have not experienced abuse [27].

Globally, around 700 million women alive today were married before they were 18, with almost a third of those married before they were 15 [28]. Girls forced into early marriage have restricted access to education and employment, and usually do not have the power to negotiate safe sex, increasing their risk and vulnerability to HIV and other STIs [28,29]. Transgender women may be more likely to experience intimate partner violence [30] and are almost 49 times more likely to acquire HIV [31], yet are often left out of programming and decision-making. Gender equality for women and for transgender, intersex and non-binary people is central to ending the AIDS epidemic, and the importance of tackling these gendered barriers to sexual and reproductive health information and services cannot be overstated. Achieving either Goal 3 or 5 for young people will be impossible without significant progress in the other, and HIV programming must understand how gender inequalities influence the HIV epidemic, and how women and girls seek out HIV prevention, testing and treatment services.

Service delivery, advocacy and programming for young people must take place within an enabling legal and policy environment that recognizes young people's right to live free from violence and discrimination, and to safely exercise their rights, including their reproductive rights. Progressive laws, which protect human rights and ensure access to clinical care and other forms of support, are necessary to end the HIV epidemic. Target 10.3 calls for the elimination of discriminatory laws and policies to reduce inequalities of outcome. In 72 countries, young people under a certain age must seek parental consent before accessing one or more SRHR service [26]. Such policies have been widely condemned by the global health community, including the Committee on the Rights of

the Child, and act as a significant barrier to young people's access to care. Globally, 44% of new HIV infections occur in key populations – sex workers, people who inject drugs, transgender people and men who have sex with men – and their sexual partners [5]. Criminalization of behaviours like sex work and drug use perpetuates stigma and restricts uptake of services. HIV programming should therefore include political advocacy at the highest levels to repeal and reform all laws that restrict these rights, and also address target 16.6 to strengthen justice systems and improve young people's access to formal redress and accountability mechanisms for rights violations.

Target 16.7 calls for inclusive, representative and decision-making at all levels – and this includes in the design, implementation and monitoring of HIV interventions. As we work towards ending the HIV epidemic for adolescents and young people, it is our responsibility to use a bottom-up approach, ensuring that advocacy and programming reflects the voices of young people who are most at risk of HIV. Meaningful youth engagement in design and delivery of HIV interventions can lead to increased acceptance from other young people, as well as higher levels of uptake and effectiveness [31]. It also fulfils young people's right under the Convention on the Rights of the Child to freely express their views on topics that affect them, and to have those views listened to.

In 2010, the Youth Civil Society Working Group of the UK Department for International Development in conjunction with other civil society organizations developed the "three-lens" approach to youth participation, which articulates three dimensions of working with young people to ensure effective, sustainable development programmes (Figure 1). Good practice participation considers all three lenses and is implemented throughout the lifecycle of development. Working *for* youth as beneficiaries (the first lens) sets the scene for working *with* youth as partners (the second lens), where young people work collaboratively throughout the intervention in a supporting role. Ultimately, we must aim to equip young people with the skills and resources to design and implement programmes which are bottom-up and youth-led (the third lens). This includes technical as well as financial support for community-led and youth-led service delivery.

Establishing mechanisms for sustainable and meaningful youth engagement in development furthers global progress towards targets 16.7 and target 10.2 on political inclusion, while also supporting the achievement of target 3.3 in a comprehensive and collaborative way. We must pay particular attention to facilitating participation of young people living with, and most affected by, HIV, including adolescent girls and young women, LGBTI people, people with disabilities and migrants, who are further excluded from participating in decision making. Efforts should be made to fit engagement opportunities into the daily lives of young people, for example at schools, clinics and community centres.

The 17th and final SDG focuses on the means of implementation of the 2030 Agenda, and is an overarching goal which draws attention to the need for sustainable financing, strong cross-sector partnerships and capacity-building, among other systemic issues. Here we particularly note target 17.18, on "high-quality, timely and reliable" disaggregated data. We will not end AIDS among young people without an accurate and comprehensive picture of what is going on in young people's lives, the factors that increase their risk and vulnerability to HIV and violence, and the key barriers to progress. There is an urgent need for data on young people – in particular 10 to 14 and 15 to 19 year olds – that is disaggregated by age, sex and key population status. It is also important to support young people to develop skills to collect and analyze their own data, as this can give insight into their lives that is not reflected in large scale surveys, and also allows a transition to the third lens of youth engagement, with young people designing and implementing programmes based on their unique needs and experiences.

3 | CONCLUSIONS

The end of AIDS is within reach, but structural barriers hinder our progress. Reframing the HIV response within a broader

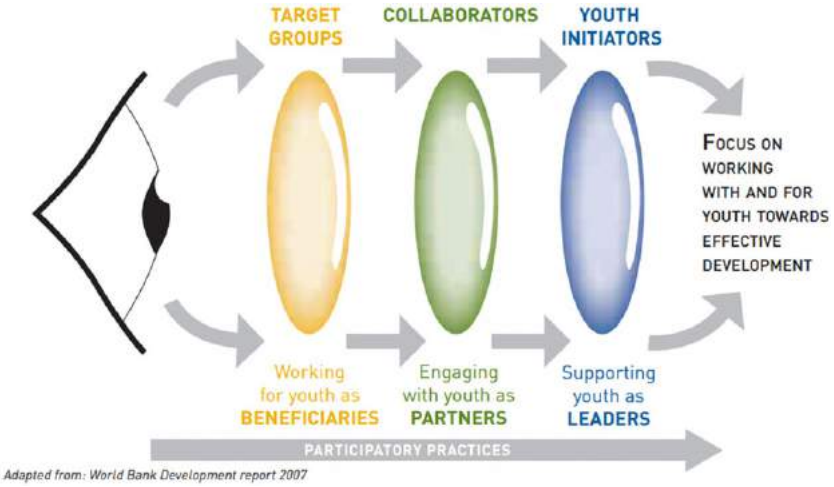

Figure 1. The three-lens approach to youth participation. This model outlines how young people should be engaged in development programmes as beneficiaries, partners and leaders [32].

context of the 2030 Agenda can support progress towards the end of AIDS as well as towards poverty eradication, education and gender equality.

We are all accountable for achieving the 2030 Agenda and leaving no one behind. As the Adolescent HIV Treatment Coalition, we call on all development stakeholders to continue building the evidence base on interlinkages of HIV across the 2030 Agenda, and how best to provide holistic, cross-sectoral programming that recognizes the unique challenges that young people face. We must create enabling legal and policy environments that uphold young people's rights, and uproot the systemic inequalities that keep them at risk and inadequately served. We must facilitate inclusive and participatory decision-making, recognizing that young people can collaborate with governments to achieve the SDGs together, and invest in young people not just as beneficiaries of HIV programmes, but as partners and leaders in the response. Finally, we must ensure a fully-funded, youth- and gender-sensitive HIV response, and build capacity of young people to hold their governments accountable, equipping them with the skills and tools to carry the HIV response forward in an effective and sustainable way.

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COMPETING INTERESTS

The authors have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

HG contributed to the concept, research, writing and revision. COR contributed to the concept, research, writing and revision, and coordination of authors. LH contributed to the concept, technical input and revision of drafts. DTH contributed to the concept, technical input and revision of drafts. All authors have read and approved the final manuscript.

ACKNOWLEDGEMENTS

The authors thank youth advocates Lorraine Anyango (Y+, The PACT) and Shaun Bera (Youth Rise), who provided input in the early stages of this manuscript. Dr Annette Sohn (TREAT Asia) provided feedback and guidance during the writing process. We also thank Professor Lucie Cluver who provided input and support during final revision stages. Finally, we acknowledge all the adolescents and young people with whom we work, and whose experiences greatly informed the viewpoints expressed in this article.

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Hodes R et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25057
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25057/full | https://doi.org/10.1002/jia2.25057

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

RESEARCH ARTICLE

The stuff that dreams are made of: HIV-positive adolescents' aspirations for development

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Abstract

Background: The Sustainable Development Goals (SDGs) commit to strengthening collaborations between governments and civil society. Adolescents are among the key target populations for global development initiatives, but research studies and programmes rarely include their direct perspectives on how to promote health and wellbeing. This article explores how both the methods and the findings of participatory research provide insights into adolescents' aspirations across the domains of health and social development. It investigates how adolescents conceive of health and social services as interconnected, and how this reflects the multisectoral objectives of the SDGs.

Methods: This research was conducted within a longitudinal, mixed-methods study of HIV-positive adolescents (n = 80 qualitative participants, n = 1060 quantitative interviews). Between November 2013 and February 2014, a participatory exercise – the "dream clinic" – was piloted with 25 adolescents in South Africa's Eastern Cape. Key themes were identified based on the insights shared by participants, and through visual and thematic analysis. These findings were explored through a second participatory exercise, "Yummy or crummy? You are the Mzantsi Wakho masterchef!," conducted in January 2016. Findings are described in relation to emerging quantitative results.

Results: Mixed methods explored associations between access to food, medicines, clean water and sanitation in HIV-positive adolescents' aspirations for development. The exercises produced practicable recommendations for innovations in development, based on associations between healthcare, food security, clean water and sanitation, while illustrating the value of partnership and collaboration (the objective of SDG17). Findings capture strong interlinkages between SDGs 2, 3 and 6 – confirming the importance of specific SDGs for HIV-positive adolescents. Study results informed the objectives of South Africa's National and Adolescent and Youth Health Policy (2017).

Conclusions: Participatory research may be used to leverage the perspectives and experiences of adolescents. The methods described here provide potential for co-design and implementation of developmental initiatives to fulfil the ambitious mandate of the SDGs. They may also create new opportunities to strengthen the engagement of adolescents in policy and programming.

Keywords: HIV-positive adolescents; participatory research; Sustainable Development Goals; development interlinkages; health access; food security; water and sanitation

Received 9 May 2017; **Accepted** 11 November 2017; **Published** 27 February 2018

1 | INTRODUCTION

1.1 | Public participation and the SDGs

The Sustainable Development Goals (SDGs) are designed to promote economic, social, and environmental wellbeing on a global scale [1,2]. In designing the SDGs, the United Nations sought to elicit the perspectives of vulnerable and marginalized groups, including diverse members of civil society, alongside consultations with government partners [3,4]. The importance of inclusivity was noted in the process of both conceiving [5] and prospective monitoring of the goals [6], and is further articulated in SDG 16, which includes a commitment to inclusivity in the promotion of peace, justice, and the building of strong and responsive institutions. But how is this greater inclusivity to be practicably realized, particularly among "hard-to-reach populations" such as adolescents?

The necessity of improving the effectiveness and scalability of health programmes for adolescents is apparent in numerous health and development indicators, including those that focus on HIV transmission and treatment. A growing research base demonstrates high rates of defaulting from antiretroviral treatment (ART) among adolescents in public settings [7,8]. The effectiveness of HIV treatment does not depend solely on the provision of medicines and healthcare, but is also linked to food security and access to health facilities [8-10]. The successes of

health and social initiatives for adolescents depend further on their ability to respond to adolescent needs in ways that resonate with their own ideas about, and aspirations for, health and wellbeing.

This article describes how both the methods and the findings of participatory exercises may provide insights into adolescents' aspirations for development. Combining data from the qualitative and quantitative components of the Mzantsi Wakho study, it explores how adolescents conceive of health and social services as interconnected. It questions how the domains of health and social development intersect for adolescents, and what this reflects about the multisectoral objectives of the SDGs.

1.2 | Adolescents and the SDGs

Creative forms of participatory research may be used to expand the evidence base within public health and development to include those who are marginalized by socio-economic and structural circumstances, such as poverty, gender and disability [11]. These methods may foster greater reflexivity between researchers and subjects [12], helping to bridge divides between global and national policy-makers and programmers, and local beneficiaries. Participatory research methods include visual or performance-based data collection tools that enable participants to document and analyse their experiences, identify solutions to local problems, and critically assess development initiatives [13-16].

2 | METHODS: PARTICIPATORY RESEARCH AND THE MZANTSI WAKHO STUDY

This article focuses principally on a participatory research exercise entitled the "dream clinic", triangulating findings with a second participatory exercise, "Yummy or crummy? You are the Mzantsi Wakho masterchef!." We combine results from these exercises with wider themes and emerging findings from a mixed methods, cohort study about youth health in South Africa. The study name, "Mzantsi Wakho" – meaning "Your South Africa," captures its intention to engage youth in conceiving and relating their own goals for health and social development.

Mzantsi Wakho is a partnership of qualitative and quantitative researchers. The study is advised by the South African Departments of Basic Education, Health, Social Development and the Human Sciences Research Council, bilateral agencies UNICEF and UNAIDS, and non-governmental organisations, including Pediatric-Adolescent Treatment for Africa (PATA). These partnerships have informed the study's focus on interconnections between the domains of health and social development for adolescents.

Starting in 2013, the study has combined multiple qualitative methods, including in-depth interviews, observations and focus groups, to investigate the healthcare practices and experiences of adolescents and young people [17-20]. From 2014 to 2015, the study established a quantitative cohort of 1060 HIV-positive 10 to 19 year-olds. A structured questionnaire captures the health and social factors associated with medicines-taking and sexual health [8,9]. The sample was 55% female, and had a mean age of 13.8. 97% of participants spoke isiXhosa as their first language. About 19% lived in informal housing, and 21% were based in rural areas. Nearly half were maternal orphans (44%) and 30% paternal orphans. All HIV-positive participants had been initiated onto ART, with an average of 5.9 years on treatment. 75% knew their HIV-positive status [21], defined as having been disclosed to by an adult caregiver or healthcare worker, and by adolescent self-reported knowledge of HIV-positive status and understanding ART as medicine to treat HIV [22,23]. Findings from both the qualitative and quantitative components of the study informed the adaptation and integration of research tools with multiple sources of data analysed by inter-disciplinary investigators [22-25].

Due to the legal and ethical challenges of working with young people, studies about health often use adults as "proxies" for adolescent experiences. Mzantsi Wakho's approach is different: positioning adolescents as the primary experts on their own health behaviours, conducting research both within and beyond clinical contexts, in homes and in leisure spaces, and seeking new ways of documenting adolescents' experiences and perspectives. Ethical approval for this study was provided by Research Ethics Committees at the Universities of Oxford (SSD/CUREC2/12-21) and Cape Town (CSSR 2013/4), Eastern Cape Departments of Health and Basic Education, and ethical review boards of participating hospitals. The study follows a deliberative approach to ethical permissions, seeking ongoing guidance to ensure consent and protect confidentiality during primary research, analysis, and dissemination.

2.1 | "Dream clinics"

The "dream clinic" used visual media to capture and convey adolescents' aspirations for health and social services. The exercise drew on the utility of participatory, socio-spatial mapping exercises as research tools [14,26]. The exercise was piloted in a workshop held in the Eastern Cape, in November 2013, with 9 adolescents from a rural area. It was repeated with 16 adolescents from a peri-urban area within the same health district in February 2014. Adolescent participants of mixed gender, ranging in age from 10 to 19, were recruited from local community-based organizations that provided HIV care and treatment. Adolescents in the first workshop knew their HIV-status, were openly disclosed, and knew one another's status as a consequence of being in the same support group. The second workshop combined openly-disclosed, partially-disclosed and undisclosed adolescents, and no specific references were made to HIV or to ART. For adolescents younger than 18-years, voluntary informed consent for participation was obtained from caregivers, alongside voluntary, informed assent from adolescents.

The "dream clinic" exercise used a series of open-ended prompts to facilitate adolescents in designing and drawing their ideal health facilities. Adolescents were invited to imagine the location and structure of the clinic, and to recreate its surroundings and interior. The exercise was conducted in three languages – isiXhosa, English, and Afrikaans. Facilitators gave prompts principally in English and isiXhosa, with additional explanations given to individuals and groups in their primary languages. All facilitators were trained on how to engage

adolescent participants, including how to avoid dominating or directing participation. Participants chose to work alone, or within groups of two to five. Groups included a dispersion of participants according to age and gender, and produced a total of fourteen "dream clinic" illustrations (10 individual drawings in the first workshop, and four group drawings in the second).

At the end of the exercise, each drawing was presented to the broader group, with participants explaining its particular features and significance. Researchers made notes of participants' responses and interpolations. One of the challenges of this exercise was that many adolescents began by drawing their clinics as they existed. Distinguishing reality from aspiration in analysing the drawings could therefore be difficult. Thematic notes helped to convey participants' intentions and to differentiate between what they hoped for, and what they experienced directly. Following Martin-Hilber *et al*. [27], notes were later collated and compared, and key themes identified based on the insights shared by participants, and through visual and discursive analyses of the drawings. Themes identified through the "dream clinics" were explored further with participants through participatory research on the experiential components of medicines-taking, including through the "Yummy or crummy" exercise described below.

2.2 | Yummy or crummy?

From November 2015 to January 2016, we designed a participatory research tool to explore the experiential components of medicines-taking. Named "Yummy or crummy? You are the Mzantsi Wakho masterchef**!**," the exercise combined role-playing with the preference-ranking features of social media forums. Drawing on the rubric for participatory research developed by Skovdal and Cornish [13], it merged "linkages and relationship tools," "experiential tools," and "prioritization and quantification tools." Through incorporating visual and performative components, the exercise aimed to provide participants with new ways to relate the multisensory experiences of medicines-taking. Feedback forms used various techniques for assessing medicines-preferences among young patients [28], including emoticons from social media applications. The content of forms was transcribed, translated, and coded, with key themes identified collectively by researchers who designed and facilitated the exercise. It was piloted with a group of adolescents and young adults (n = 17, male 7, female 9), part of the Teen Advisory Group (TAG), in January 2016. TAG was established within the Young Carers study in 2008, and participants played an advisory role in the Mzantsi Wakho study, taking part in annual workshops from 2012. "Yummy or crummy?" findings are used here to triangulate "dream clinic" findings, with a focus on the intersection of health programming with sanitation and social development from the perspectives of HIV-positive adolescents.

3 | RESULTS

3.1 | Food and water

In numerous "dream clinics", participants drew food gardens growing next to facilities, with ready access to fresh produce. Bathrooms with sinks and taps, and brimming water tanks, were portrayed (Figures 1-3). Most drawings included a "tuck shop" or kiosk and food garden in close proximity to the clinic. In one drawing, the entrance to the clinic was pictured not at the clinic's centre, but at its side, next to a soup kitchen (Figure 4). Adolescents' desires for comprehensive healthcare were conceived in relation to adequate nutrition and food security.

Both within one-on-one discussions between facilitators and individual participants, and within group discussions conducted as part of the "dream clinic" exercise, the provision of food and clean water was prioritized (group discussion, "dream clinic" exercise, Mzantsi Wakho workshops November 2013; February 2014). Within the drawings themselves, soup kitchens, tuck shops, and gardens were rendered with the same intricacy and precision as pharmacies and folder rooms within clinics. The inclusion of food and water supplies as features of the "dream clinic" illuminates both the value and the potential scarcity of these resources.

Findings from other components of the Mzantsi Wakho study emphasized the importance of food and water as prerequisites for adherence to medicines, suggesting an inter-

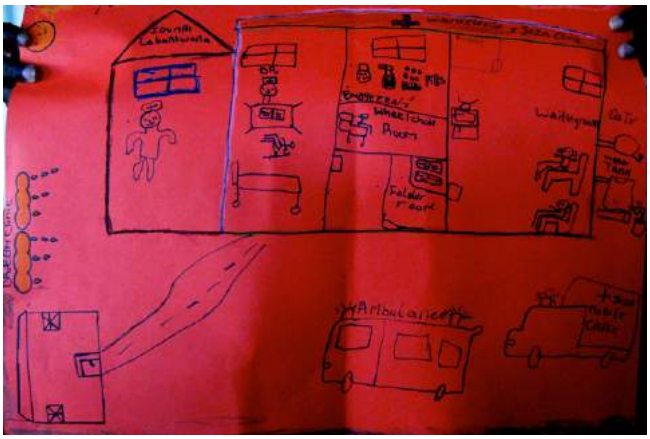

Figure 1. A "dream clinic" (November 2013), including water tanks and taps (far right), a wheelchair room (centre) and an ambulance and mobile clinic (bottom right).

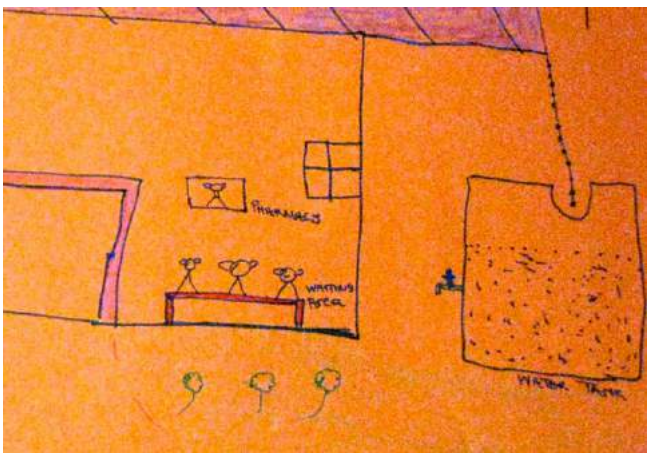

Figure 2. Detail from a "dream clinic" (November 2013) shows a large and full water tank and a tap adjacent to the patient's waiting area.

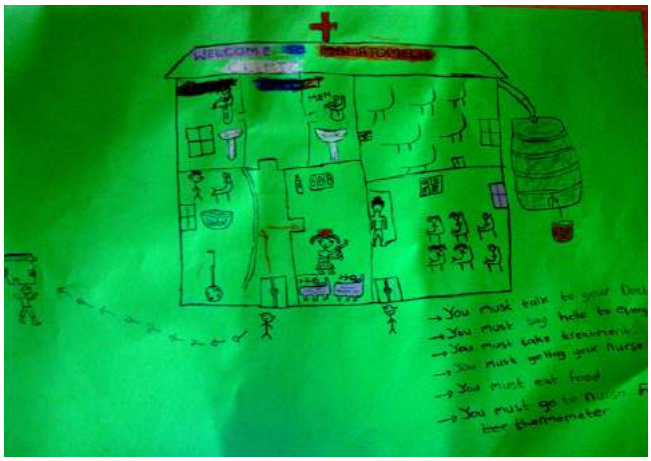

Figure 3. A "dream clinic" (November 2013) features a water tank and a bucket for easy distribution (far right), separate and well-appointed ablutions for men and women (with taps and toilets, centre top), and a basin with water in the consulting room (centre).

Figure 4. Detail from a "dream clinic" (February 2014) shows the route to the clinic from participants' homes. The first stop on the route is a soup kitchen, the second is a school.

linkage between SDGs 2 (food security), 3 (health), and 6 (water and sanitation). Over a fifth (22.6%) of the 1060 HIV-positive adolescents in the sample reported hunger and food insecurity [9]. Many participants relied on school feeding programmes as vital nutritional support, with 93% reporting receiving at least one meal a day at school.

The "Yummy or crummy?" exercise reified adolescents' emphasis on access to water and sanitation, not just as a medium for swallowing pills, but of agency and mobility. In areas that lacked running water, adolescents on ART were required to plan their movements to ensure that they were close to a water supply at dosing times – especially as their regimens commonly included numerous large pills, making "dry swallowing" difficult. This curtailed the mobility of adolescents in areas with restricted access to water and sanitation where they were, in essence, tethered to taps.

3.2 | Access

All of the dream clinic drawings portrayed transport routes as roads which were smoothly paved and well-marked. A short distance between healthcare facilities and homes conveyed some participants' desire for proximate, readily accessible facilities, although in-depth interviews conveyed the desire of other participants for facilities distanced from their homes, to ensure greater privacy and avert potential HIV-related stigma. Wheelchairs were represented in one drawing, relaying the need for equipment and healthcare services for those with disabilities and injuries that impaired movement. Ambulances, pictures in numerous drawings, conveyed the desire for mobile services. Some participants felt, however, that mobile clinics would be less reliable than "fixed" facilities, and the misuse of ambulances as private taxis was reported.

The "dream clinics" revealed adolescents' aspirations for health services as interconnected with education and social services. One "dream clinic" featured a long and winding road. The first stop on the route to the clinic was a soup kitchen (Figure 4). The second stop was a school. Within this rendition, access to food, education, and healthcare were associated.

3.3 | Comprehensive services

Representations of clinics as sources of food, water, and social services reflected adolescents' aspirations for a strong, supportive, and integrated health service that could meet the diverse needs of its users. The clinic was imagined as a site of multiple, interlinking forms of care and support. Reflecting during a workshop (November 2013) on what clinic staff should be expected to do, one adolescent participant gave the following list: "lend us money to go home, give us some lunch… give us pills, take blood tests." Another participant stated: "I would like the clinic to have food, water; to have medication because they don't give medication; clean toilets; gardens for veg!"

Desires for food security and access to clean water were represented concurrently with objectives for accessible and comprehensive health services, such as well-stocked pharmacies and ample staff. In Figure 5, a group of participants envisioned a flourishing vegetable garden ("groentes" in Afrikaans) next to an image of nurses dispensing medicines to patients. These explicit linkages between food, water, and pill-taking reflect a related finding in the Mzantsi Wakho study: that adolescents perceived ability to swallow pills and thus adhere to their ART regimens as reliant on having clean water and "good" food to eat.

3.4 | Participation

In Figure 5, the speech bubble (in Afrikaans) captures a conversation between a nurse and a patient. Using the formal and respectful tense pronoun, "u," as opposed to the casual "jy," the implication is that patients wish to be addressed respectfully by healthcare workers. Adolescents aspired for greater agency in their interactions with healthcare workers, which resonated with the commitment of SDG 16 to create more effective, accountable and inclusive institutions and partnerships for development. While focused on their own

priorities in the clinic setting, adolescents in this exercise also (sometimes reluctantly) paid attention to the needs of other vulnerable groups, particularly young mothers and patients with disabilities.

4 | DISCUSSION

Participatory visual methods have numerous limitations, including questions regarding interpretation, validity, reliability, and integration with other datasets and disciplinary approaches. However, in their potential to engage adolescents directly in the research sphere, participatory techniques have much to offer. This includes the means of exploring experiential associations and aspirations, and of translating research beyond surveys and researcher-led interviews or focus groups, to forms of investigation that offer participants new channels of engagement and representation. As such these forms of enquiry may provide a means to pursue the more "human-rights based approach" [29] called for in implementing and evaluating the SDGs. They offer another opportunity to include the views and perspectives of marginalized population groups such as HIV-affected adolescents, and to design responsive and effective programmes accordingly.

Findings from the "dream clinics" and "Yummy or crummy?" reveal synergies between healthcare provision and access, infrastructure, water and sanitation, and nutrition. Food and water are critical to adherence for participants in this study, interlinking SDGs 2 (food security), 3 (health), and 6 (water and sanitation). This finding is similar to another study conducted in South Africa, in which HIV-positive patients hoped to access food and drink, such as bread and tea, while waiting in clinic queues. This was not just to staunch hunger built up in the course of long delays to see healthcare workers, but also to eat something before taking ART [30]. Associations between hunger, thirst and ART defaulting are documented in the growing literature on ART adherence [31]. Within the Mzantsi Waho study, adolescents who reported food insecurity were nearly twice as likely to report past-week non-adherence [8]. It is increasingly evident that a lack of food is associated with perceived side-effects from ART, and with missing doses [32-34].

Figure 5. Detail from a "dream clinic" (February 2013) shows a flourishing vegetable garden and plants and trees next to the healthcare facility. It portrays a respectful dialogue between a nurse and patient.

These findings should be considered in the context of the SDG agenda given the requirement to address the "interconnected factors" of the SDGs, and to explore the experiences of marginalized constituencies, including children and adolescents [5]. Understanding what the intended recipients of development initiatives want and need, and partnering with them in their design, adaptation and implementation, is imperative to realize the ambitious objectives of the SDGs.

The participatory exercises described here encouraged a greater plurality of conceptions of healthcare services and their potential improvement [35]. Findings from the "dream clinic," translated into policy recommendations, were incorporated in South Africa's Adolescent and Youth Health Policy for 2017 [36], and the UNICEF-led platform, All-In to #EndAdolescentAIDS [37]. The form and the findings of these "dream clinics" have therefore influenced policy and programming at national and regional levels, propelling the experiences and aspirations of adolescents directly into policy goals and programmatic recommendations. This exercise has been repeated in skills-development programmes for adolescents and healthcare workers in South Africa by other organizations.

5 | CONCLUSION

The formulation of the SDGs reflects a participatory impetus of the broader development agenda. This study proposes ways to include of adolescents in implementing and monitoring the SDGs.

In addition to more structured and traditional research methods, Mzantsi Wakho's "dream clinic" and "Yummy or crummy?" exercises aimed to combine the components of participatory research in partnership with HIV-positive teenagers in South Africa, encouraging a greater plurality of conceptions of healthcare interventions and their potential improvement. Methods such as these provide an opportunity for researchers, programme implementers, and government representatives to bridge the gap between the rhetorical commitment to broad-based and inclusive partnerships for development, and their practicable rendition.

Findings from the exercises captured how participants conceived of healthcare as far broader than access to medicines or clinical care. Rather, participants imagined healthcare as part of a developmental lattice that connects sound infrastructure, access to education, and nutrition. Adolescents conceived of themselves as partners in the design and implementation of development initiatives – and as a binding force within this lattice.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

RH, JD, ET, BV and LC conducted primary research and analysis. NZ guided methods and analysis. All authors wrote, edited and approved the final manuscript.

ACKNOWLEDGEMENTS

Authors thank participants and their families, and acknowledge the support of the Mzantsi Wakho research team: M Ashorn, W Booi, N Bungane, L Button, KE Chademana, N Galela, L Gittings, N Gwebecimele, R Haghighat, E He, A Heusel, S Hoeksma, M Isaacsohn, Z Jantjies, R Jopling, C Kama, B Kamile, B Kinana, V Luke, B Madondo, K Makabane, B Makwenkwe, T Mampangashe, Z Marikeni, D Mark, A Mayekiso, A Mbiko, A Mboyiya, D Mhlauli, S Medley, P Mngese, S Mngese, P Mjo, S Mona, T Moyikwa, S Mpimpilashe, M Mpumlwana, S Mqalo, S Mwellie, P Myoyo, M Neel, U Ngesi, S Ngozi, P Nobatye, N Nurova, M Pantelic, T Ramncwana, J Rosenfeld, B Saliwe, J Sandelson, L Sidloyi, I Skracic, R Smith, N Sontsonga, J Steinert, B Taleni, M Thabeng, S Tshaka and T Tsiba. We are grateful for the support of the Clarendon-Green Templeton College Scholarship Fund, Paediatric-Adolescent Treatment Africa (PATA), the Regional Inter-Agency Task Team (RIATT-ESA) for Children Affected by AIDS in Eastern and Southern Africa, the South African National Departments of Basic Education, Health and Social Development, UNICEF and UNFPA. Our thanks to three anonymous reviewers.

FUNDING

This study was supported by the Nuffield Foundation under grant CPF/41513, the International AIDS Society through the CIPHER grant (155-Hod), Janssen Pharmaceutica N.V., part of the Janssen Pharmaceutical Companies of Johnson & Johnson, Evidence for HIV Prevention in Southern Africa (EHPSA), a UK aid programme managed by Mott MacDonald (MM/EHPSA/UCT/05150014), the Economic and Social Research Council (IAA-MT13- 003), the Regional Inter-Agency Task Team (RIATT-ESA) for Children Affected by AIDS in Eastern and Southern Africa, UNICEF, UNFPA, the European Research Council under the European Union's Seventh Framework Programme (FP7/2007-2013)/ERC grant agreement no. 313421, the Oak Foundation (R46194/AA001), the Claude Leon Foundation, the John Fell Fund (103/757) and the Philip Leverhulme Trust (PLP-2014-095).

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Penazzato M et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25049
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25049/full | https://doi.org/10.1002/jia2.25049

JIAS
JOURNAL OF THE INTERNATIONAL AIDS SOCIETY

COMMENTARY

Shortening the decade-long gap between adult and paediatric drug formulations: a new framework based on the HIV experience in low- and middle-income countries

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Abstract

Introduction: Despite the coordinated efforts by several stakeholders to speed up access to HIV treatment for children, development of optimal paediatric formulations still lags 8 to 10 years behind that of adults, due mainly to lack of market incentives and technical complexities in manufacturing. The small and fragmented paediatric market also hinders launch and uptake of new formulations. Moreover, the problems affecting HIV similarly affect other disease areas where development and introduction of optimal paediatric formulations is even slower. Therefore, accelerating processes for developing and commercializing optimal paediatric drug formulations for HIV and other disease areas is urgently needed.

Discussion: The Global Accelerator for Paediatric Formulations (GAP-f) is an innovative collaborative model that will accelerate availability of optimized treatment options for infectious diseases, such as HIV, tuberculosis and viral hepatitis, affecting children in low- and middle-income countries (LMICs). It builds on the HIV experience and existing efforts in paediatric drug development, formalizing collaboration between normative bodies, research networks, regulatory agencies, industry, supply and procurement organizations and funding bodies. Upstream, the GAP-f will coordinate technical support to companies to design and study optimal paediatric formulations, harmonize efforts with regulators and incentivize manufacturers to conduct formulation development. Downstream, the GAP-f will reinforce coordinated procurement and communication with suppliers. The GAP-f will be implemented in a three-stage process: (1) development of a strategic framework and promotion of key regulatory efficiencies; (2) testing of feasibility and results, building on the work of existing platforms such as the Paediatric HIV Treatment Initiative (PHTI) including innovative approaches to incentivize generic development and (3) launch as a fully functioning structure.

Conclusions: GAP-f is a key partnership example enhancing North-South and international cooperation on and access to science and technology and capacity building, responding to Sustainable Development Goal (SDG) 17.6 (technology) and 17.9. (capacity-building). By promoting access to the most needed paediatric formulations for HIV and high-burden infectious diseases in low-and middle-income countries, GAP-f will support achievement of SDG 3.2 (infant mortality), 3.3 (end of AIDS and combat other communicable diseases) and 3.8 (access to essential medicines), and be an essential component of meeting the global Start Free, Stay Free, AIDS Free super-fast-track targets.

Keywords: paediatric drugs; drug development; drug formulations; regulatory approval; Global Accelerator for Paediatric Formulations; HIV; tuberculosis; viral hepatitis

Received 22 May 2017; **Accepted** 18 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

Prompt treatment of people living with HIV (PLHIV) with appropriate antiretroviral drugs (ARVs) saves lives and improves health, but the 43% ARV treatment (ART) coverage of children living with HIV (CLHIV, <15 years old) continues to lag behind adult coverage [1], and many CLHIV in low- and middle-income countries (LMIC) still do not receive optimal paediatric formulations. In an era that has seen the major public health achievement of 18.2 million people accessing ARVs worldwide in 2016 [1] and new fast track targets to end AIDS by 2030 [2], drug development for children surprisingly still lags 8 to 10 years behind that of adults [3]. There are many demographic, structural, regulatory, technical and economic challenges slowing drug development for children. The 2.1 million CLHIV globally make up less than 10% of all PLHIV, but require combinations, strengths and formulations of ARVs that vary by age and weight. The result is a

fragmented, low-volume market that typical economic incentives will not address, making it difficult for generic drug manufacturers to engage [4], even when there are no intellectual property barriers. Declining numbers of new infections in children coupled with technical challenges in making child-friendly formulations and the need to investigate safety and dosing across the paediatric spectrum of ages and weights contribute to delays in testing of new ARVs in children, despite regulatory incentives and requirements for paediatric development plans for new drugs by innovator companies [5]. Individual country regulatory approvals, national HIV treatment policies and supply chain management strategies can lead to further delays in uptake into treatment programmes. These challenges are not unique to HIV; similar barriers have been encountered in developing optimal formulations for the treatment of tuberculosis and viral hepatitis in children. Small markets, particularly for multi-drug resistant (MDR) tuberculosis, and unclear treatment recommendations for children, such as for hepatitis B and hepatitis C, have resulted in very slow progress and lack of access to paediatric formulations.

Stakeholders working in the area of paediatric HIV have come together in an unprecedented effort of cross-sectoral collaboration to develop and articulate solutions to these challenges. The work stream has been unified by linking core activities of policymakers, research networks, regulatory agencies, manufacturers, supply and procurement organizations and funding bodies with the aim of ensuring accelerated development and uptake of optimal ARVs for children. A proposal now stands to take this to the next level with a more formalized, sustainable, coordinated framework aiming to accelerate processes for development and uptake of prioritized paediatric drug formulations for use in LMICs and globally by 2020: the Global Accelerator for Paediatric Formulations (GAP-f). GAP-f will accelerate both upstream and downstream processes for developing paediatric drug formulations for HIV and for other disease areas, like hepatitis C and tuberculosis that face the similar challenges of young target populations, high burden in LMICs, small-volume markets and lack of market incentives for development and manufacturing.

GAP-f will make an important contribution to ensure success of Sustainable Development Goal (SDG) 3: ensure healthy lives for all and promote wellbeing. Ensuring access to the most needed paediatric formulations for HIV and other high-burden infectious diseases in LMICs directly responds to SDG 3.8 (access to essential medicines, indicator 3.8.1), as development and uptake of the most needed paediatric formulations will overcome the principal barrier to access for these populations. It will help to reduce HIV-related infant and child mortality in support of SDG 3.2 (indicators 3.2.1, Under-five mortality rate and 3.2.2 Neonatal mortality rate) and is necessary to help end AIDS and combat other communicable diseases (SDG 3.3, indicators 3.3.1, 3.3.2 and 3.3.3). Finally, it is an essential component of meeting the global Start Free, Stay Free, AIDS Free super-fast-track targets for paediatric HIV [6].

GAP-f exemplifies partnership and collaboration that enhance North-South and international cooperation on and access to science and technology, and thus it directly responds to SDGs 17.6 (technology, indicator 17.6.1) and 17.9 (capacity-building, indicator 17.9.1).

2 | DISCUSSION

2.1 | What is GAP-f?

Since 2013, under the coordination of the World Health Organization (WHO), cross-sectoral collaboration in paediatric HIV has increased among key stakeholders addressing medium- and long-term prioritization of most needed paediatric formulations for development. This has been accomplished through several ongoing initiatives:

1 The Paediatric ARV Drug Optimization (PADO) group sets priorities for development of new ARV drug formulation for children.
2 The Paediatric ARV Working Group (PAWG) provides technical guidance on weight-band dosing and pharmacokinetic and acceptability studies of ARV drugs in children.
3 The Interagency Task Team on Prevention of HIV Transmission in Pregnant Women, Mothers and their Children (IATT) develops a Paediatric ARV Formulary of existing drug formulations needed from manufacturers to enable optimal treatment of children.
4 The Paediatric ARV Procurement Working Group (PAPWG) coordinates procurement of paediatric ARVs for approximately 70 LMIC programmes.

In 2014, UNITAID, the Drugs for Neglected Diseases initiative (DNDi) and the Medicines Patent Pool (MPP), launched the Paediatric HIV Treatment Initiative (PHTI), to develop and deliver specific paediatric formulations; the Clinton Health Access Initiative (CHAI) joined the PHTI later. Later in 2014, partners came together to advance the paediatric HIV agenda under the umbrella of the Global Pediatric Antiretroviral Commitment-to-Action (CTA). Several broad consultations held in 2016 [7-9] explored mechanisms to advance paediatric formulation development and introduction. In parallel, two meetings organized under the leadership of the Holy See [10] generated high-level support to facilitate closer collaboration between the private sector and relevant stakeholders. These efforts to support paediatric formulation development and uptake are essential elements of the AIDS Free agenda of the Start Free, Stay Free, AIDS Free super-fast-track framework for ending AIDS in children, adolescents and young women by 2020, launched by UNAIDS and PEPFAR in 2016 [11].

The GAP-f brings together these efforts through establishment of a more formalized mechanism with collaboration upstream (clinical and formulation development by innovators and generics; stringent drug regulatory authority filing and approval processes; optimized paediatric product testing and generic manufacturing) and downstream (country-level drug regulatory approval; national treatment policy; supply chain management; programme sensitization; market uptake and incentives). The GAP-f will streamline efforts currently underway, integrating and consolidating all stakeholders invested in different steps of the pathway of paediatric drug prioritization, development, manufacture and uptake into a coherent, single-framework mechanism (see Figure 1).

2.2 | Finding efficiencies upstream

Currently, the development of paediatric products is closely dependent on development of products for adults, although it

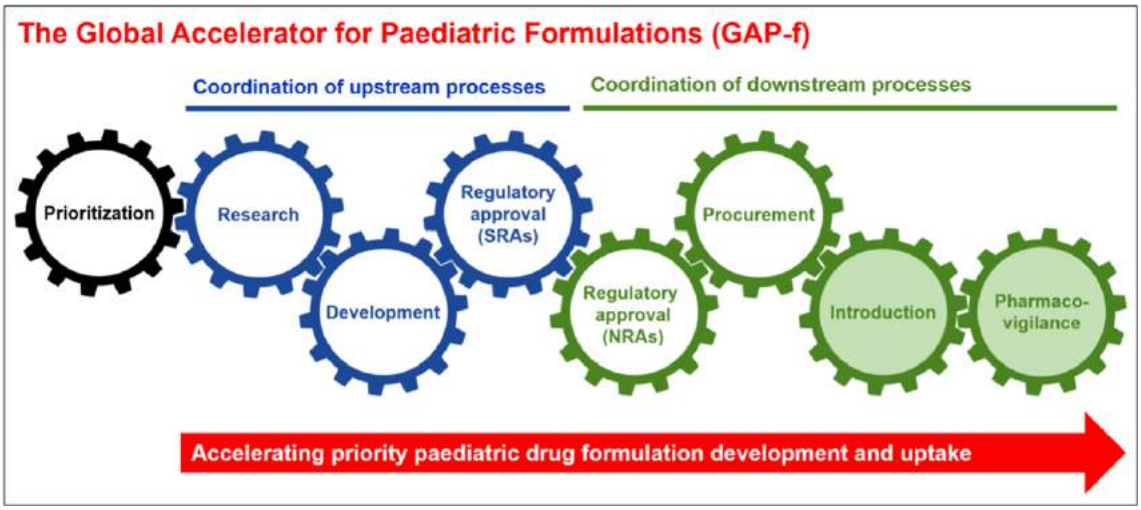

Figure 1. The Global Accelerator for Paediatric Formulations (GAP-f). The GAP-f formalizes collaboration across sectors to ensure accelerated development and uptake of the most needed drugs and formulations for children. SRAs, stringent regulatory authorities; NRAs, national regulatory authorities (in high-burden countries).

presents additional challenges (see Figure 2). Efficacy of most drugs (including ARVs) in children is extrapolated from results of clinical trials conducted in adults; direct studies of safety and dosing in children across the paediatric age and weight spectrum are then required. Through the submission of paediatric investigation plans [PIP, at the European Medicines Agency (EMA)] or paediatric study plans [PSP, at the United States Food and Drug Administration (US FDA)], innovator companies commit to generate supportive data in children required for authorization of a medicine for paediatric use. These plans, compulsory for all companies seeking marketing approval unless they obtain a waiver or a deferral, are submitted very early in drug development, and include non-clinical and clinical study plans [12,13]. The execution of these plans starts after proof of concept of the adult product and represents a large investment from pharmaceutical companies.

Formulation development is also a critical element of paediatric drug development. Paediatric products must be age-appropriate formulations for the intended age groups, palatable and easy to administer in appropriate doses. In the past, most paediatric formulations were oral liquids, which are difficult to store, may need refrigeration, entail more complex administration (with higher risk of dosing errors) and are more difficult for making fixed-dose combination (FDC) products. However, WHO currently recommends dispersible tablets, granules or other solid formulations (that do not require whole pill swallowing), preferably in FDCs, to avoid the complexities linked to liquid administration [14]. Currently, there are several key regimens recommended by WHO available in such child-friendly formulations (e.g. ABC/3TC dispersible tablets, LPV/r pellets), but still more are needed. In addition, it is important to ensure that future products are developed following these recommendations.

Because the paediatric market for HIV and other infectious disease products is small, innovator companies that have previously developed and launched paediatric formulations imperfectly adapted for use in LMICs are unlikely to reformulate their products. In such cases, generic companies may be best placed to manufacture alternate formulations for existing products when patents expire or when the innovator companies grant voluntary licences (VL) permitting generic versions of drugs with remaining patent protection. Since 2010, the MPP has been striving to negotiate VL agreements with innovators of HIV, hepatitis C and tuberculosis medicines [15]. To date, all innovators have granted VLs to the MPP for all WHO-recommended paediatric ARVs still under patent (except for darunavir, for which Janssen announced intent not to enforce patents in resource-limited settings [16]).

Regulatory approval of novel formulations, especially new FDC products for which component drugs are owned by different innovators, was previously out of the scope of stringent regulatory authorities (SRA). In the last decade, several initiatives have addressed some of these limitations mainly in the field of HIV. In 2006, as part of the President's Emergency Plan for AIDS Relief (PEPFAR), the US FDA identified a mechanism to grant tentative approval to ARV products intended for procurement in developing countries while maintaining patent protection within the US [17]. EMA now gives to manufacturers, scientific opinion on the regulatory requirements for products intended for non-EU markets through the Article 58 procedure. In addition, the WHO prequalification team assesses products and inspects manufacturing plants. As a result, several paediatric-adapted formulations, including several dispersible FDCs for HIV, TB and malaria, that meet the high SRA standards for efficacy, safety and quality are available to children in LMICs.

A good illustration of the paediatric development process is the FDC containing abacavir (ABC) and lamivudine (3TC), key components of WHO-recommended first-line HIV treatment for children (see Figure 3). The innovator conducted clinical trials in the 1990s to establish the appropriate dose for children. The US FDA approved the oral solutions in 1995 (3TC) and 1998 (ABC). The first generic dispersible tablet containing a combination of the two products was approved in 2011 and was only available in countries where there was no patent restriction. Only in 2014, four years after WHO

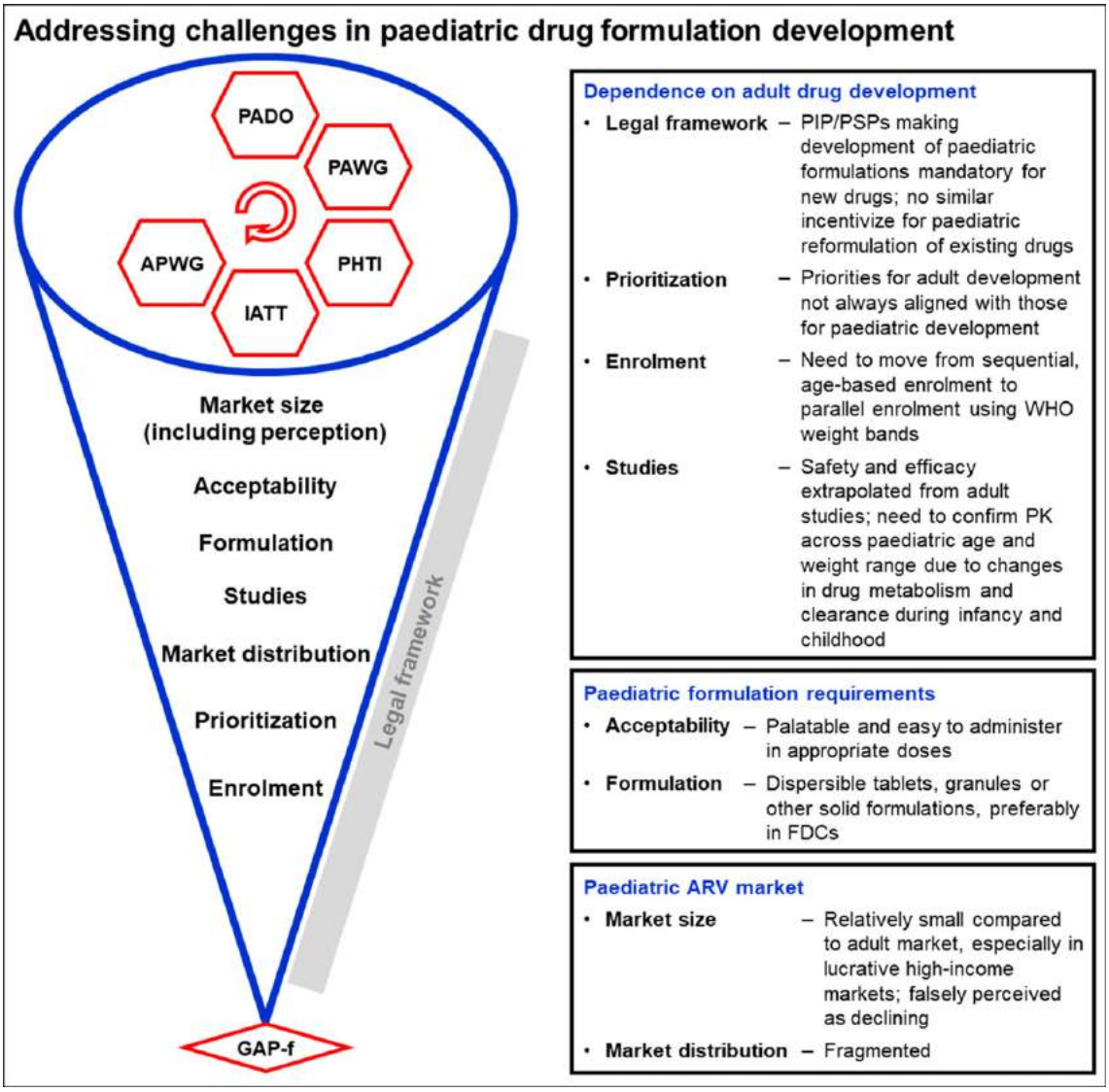

Figure 2. The GAP-f represents an opportunity to address challenges in paediatric drug formulation development. Challenges are grouped around three areas: dependence on adult drug development, paediatric formulation requirements and paediatric ARV market. Progress to-date in addressing these challenges is depicted along a funnel originating from precursor mechanisms and leading up to the GAP-f collaborative model. Legal framework challenges are placed outside of the funnel because of the limited influence of the GAP-f to directly address these. PK, pharmacokinetic; GAP-f, Global Accelerator for Paediatric Formulations; ARV, antiretroviral.

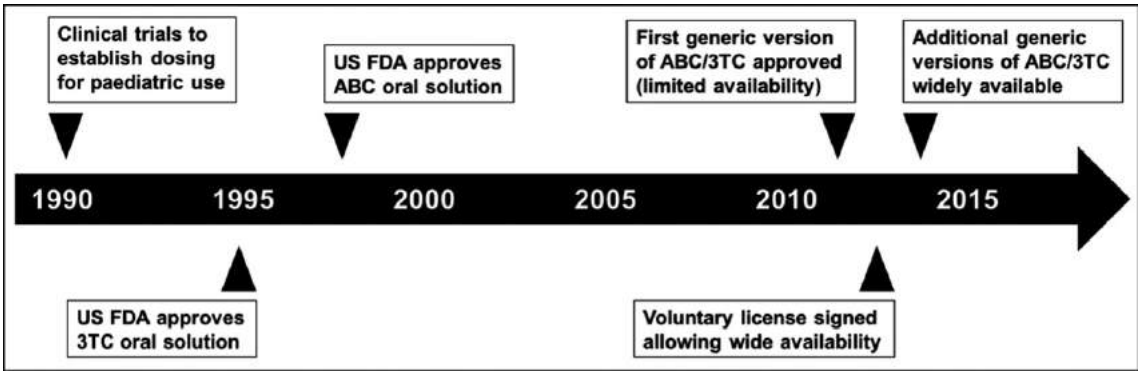

Figure 3. Timeline for ABC/3TC development. It took almost 15 years after ABC and 3TC were first approved for use in children until enough generic versions of child-friendly formulations were produced to make these drugs widely available to children in LMIC. ABC, abacavir; 3TC, lamivudine; LMIC, low- and middle-income countries.

recommended the use of this combination as a preferred backbone in first-line treatment for all children [18] were other generic versions made more widely available. Bilateral licensing agreements between the innovator and generic companies and VLs with the MPP for ABC expanded access to these formulations to 121 countries.

This example shows the need to accelerate the development of new products and formulations in HIV, and even more in other disease areas where progress has been slower. Newer generation ARVs and direct-acting antivirals for hepatitis C infection, among others, offer the possibility of testing new models, such as the one proposed by the GAP-f, to accelerate development of optimal formulations. Direct and early technical support by the PAWG can help define and accelerate paediatric development plans (PIP and PSP) and clinical studies. It is also important that innovator companies develop formulations and combinations appropriate for the global population ensuring intellectual property is not a barrier. Coordination between regulators to exchange information on paediatric development plans must occur regularly and early enough so plans can be aligned to product needs. Harmonized protocols for paediatric trials can optimize safety and efficacy data, and thus simplify development. Finally, incentivizing generic manufacturers to conduct formulation development can mitigate the negative effects of the small market size. The incentives could include technical assistance in the design of studies needed to obtain regulatory approval that rely on published literature or on data supporting a previous approval, as well as financial support to conduct such studies.

2.3 | Increased coordination downstream

In-country registration is often the bottle neck for rapid market introduction. More systematic use of existing (Collaborative Registration Procedure CRP for WHO-prequalified products: http://apps.who.int/medicinedocs/en/d/Js21317en/) mechanisms to enable increasing reliance by NRAs on regulatory approval granted by SRAs is expected to significantly accelerate approval processes. These mechanisms would, in fact minimize the need to undertake additional local clinical studies when robust evidence already exists.

The impact of new products on patients' lives relies as much on what happens downstream of development and regulatory approval as upstream. Careful procurement planning and clear communication between procurers, programmes and suppliers can ease the launch of a new paediatric formulation. In the absence of this, suppliers can be hesitant to take on inventory risk and commit production resources to the new product(s) until larger orders are received, increasing lead times, and risking loss of interest from programmes to adopt new product(s), or worse still, stock-outs. Avoiding stock-outs and delivering optimal products facilitates achievement of the SDG 3, including ending preventable deaths of newborns and children <5 years of age, and ending the AIDS epidemic by 2030.

The paediatric ARV market, despite growth over the last 10 years, remains relatively small and fragile. To address procurement and access challenges, the PAPWG was created to lead global collaboration and coordination among key partners, including procurement that promotes optimal products. This effort has succeeded in consolidating the number of different paediatric ARV products procured and increasing the share of paediatric products procured that correspond to WHO-preferred products for children. Following success in the paediatric market, in 2016, the group expanded its scope to include low-volume adult ARV products, and was renamed the ARV Procurement Working Group (APWG).

The theory of change underpinning the APWG is that coordinated procurement, where orders are consolidated with predictable ordering schedules, reduces lead times and avoids stock-outs. Coordination occurs at the global level between member procurers, who in turn coordinate with their client programmes to negotiate acceptability of any adjustments. Sharing market intelligence across large funders and buyers ensures both visibility and confidence for manufacturers and supplier accountability. Supply disruptions are minimized and ARV markets are shepherded towards optimal formulations that benefit patients the most. The APWG consists of major funders and buyers like the Global Fund to Fight AIDS, Tuberculosis and Malaria, PEPFAR, UNICEF, national procurement units from Kenya and Ethiopia, and partners like UNITAID and CHAI. (It does not currently include South Africa procurement units.) Its approach includes:

1 Consolidated ordering at set times each quarter to ensure any one product has sufficient orders to fulfil a supplier's minimum batch size (ranging from 5000 to 50,000 packs). A quarterly review of planned procurements identifies potential issues around sub-batch size and extended lead times are flagged early for corrective action. Buying plans can be adjusted while allowing members to adhere to their respective organizational policies.
2 Optimizing product selection using the formulary list developed by the IATT [19], and WHO guidelines on ART [14].
3 Aggregating a rolling quarterly forecast across procurers of demand by delivery quarter for the next 12 to 18 months to help suppliers with market visibility and production planning.
4 Regular structured dialogue between buyers, programmes and manufacturers to ensure timeliness and consistency of information sharing.
5 Collaboration with procurement partners to support improvement of country paediatric forecasting, procurement practices and supply management.

The APWG, responsible for well over half the global demand, has made great strides in stabilizing and streamlining the paediatric ARV market by consolidating volumes: lead times have reduced sharply, there is less fragmentation in product selection, and in 2016 less than 5% of orders by volume were "non-essential" formulations as defined by the IATT. The APWG is an important body for downstream efforts to ensure that the new paediatric products are not only developed, but also realize their full potential in improving the lives of CLHIV, consistent with the targets of SDG 3.

2.4 | Implementing the GAP-f

The GAP-f will ensure coordination among partners working in different areas in the paediatric field to achieve faster development and uptake of the most needed drugs for children. Implementation of the GAP-f is conceptualized as a 3-stage process:

1 Stage 1: Strategic development, consensus on activities to accelerate paediatric drug optimization and formalization of partner and stakeholder engagement.
2 Stage 2: Testing acceleration model for feasibility and results.
3 Stage 3: Launch of the GAP-f as a fully functioning, sustainable structure informed by the evaluations of Stages 1 and 2.

The first stage will promote more visibility on the future market of individual priority products and regulatory efficiencies through increased coordination of the PIP/PSP processes in the European Union (EU) and the US:

1 Development of a harmonized master protocol for paediatric clinical, bioequivalence and palatability studies;
2 Increased engagement in high-burden countries towards prioritizing registration of PADO priority products for children; and
3 Strategic assessment of timelines and durability of priority products (as prioritized by PADO).

In Stage 2, GAP-f will build on the work of the PHTI to test its model for feasibility and results. This will include facilitation of early, effective engagement between innovators and paediatric HIV clinical trials networks to collaborate on the design of initial paediatric studies. Innovative approaches to incentivize generic development of priority products and promotion of earlier collaboration between innovators and generic manufacturers so that the generics can potentially be part of innovators' development team and perform early child-friendly formulation development will be considered. In collaboration with country partners, GAP-f will develop harmonized messaging to ensure future market demand for priority products, simplified guidance for product introduction and product scale-up plans.

In its full genesis as an independent entity (Stage 3), the GAP-f will sustain and support activities and interventions proven to be effective in its initial stages. The experiences and lessons learned will inform the design of a fully functioning structure, which will coordinate and facilitate upstream and downstream activities detailed above. Evaluation of the impact of Stage 1 coordination efforts and promotion of more efficient drug trial designs in children and of Stage 2 examples of innovative financing and facilitated innovator-generic manufacturer collaboration in paediatric formulation development will be incorporated into the final design of Stage 3 of GAP-f. The GAP-f mechanism will build on the HIV experience and subsequently expand its scope to include paediatric formulations of drugs for other critical disease areas, such as tuberculosis and viral hepatitis, which present a number of similar challenges.

3 | CONCLUSIONS

The experience gained in paediatric HIV showed that the current separate work streams for development and uptake of paediatric formulations fall short to deliver optimal formulations for children and that a more structured and efficient collaboration is required. The GAP-f proposes an innovative collaborative model, endorsed by key stakeholders, which will allow accelerated availability of safe, effective, quality-assured and affordable paediatric medicines. It is essential to achieve the Start Free, Stay Free, AIDS Free super-fast-track targets of ending AIDS in children and adolescents by 2020 and will contribute to SDG 3 of reducing child mortality, ending AIDS and tuberculosis, and combating hepatitis. In addition, the GAP-f represents an example of international access to innovation and effective public-private partnerships, thus contributing also to SDG 17. The GAP-f represents an example of extensive collaboration built on existing initiatives and partners' expertise, with an ambitious overarching goal of accelerating access to best treatment options for diseases affecting children primarily in LMICs, such as HIV, tuberculosis, viral hepatitis and other infectious (and non-communicable) diseases subject to similar market failures.

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COMPETING INTERESTS

MP, LL, MW, VP, FP, MA, WK, SM, MV, JL, DJ and GS have no competing interests to declare.

AUTHORS' CONTRIBUTIONS

All authors contributed equally to drafting the content, editing and reviewing the manuscript for final endorsement.

ACKNOWLEDGEMENTS

The authors thank all stakeholders who have contributed to the development of the GAP-f concept.

FUNDING

Part of this work (SM, MV) was supported by the International AIDS Society's Collaborative Initiative for Paediatric HIV Education and Research which is made possible through funding from founding sponsor ViiV Healthcare and from Janssen, and Industry Liaison Forum, through contributions from its 2016 and 2017 Gold Partners (Gilead Sciences, MSD and ViiV Healthcare), Silver Partners (AbbVie, Alere and Janssen) and Bronze Partners (Abbott, Beckman Coulter, bioLytical Laboratories, Cepheid, Cipla, Female Health Company, Lupin Pharmaceuticals, Omega Diagnostics, Roche Molecular Systems and Sysmex Corporation). Technical expertise for this document was supported in part (GS) by the U.S. President's Emergency Plan for AIDS Relief (PEPFAR).

DISCLAIMER

This manuscript represents the views of the authors, and the findings and conclusions included here do not necessarily represent the views of the World Health Organization or the United States government.

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Tinasti K *Journal of the International AIDS Society* 2018, **21**(S1):e25045
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25045/full | https://doi.org/10.1002/jia2.25045

COMMENTARY

HIV and AIDS among adolescents who use drugs: opportunities for drug policy reform within the sustainable development agenda

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Abstract

Introduction: The international community's commitment to halve by 2015 the HIV transmission among people who inject drugs has not only been largely missed, instead new HIV infections have increased by 30%. Moreover, drug injection remains one of the drivers of new HIV infections due to punitive responses and lack of harm reduction resourcing. In the midst of this situation, adolescents are a forgotten component of the global response to illegal drugs and their link with HIV infection. The Sustainable Development Goals (SDGs) present an opportunity to achieve the global objective of ending AIDS among adolescents who use drugs, by addressing the structural vulnerabilities they face be they economic, social, criminal, health-related or environmental.

Discussion: The implementation of the SDGs presents an opportunity to address the horizontal nature of drug policy and to efficiently address the drugs-adolescents-HIV risk nexus. Adolescent-focused drug policies are linked to goals 1, 3, 4, 10, 16 and 17. Goals 3 and 16 are the most relevant; the targets of the latter link to the criminalization of drug use and punitive policy environments and their impact on adolescents' health and HIV transmission risks. Moreover, it presents an opportunity to include adolescent needs that are missing in the three drug control conventions (1961, 1971 and 1988), and link them with the provisions of the Convention on the Rights of the Child (1989). Finally, the six principles to deliver on sustainable development are also an opportunity to divert adolescents who use drugs away from criminalization and punitive environments in which their vulnerability to HIV is greater.

Conclusions: Addressing HIV among adolescents who use drugs is an extremely complex policy issue depending on different sets of binding and non-binding commitments, interventions and stakeholders. The complexity requires a horizontal response provided by the SDGs framework, starting with the collection of disaggregated data on this specific subgroup. Ending AIDS among adolescents who use drugs requires the implementation of national drugs and HIV plans based on the multi-sectoral approach and the transformative nature of the SDGs, to provide a comprehensive response to the epidemic among this key affected subgroup.

Keywords: SDGs; drug policy; people who inject drugs; adolescents who use drugs; drug control conventions; HIV key population

Received 10 May 2017; **Accepted** 11 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

Responding to paediatric HIV has been high on every national political agenda for the last decade, with encouraging results in terms of declining new infections among children by 70% between 2000 and 2015 [1]. Yet, adolescents aged 10 to 19 years old continue to pay a high toll to HIV in terms of new infections, AIDS-related deaths and lack of access to antiretroviral therapy (ART) and other relevant services. This age group represented 260,000 [81,000 to 450,000] of the total 1,800,000 [1,600,000 to 210,000] new infections (all ages) in 2016, with new infections and AIDS-related deaths expected to continue to increase [2]. Among adolescents and young people, subgroups most at risk of acquiring HIV such as those who use drugs have not been adequately addressed yet, prompting an increase in HIV infections through injecting and non-injecting drug use.

However, new HIV infections among adolescents are not all related to drug use, as illustrated in sub-Saharan Africa, where new HIV infections are high among young women and adolescent girls. In South Africa alone, adolescent girls represented 24% of all new infections in 2012 [3]. International organizations, funders, civil society and national authorities are teaming to address the stigma, the policy barriers and the lack of gender- and age-tailored interventions for this subgroup, while their investments in other subgroups, such as those who use drugs, remain marginal.

It is accurate, nevertheless, that the policy response to HIV among adolescents who use drugs (AWUD), at the international level, is extremely complex. The complexity of the response is based on multilayered interactions between a large set of conventions, political declarations and resolutions from the HIV and AIDS, drug control, and children's and human rights sectors. However, this complex response needs to be efficient, as it is necessary to address an alarming situation. While there is no disaggregated data on the prevalence of drug use or injection among adolescents, or on the prevalence of HIV among adolescents who use or inject drugs, people who inject drugs (PWID) of all age groups are the key population with new infections increasing by 30% between 2011 and 2015 [4], while the 2011 political declaration on HIV and AIDS committed its signatory countries to halve the transmission among this population [5]. Moreover, 86% of PWID who know their status did not have access to ART in 2013 [6].

To achieve the *All In* 2020 targets [7] and end AIDS among AWUD by 2030, this commentary will focus exclusively on policy development by reviewing countries' obligations through legally binding conventions (Convention on the Rights of the Child (CRC), 1989; drug control conventions, 1961, 1971, 1988) as well as non-binding commitments countries took through designated political declarations (on the world drug problem, 2009 as complemented by the UNGASS 2016 outcome document; on ending AIDS by 2030, 2016; and on the public health dimension of drugs at the WHA, 2017). It will then lay down the role of the Sustainable Development Goals (SDGs) as a general policy framework allowing a multisectoral response to HIV among AWUD, before framing HIV and drug use within the SDGs agenda to illustrate the needed policy interventions to end AIDS among adolescents by 2030.

2 | DISCUSSION

The situation of people who use drugs (PWUD), injecting and non-injecting, adults or adolescents, varies from one country to another, depending on the nature of each national epidemic, the mode of consumption of drugs, but mostly on the policy framework. In 2014, there were 11.7 million (8.4 to 19.0 million) people who inject drugs (PWID) (aged 15 to 64) globally, of which 24% resided in Eastern Europe alone. This region is highlighted as it faces the largest number of new HIV infections through drug injection as a mode of transmission in the world, and concentrates countries that oppose in policy and in practice the evidence-based harm reduction measures [8]. For instance in the Russian Federation, the country with the highest injection burden in the world with 2 million PWID (1.8 to 2.2 million) [9], HIV prevalence among young people aged less than 25 in Moscow reached 12% in 2012 [10], while it reached 37.4% – strongly linked to drug injection – among homeless AWUDs in Saint Petersburg [11]. In comparison, in France, where harm reduction services were introduced in the 1990s, PWID represented 1% of all new HIV infections in 2014 [12].

These national laws and policies to address drug use are interpreted from the drug control conventions (namely the Single Convention on Narcotic Drugs of 1961, the Convention on Psychotropic Substances of 1971 and the Convention against Illicit Traffic of 1988) [13]. These conventions objectives, as stated in the non-binding preamble, are: preserving the health and wellbeing of all; ensuring access to illegal drugs for medical and scientific needs; and fighting the "evil" of addiction. The articles of the conventions, which are legally binding for countries that ratified them, gave prominence to the latter and resulted in measures that harshly counter drug use through the "war on drugs" and the militarization of the response to drugs on a global scale. This approach to drug control among adolescents has resulted in more health and social harms than it provided solutions [14], as illustrated by the high burden of HIV and HCV among AWUD.

The 1988 Convention against illicit traffic is the only one that refers directly to underage minors, addressing the inclusion of minors in the illicit trade or the delivery of illicit drugs to them [15]. These provisions are aligned, in the text, with the article 33 of the CRC [16]. They differ in practice. Indeed, the CRC provision needs to be interpreted in terms of the whole convention: to be based on human rights and to have a positive impact on children and adolescents [17]. The Committee of the Rights of the Child has further reminded that in most countries children do not have access to drug use-related HIV prevention, and has called for harm reduction services to be available to children and AWUD, the decriminalization of drug use among this subgroup [18], as well as the need to take the best interest of adolescents as a primary consideration in all decisions that concern them [19].

And while the 2009 political declaration on countering the world drug problem does not address adolescents, the outcome document of UNGASS 2016 introduced a new chapter to address drugs and youth. Signatory countries approved to provide health services to dependent adolescent during custody or arrest, but also to address their age-specific needs and other social determinants of their involvement in the drug trade, gang-related violence and urban crime [20], elements that enhance their vulnerability to HIV as well. The UNGASS outcome document provides the first-ever negotiated agreed language on youth and drugs at the international level, and aligns with the SDG agenda in promoting universal and equitable access to health services for youth. The 2016 political declaration on ending AIDS reminded that access to HIV services is hindered for adolescents in many settings. It called for policy environment to take into account the HIV vulnerability of this group, while providing comprehensive harm reduction services to PWID – the UNGASS 2016 outcome document has failed to mention harm reduction, some countries arguing that providing paraphernalia promotes drug use. It also set target dates and treatment coverage by region for adolescents living with HIV or in risk of infection [21].

During the Post-2015 Development Agenda process, the HIV community advocated for the inclusion of the Fast-Track Strategy as a target to end AIDS [22] – currently target 3.3 – while the drug policy community did not engage in the process. During the discussions of the UN General Assembly's Open Working Group (OWG), the response to drugs appeared on the 11th session under goal 3: "by 2030, eliminate narcotic drug and substance abuse" and goal 16: "significantly reduce the irresponsible trade in arms and conflict commodities, and reduce violence and other negative impacts associated with trade in illicit drugs." [23] This prohibition-

based language was later reviewed by UN Member States who have failed to achieve their former commitments – in the 1998 and 2009 political declarations on the world drug problem – to eliminate or significantly reduce drug use globally. The final text under goal 3 is the current target 3.5: "strengthen prevention and treatment of substance abuse, including narcotic drug abuse [. . .]" [24].

The SDGs being the framework within which all new policies need to develop [25], how to use them practically to address HIV among AWUD? Here are some ways forward using existing international agreements and mechanisms to achieve ending the epidemic among youth by 2030. Being integrated and indivisible, the SDGs cover AWUD and HIV through directly two targets – 3.3 and 3.5 – but their needs cut across all the goals, while they are influenced by far more targets.

Central to addressing HIV among AWUD is target 17.18, on the need to enhance data collection in developing countries, focusing on adolescent's health, mental health and substance use [26]. For example, it remains difficult to assess the situation of growing methamphetamine use among adolescents in Myanmar, sparking a risk of an HIV epidemic through risky sexual behaviour [27], without clear and disaggregated data. The issue of data collection among this age group is a serious barrier to the HIV response in developed countries as well. Indeed, the current collection of data is based on arrests, seizures and access to treatment [28] mainly. For adolescents, the UN has called on countries to move beyond school surveys [29] to collect data. Therefore, the indicator 3.5.1 (Coverage of treatment interventions for substance use disorders to prevent substance abuse by 2030) will not support the aim of the target unless it is complemented by disaggregated data. The issue of metrics and data collection is central to the future drug policy architecture and the response to HIV among all PWID age groups, pushing countries to trigger the discussion on their global review [30].

The second most important barrier to ending AIDS among AWUD remains the equitable access to quality harm reduction, HIV and other healthcare services for this population. This is where the interaction between HIV programming, health resourcing and financing, youth protection and drug control culminate, and where the use of the SDG agenda becomes clearest on a programmatic and policy level. To achieve targets 3.3 (end AIDS) and 3.5 (prevent substance abuse) for adolescents, there is a need for an enabling policy environment to enhance access to effective harm reduction services. On the financial implications, Harm Reduction International calculated that shifting 10% of the USD 100 billion currently devoted to drug law enforcement would allow for the coverage of all harm reduction needs in the world by 2020, including for adolescents [31]. This becomes more urgent since the HIV epidemic among PWID continues to increase while no additional country introduced needle and syringe programmes (NSP) since 2014. These evidence-based services and their access are hindered by the criminalization of drug use [32], and are further refused to adolescents depending on the cultural and political contexts [33].

Moreover, the UNGASS 2016 outcome document and the 2009 drug control political declaration do not refer to harm reduction, countries not being able to get along on the use of this terminology during the negotiations for these documents. Thus, the implementation of the 2016 HIV political declaration in conjunction with drug control mechanisms at the national level is central to allow for the establishment of prevention and harm reduction services at the national level. Moreover, using the six principles to deliver on sustainable development [34] will allow for equitable access to quality services, as they call for people-based policies. Such an approach, which is starting to take place in countries as diverse as Colombia, Thailand or Ghana results in policies that focus on the needs of PWUD rather than on eliminating the substance they use regardless of the negative impact on their health and human rights.

Finally, it is necessary to remind here that to prevent HIV infection and substance abuse among adolescents, better management of their mental health is necessary, since up to 20% experience mental health disorders starting the age of 14 [35], and suicide rates are higher than among other age groups.

Another major interaction of SDGs to prevent HIV transmission among AWUD is the policy environment enabling the delivery of needed health services. This policy environment is decided through goal 16 and its targets' implementation. As currently illustrated in the Philippines, where the government envisages lowering the criminal liability age to 9 years old in an effort to enhance its "war on drugs" [36], the social determinants of the vulnerability of AWUD to organized crime and authorities' abuse are not addressed.

More practically, this means addressing the policy barriers for effective rights-based responses to HIV among AWUD: the violence (16.1) and abuse (16.2) experienced by adolescents need to be effectively countered through fair access to justice and the rule of law (16.3), accountable institutions (16.6) and non-discriminatory policies (16.b). In the case of the Philippines, the central government as well as provincial governments in charge of delivering health services need to work in collaboration with law enforcement, the judiciary, children protection services and social workers to provide an environment where AWUD are not afraid to seek services they need, that these services are available and of quality, that the criminal responsibility is lifted for use and possession of illegal drugs, and that the social and economic empowerment (10.2) and quality education (4.1) are pursued while protecting youth of legal liability for drug-related small-scale offences, in order to avoid putting them in a situation of risky sexual behaviour and prevent HIV infection and violence.

3 | CONCLUSIONS

Addressing HIV among adolescents who use drugs is an extremely complex policy issue, especially since it relies on different sets of binding and non-binding commitments by countries, and on different sets of interventions provided by different stakeholders. It needs effective coordination as well as political will and commitment. It also requires better metrics to collect data on adolescents and drug use, adolescents with dependence, as well as data on access of AWUD to healthcare and social services in all regions of the world. Most importantly, it needs the inclusion of adolescents who use drugs themselves (along with the parent or legal guardian) in the design and implementation of drug policies, in accordance with

the right of the child to be heard (article 12 of the CRC) and SDG target 16.7 on ensuring inclusive decision-making.

The SDGs provide a framework allowing for a horizontal response, taking into account all needed policies, health and social interventions, and the legislative reforms. Ending AIDS among AWUD needs to be based on the implementation of the SDGs in national drugs and HIV plans, since the SDGs are a transformational agenda for all public policies, that no target is considered met until it is met for all economic and social groups – including by PLHIV, PWID and adolescents – and that all actions advance human rights. This is the only way forward in order to reach the AWUD furthest behind in the HIV response and not to leave anyone behind and, especially key populations and their subgroups.

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COMPETING INTERESTS

The author declares no competing interests.

AUTHOR'S CONTRIBUTIONS

KT researched, analysed data and drafted this commentary.

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Chamla D et al. *Journal of the International AIDS Society* 2018, **21**(S1):e25046
http://onlinelibrary.wiley.com/doi/10.1002/jia2.25046/full | https://doi.org/10.1002/jia2.25046

VIEWPOINT

Children, HIV, emergencies and Sustainable Development Goals: roadblocks ahead and possible solutions

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Keywords: children; adolescents; HIV; SDG; climate change; emergencies

Received 9 May 2017; **Accepted** 14 December 2017; **Published** 27 February 2018

1 | INTRODUCTION

Climate change, violent conflicts, and HIV/AIDS are linked to multiple Sustainable Development Goals (SDGs) through complex pathways (Figure 1) that include food insecurity, population displacements and migration, disruptions of health and HIV services, and increased incidences of sexual based violence. This interlinkage has the potential to result in high newborn and under five mortality rates and increased burden of HIV, directly affecting SDG 3.2 and 3.3 with children and adolescents being primarily affected.

In the past two years, five severe (classified by the UN as L3) emergencies were declared with over 50 million children caught up in major conflicts and other humanitarian crises [1]. Nine of 21 countries deemed "high priority" for HIV by UNAIDS are fragile, conflict-affected, or affected by climate-related hazards. Today, more than 59 million people are displaced – 22 million more than a decade ago [2], while more than 70 million people in 45 countries are food insecure – 40% more than in 2015. There are more than 1.8 million people living with HIV in emergency settings, with children under the age of 15 years accounting for around 10% [3]. Emergencies have increasingly become protracted (long term) with an average stay in refugee camps reaching 20 years [4] – implying that children could face more HIV risks throughout their adolescence in a refugee camp. The road towards the SDGs is further constrained by rapid population growth with an estimated one billion children likely to live in Africa by mid-century, of which 217 million will be under-five and over one third living in conflict-affected zones [5].

Yet, most humanitarian plans and appeals have not been included in national development strategies, HIV interventions are largely underfunded despite high HIV vulnerability in emergency contexts [6], and most funding opportunities have been short term and focussed on immediate life-saving interventions. Similarly, the opportunities provided by investments in SDGs are not optimal in humanitarian settings. These include medium-long term funding by global financial instruments such as the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) and novel service delivery models, including enabled community systems that have had remarkable impact on improving HIV service delivery and access in countries such as South Africa [7].

These roadblocks, and a divide between humanitarian and development fields have tremendous implications for children and adolescents living with HIV in emergency contexts such that a clear way forward, building on the current global discourse on humanitarian-development nexus, remains critical.

2 | IMPLICATIONS FOR HIV

Most L3 emergencies have a potential to reverse gains in the global HIV response – including the legacy of the global plan on the elimination of new paediatric HIV infections. This five-year plan was developed in 2011 with the aim of reducing new paediatric HIV infections by 90% and AIDS-related maternal and paediatric mortality by 50% [11]. Over the course of the Global Plan, more than 60% of annual new HIV infections were reduced, translating to 1.2 million new infections among children averted [8]. However, among countries affected by emergencies such as Nigeria, the reduction in new infections remains as low as 40% [8]. The effects of climate change are more profound in Africa and Asia, where there is a disproportionately high burden of HIV. Of the nine fragile countries with high HIV burden, five are in Central and West Africa, contributing 45% of the global number of new paediatric HIV infections with Nigeria alone accounting for more than 27% [9].

As more fragile countries have graduated to middle income status, development assistance for HIV will likely reduce, as for instance, domestic contribution thresholds by

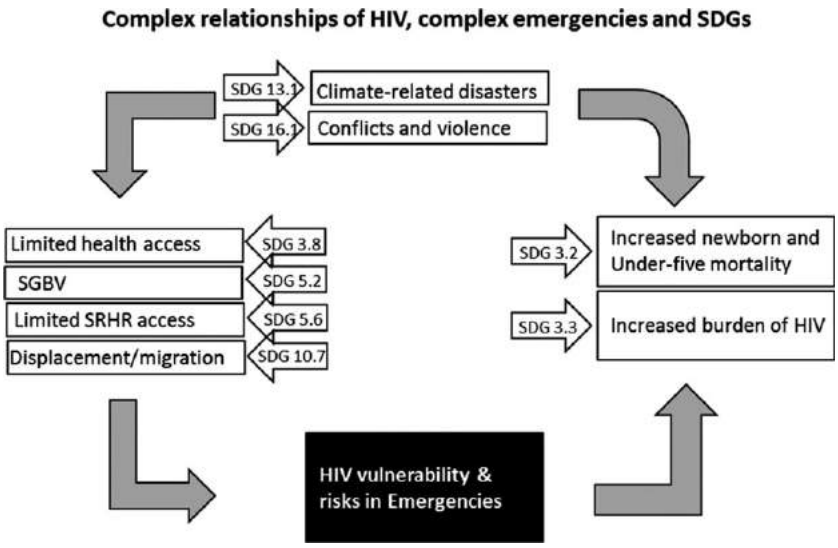

Figure 1. Complex relationship of HIV, emergencies and SDGs. SGBV, sexual and gender-based violence; SRHR, sexual reproductive health and rights; SDG, Sustainable Development Goals.

eligible middle income countries for grants from the GFATM is 20% to 60% – a significant rise from 5% for developing economies [10]. Without significant financial resources, these fragile states will not be able to sustain their HIV response.

3 | WAY FORWARD: HUMANITARIAN-DEVELOPMENT NEXUS AND HIV RESPONSE

The humanitarian-development nexus provides an important framework that could bridge a divide between these two fields that are guided by two separate, but complementary global processes – Agenda 2030 for sustainable development [16] and Agenda for Humanity [17], endorsed during the World Humanitarian Summit in 2016. The nexus calls for joint analysis and planning; defining collective outcomes; and joined-up programming [18]. Adapting this nexus in HIV responses during the emergencies could provide a way forward for addressing the roadblocks previously mentioned. The first step could be understanding the climate change or conflict risks that could impact HIV response through a joint analysis using current evidence and existing analytical frameworks. It is also important to note during the analysis that different types of emergencies such as *acute* or *protracted*, could have different needs requiring different programme designs. This risk analysis could form the basis of risk-informed joint planning, allowing synergies between HIV and humanitarian interventions.

Joined-up programming could be facilitated with sustainable financing by optimizing development and humanitarian funding mechanisms [14], and ensuring systematic integration and transition of humanitarian interventions to national or local authorities. Linking early recovery, resilience building and health system strengthening will ensure a quick development pathway after an emergency. Empowering communities and their infrastructure is equally important for resilience and improved outcomes. There is mounting evidence of the importance of community health workers in the reduction in under-5 mortality rate [15] that could also benefit children and adolescents living with HIV. Some promising practices are also emerging such as GFATM's establishment of a special envelope for "challenging operating environments" [19] that aims to expand access to services in manmade or natural crises. New models of service delivery and innovations such as Point-of-Care diagnostics for dual HIV and syphilis testing [20], could also be adapted in emergencies.

Collective outcomes should be defined from the onset of the emergencies, and a robust monitoring and evaluation system put in place to track progress towards SDGs. Sustaining peace resolutions, is critical for maintaining this progress. The renewed momentum in HIV workstreams spearheaded by the new post-Global Plan programming framework, *Start Free, Stay Free, AIDS Free* [12], provides an opportunity for moving forward with this agenda. Creating a humanitarian-development nexus is the centrepiece for the *new way of working* arising from the global humanitarian summit and a major theme in the Sendai framework for Disaster Risk Reduction 2015 to 2030 [13]. These are critical elements for achieving SDGs without leaving behind children and adolescents living with HIV in humanitarian crises.

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COMPETING INTERESTS

Authors declare no competing interests DC, CL and PI have not received grants or speakers fees from any commercial body in the preparation or submission of this manuscript

AUTHORS' CONTRIBUTIONS

DC conceptualized the article, established links between emergencies and HIV, and drafted the first draft. CL and PI reviewed the draft, elaborated links with SDGs and contributed to the writing of the manuscript

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Website: www.jiasociety.org

eISSN: 1758-2652

Contact details

Editorial office:
Avenue de France, 23
CH-1202 Geneva
Switzerland

Email: editorial@jiasociety.org

Tel: +41 (0) 22 710 0800

Publisher

The *Journal of the International AIDS Society* is published by John Wiley & Sons Ltd on behalf of the International AIDS Society

John Wiley & Sons Ltd
9600 Garsington Road
Oxford, OX4 2DQ UK

Telephone: +44 1865 776868

Email: customer@wiley.com

Production Editor

Jose Pedro Costa Moreira (email: jcostamore@wiley.com)

Abstracting and Indexing Services

The *Journal of the International AIDS Society* is indexed in a variety of databases including PubMed, PubMed Central, MEDLINE, Science Citation Index Expanded and Google Scholar. The journal's impact factor is 6.296 (*2016 Journal Citation Report® Science Edition – a Clarivate Analytics product).

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